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LIQUID CRYSTAL AND HYDROPHILIC GEL MEDIA FOR IONTOPHORESIS

DISSERTATION

Presented in Partial Fulfillment of the Requirements for
the Degree Doctor of Philosophy in the Graduate
School of The Ohio State University

By

Manesh A. Dixit, B.Pharm.

*****

The Ohio State University

1999

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ABSTRACT

The necessity of parenteral administration of certain drugs due to their physical-chemical properties, especially proteins and peptides, motivates the quest for more efficient and versatile transdermal drug delivery systems. Iontophoresis, electrically facilitated transdermal drug delivery, is one such system. Most research in iontophoresis has focused on parameters such as electrical factors, effects of current on the skin and on the device used, but with few exceptions on the donor formulations used. This study was conducted therefore to develop non-solution donor media suitable for iontophoresis, but with a transport environment similar to that of a fluid, and free of extraneous ions which can compete with drug for the current. This study is intended to provide additional possibilities for managing drug delivery, not only in iontophoresis, but also in other types of electrically assisted drug delivery system. The work presented herein focuses on the in vitro iontophoretic and passive release of lidocaine H⁺, a model drug, from various liquid crystalline and gel formulations across an artificial membrane in a newly designed iontophoretic apparatus.

The custom designed iontophoretic cell was characterized and the iontophoretic data was compared with that reported in the literature. The pulling of drug ions out of the receiver compartment by the charge on the electrode of opposite polarity does not appear to affect
iontophoretic drug delivery. The reason for this is that migration of drug ions out of the membrane toward the electrode of opposite polarity does not occur to a significant extent. These findings are significant for the positioning of electrodes in clinical applications and for in vitro studies.

Lamellar liquid crystalline formulation of monoolein showed a nonlinear increase in lidocaine H\(^+\) flux with increases in current. Furthermore, formulations consisting of cubic, hexagonal and lamellar mesophases of poloxamer were prepared. The cubic mesophase formulation contained poloxamer 334, whereas, the hexagonal and lamellar contained poloxamer 184. These mesophases were identified by polarized light microscopy and \(^3\)H-NMR method. Cubic, hexagonal and lamellar mesophases were formed progressively as the water content of system decreased. The observed decreases in passive diffusional fluxes and conductivity of these mesophases were consistent with decreases in the water contents and increased resistance to ion transport resulting from the characteristic structure of liquid crystals. During ionic transference controlled drug release, the poloxamer mesophase formulations behaved as if no liquid crystalline structure was present and followed electrodiffusion theory, as would an aqueous solution. This behavior demonstrates the potential of poloxamer mesophases as drug containing media for iontophoresis which due to their physical-chemical properties may have advantages over conventional iontophoretic drug delivery media.

Gel matrixes consisting of agarose (high EEO) in conjunctions with carbomer 934 were loaded with lidocaine HCl. Presence of carbomer in agarose gel increased steady state
iontophoretic fluxes upto 40% while passive diffusional fluxes remained relatively constant. The increases in iontophoretic fluxes were attributed to the effect of carbomer on the structure of agarose gel, increased endoelectroosmotic flux and electrostatic barrier to the transport of counter-ions due to the fixed negative charges on the carbomer chains. Thus, data suggests that manipulating ionic charges of the donor formulations provides a means of enhancing iontophoretic fluxes.
To my parents
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CHAPTER 1

BACKGROUND

1.1 Facilitated transdermal drug delivery

In recent years, there has been growing interest in the development of alternative routes of drug administration which are comparable to intravenous infusion but without its potential problems and inconveniences. The skin is a site for regional therapy of skin disorders, but because of its immense surface area, voluminous blood flow and easy accessibility it has become the focus of drug delivery research as an inlet for painless, continuous administration of drugs for systemic purposes (1, 2).

Transdermal drug delivery systems for the systemic administration of several drugs including scopolamine, nitroglycerin, isosorbide dinitrate and estradiol have been developed and marketed (3). The advantages of such controlled percutaneous drug delivery systems are as follows (4):

1. They are free of the risks and inconveniences of intravenous therapy.

2. They avoid the first pass effect and variations in bioavailability associated with
the oral route of administration.

3. They provide controlled drug administration and reduce the frequency of dosing including those with short biological half-lives.

4. Patient compliance improves because of their simplified therapeutic regimens and administration.

5. They allow easy and rapid termination of drug administration, if needed.

Transporting large, hydrophilic drugs across formidable barriers such as skin requires energy. Passive transdermal drug delivery of several drugs based on a concentration gradient, or more specifically, an effective concentration (thermodynamic activity) gradient has been successful for drugs with small molecular size and a lipophilic nature. The delivery of large and hydrophilic drug molecules across the skin can be energetically difficult. The additional source of needed energy can be supplied in the form of a sound wave (phonophoresis), light, heat, and electric fields (5, 6). By contrast, other materials, such as ion-pairing complexers, prodrugs and permeation enhancers act by reducing the activation energy of the transport barrier (7).

The advantage of modulating drug delivery by the aid of an external electric field has made electrically assisted transdermal drug delivery popular in pharmaceutical research (Figure 1.1). Electrically assisted transdermal drug delivery primarily includes iontophoresis, electroporation and electroincorporation. In electroporation, high voltages applied momentarily across the skin reduce its barrier properties (8-10). This approach does not
provide a driving force for drug transport, but rather increases skin permeability by creating transient pores. A concentration gradient is still needed to force the drug across aqueous pores. Electroincorporation is similar to electroporation except particles such as liposomes are used to carry the drug (11). Currently, most electric assisted transdermal drug delivery is based on iontophoretic delivery and that will be the focus of this study.

1.2 Iontophoresis

Transdermal iontophoresis mainly refers to the transfer of ionic compounds through the skin using low levels of an electric field (12). Although the usefulness of small magnitudes of current in enhancing tissue penetration of charged compounds was first demonstrated almost hundred years ago, recent developments in electrical and electronic instrumentation, electrochemistry, and polymer sciences have advanced iontophoretic technology and made it a center of attention of drug delivery research (13).

In iontophoresis, drug formulation traditionally is placed in contact with an electrode of the same polarity as the drug ions, with an electrode of the opposite polarity with respect to drug ions is placed with an electrolyte formulation at a nearby site on the body surface. These two electrodes are connected to a power supply capable of delivering small amounts of current. The magnitude of the current is well below the pain threshold. The current is applied for an appropriate amount of time to carry drug ions through the skin to the dermal layer where they can diffuse into blood capillaries (Figure 1.2).
There are several advantages as well as disadvantages of iontophoresis compared with those of passive transdermal iontophoresis (14). The potential advantages are:

1. It is capable of delivering higher doses of therapeutic agents per unit time and area of applications.
2. It is able to administer relatively high molecular weight hydrophilic compounds such as insulin.
3. The delivery of drugs can be programmed for intervals of time, for use on demand, for pulsatile release, etc.

The potential disadvantages include:

1. It is a relatively complex and instrumentation intense system.
2. The electrical instability of drugs is still a relatively unknown factor.
3. Unknown local and possibly systemic toxic effects resulting from prolonged exposure to current.
4. High cost of development and manufacture.
5. Can not be used by patients using heart pace-makers or other electrical devices.

1.2.1 History of iontophoresis

In 1747 Veratti proposed the idea of using current to deliver drug into a tissue (12). The first scientific experiment of transdermal iontophoresis was performed by LeDuc in 1908 who introduced the term ‘ionotherapy’ (15). He was able to kill rabbits by the delivery of
strychnine sulfate and potassium cyanide from positive and negative electrode compartments, respectively. His experiments proved that ionic medications penetrate the skin under the influence of an electric field and may exert local as well as systemic effects. Licht S., et al, has given exhaustive review on electrotherapy including iontophoresis upto 1965 (16). More recent reviews have been published by Chien (17), Tyle (18), Singh and Roberts (19).

Line-operated units for iontophoresis of pilocarpine were approved by the FDA in the 1980's and were widely used by physicians to assist the transport of pilocarpine into the skin to induce sweat for chloride assays diagnostic in cystic fibrosis (20). A battery-operated device, Drionic®, was introduced by General Medical Company for home treatment of hyperhidrosis in 1982 (21). Medtronic, Inc. markets a cystic fibrosis iontophoretic diagnosis device (22), and Phoresor®, a sophisticated multipurpose iontophoresis device for medicine, dentistry and physical therapy has been developed by Motion Control, Inc. (23). Recently, Iomed, Inc. introduced an iontophoretic transdermal patch-like device for the administration of lidocaine or dexamethasone (24, 94).

1.2.2 Electrophysicochemical aspects of iontophoresis

Recent developments in empirical and theoretical studies of iontophoresis have helped identify the important parameters affecting iontophoretic drug transport. The critical parameters of this process include the nature and composition of the contents of the donor and receiver compartments; the physical and chemical properties of the target drugs; the characteristics of the skin barrier; and electrical factors as will be discussed below.
1.2.2.1 Physicochemical aspects

1.2.2.1.1 Drug
Iontophoresis requires that drug be ionized for effective iontophoretic delivery and electrochemically stable to prevent production of toxic byproducts. The mobility of ions increases with increases in the number of charges on the ions and can be estimated from conductivity measurements. Gangarosa, et al, measured the conductivities of several drugs, such as local anaesthetics, vasoconstrictors, corticosteroids, anticancer drugs and antiviral agents, to determine their suitability for iontophoretic drug delivery (25). Del Terzo, et al, have shown an inverse relationship of the hydrophobicity of a series of alkanoic acids of increasing chain length with iontophoretic delivery due to decreasing convective bulk flow (26). Guy, et al, proposed the presence of adjacent hydrophobic and cationic groups in a LHRH oligopeptide was responsible for the neutralization of the skin's negative charge, thereby, resulting in decreased drug delivery (27). It has been reported that iontophoretic delivery is inversely related to a compound’s molecular weight or molar volume due to decrease in mobility (28).

1.2.2.1.2 Drug concentration
The Nernst-Planck equation indicates that increases in iontophoretic transport rates occur with increases in drug concentration (see Equation 1.2). This direct relationship has been shown by Miller and Smith (29), Wearley, et al, (30), and others (31). Drug concentration
in these studies was less than 100 μM. On the other hand, hydromorphone delivery from unbuffered solutions having hydromorphone concentrations in the range of 10-800 mM through porcine skin was independent of drug concentration (32).

In iontophoresis, an electric potential gradient is the main driving force behind the flux across the skin and increasing drug concentration leads to increases in the flux up to a limit after which flux remains essentially constant or sometimes decreases (33). This nonlinear dependency of iontophoretic flux on concentration appears to correlate with drug aggregation, alterations in electroosmosis, ion-pairing/complexing, and saturation of ion-conducting pathways in the membrane (34, 35).

Iontophoretic fluxes at moderate currents are mainly determined by the diffusivity of the drug and the counterions on the opposite side of the membrane in the receiver compartment. If drug diffusivity is relatively smaller than that of the counterions in the receiver compartment, then iontophoretic drug delivery becomes less dependent on drug concentration (36).

1.2.2.1.3 pH

pH has a direct influence on iontophoretic drug transport as it determines the degree of ionization of the drug and of the charged groups in the barrier, if any are present. The charged groups of the barrier, depending on their ionization, can control solvent flow through the barrier when under the influence of electric field. In some cases, drug stability is also highly dependent on pH. The pH changes during iontophoresis generally result from the
electrolysis of water. The H\(^+\) and OH\(^-\) ions generated by the electrolysis of water are highly mobile because of their small ionic sizes and unique mechanism of aqueous ionic transport (37). Inorganic ions, such as Na\(^+\), K\(^+\), and Cl\(^-\), which are common culprits that can reduce drug transport, have 3-5 times smaller mobilities than do H\(^+\) or OH\(^-\) ions.

1.2.2.1.4 Extraneous ions

Extraneous ions are generated by the addition of buffer or other salts to the formulation, and are competitors to the drug ions for the available current. In this context, lower iontophoretic fluxes result from increasing the ionic strength of a formulation (38, 39). This results from decreases in drug mobility due to the presence of extraneous ions in the hydration radius of the drug ions. The simple solution to this problem is to avoid the use of a buffer or to use a buffer with a minimum ionic strength, if possible. In case of necessity, large size extraneous ions should be used since they are less mobile. Polymeric buffers have been used to enhance iontophoretic drug delivery (40). Polymeric buffers are large molecular weight compounds carrying multiple charges, therefore, they are effective at small concentrations and do not compete with drug ions to a significant extent. For example, the use of a poly(methyl vinyl ether maleic anhydride) buffer increased the iontophoretic delivery of thyrotropin releasing hormone (MW 362; pKa 6.2) and desamino tyrosyl lysyl prolineamide (MW 414; pKa 10.5) about 4 to 6 fold compared to that when McIlvaine buffer (citric acid and Na\(_2\)HPO\(_4\)) was used (41).
1.2.2.2 Electrical factors

1.2.2.2.1 Current

It is well known and accepted that iontophoretic fluxes are proportional to the duration and magnitude of the applied current (39, 42-44). The iontophoretic flux can be determined from the transport number as given below in Equation 1.1:

\[ J_i = \frac{t_i \times I}{|Z_i| \times F} \]

[1.1]

where, \( J_i \) is the iontophoretic flux; \( t_i \) is the transport number of drug; \( I \) is the current; \( Z_i \) is the ionic charge; and \( F \) is the Faraday constant. The fraction of current carried by drug ions, i.e., the drug delivery efficiency, depends on the mobility and concentration of the drug and other ions present in the system (45). In addition to the duration and magnitude of the applied current, drug delivery depends also on the nature of applied current. Direct, alternating and pulsed current of various waveforms, such as square and sine, have been used in iontophoresis (46-48). Contrary reports of the effectiveness of a pulsed current in iontophoresis has been reported (49). Pulsed current iontophoretic drug delivery is also dependent on the waveform frequency and on:off ratio of an applied pulsed current. Chien, et al, found a pulse current of 2 kHz frequency having a 1:1 on:off ratio gave a higher iontophoretic delivery of insulin (50). Local skin damage due to application of current in iontophoresis was shown to be reduced by the use of a periodical current since skin can depolarize and recover during the off periods (51).
1.2.2.2 Electrodes

The electrodes transform electronic current into ionic current at their interface with an aqueous solution. Inert electrodes such as platinum and carbon electrolyze water and generate hydroxyl and hydronium ions (29, 45, 51). Therefore, the pH in the cathode compartment becomes more basic while that in the anode compartment becomes more acidic. These ionic byproducts not only alter the pH but also create a drag on drug delivery by competing with drug ions for current. In addition, the pH shifts are also detrimental to drug stability. Salt bridges and ionic exchange membranes have been used to alleviate this problem (52, 53). Active electrodes such as Ag/AgCl do not cause electrolysis of water and are widely used in iontophoresis. However, Ag/AgCl electrodes have been reported to cause precipitation of peptides (29, 51). The surface area of electrodes should be properly designed so that the ionic current is uniformly distributed over the entire surface area.

1.2.3 Theoretical considerations

1.2.3.1 Iontophoretic models

Various mathematical models have been developed and investigated for the prediction of iontophoresic drug transport. These models, along with varying degrees of complex assumptions associated with them, are useful in predicting reasonably accurate values for parameters such as flux and lag time (54, 55). The most commonly used form of the Nernst-Planck equation for electrodiffusion is given below (Equation 1.2). From this, the unidirectional transport of ions in a dilute solution under an influence of electric field can be
characterized.

\[ J_i = -D_i \frac{dc_i}{dx} - \frac{D_i Z_i F c_i}{RT} \frac{d\Phi}{dx} \]  \[1.2\]

where, \( J_i \) is the flux of ionic species \( i \) in a convective free medium; \( D_i \) and \( c_i \) are its diffusion coefficient and concentration, respectively; \( R \) is the gas constant; \( T \) is the absolute temperature and \( d\phi \) is an electric potential over the distance \( x \). The concentration (\( c_i \)) and electric field strength (\( E = d\phi/dx \)) at any point within the membrane are functions of position within the system (55).

The Nernst-Planck equation is a combination of Fick's first law of diffusional force (first term in Equation 1.2) and additional force proportional to the electric field at any point in the medium (second term in Equation 1.2). The Nernst-Planck equation assumes that ionic mobility is directly proportional to its diffusion coefficient, that the activity coefficient is constant throughout the medium and that solvent velocity is zero, i.e., a convection free medium (55). Ionic transport in a convection free medium is completely specified by Equation 1.2 and the Poisson equation (Equation 1.3) together.

\[ \frac{d^2 \Phi}{dx^2} = -\frac{\rho}{\varepsilon} \]  \[1.3\]

where, \( \varepsilon \) is the permittivity of the membrane and \( \rho \) is the local space charge density.
Equations 1.2 and 1.3 can be solved by making assumptions of electroneutrality or constant electric field in the membrane (55). The constant electric field approximation is appropriate when membranes are thinner than space charge layers at the boundaries of the membrane, i.e., the Debye length or when the total ionic concentrations on both sides of the membrane are equal. In an electroneutrality approximation to the Nernst-Planck and Poisson equations, the bulk of the membrane is assumed to be electroneutral since the membrane is thicker than the space charge layers at its boundaries.

Solvent flow in ion transport across a charged membrane upon the application of an electric field (electroosmosis) can be accounted for by simply incorporating an additional term in Equation 1.2 (56). The modified Nernst-Planck equation is then:

$$J_i = D_i \frac{dc_i}{dx} - \frac{D_i Z_i F c_i}{RT} \frac{d\Phi}{dx} + v_c (1 - \sigma_i)$$

[1.4]

where, $v$ is the solvent velocity and $\sigma_i$ is the reflection coefficient of solute at the solution-membrane boundary. The reflection coefficient is an indicator of the efficiency with which solvent carries solute through the membrane. The transport models mentioned above can be further simplified by making the concentration of ions in the membrane functions of ionic concentration in the external phases surrounding the membrane. Establishing boundary conditions relating electrochemical potentials across membrane-solution interfaces is a simple approach in the absence of an external electric field (57). Kinetic equations have been derived for ion transport in the presence of an electric field to provide the boundary conditions (58).
1.2.3.2 Electroosmosis

Electroosmosis is bulk fluid flow coupled with electrically induced migration of ions in an anticonvective medium, i.e., a porous medium having fixed charges (59-63). This bulk fluid flow always occurs in the direction of migration of counterions and could be in the same direction of current (positive electroosmotic flow) or against the direction of current (negative) depending on the charge of the membrane. Thus, it could enhance or decrease drug transport depending on the charge of the drug molecules. The isoelectric point of a skin is between pH 3 and 4. Therefore the pores in skin are negatively charged at physiological pH which facilitates the transport of cations compared to anions (64). Electroosmotic flow is caused by an electrical volume force acting on the mobile counterions to maintain electroneutrality in a medium bearing net charges. It is not dependent on a concentration gradient, but is proportional to a potential gradient under conditions of equal temperature, pressure and fluid composition on both sides of the membrane (65). Convective fluid flow results from pressure differences induced by an applied voltage (66, 67). The terms electroosmotic and convective flow are used interchangeably. The primary physico-chemical factors which determine electroosmotic flux are the net charge density of the anticonvective medium, the ionic strength and viscosity of the electrolyte, and the magnitude of the applied electric potential (68). The role of electroosmotic flow in transdermal iontophoresis has been widely discussed. Higuchi, et al, proposed a modified Nernst-Planck equation by incorporating the effect of convective solvent flow (62). The dimensionless Pelcet numbers characterize the effect of convective solvent flow on the flux of the drug permeant as given by Equation 1.5 below (62):
\[ P = \frac{v^2 x}{D} \]  

where, \( P \) is the Pelcet number; \( v \) the velocity of the solvent; \( x \) the membrane thickness; and \( D \) the diffusion coefficient of the drug. This equation predicts that the effect of electroosmosis on iontophoretic drug delivery is inversely related to drug diffusivity, i.e., directly proportional to molecular size, which was later proved by Peck, \textit{et al.} (69).

### 1.2.4 Skin permeation chemical enhancers

Iontophoretic flux through the skin can be influenced by the pretreatment of the skin or the co-iontophoresis of another compound with the drug (71-76). Riviere, \textit{et al.}, reported that vasoconstrictors such as epinephrine reduced the iontophoretic delivery of drug when administered together; whereas, vasodilators such as tolazoline increased iontophoretic drug delivery in the isolated, perfused skin flap model (75). Wearly, \textit{et al.}, used N-decylmethyl sulfoxide as a skin permeation enhancer for the iontophoretic transport of azidothymidine (73). Hydration of the skin has also resulted in enhanced iontophoretic drug delivery (71). Srinivisan, \textit{et al.}, pretreated hairless mouse skin for two hours with ethanol and found an increased iontophoretic delivery of insulin compared to iontophoresis without pretreatment (71). Gay, \textit{et al.}, reported that the iontophoretic delivery of piroxicam was increased at higher currents upon the addition of oleic acid; whereas, at lower currents it was reduced (74). It was proposed therefore that negatively charged oleate ions competed with piroxicam for the current, resulting in reduced iontophoretic delivery at low currents. At higher currents,
however, enough oleic acid had apparently entered the skin to modify lipoidal pathways, thereby, enhancing piroxicam delivery (74). Other mechanisms for such synergistic effects include vasomodulation, extraction of skin lipids and enhanced lipid fluidity (76).

1.2.5 Skin barrier

Stratum corneum, the outer layer of the skin, is the major obstacle to drug transport in transdermal drug delivery and the determinant of the electrical resistance for current conduction through the skin. Drug molecules can cross the stratum corneum by the transappendageal shunts, or by intracellular or transcellular and/or intercellular or paracellular pathways (77, 78). Hair follicles and sweat glands (the transappendageal shunts) are paths of low resistance since they provide an aqueous environment for compounds to traverse the stratum corneum (79, 80). Charged dyes have been used to identify the sweat gland pathways in iontophoresis (81). In vitro experiments with vibrating probe electrodes indicated that appendageal pathways were prime conduits of current transport in hairless mouse skin (82). Scott, et al, studied the transport of Fe(CN)$_6^{4-}$ and Fe$^{3+}$ in opposite directions and recorded the presence of prussin blue precipitate (Fe(Fe(CN)$_6$)$_3$) by video microscopy which indicated the pathways of low resistance (83). All of these and other studies suggested that the appendageal pathways were the major routes of current transport under the influence of an electrical field (84). However, intercellular and intracellular pathways also provide routes for iontophoretic transport as has been shown for excised human skin, and for in vivo pig skin by transmission electron microscopy (85, 86).
1.2.6 Applications of iontophoresis

Iontophoresis is a promising alternative to parenteral drug delivery for certain drugs and therapies. It has been explored for the administration of peptides and proteins since they are charged and require parenteral administration (87). Insulin, arginine-vasopressin, thyrotropin releasing hormone, gonadotropin releasing hormone, leuprolide, cholecystokinin-8analogue, α-chymotrypsin, and other small peptides have been administered by iontophoresis (88-91). In dentistry, iontophoresis of local anesthetics is employed (92). For hyperhidrosis treatment, iontophoresis of water, polidine methyl sulfate, atropine sulfate and glycopyrrnium bromide has been used (93). Antiinflammatory drugs such as hydrocortisone, dexamethasone, xylocaine and salicylate have been delivered by iontophoresis (94). Iontophoresis has also been suggested for delivering drugs for ocular infection, arrhythmia and Parkinson’s diseases (95-99). The advent of genetically engineered small therapeutic molecules may further drive the interest in iontophoresis.

1.2.7 Skin toxicity

The most commonly reported unwanted cutaneous effects due to the passage of current are skin irritation and burning (100). Other effects include erythema, contact dermatitis, discoloration of the skin and ‘red mottling’ under the drug containing electrode (101-106). Iontophoretic therapy is reported to be innocuous when currents of less than 0.5 mA cm^-2 are used for a short period of time (about 20 minutes) (107). Possible toxic effects due to the penetration of metal ions from the electrodes into the skin and tissues are not known.
1.3 Liquid crystals

“Liquid crystal is a phase structure possessing long range order along at least one direction, while at the same time being disordered relative to crystal states” (108). This intriguing state of matter exhibits the properties of both the solid and liquid states. Besides these, liquid crystals exhibit properties that are unique to this phase, e.g., temperature sensitive color changes (109). In addition, liquid crystalline phases are thermodynamically stable (108). They are also sensitive to external forces such as magnetic and electric fields, which can cause significant changes in their properties, e.g., viscosity (110-113). Attempts have been made to establish the relation of liquid crystals to living cells (109). In addition to their roles as analytical and diagnostic tools in medicine and pharmacy, liquid crystals have been used in drug delivery systems including transdermal delivery, for various purposes such as to enhance solubility, stability, and to achieve controlled release (114). In the transdermal delivery area, liquid crystals are also finding applications as model membranes not only for screening drugs for transdermal delivery, but also for elucidating relationships in basic studies involving skin (115, 163). There are two kinds of liquid crystalline phases, thermotropic and lyotropic (108). The thermotropic liquid crystals are temperature dependent. For example, when cholesteric materials are heated, they form liquid crystalline phases before melting. Thermotropic liquid crystals are further subdivided into smectic, i.e., a threadlike structure, and nematic, i.e., a stratified structure. Lyotropic liquid crystals require solvent along with a minimum thermal energy to form the liquid crystalline state. Therefore, they are also called
as thermolyotropic liquid crystals. Solutions of various surfactants form lyotropic liquid crystalline phases. Lyotropic crystals are divided into cubic, hexagonal and lamellar liquid crystals. The characteristics of these phases are given in Table 1.1 (109).

1.4 Physical gels

"Gel is an infinitely large macromolecule or supermacromolecule, which forms a network extending from one end to the other and occupying the whole reaction vessel" (116). There are two kinds of gels, chemical and physical. Chemical gels consist of covalently cross linked networks; whereas, in physical gels, three-dimensional structure is maintained by noncovalent interactions such as ionic associations, hydrophobic interactions, stereocomplex formation and hydrogen bonding between the macromolecular segments (117). The structure of physical gels is bolstered further by associations of fractions of polymer chains to form "junction zones". The nature and number of junction zones determine the macroscopic and microscopic properties of the gels. These junction zones can be altered by changes in the pH, ionic strength, temperature, electric field and composition of the gels, leading to phase transitions (117). These phase transitions result from changes of both the repulsive intermolecular forces and the attractive forces which act against each other in maintaining gel structure. Physical gels can be formed by first dissolving a polymer in a suitable solvent and then precipitating it out. This can be generally achieved by dissolving polymer in a solvent at high temperature followed by cooling the mixture to form a gel, or by adding an unfavorable solvent to a solution of the polymer (117). Agaroses, alginates, gelatins, pectins,
chitosans, carageenans, poloxamers and polyphosphazenes form physical gels in water (117). Chien, et al, used chemical gels of polyacrylamide, PHEMA (poly(2-hydroxyethyl methacrylate) and carbomer 934 for the iontophoretic delivery of peptides and proteins (118). Bannon, et al, have quantified the iontophoretic release of nicotine and salbutamol sulfate from agar gels (119).
### Characteristics of Lyotropic Liquid Crystalline Phases

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cubic liquid crystal</th>
<th>Hexagonal liquid crystal</th>
<th>Lamellar liquid crystal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long range order</td>
<td>Three dimensional</td>
<td>Two dimensional</td>
<td>One dimensional</td>
</tr>
<tr>
<td>Freedom of movement</td>
<td>None</td>
<td>One direction</td>
<td>Two directions</td>
</tr>
<tr>
<td>Surfactant concentration</td>
<td>Low</td>
<td>Intermediate</td>
<td>High</td>
</tr>
<tr>
<td>Viscosity</td>
<td>Very viscous</td>
<td>Viscous</td>
<td>Moderately viscous</td>
</tr>
<tr>
<td>Microscopic properties</td>
<td>Isotropic</td>
<td>Middle soap texture</td>
<td>Neat soap texture</td>
</tr>
</tbody>
</table>

**Table 1.1** Characteristics of lyotropic liquid crystalline phases.
Figure 1.1  Total number of research articles on facilitated transdermal drug delivery from 1970 to 1998 (source: IPA).
Figure 1.2 A schematic diagram of conventional iontophoresis.
CHAPTER 2

STATEMENT OF THE PROBLEM

By necessity, certain drugs due to their physical-chemical properties, especially proteins and peptides, must be administered by the parenteral route. As a result, there is a need for more efficient and versatile transdermal drug delivery systems capable of delivering these drugs in therapeutic amounts. Iontophoresis, electrically facilitated transdermal drug delivery, is one such system. Most research in iontophoresis has focused on parameters such as electrical factors, effects of current on the skin and on the device used, but with few exceptions on the donor formulations used (49, 100, 120-126). Factors such as the electrochemical stability of the formulation and competition for current by other ions which reduces drug transport, offer additional challenges to the formulation of an iontophoretic drug donor media over traditional transdermal formulations. Commonly used iontophoretic formulations are either solutions or hydrogels (118, 119). The loading of a drug solution into an iontophoretic device and enclosing it uniformly between the electrodes and the skin in order to complete an electrical circuit without seepage has always been troublesome. Most hydrogels used in iontophoresis are chemical gels consisting of extraneous ions such as free radicals, polymerization initiators, cross linking agents, residual monomers, buffer ions and other materials required for
polymerization but generally not regarded as safe can create a drag on drug transport and delivery (118). The work herein is intended to provide additional possibilities for managing drug delivery, not only in iontophoresis, but also in other types of electrically assisted drug delivery system to make these modes of administration more useful and adaptable. The objectives of this research project were as follows:

- To develop electrically conductive, physiologically acceptable, clinically applicable, semisolid or non-solution donor media suitable for iontophoresis, but with a transport environment similar to that of a fluid, and free of extraneous ions which can compete with drug for the current.

- To investigate both the passive diffusional and iontophoretic drug transport from these donor systems in a custom designed in vitro model for iontophoresis.

- To optimize drug delivery from these media and to characterize in vitro their applications in electrically assisted drug delivery.
CHAPTER 3

IONTOPHORESIS APPARATUS

3.1 Introduction

In clinical iontophoresis, the drug formulation is traditionally placed under an electrode of the same polarity as the drug and an electrode with opposite polarity with respect to the drug ions is placed in contact with an electrically conductive placebo formulation at a nearby site on the body surface. These two electrodes are connected to a power supply capable of delivering small accurate amounts of current. A current of magnitude well below the pain threshold is allowed to pass through the circuit for an appropriate amount of time to drive the drug ions through the skin barrier. To model this arrangement, a commonly used in vitro iontophoresis apparatus contains a membrane (artificial or skin) positioned between two half cells (donor and receiver) placed side-by-side (45). Each half cell contains one of a pair of electrodes, thereby making this arrangement a poor simulation of the clinical configuration. This kind of arrangement has other drawbacks such as the absence of the removal of drug ions from the receiver compartment through the skin, if any, by the electrode of opposite polarity; the possibility that electrochemical degradation of the drug can occur at the electrode surface of
opposite polarity with respect to drug ions and therefore be a component of the receiver compartment fluid; and a cumbersome loading of non-liquid formulations into the half cells.

Several new static or flow through, horizontal or vertical types of cells consisting of up to three compartments that are capable of good temperature control and ease of sampling have been designed to mimic clinical conditions more closely (121, 124, 125). However, these cells are generally rather complex in their design, the experimental procedures are complicated, solvent evaporation from the electrode chambers can occur with resulting changes in the composition of the fluid in the electrode chambers, and there is generally poor control of the distance between the electrodes and the membrane.

A newly designed iontophoretic cell was therefore used for this research. A brief description of this novel custom designed cell and iontophoresis apparatus and procedures will be given in a following section. A detailed description has been given by Wen-Hsia Chen (126). The iontophoretic data was compared with that reported in the literature. Concerns related to the possible extraction of drug ions from the receiver compartment through the membrane are evaluated and its implications in the comparison of iontophoretic transport data reported from different kinds of cells will be discussed.

3.1.1 Lidocaine HCl monohydrate

Lidocaine HCl monohydrate (MW 288.82) was used as the model drug in this study. Lidocaine (127-129) is a weakly basic tertiary amine with a pKa of 7.8 and exists
predominantly in the ionized form at physiological pH, i.e., epidermal pH 5.2. Its structure is given in Figure 3.1. Besides commonly used the HCl salt, several other salts of lidocaine such as the adipate, maleate, malonate and tosylate have been synthesized to enhance skin permeation (130). Lidocaine HCl monohydrate ("lidocaine HCl") is highly soluble in water (0.68 g mL\(^{-1}\)) and has a melting point of about 78 °C. It is stable in the presence of heat, an electric field, moisture, acid and alkali (131). Lidocaine HCl dissociates into lidocaine H\(^+\), a cation, and Cl\(^-\) ions when dissolved in water.

Lidocaine undergoes extensively first-pass metabolism when given orally (132). It is generally used for local anesthesia (133). Several kinds of formulations of lidocaine such as creams, emulsions and gels have been developed for controlled release (134-136). Iontophoresis of lidocaine H\(^+\) has been studied extensively for primarily two reasons: the properties of lidocaine make it an ideal candidate for the study of iontophoresis, (137-138) and secondly, there is a need for painless modes for the induction of local anaesthesia (139-144). Siddiqui, \textit{et al}, studied iontophoresis of lidocaine HCl as a function of the pH of various formulations, i.e., the degree of ionization of lidocaine (145). Riviere, \textit{et al}, used lidocaine HCl as a model drug to study the effects of vasoactive drugs on iontophoretic transport (75). Comeau, \textit{et al}, found anesthesia induced by iontophoresis of lidocaine H\(^+\) is dependent on the concentration of lidocaine HCl and on electrical factors such as the duration and magnitude of current application (146, 147).
3.1.2 Nuclepore® membranes

Nuclepore® membrane has a polyvinylpyrrolidone-coated polycarbonate backbone and has ionogenic surfaces of low ionic charge density. Ionization of carboxyl groups at the surface gives rise to a surface charge dependent upon the pH and ionic strength of the solution in which it is in contact. These membranes therefore have a small net negative surface charge (148). Higuchi, et al, reported the resistance of a 6 μm thick Nuclepore® membrane with a pore radius of 75 Å and a porosity 0.001 to be approximately 30 Ω, which is of the order of magnitude of the adjacent solution (63). They also reported a linear voltage-current profile for these membranes. The same kinds of Nuclepore® membrane have been used in this study.

3.2 Experimental

3.2.1 Materials

All materials obtained commercially are listed in Table 3.1 and were used as received. The SpectraPor® I membranes were stored in a refrigerator. All other materials were stored at ambient temperature according to the recommendations of the manufacturers. Distilled/Deionized water with a specific resistance of no less than 18 MΩ cm was obtained from a Millipore® (Bedford, MA) Milli-Q2® system.

3.2.2 Eluant

The eluant in the flow-through receiver compartment was isotonic phosphate buffer saline (pH = 7.4) which consisted of 70 mM of NaCl, 53 mM Na₂HPO₄, and 13 mM KH₂PO₄. This
buffer was used as an eluant in this entire study unless otherwise stated. The cathode compartment contained the eluant buffer as a conductive medium to complete the electrical circuit.

3.2.3 Equipment

Equipment is given in Table 3.2.

3.2.3.1 Iontophoretic cell

The iontophoretic cells were made of Kel-F® 81 plastic. The cell was designed so that two electrodes can be placed on the same side of two separate pieces of membrane. The cell consists of three compartments (Figure 3.2). The receiver compartment which represents the systemic circulation has a volume of 2 mL and two openings with a diameter of 9 mm (0.64 cm² area each) connecting to two separate electrode compartments. Each electrode compartment has a volume of 1.9 mL (Figure 3.3). However, since the volume between the electrode surface and the membrane after the electrode containing plugs are inserted into the electrode compartments is 0.32 mL, therefore, excess formulation in the electrode compartments moves into the adjacent overflow chambers. Two membranes mounted horizontally in the openings between the electrode and receiver compartments. The tortuous pathway of the flow of eluant in the receiver compartment achieves adequate mixing.
### 3.2.3.2 Electrodes

The Ag/AgCl electrode containing plugs are inserted directly into the electrode compartments (Figure 3.3). The electrode plugs fit tightly and reproducibly in the openings of the electrode compartments and thereby reduce evaporation of solvent.

### 3.2.3.3 Power supply

A computerized power source with Scepter® software was used for controlling the electric current and voltages, and for logging data. There are 12 channels capable of providing constant voltage and current (AC or DC) individually. The maximum voltage and current for each channel were 10 V and 10 mA respectively. The currents and voltages were checked with a precision no-load digital multimeter.

### 3.2.3.4 Iontophoresis apparatus

A schematic diagram of the iontophoresis apparatus is shown in Figure 3.4. The apparatus consists of a cell warmer/holder, fraction collector, constant temperature waterbath and pump for the eluant, in addition to those portions indicated above.

### 3.2.4 Methods

#### 3.2.4.1 HPLC analysis

Lidocaine H⁺ was analyzed by HPLC (128, 135, 149, 150). The calibration curve is shown in Figure 3.5. The retention time of lidocaine H⁺ was about 2.8 minutes and the conditions
for analysis were as follows:

- **Column**: Hamilton PRP-1 column
- **Mobile Phase**: 47% formate buffer (0.1 M, pH 3) containing 20 mM triethylamine and 53% methanol
- **Flow rate**: 1.5 mL min⁻¹
- **Detector**: UV at 254 nm

### 3.2.4.2 Preparation of the membranes

Nuclepore® membranes (18 x 20 mm) were soaked in phosphate buffer for 24 hours. Fresh membranes were used for each experiment. The stack of membranes was prepared by placing the membranes on a glass microscope slide and then gently rolling a clean glass test tube over the stack to remove excess solvent and air bubbles between the layers.

### 3.2.4.3 Iontophoresis

The anode (donor) compartment was filled with 0.8 mL of 1% w/w lidocaine HCl solution and the same volume of phosphate buffer was placed in the cathode compartment. Care was taken to ensure that all three compartments, anode, cathode and receiver, were free of air-bubbles. The temperature of the cell and eluant was maintained at 32 °C by circulating water at 37 °C through the cell warmer, and the flow rate of eluant was controlled at 0.2 or 1.0 mL min⁻¹. Flow of eluant was started as soon as the donor compartment was filled, following
which it was collected at either 5 or 15 minute intervals. Current of 0.5 mA DC was applied for 1 hour and samples of eluant were collected for up to 1 hour after the current had been turned off. In addition, passive diffusional release was also studied.

3.2.4.4 Cleaning of electrodes

The electrodes were washed several times with distilled, deionized water after each iontophoresis experiment. The cleaned electrodes were kept in distilled, deionized water and then air-dried at room temperature prior to use. The polarity of the electrodes was reversed for each reuse.

3.2.5 Data analysis

Steady state fluxes of lidocaine H+ were determined by linear regression of the straight line portions of plots of the cumulative amounts of lidocaine H+ transported (µg) as functions of time (minute). The data is presented as the mean ± standard deviation. All experiments were done at least in triplicates.

3.3 Results and Discussion

3.3.1 Drug transport barrier

In vitro iontophoretic studies reported in the literature have been conducted with either biological or artificial membranes. In vitro iontophoretic transport across biological membranes such as human or porcine skin is useful for elucidating the mechanisms of
iontophoretic drug transport \textit{in vivo} \cite{75, 151-153}. Artificial membranes such as cellophane and Nuclepore* differ from biological membranes in various aspects such as chemical compositions, charge, physical structure and transport pathways. Their consistent compositions, uniform structure, good stability and ease of handling have made them ideal barriers for drug transport studies \cite{63, 154-156}. The \textit{in vitro} experiments herein were conducted with stacked layers of Nuclepore* membranes in order to determine the effect of formulation factors on iontophoretic and passive drug release without the variability of biological membranes. Stacked layers of an appropriate number of Nuclepore* membranes were selected in order to differentiate ionic transference controlled processes from diffusion controlled processes at clinically applicable current levels.

3.3.2 \textbf{Features of the iontophoresis apparatus}

As indicated, the \textit{in vitro} iontophoretic experiments were carried out with a custom designed iontophoresis apparatus. The features of this novel system are as follows:

- Good simulation of clinical application.
- Reduced electrochemical degradation of the drug at the electrode surface of opposite polarity to that of the drug ions.
- Complete physical and electrical isolation of two pieces of membranes.
- Ease of loading of formulations such as gels into the electrode compartments due to their horizontal geometry.
- Consistent placement of electrodes with respect to membranes.
- Reduced evaporation of solvent from electrode compartments.
• Ease of control of temperature, flow rate and electrical parameters.
• Automated experimental procedure.

3.3.3 Flow rate of eluant and collection intervals

Experimental parameters such as the flow rate of eluant and the collection intervals may influence the apparent fluxes which may be significantly different from the true, intrinsic fluxes under non steady-state conditions (157-160). Figure 3.6 shows the effect of flow rate and collection intervals on steady state iontophoretic flux. Drug fluxes derived from drug concentrations in the eluant have been adjusted for the amount of drug in the receiver compartment. The intrinsic flux is given by the following:

\[ J = V \times \frac{dc}{dt} + F \times c \]  

[3.1]

where, \( J \) is the intrinsic flux (\( \mu g \) min\(^{-1} \)); \( V \) is the volume of the receiver compartment (mL); \( F \) is the flow rate (mL min\(^{-1} \)); and, \( c \) is the drug concentration in eluant (\( \mu g \) mL\(^{-1} \)). At steady state, the change in drug concentration in the receiver compartment (\( dc/dt \)) is zero and therefore, the intrinsic flux can be calculated directly from the drug concentration in the eluant. The steady state iontophoretic fluxes at two different flow rates and collection intervals as shown in Figure 3.6 are similar. This reason for this is that in ionic transference controlled processes, potential differences are the primary driving forces for drug transport. Hydrodynamic forces created by the flow of eluant and/or the drug concentration gradient do not significantly influence drug transport in such processes.
3.3.4 Literature data

Riviere, et al., have studied the iontophoresis of lidocaine H\(^+\) across human and porcine skin (75). The data reproduced from their work is shown in Figure 3.7. For comparison purposes, the iontophoresis of lidocaine H\(^+\) across stacked membranes of different numbers of layers of Nuclepore\(^\circledast\) membranes was studied and is shown also in Figure 3.7. The iontophoretic conditions of these two experiments are summarized in Table 3.4. Riviere, et al., used a side-by-side two compartment cell with a dermatomed skin positioned between the two compartments. To simulate such a condition in this custom designed cell, a layer of porous membrane, SpectraPor\(^\circledast\) 1, was mounted between the cathode compartment and receiver compartment in place of the layers of Nuclepore\(^\circledast\) membrane. A membrane was necessary to retain the conductive buffer solution in the cathode compartment. As usual, the anode compartment was separated from the receiver compartment by stacked layers of Nuclepore\(^\circledast\) membrane. The iontophoretic fluxes across layers of Nuclepore\(^\circledast\) membrane were different from those across porcine or human skin. The iontophoretic permeability of lidocaine H\(^+\) across stacked layers of Nuclepore\(^\circledast\) membrane was about 2.5 times its iontophoretic permeability across human or porcine skin if the effects of iontophoretic cell design are ignored. These differences in iontophoretic permeability are due to differences in chemical compositions, charge, physical structure and transport pathways between the layers of Nuclepore\(^\circledast\) membrane, and the porcine and human skins. The steady state iontophoretic fluxes were independent of the number of layers of Nuclepore\(^\circledast\) membrane (see Table 3.4). In constant current experiments, higher resistances due to an increased number of layers of Nuclepore\(^\circledast\) membrane appear to be compensated for by the higher voltages.
3.3.5 ‘Pulling out’ effect

The electrode of opposite polarity with respect to the drug ions can pull drug ions through the membrane and therefore out of the receiver compartment. To investigate the effects of this ‘pulling out’ effect on iontophoretic drug delivery, two experiments were conducted, one with a layer of SpectraPor membrane, and the second with a stacked layers of Nuclepore membranes between the cathode compartment (the electrical continuity compartment) and the receiver compartment. SpectraPor membrane is more porous than Nuclepore membrane. The anode compartment (donor compartment) was separated from the receiver compartment by stacked layers of Nuclepore membrane (see Table 3.5). The iontophoretic cell consists of three compartments: 1) the donor compartment; 2) the electrical continuity compartment, both of which are separated but essentially on the same side of the membrane; and 3) the flow through receiver compartment. If drug is pulled out of the receiver compartment by the cathode, lower iontophoretic drug delivery would be expected for all experiments conducted with the more porous membrane between the cathode compartment and the receiver compartment. Instead, the iontophoretic fluxes were found to be unaffected by the thickness and type of membrane between the cathode compartment and the receiver compartment. This suggests that migration of lidocaine \( H^+ \) occurring from the receiver compartment to the cathode compartment is not significant. These findings are consistent with the extremely low concentrations of drug ions compared with those of the competitive ions in the receiver compartment. However, minute amounts of lidocaine \( H^+ \) were found in the cathode compartments after iontophoresis (see Table 4.5). These amounts of lidocaine \( H^+ \) were independent of the type and thickness of the membrane. Chen has traced the source
of lidocaine H⁺ in cathode compartments to the Ag/AgCl electrodes (126). These electrodes were used as the anode and therefore had been exposed to lidocaine HCl solutions in previous experiments.

All the iontophoretic experiments in this research were done with the same type of membrane between the anode compartment and the receiver compartment, and, the cathode compartment and the receiver compartment, unless otherwise indicated. This was done to mimic clinical applications although iontophoretic fluxes were found to be independent of the number of layers of membrane.

Most of the in vitro iontophoretic data reported in the literature was collected by placing electrodes across the membrane, a situation which is clinically unrealistic. The general assumption in those studies was that the placement of electrodes on the same side of the membrane is as effective as placing them on either side of the membrane. Recently, there is growing interest in performing iontophoretic studies under conditions which simulate clinical applications closely. However, the in vitro iontophoretic data from these two different kinds of cell design can be equated, since there is no significant extraction of drug ions out of the membrane by the electrode of opposite polarity. This is true only if electrical current is transported through the membrane and there is no significant electrochemical degradation of drug at the surface of the electrode of opposite polarity.
3.4 Summary

The novel custom designed iontophoresis apparatus has several advantages. It not only more closely simulates the clinical application of iontophoretic devices, but it also permits automation of data collection. It has unique features such as a nearly enclosed environment in the electrode compartments and consistent placement of the electrodes with respect to membranes.

Influence of experimental parameters such as flow rate and sampling time on steady state iontophoretic fluxes in this iontophoresis apparatus has been evaluated. The steady state iontophoretic fluxes were found to be independent of these parameters as well as the number of layers of membrane. An enhanced resistance due to an increased number of stacked membranes in constant current experiments appears to be compensated for by increased voltages.

The pulling of drug ions out of the receiver compartment by the charge on the electrode of opposite polarity does not appear to affect iontophoretic drug delivery. The reason for this is that migration of drug ions out of the membrane toward the electrode of opposite polarity does not occur to a significant extent. These findings are significant for the positioning of electrodes in clinical applications and for in vitro studies. The data from two different experiments in which electrodes were placed either across the membrane or on the same side
of the membrane can be correlated as long as the electrical circuit is completed through the membranes and there is no significant degradation of drug ions at the electrode surface of opposite polarity.
### Materials

<table>
<thead>
<tr>
<th>Materials</th>
<th>Supplier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine HCl</td>
<td>Astra Pain Control AB</td>
</tr>
<tr>
<td></td>
<td>Södertälje, Sweden</td>
</tr>
<tr>
<td>Sodium phosphate, dibasic, 12-hydrate</td>
<td>J. T. Baker</td>
</tr>
<tr>
<td></td>
<td>Phillipsburg, NJ</td>
</tr>
<tr>
<td>Potassium phosphate, monobasic</td>
<td>J. T. Baker</td>
</tr>
<tr>
<td></td>
<td>Phillipsburg, NJ</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>Fisher Scientific</td>
</tr>
<tr>
<td></td>
<td>Pittsburgh, PA</td>
</tr>
<tr>
<td>Sodium formate</td>
<td>Sigma Chemical Company</td>
</tr>
<tr>
<td></td>
<td>St. Louis, MO</td>
</tr>
<tr>
<td>Formic acid</td>
<td>Sigma Chemical Company</td>
</tr>
<tr>
<td></td>
<td>St. Louis, MO</td>
</tr>
<tr>
<td>Methanol HPLC grade</td>
<td>Fisher Scientific</td>
</tr>
<tr>
<td></td>
<td>Pittsburgh, PA</td>
</tr>
<tr>
<td>Nuclepore® polycarbonate membrane</td>
<td>Corning, Inc.</td>
</tr>
<tr>
<td></td>
<td>Acton, MA</td>
</tr>
<tr>
<td>SpectraPor® 1 membrane tubing</td>
<td>Spectrum Medical Industries</td>
</tr>
<tr>
<td></td>
<td>Los Angeles, CA</td>
</tr>
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</table>

**Table 3.1** Materials.
<table>
<thead>
<tr>
<th>Equipment</th>
<th>Manufacturer/Supplier</th>
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<tbody>
<tr>
<td>Iontophoretic cells</td>
<td>AMIE Systems</td>
</tr>
<tr>
<td></td>
<td>Riegelsville, PA</td>
</tr>
<tr>
<td>Ag/AgCl embedded electrodes</td>
<td>AMIE Systems</td>
</tr>
<tr>
<td></td>
<td>Riegelsville, PA</td>
</tr>
<tr>
<td>Scepter™ 12 channel programmable power supply</td>
<td>Keltronic Corp.</td>
</tr>
<tr>
<td></td>
<td>Oklahoma City, OK</td>
</tr>
<tr>
<td>Multimeter, Model 2001</td>
<td>Keithley Instruments, Inc.</td>
</tr>
<tr>
<td></td>
<td>Cleveland, OH</td>
</tr>
<tr>
<td>Multi-channel peristaltic cassette pump, Model IPN</td>
<td>ISMATEC SA</td>
</tr>
<tr>
<td></td>
<td>Zürich, Switzerland</td>
</tr>
<tr>
<td></td>
<td>Karlsruhe, Germany</td>
</tr>
<tr>
<td>Fraction collector, Retriever IV</td>
<td>ISCO, Inc.</td>
</tr>
<tr>
<td></td>
<td>Lincoln, NB</td>
</tr>
<tr>
<td>Refrigerated circulating bath, Model RTE-90D</td>
<td>Neslab Instruments</td>
</tr>
<tr>
<td></td>
<td>Portsmouth, NH</td>
</tr>
<tr>
<td>Magnetic stirrer, IKAMAG Model RET with revolution counter, IKA-TRON Model DZM 1</td>
<td>IKA-Works, Inc.</td>
</tr>
<tr>
<td></td>
<td>Cincinnati, OH</td>
</tr>
<tr>
<td>Temperature indicator and controller</td>
<td>IKA-Works, Inc.</td>
</tr>
<tr>
<td>IKA-TRON Model ETS-D2</td>
<td>Cincinnati, OH</td>
</tr>
</tbody>
</table>

Table 3.2  Equipment.

(continued)
Table 3.2 Equipment (continued).

<table>
<thead>
<tr>
<th>Equipment</th>
<th>Manufacturer/Supplier</th>
</tr>
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<tbody>
<tr>
<td>Microbalance,</td>
<td>Mettler Hightstown, NJ</td>
</tr>
<tr>
<td>Model UM-3, sensitivity 0.1 μg</td>
<td></td>
</tr>
<tr>
<td>Model AE 240, sensitivity 1.0 μg</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>Beckman San Ramon, CA</td>
</tr>
<tr>
<td>Meter, Model Φ 72</td>
<td></td>
</tr>
<tr>
<td>Electrode, semimicro ROSS combination, glass</td>
<td>Orion Boston, MA</td>
</tr>
<tr>
<td>HPLC</td>
<td>Beckman San Ramon, CA</td>
</tr>
<tr>
<td>Solvent pumps, Model 110B</td>
<td></td>
</tr>
<tr>
<td>Injector, (250μL loop)</td>
<td></td>
</tr>
<tr>
<td>Detector, Model 607</td>
<td></td>
</tr>
<tr>
<td>Analog interface, Model 406</td>
<td></td>
</tr>
<tr>
<td>Software, System Gold™</td>
<td></td>
</tr>
<tr>
<td>Column, reverse phase, PRP-1, 4.1 mm × 25 cm, 10 μm part.</td>
<td>Hamilton Reno, NV IBM Armonk, NY</td>
</tr>
<tr>
<td>Computer, PS/2, Model 30</td>
<td></td>
</tr>
<tr>
<td>Experimental apparatus</td>
<td>Riviere, et al, (75)</td>
</tr>
<tr>
<td>------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Cell</td>
<td>Side-by-side, static</td>
</tr>
<tr>
<td>Membranes</td>
<td>Human skin (210 μm) and porcine skin (295 μm)</td>
</tr>
<tr>
<td>Membrane area</td>
<td>0.64 cm²</td>
</tr>
<tr>
<td>Formulation in anode compartment</td>
<td>1.0 % w/w Lidocaine HCl</td>
</tr>
<tr>
<td>Buffer in cathode compartment and/or in receiver compartment</td>
<td>0.150 M phosphate buffer, pH 6.8</td>
</tr>
<tr>
<td>Electrodes</td>
<td>Ag/AgCl wire mesh</td>
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<tr>
<td>Temperature</td>
<td>32 °C</td>
</tr>
</tbody>
</table>

Table 3.3  Comparisons of the experimental conditions for iontophoresis. The data is shown in Figure 3.7.
### Table 3.4

Iontophoretic fluxes of lidocaine H\(^+\) across various membranes. The human and porcine skin data is taken from work of Riviere, *et al.*, (75), while the iontophoretic fluxes were calculated from the data shown in Figure 3.7.

<table>
<thead>
<tr>
<th>Membranes</th>
<th>Iontophoretic flux (µg min(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclepore(^*) (5 layers)</td>
<td>27.67±1.31</td>
</tr>
<tr>
<td>Nuclepore(^*) (10 layers)</td>
<td>27.29±1.14</td>
</tr>
<tr>
<td>Nuclepore(^*) (50 layers)</td>
<td>25.85±0.86</td>
</tr>
<tr>
<td>Human skin (210 µm)</td>
<td>10.42</td>
</tr>
<tr>
<td>Porcine skin (295 µm)</td>
<td>10.62</td>
</tr>
<tr>
<td>Membranes</td>
<td>Anode</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Nuclepore® (5 layers)</td>
<td>Nuclepore® (5 layers)</td>
</tr>
<tr>
<td>Nuclepore® (5 layers)</td>
<td>SpectraPor® 1 (1 layer)</td>
</tr>
<tr>
<td>Nuclepore® (10 layers)</td>
<td>Nuclepore® (10 layers)</td>
</tr>
<tr>
<td>Nuclepore® (10 layers)</td>
<td>SpectraPor® 1 (1 layer)</td>
</tr>
<tr>
<td>Nuclepore® (50 layers)</td>
<td>Nuclepore® (50 layers)</td>
</tr>
<tr>
<td>Nuclepore® (50 layers)</td>
<td>SpectraPor® 1 (1 layer)</td>
</tr>
</tbody>
</table>

Table 3.5  Iontophoretic fluxes across various membranes and the amounts of lidocaine H⁺ in the cathode compartments after iontophoresis. The flow rate of eluant (0.15 M phosphate buffer, pH 6.8) was controlled at 0.2 mL min⁻¹. Iontophoresis was performed for 60 minutes at 0.5 mA DC, and the samples were collected every fifteen minutes.
Figure 3.1 Structure of lidocaine.
Figure 3.2  Schematic illustration of an iontophoresis cell (top view).
Figure 3.3  Schematic illustration of the electrode compartment, Ag/AgCl electrode and their assembly (top and cross views).
Figure 3.4  Schematic illustration of iontophoresis apparatus.
Figure 3.5 HPLC calibration curve.
Figure 3.6  Iontophoresis of lidocaine H+ across 10 stacked layers of Nuclepore® membranes at different flow rates of isotonic phosphate buffer saline eluant and at different collection intervals.
Figure 3.7 Comparisons of iontophoretic fluxes across various membranes. The human and porcine skin data is reproduced from work of Riviere, et al. (75). The experimental conditions are given in Table 3.3.
CHAPTER 4

LIQUID CRYSTALS AS DRUG DELIVERY MEDIA FOR IONTOPHORESIS

4.1 Introduction

4.1.1 Liquid crystalline phases in drug delivery

Liquid crystalline phases have been used as drug delivery systems for oral and topical administration for various therapeutic purposes (114, 149, 161, 162). Liquid crystalline matrixes of lipidic materials have been suggested also as models for the stratum corneum (115, 163). They have been used also as templates for the formation of smaller and more uniform particles than can be obtained by other means (164). Liquid crystals are also being used in a variety of ways in the instrumentation of pharmaceutical processes such as sensors for control of certain tableting processes by non-contact gauging of tablet surface temperatures (165). Despite their interesting physical-chemical properties, liquid crystalline phases do not appear to have been studied as the donor media in iontophoresis.

Engstrom, et al., advocated the use of liquid crystalline phases such as those formed by monoolein with water as delivery systems for peptides and proteins (166). Liquid crystalline
vehicles were found to be useful also for sustained vaginal delivery of antimuscarinic drugs since their physical integrity remained intact despite absorption of fluid secretions (167). Mueller-Goymann, et al., have studied the transition of reverse micellar solutions consisting of fenoprofen sodium, isopropyl myristate and phospholipids into lamellar liquid crystals upon the addition of water as easily administered, sustained release delivery systems (168). Various materials such as poloxamers, cetomacrogols, nonoxynols, phytosterols, cholesterol, phospholipids, glycerates and ionic surfactants, capable of forming lyotropic and thermotropic liquid crystalline phases are useful in drug delivery (114, 169, 170).

4.1.2 Advantages of liquid crystalline phases as donor media in iontophoresis

Liquid crystalline formulations have potential for use in iontophoresis as a means of enhancing bioavailability; for example, by increasing the stability and/or solubility of a drug (171-173). Lyotropic liquid crystalline phases or mesophases consist of micelles or other structural arrays of the appropriate materials assembled in specific degrees of order within a continuous solvent phase. The micellar structures can solubilize drugs in their interiors, and thereby can also reduce the hydrolysis of various drugs (172). Surfactant-based liquid crystalline phases also possess surface active properties which can assist in decreasing aggregation and the subsequent inactivation of peptides and proteins (173). They can enhance the permeability of drugs through the skin by interacting with the skin lipids (174). In addition, these systems can act as drug reservoirs from which drug diffusion can be controlled by changing the characteristics of the mesophase formulations. The drug reservoir feature could function to provide multiple doses of drug for extended periods since liquid crystalline systems are
inherently thermodynamically stable. Therefore, they could be used to control passive diffusional fluxes occurring between periods of iontophoretic drug release. The most exciting aspect of the behavior of liquid crystals is their sensitivity to external forces such as electric and magnetic fields. Electrical fields can create various phenomena in liquid crystals such as electrohydrodynamic effects and affect both their microscopic and macroscopic properties, including their rheological characteristics (175). Electrically induced effects along with the anisotropy of electrical conductivity, i.e., conductivity parallel to the direction of alignment of the structural elements of the liquid crystalline phase, which differs from conductivity perpendicular to this direction, could affect the transport of drug ions, and subsequently, drug delivery.

4.1.3 Monoolein

Lipid materials have been used for some time as drug carriers because they are available with varying degrees of polarity and are easy to process without the need for organic solvents due to the low viscosities of their melts. Monoolein or glyceryl monooleate is a water insoluble, amphiphilic, unsaturated polar lipid. It is non-toxic and has been used in emulsions for topical applications (176). Monoolein swells in water giving rise to reversed micellar, lamellar, cubic and reversed hexagonal phase depending on water content and temperature (177). A large region of cubic phase dominates the phase diagram, however, the addition of lidocaine HCl promotes the formation of a lamellar liquid crystalline phase. Engstrom, et al, studied the phase behavior of lidocaine-monoolein-water system and advocated the use of cubic phases of monoolein as delivery systems for peptide drugs (178). Because of its
hydrophobic/hydrophilic domains and viscous nature, it has been evaluated as drug delivery systems for both hydrophobic and hydrophilic drugs, but there is no indication in the literature that it has been used as the donor medium in iontophoresis (180, 181).

4.1.4 Poloxamers

Poloxamers are non-ionic, water soluble surface-active poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene) polymers and form various mesophases at skin temperature (32 °C) (182). Poloxamers are commercially available and biologically compatible (183). They exhibit reverse thermal gelation behavior, i.e., their macroscopic viscosity increases with increases in temperature. This property has been attributed to enhanced entanglement, desolvation and intermolecular hydrogen bonding of the poloxamer polymers as temperature is increased (184, 185).

Various poloxamer formulations have been evaluated for topical and parenteral applications to achieve controlled release of drug, and they have been used also to inhibit postsurgical adhesion formation and as an artificial skin particularly in burn therapy (186-195). Chen-Chow and Frank investigated the release of lidocaine from gels consisting of poloxamer 407 (196). In addition, poloxamers have been reported to increase the stability of various peptides such as interleukin-2 and recombinant human growth hormone (173, 197). Being surface active, the poloxamers can also act as skin permeability enhancers (174). The poloxamers are cost effective and have other advantages including their non-occlusive properties, ease of application, good water solubility and the option of not having to use heat and/or organic
solvents which could be deleterious to the activity of a drug during preparation of a formulation. Formulations can be easily prepared and handled in a liquid form which transforms into a liquid crystalline phase (gel) when warmed to skin temperature. Since the gels are thermoreversible, removal from the skin is facilitated by immersion in, or irrigation with, cool water. The reversible thermogelation also facilitates retention of a poloxamer system at the site of application due to its aqueous semisolid consistency and bioadhesive properties. Poloxamers are also useful in topical formulations since they form elegant clear gels in aqueous media, and have excellent chemical and physical stability in single phase systems (198, 199).

4.1.5 Objectives

Although liquid crystalline formulations have been used in various controlled drug delivery applications, there is no evidence that they have been utilized in iontophoresis. There are however several advantages for using liquid crystalline systems as the donor formulations in iontophoresis because of their unique physicochemical properties, as discussed above. This study was therefore undertaken with the following goals:

- To develop lyotropic liquid crystalline formulations as donor drug delivery media for iontophoresis.
- To investigate the effects of parameters such as the compositions of the liquid crystalline system, drug concentration, electrical current, water content, and liquid crystalline structure on in vitro passive diffusional and iontophoretic drug release from these systems.
• To examine the effect of liquid crystalline structure on the conductivity of mesophase formulations, and the role of conductivity in predicting iontophoretic drug flux from these formulations.

• To compare passive diffusional and iontophoretic drug release from these systems with those from a simple solution and to evaluate such release in terms of electrodiffusion theory.

4.2 Experimental

4.2.1 Materials

All materials obtained commercially are listed in Table 4.1 and were used as received. Monoolein was stored in light protective vials in a refrigerator. All other materials were stored at ambient temperature according to the recommendations of the manufacturers. Distilled/Deionized water with a specific resistance of no less than 18 MΩ cm was obtained from a Millipore® (Bedford, MA) Milli-Q2® system.

4.2.2 Equipment

Equipment is given in Table 4.2.
4.2.3 Methods

4.2.3.1 Monoolein liquid crystalline systems

4.2.3.1.1 Preparation of liquid crystalline systems

Lidocaine HCl and NaCl were dissolved in water contained in a glass vial (~20 mL) and then the solution was warmed to 30-35 °C, following which monoolein was added. The mixture was centrifuged and stored in airtight vials at room temperature. Care was taken to ensure that the mixture was homogenous, yet free of air bubbles. There were no signs of degradation when the samples were observed periodically over two weeks. The formulation was as follows.

- Lidocaine HCl: 15% w/w
- Sodium chloride: 2% w/w
- Water: 33% w/w
- Monoolein: 50% w/w

4.2.3.1.2 Polarized light microscopy

Optical microscopy techniques, particularly the use of polarized light and a heating and/or cooling stages are widely used for the identification of liquid crystalline phases and in the study of phase equilibria (200). As a result of their ordered molecular arrangement, mesophases are birefringent, i.e., appear bright when viewed between crossed polars. When polarized light passes through anisotropic or birefringent materials it is split into two parallel
rays which vibrate at right angles to each other and at different speeds. The resulting nonzero vector component of the emergent light is transmitted by the analyzer, making these materials appear bright. The liquid crystalline materials can be identified by the textures observed by polarized light microscopy since the optical properties of a phase are dictated by its structure. Phases that appear dark when viewed between cross polars is isotropic or nonbirefringent. Isotropic phase states are gases, liquids, cubic liquid crystals and cubic crystals. The monoolein liquid crystalline formulation was identified by observation between cross polarizers in an optical microscope at 32 °C. A Mettler FP2 hot stage and FP21 temperature controller were used to control temperature during microscopy.

4.2.3.1.3 Iontophoresis

The anode (donor) compartment was filled with 0.8 mL of warmed (32 °C) liquid crystalline formulation and the same volume of isotonic phosphate buffer saline was placed in the cathode compartment. Since the volume of the anode and the cathode compartments is actually 0.32 mL, the remainder of the sample added to these compartments moves into the overflow chambers of the cell when the electrode is inserted. All experiments were conducted with five stacked layers of Nuclepore* membranes that had been presoaked in isotonic phosphate buffer saline (PBS). Fresh membranes were used for each experiment. The temperature of the cell and eluant was maintained at 32 °C and the flow rate of isotonic phosphate buffer saline was controlled at 1 mL min⁻¹. The flow of eluant was started as soon as the donor compartment was filled, following which it was collected at 3 minute intervals and assayed for lidocaine H⁺ by HPLC.
4.2.3.1.4 Electrical factors

Iontophoretic drug release from monoolein mesophase systems was studied as a function of constant current to investigate the effects of current on release. In addition, passive diffusional release was also studied. Currents of 0.1, 0.25, 0.4 and 0.5 mA DC, which corresponded to current densities of 0.15, 0.39, 0.63 and 0.78 mA cm\(^{-2}\), respectively, were used. A continuous constant current was provided by a computerized power source with Scepter\textsuperscript{®} software. In all experiments, current was applied for 60 minutes and samples of the eluant were collected for up to 30 minutes after the current had been turned off.

4.2.3.2 Poloxamer liquid crystalline systems.

4.2.3.2.1 Preparation of liquid crystalline systems.

Lidocaine HCl was dissolved in water contained in a glass vial (~20 mL), after which a poloxamer was added. The mixture was heated to 90 °C for 5 hours in a waterbath under continuous stirring with a magnetic stirrer. After cooling to room temperature, the vial was reweighed to check for loss of ingredients, sealed and stored in a refrigerator at about 5 °C. Care was taken to ensure that the mixture was homogenous, yet free of air bubbles. In addition, solutions of lidocaine HCl were prepared for comparison of drug release from the liquid crystal system.
4.2.3.2.2 Composition of liquid crystalline systems

Cubic, hexagonal and lamellar mesophase formulations; and aqueous solutions were prepared at 2.5, 5.0, 7.5 and 10.0 % w/w concentrations of lidocaine HCl. The cubic liquid crystalline formulation consisted of poloxamer 334, whereas the hexagonal and lamellar liquid crystalline formulation contained poloxamer 184. The ratios (w:w) of poloxamer and water were 1:2, 1:1 and 2.33:1 in the cubic, hexagonal and lamellar liquid crystalline formulations, respectively (Table 4.3).

4.2.3.2.3 Polarized light microscopy

The mesophase formulations were identified by the absence or presence of characteristic birefringence when observed through cross polarizers in an optical microscope at 32° C.

4.2.3.2.4 $^2$H-NMR

$^2$H-NMR of deuterated water is a well-established method for the study of phase equilibria, phase boundaries and the properties of different phases in a multiphasic system (201). It has been used in studies of the phase behavior of lecithin/water systems, calcium octyl sulfate/decan-1-ol/water systems, water/oil systems containing amphiphilic block copolymers and also in investigations of membrane structure and dynamics (202-204). $^2$H-NMR measurements are intramolecular in nature, i.e., the quadrupolar interaction at the position of the deuteron for a given C-D bond is measured. If the C-D bond orientation fluctuates, the quadrupolar interaction averages out and thus gives rise to spectral signatures, depending on the rate of a given type of molecular motion as well as its symmetry (201).
A deuteron has a spin quantum number (I) of one. Therefore, there are three \((2I + 1)\) energy levels, up, down and sideways, in the magnetic field. The interaction dominating deuterium NMR spectroscopy is between the nuclear quadrapole moment, which results from the nonspherical symmetric distribution of nuclear charge, and the electrical field gradient at the deuterium nucleus. This quadrapolar interaction modifies the separation of Zeeman nuclear energy levels so that it gives rise to a doublet spectrum (201).

Standard NMR measurements of samples dissolved in a liquid give sharp spectral lines because of an isotropic motion of molecules on the NMR measurement time scale \((10^{-4} \text{ to } 10^{-5} \text{ s})\). By contrast, for an anisotropic liquid crystalline phase, all directions of a D\(_2\)O molecule do not have the same probability (anisotropy) and there will remain a residual quadrapolar interaction not averaged out by the molecular motion. This generates two equally intense peaks with widths on the order of kilohertz. Intensity measurements, which would give information on the relative proportions of the two phases in a sample, are difficult to make due to overlap effects and the very different nature of the two parts of a spectrum. Therefore, it is not possible to determine phases quantitatively with \(^2\)H NMR (202-204).

Liquid crystalline formulations containing 2.5 and 10\% w/w lidocaine HCl were prepared for each type of mesophase without correction for the molecular weight difference between D\(_2\)O and H\(_2\)O. \(^2\)H-NMR experiments were performed on a DRX 500 instrument operating in the Fourier transform (FT) mode. Sample temperature was maintained at 32 °C by controlled temperature air passing through the sample holder.
4.2.3.2.5 Conductivity

The measurement of conductivity is useful in estimating electrochemical properties such as the mobility and transport number of drug ions (205). It has been used to determine the suitability of drugs for iontophoresis. Conductivity has been suggested also as an important tool for predicting iontophoretic flux and estimating the competitive transport between a drug and other ions during transdermal iontophoresis (25, 120, 151, 206). The conductance of all formulations was measured with an Extech 480 conductivity meter at 32 °C. Potassium chloride solutions (0.1 and 0.02 N) were used to calibrate the conductivity meter. The specific conductance of the deionized distilled water used for all formulations was about 2-3 μS cm⁻¹. The temperature of the formulations was monitored continuously during conductivity measurement. After immersion of the conductance cell in a formulation, the open end of the sample vial was wrapped with Parafilm® to minimize solvent evaporation. Specific conductivity or the conductivity, κ, was measured by direct meter reading.

4.2.3.2.6 pH measurement

The pH values of poloxamer liquid crystalline formulations were measured (Beckman Model Φ 72) when the formulations were in their fluid state. This was done by placing the liquid crystalline formulations in a cooling chamber maintained at 4 °C by circulating cold water due to their reverse thermal behavior. The pH values of the other types of formulations were measured at room temperature.
4.2.3.2.7 Iontophoresis

The anode (donor) compartment was filled with 0.8 mL of cold liquid crystalline formulation and the same volume of isotonic phosphate buffer saline was placed in the cathode compartment. The formulations underwent gelation immediately to form their liquid crystalline phases in the donor compartment. Since the volume of the anode and the cathode compartments is actually 0.32 mL, the remainder of the sample added to these compartments moves into the overflow chambers of the cell when the electrode is inserted. All experiments were conducted with five stacked layers of Nuclepore* membranes that had been presoaked in isotonic phosphate buffer saline. Fresh membranes were used for each experiment. Enough care was taken to ensure that all three compartments, anode, cathode and receiver compartment were free of air-bubbles. The temperature of the cell and eluant was maintained at 32 °C by circulating water at 37 °C through the cell warmer, and the flow rate of isotonic phosphate buffer saline eluant was controlled at 1 mL min⁻¹. Flow of eluant was started as soon as the donor compartment was filled, following which it was collected at 5 minute intervals and assayed for lidocaine H⁺ by HPLC.

4.2.3.2.8 Electrical factors

Iontophoretic release was studied as a function of current to investigate the effects of current strength on drug release from the poloxamer liquid crystalline systems. In addition, passive diffusional release was also studied. Currents of 0.25, 0.5, 0.75 and 1.0 mA DC, which corresponded to current densities of 0.39, 0.79, 1.18 and 1.57 mA cm⁻², respectively, were used. A continuous constant current was provided by a computerized power source with
Scepter® software. In all experiments, after an initial 45 minutes of passive diffusion, current was then applied for another 45 minutes; samples of eluant were collected for up to 30 minutes after the current had been turned off (Protocol 1). In addition to this protocol, a second programmed incremental current protocol, given below, was also used.

Protocol 2: 0-45 min at 0 mA DC, 45-75 min at 0.5 mA DC, 75-105 min at 0 mA DC, 105-135 min at 0.75 mA DC, 135-165 min at 0 mA DC, 165-195 min at 1.0 mA DC, 195-225 min at 0 mA DC, 225-255 min at 0.25 mA DC, and 255-285 min at 0 mA DC.

4.2.4 Data analysis

Steady state fluxes were determined by linear regression of the straight line portions of plots of the cumulative amounts of lidocaine H⁺ transported (µg) as functions of time (minute). The data is presented as the mean ± standard deviation. The number of experiments (n) varied from three to six.

4.3 Results and Discussion

4.3.1 Drug transport barrier

Diffusional drug transport can be either membrane-controlled, e.g., transdermal peptide delivery or vehicle-controlled, e.g., transdermal nitroglycerin delivery. Several days may be necessary to establish a steady-state diffusional flux across the skin. By contrast,
Iontophoretic transport of drug across the skin takes a few hours to attain steady state flux. In a typical iontophoresis experiment, skin, or more specifically, the stratum corneum is the main barrier to transport, rather than diffusion of the drug through the vehicle. However, for the systems described herein, a barrier within the formulation itself would also appear to be an important factor. Although such systems deviate from a typical iontophoresis, as will be seen they have the advantage of demonstrating the effect of current on the formulation, and in turn, on drug release.

4.3.2 **Monoolein liquid crystalline systems**

4.3.2.1 **Preparation**

A lamellar liquid crystalline phase based on monoolein was chosen as the initial vehicle for iontophoresis because of its rather simple structure compared with other liquid crystalline phases. Furthermore, in monoolein-water systems, lidocaine HCl alters the geometry of the liquid crystals, thereby promoting the formation of a lamellar phase which occupies a large portion of the phase diagram for this system (178). A formulation was chosen that contained a maximal ratio of water to monoolein, while still lying near the center of the lamellar phase region. It was found however that the formulation did not have sufficient conductivity, and therefore offered too high resistance for iontophoresis due to the rather larger content of monoolein, a semipolar oily compound. To correct for this, NaCl was added.
Since pure 1-monoolein is a very expensive compound, monoolein containing 2-monoolein along with 1-monoolein was used instead. In addition to monoesters, this material also contained minute amounts of free glycerin, free fatty acids and diglycerides. The fatty acid distribution of the monoglyceride is not critical as long as it contains 90% unsaturated fatty acids such as oleic acid (18:1) and linoleic acid (18:2) and about 5% saturated fatty acids because of the similar properties of the fatty acids. Differences in the content of fatty acids show up in the precise location of the phase boundaries (177). Due to their similarities, it was assumed that the phase diagram of the monoolein-water system would be similar in nature to that reported in the literature. As long as compositions are chosen that are sufficiently distant from the phase boundaries of the monoolein-water systems, this assumption should be safe.

4.3.2.2 Identification

A lamellar monoolein liquid crystalline formulation containing 15% w/w lidocaine HCl was a bright yellow, free flowing fluid. The liquid crystalline phase was identified by its texture observed by polarized light microscopy (Figure 4.1). The formulations displayed birefringence characteristic of a lamellar liquid crystalline phase even after application of an electrical current for one hour.

4.3.2.3 Drug release

The cumulative release profile of lidocaine H+ from this formulation at various current densities along with the release profile by passive diffusion is shown in Figure 4.2. It can be
seen that the steady state flux of lidocaine H\(^+\) is enhanced over that by diffusion upon the application of current. While there is an increase in the steady state flux by the application of 0.5 mA DC when compared with 0.25 and 0.1 mA DC, the flux at 0.25 mA DC is actually less than that by 0.1 mA DC (Figure 4.4). The nonlinear relationship between iontophoretic flux and applied current might then be due to electrorheological changes and/or electrohydrodynamic effects induced in the formulation, as will be discussed below.

4.3.2.3.1 Electrorheological effects

Transport rates in liquid crystals depend not only on the microscopic structure or ultrastructure of a phase, but also on aspects of their macroscopic structure. In liquid crystals of fixed composition, rheological properties depend on the size and arrangement of aligned domains within a sample. The particular arrangement of domains of varying orientations and the existence of structural defects might enhance or retard transport of molecules through a liquid crystalline phase (175). Therefore, the transport of molecules can be greatly influenced by such structural characteristics.

Iontophoretic flux consists of two parts: electrically facilitated flux, which has a contribution from electroosmosis, and diffusional flux. By their nature, liquid crystals are sensitive to external forces which can cause significant changes in their viscosities and refractive indices. In this context, lamellar liquid crystals are Newtonian at low shear rates, but are shear thickening (dilatant) at high shear rates. It is quite possible that the application of an electrical current to a liquid crystal formulation would affect its viscosity to an extent dependent on the
magnitude and type of current. Both electrically facilitated flux and diffusional flux depend on the viscosity of the medium since it affects the mobility of drug ions. It would be expected that increases in the magnitude of the current will cause higher electrically facilitated fluxes, although they may not necessarily be linear, whereas diffusional flux would be enhanced or reduced due to decreases or increases in viscosity, respectively. Such electrorheologic changes could be at the micro and/or macro level and will be of importance only when drug transport is not restricted by membrane resistance.

At higher magnitudes of current, diffusional flux would decrease due to increases in viscosity and the fluxes would be predominantly due to movement of ions and to electroosmosis induced by the applied current. On the other hand, at low currents, both diffusional flux and electrically facilitated flux would contribute to the total flux. As such, the higher flux (normalized) at 0.1 mA DC, than at 0.25 and 0.5 mA DC, might be due to these combined fluxes; whereas at the higher currents, the contribution of diffusional flux toward the total iontophoretic flux becomes small. This conclusion is supported by an experiment at 0.4 mA DC in which the steady state flux agreed with those at 0.25 and 0.5 mA DC (Figures 4.3 and 4.4). A good relationship \( (r^2 = 0.992) \) exists between the steady state fluxes and the applied currents (0.25, 0.4 and 0.5 mA DC) with a Y-intercept of 0.0381 \( \mu g \text{ min}^{-1} \), indicating diffusional flux is depressed when higher magnitudes of current are applied.
4.3.2.32 Electrohydrodynamic effects

A significant aspect of the electrical conductivity of liquid crystalline materials is that unlike isotropic liquids, electrical conduction in these anisotropic systems is highly dependent on the direction of current flow. In this respect, electrical conductivity in lamellar phases is minimal in directions normal to the lamellae along the optic axis. In such materials, a negative anisotropy of properties such as diffusivity and conductivity are exhibited to a greater extent because of the presence of alternating aqueous and lipid layers. Since ions are more easily transported through the aqueous layers between the lipid layers than across the lipid layers themselves, structural alterations could greatly influence the kinds of effects induced by an electric field (110, 175).

Several phenomena in liquid crystals can be explained by elastic deformations caused by external forces such as electrical and magnetic fields. In liquid crystals, elastic properties are due to changes in density, as in the case of isotropic liquids and in variations of the direction of the "director". If in the original state, the direction of the director with respect to field direction does not satisfy the condition of minimum free energy, then a sufficiently strong electric field produces torque on the liquid crystal which leads to reorientation of the director so that the deformed state with a lower free energy than the initial state is formed. In comparison to solid crystals, the energies of elastic deformation in liquid crystals are several orders of magnitude smaller.
External forces such as electric or magnetic fields alter the direction of the local director, giving rise to charge separation. The applied electric field causes these charged volumes to flow in alternating directions, in turn leading to a viscous torque on the local directors in such a way that deformation in the liquid crystal takes place. Transverse fields created by the space charge distribution bolster this deformation. These forces are countered by an elastic torque which is due to surface interaction and a dielectric torque resulting from negative dielectric anisotropy. Above the threshold field, deforming torques overcome the stabilizing torques. A potential difference of a few volts leads to cellular convection in liquid crystals causing disruption of the original molecular alignment. Further increases in voltage will result in more disruption, leading to a turbid appearance. The occurrence of such a convective instability can be determined by the anisotropy of electrical conductivity, i.e., conductivity parallel to the direction of alignment which differs from conductivity perpendicular to this direction, and by dielectric properties in the initially aligned material. Small spherical ions like Na⁺ possess a relatively low conductivity anisotropy, whereas nonspherical ions exhibit a relatively high conductivity anisotropy because of steric impedances (110).

4.3.2.3.3 Voltage

In the initial phase of iontophoresis, voltage was found to increase continuously. These initial increases in voltage can be explained by gradual orientation of layers in the liquid crystalline material, and to distribution of lidocaine HCl in the hydrophilic and hydrophobic domains of the monoolein/water lamellar liquid crystalline phase.
It has been reported that the conductivity of lamellar lyotropic phases decreases with time, and this has been attributed to a gradual tendency for these systems to assume a homeotropic arrangement between the electrodes in which the lamellae lie parallel to the electrodes. Initially, lamellar phases will be oriented in many directions. Upon standing, a homeotropic condition with the director perpendicular to the bounding wall, which arises from surface effects close to the electrode, will gradually spread outwards. Under these conditions, the sample will gradually assume the preferred orientation which unfortunately is the one which offers maximum resistance to passage of current (207).

Given the solubility of lidocaine hydrochloride in water and its polar character, most of the drug is dissolved in the water and this dissolved drug is then entrapped between the lipid layers. Entrapped drug will be released slowly since it has to diffuse through tortuous aqueous pathways and highly lipophilic bilayers. In addition, a small amount of lidocaine $\text{H}^-$ might be loosely bound to hydrophilic groups at the surface of the bilayer because of its surface-active properties. The drug will be released at a faster rate from this surface depot since its ions do not need to penetrate into the lipophilic regions of monoolein. During application of current, drug ions will preferably move through the aqueous channels since they are the paths of least resistance rather than penetrating into lipophilic bilayers. Along with an increase in the viscosity, depletion of surface bound drug would explain the increase in voltage from its initial low value to that at which it stabilizes.
4.3.2.4 Monoolein liquid crystals as an iontophoretic drug delivery medium

Based on the release patterns observed in this work, it was proposed that lidocaine H+ binds to monoglyceride mesophases. This was later confirmed by Chang, et al, who showed that drug release was affected by the absorption of amphiphilic drugs to monoglyceride phases rather than to ionic interactions between cationic drugs and fatty acids present in the monoglycerides (208). Because of such binding, it was found that drug is not released completely from these mesophases. Monoolein because of its lipid nature makes the formulation less conductive, thereby forcing the addition of electrolytes to enhance conductivity. Drug release was then complicated in turn by the presence of NaCl. The low conductivity combined with drug binding lead to small enhancements or to even reductions in drug release from the monoolein liquid crystalline systems. Later on, Corrigan, et al, reported a similar non-linear iontophoretic release of a polar drug with respect to current from monoolein formulations (209). In fact, monoolein-water-lidocaine HCl systems do not form mesophases other than lamellar at 32 °C, thus precluding study of drug release from other types of liquid crystalline phases. In iontophoresis, it is advisable to minimize extraneous ions in order to achieve high drug delivery efficiency, and to make a formulation reasonably electrically conductive to minimize power requirements. In this context, water soluble, preferably nonionic surfactants such as the Pluronic* Polyols (poloxamers), which form a variety of mesophases at 32 °C, may be good alternative candidates for studying these effects and they will be the subject of the following discussions.
4.3.3 Poloxamer liquid crystalline formulations

4.3.3.1 Poloxamer 334

Poloxamer 334 has a molecular weight of 5,900 with a molecular composition of \((\text{poly(oxyethylene)})_{27}(\text{poly(oxypropylene)})_{56}(\text{poly(oxyethylene)})_{27}\). It forms cubic, hexagonal and lamellar liquid crystalline phases in water, in addition to micellar and mixed phases, at concentrations ranging from 25-85% w/w. All of these mesophases invariably melt below 100 °C and occupy a region in a phase diagram ranging from 5-90 °C (210). At 32 °C, globular micelles form first in aqueous solutions which exist at concentrations below 25% w/w of the poloxamer. A cubic phase forms when poloxamer concentration reaches the range of 27-38% w/w. Upon further increases in concentration, a hexagonal phase is formed which persists until poloxamer concentration is about 62% w/w at 32 °C. At concentrations between 69-88% w/w poloxamer, a lamellar phase is formed. Each phase is separated from neighboring phases by a two-phase region. A multiphase region occurs below 5 °C and above 90 °C. These desirable features of the poloxamer 334-water systems were the reasons for using this system to study the effect of mesophase structure on iontophoretic drug transport.

4.3.3.2 Preparation

The poloxamer-water liquid crystalline phases can be prepared by either a “cold” or a “hot” process (211). In the cold method, a weighed amount of poloxamer is slowly added over a period of time to cold water with gentle mixing. The container may be left overnight in a
refrigerator at 4 °C to effect complete solution or may be placed in icebath and mixed slowly until the poloxamer is dissolved. This technique is most often used in laboratories since it does not require heat which could be deleterious to the activity of the drug. Solvent evaporation is also minimized because of the low temperature. The cold process proved to be very tedious however, particularly for dissolving poloxamer 334 above 30% w/w due to increases in the viscosities of the cold solutions. By contrast, the hot process was simpler and could be completed in less than five hours. Heating lidocaine HCl for such a prolonged period does not affect its therapeutic activity (131). Water loss during heating was minimized by wrapping Parafilm® around the cap of the vial. Weight loss, if any, was checked by reweighing the vial after heating. There are no reported differences in the structures and properties of mesophases prepared by these two methods, nor were any observed.

The formulations were colorless, transparent and free flowing fluids when refrigerated and “ringing gels” at room temperature and above. That is, when one strikes a flask or bottle containing gel against a solid background, a ringing vibration can be felt. This results from the stiffness of the gel. The gels did not show birefringence when observed by optical microscopy through crossed polarizers at 32 °C. Based on these characteristics and on the location of these compositions in the phase diagram of the original poloxamer 334-water system, it was presumed to be a cubic liquid crystalline phase.
4.3.3.3 Poloxamer 184

Initially, poloxamer 334 was chosen because of its ability to form cubic, hexagonal and lamellar liquid crystalline phases at 32 °C as its concentration is increased. A cubic liquid crystalline phase of poloxamer 334 lies next to the micellar phase and therefore, preparation of such a system was facilitated. By lowering the temperature of the cubic liquid crystalline gel, a less viscous, free flowing micellar phase forms which permits homogenous mixing without entrapping air. However, the lamellar and hexagonal liquid crystalline systems of poloxamer 334 and water could not be made homogenous and air-bubble free because of the solid rubber-like consistency of the systems. By lowering the temperatures of the lamellar and hexagonal liquid crystalline formulations, hexagonal and cubic phases are formed, respectively. These phases are too stiff to mix effectively and to load into the donor compartments of iontophoretic cells without entrapping air.

Poloxamer 184 has a molecular weight of 2,900 with a molecular composition of (poly(oxyethylene))_{13}-(poly(oxypropylene))_{30}-(poly(oxyethylene))_{13}. Thus, it has the same molar ratio of poly(oxyethylene) and poly(oxypropylene) as that of poloxamer 334, but is half its molecular weight. In water it forms less viscous systems than does poloxamer 334 because it consists of smaller polymer blocks. It also forms hexagonal, cubic and lamellar liquid crystalline phases as its concentration increases (212). An isotropic micellar phase is formed below 40% w/w poloxamer 184. At higher concentrations, a hexagonal phase forms and occurs up to 69% w/w poloxamer 184. Thus, a hexagonal phase rather than a cubic phase appears as the first liquid crystalline phase at these concentrations. Between 69-82% w/w
poloxamer 184, a lamellar phase forms. A cubic phase does not form, but below 25 °C, between the regions of the hexagonal and lamellar phases. This cubic phase is presumed to consist of bicontinuous networks of water and polymer. Thus, it differs from the normal cubic phase which appears in poloxamer 334/water systems between the isotropic micellar solution and the hexagonal phase. This behavior has been attributed to differences in the micellar shapes of these poloxamers (182). Unfortunately the cubic phase of poloxamer 184 spans a very narrow range of concentration, making it difficult for practical use in studies of drug release.

4.3.3.4 Characterization

All of these formulations were colorless, transparent fluids when refrigerated, and formed colorless, transparent gels at room temperature and above. For each mesophase, the ratios of water to poloxamer were the same to allow evaluation of the effect of increasing drug concentration on drug release. As expected, the hexagonal and lamellar mesophase formulations had birefringence characteristic of each type of phase (Figures 4.5 and 4.6). The microscopic textures of these block copolymer systems were not found to be distinct, i.e., sharply defined. This has been attributed to the structure of the block copolymers (210). The interiors of the copolymer micelles are much less ordered compared to that of simple hydrocarbon surfactants. Moreover, the large-scale structure is less well developed for the copolymers than for normal single chain surfactants. However, manipulating the samples for a longer time while in the polarized light microscope often produced textures which displayed the usual characteristic features of these liquid crystalline systems.
The nature of the liquid crystalline phases was confirmed by $^2$H-NMR. As expected, an isotropic line for the cubic liquid crystalline formulations was found (Figure 4.7). The sharp spectrum line occurs because all deuterium atoms are facing the same environment, i.e., there is no anisotropic effect. Cubic phases are therefore isotropic, i.e., their structure is identical along any three orthogonal directions in space. The single spectrum line also indicates the presence of only one phase in the system. Because of the geometry of the cubic phase, quadrapolar interactions will be averaged out on the NMR time scale; therefore, splitting collapses and the spectrum consists a single resonance line (201).

Figures 4.8 and 4.9 show the deuteron NMR spectra for the hexagonal and lamellar liquid crystalline formulations, respectively. Unlike the cubic phase, the hexagonal and lamellar phases have a doublet occurring as if it is centered around the hypothetical single sharp isotropic line for the cubic phase. For the anisotropic hexagonal and lamellar phases, interactions of the deuteron quadrapole moment with the electric field gradient at the deuteron nucleus generates spectra with two equally intense peaks with widths on the order of kilohertz (202). This occurs because of residual quadrapolar interactions resulting from the anisotropy of the liquid crystalline phases that is not averaged out by molecular motions. Observed quadrapole splitting depends on the fraction of deuteron in one or more anisotropic sites, the quadrapolar coupling constant and the average molecular ordering of water molecules in these sites (203). For a lamellar liquid crystalline phase, quadrapolar splitting which is measured as peak to peak distance, is almost twice that for a hexagonal liquid crystalline phase (203, 204). It has been reported in the literature that the quadrapolar
splitting for a lamellar liquid crystalline phase is double that of a hexagonal liquid crystalline phase if the lamellae are flat, i.e., not significantly curved. In addition, local interactions and molecular ordering are the same in the two phases and translational diffusion of deuteriums around the cylinders of the hexagonal structure occurs over a time period shorter than that for inverse splitting (203, 204). This indicates the existence of only the hexagonal or lamellar phases in the respective systems.

4.3.3.5 Drug release

Steady state fluxes from the solution, and the cubic, hexagonal and lamellar liquid crystalline formulations as functions of current and lidocaine HCl concentration are shown in Figures 4.10-4.13. Passive diffusional fluxes from formulations of all of the phases were found to increase with increases in lidocaine HCl concentration. Diffusional release of a soluble drug from a liquid crystal matrix can be given by Equation 4.1 which was proposed by Baker and Lonsdale (213). Accordingly, the release rate is proportional to the concentration of drug.

\[
\frac{dQ}{dt} = 2C_0 \left( \frac{D}{\Pi t} \right)^{\frac{1}{2}}
\]

where, Q is the amount of drug released from a unity surface area during time t; D is the diffusion coefficient; C_0 is the initial drug concentration in the liquid crystalline phase; and \(\Pi\) is the geometric constant of the drug delivery device.
The trend of the passive diffusional fluxes of lidocaine H⁺ from the poloxamer/water mesophases is to decrease in the order: cubic, hexagonal, lamellar; whereas the iontophoretic fluxes remained relatively constant at the higher currents. Iontophoretic fluxes for all formulations were also linear with respect to current. The liquid crystalline system consists of three domains: a hydrophilic domain, a hydrophobic domain and an interface between the hydrophilic and hydrophobic domains. Because of its polar nature, lidocaine H⁺ is primarily in the hydrophilic domains, but may also be found at the interface due to its surface active properties. Apparently, the polar lidocaine H⁺ diffuses through aqueous channels within the liquid crystalline system (196). An increase in resistance to diffusion through these channels would be expected compared to that of a solution due to their viscosity and tortuosity.

Poloxamers are soluble/dispersible in water and dissolve as unimers at low temperatures and low concentrations. Above a critical temperature and critical concentration, micelles are formed due to the hydrophobic effect between the propyleneoxide block and water. These micelles consist of a core of propyleneoxide with a water-swollen mantle of ethyleneoxide chains. An increase in temperature or poloxamer concentration, or both, increases the volume fraction of the micelles. At a critical volume fraction, micelles undergo inverse hard sphere crystallization and ‘freeze’ into a cubic liquid crystal (214). That is, at a critical volume fraction, micelles overlap considerably and form a hard gel consisting of close-packed spherical micelles. This discontinuous cubic phase requires a higher level of hydration energy and therefore, is the most dilute liquid crystalline phase. It is a cubic liquid crystal because it is characterized by true long range correlations in the bond angles similar to that of true
crystals, but has only quasi-long range correlations which are liquid like in bond lengths (214). The structure of a matrix of “hard sphere” micelles consists of tortuous aqueous networks through which drug ions and current flow (Figure 4.14).

Upon further addition of poloxamer, i.e., by decreasing water content, fusion of micellar elements of the cubic phase might occur to form the cylindrical elements of indefinite length characteristic of a hexagonal phase (215). These cylindrical elements are assembled in a parallel, hexagonally close-packed manner. The hexagonal phase may be regarded as possessing two-dimensional long range order. As in the cubic phase, aqueous channels exist outside the cylindrical elements through which ions and current flow (Figure 4.15). Passive fluxes from these phases are less than those from cubic phases due to the higher microviscosity of the channels due to their low water contents. Therefore, increased hindrance to diffusion should occur in such structures compared with that when micelles exist in a discontinuous array.

The cylindrical elements of the hexagonal phase will undergo a transition to a lamellar bilayer structure upon further addition of poloxamer. This phase may be regarded as possessing one-dimensional long range order (Figure 4.16), and in general, it is the most concentrated liquid crystalline phase. Since lidocaine H⁺ is polar, it cannot pass easily through such bilayers, but instead diffuses through the tortuous aqueous channels between the bilayers. Domains of bilayers are arranged randomly, thereby making diffusion of lidocaine H⁺ difficult. As a result,
passive diffusion fluxes from the lamellar liquid crystalline phase are the lowest among all of
the formulations due to their very low water contents and high microviscosity of the aqueous
channels between the bilayers.

The release of lidocaine H⁺ from a cubic liquid crystalline formulation containing 10% w/w
lidocaine HCl is shown in Figure 4.17 (note the effect of the programmed current changes).
The magnitude of the post-iontophoretic passive diffusional flux indicates in general that no
irreversible changes were taking place in both the membrane and formulation due to the
passage of current. As shown in the figure, post-iontophoretic passive diffusional fluxes
attain values similar to that of the pre-iontophoretic passive flux some time after the current
had been turned off. This increased passive diffusional release during the off period may be
due to release of entrapped drug in the membrane and/or to accumulated drug in the receiver
compartment.

4.3.3.6 Conductivity
The specific conductivities of all of the formulations as functions of the molar concentrations
of lidocaine HCl are shown in Figure 4.18. The figure indicates a linear increase in the
specific conductivity of all the formulations with increasing concentration of lidocaine HCl.
The ability of electrolyte solutions to carry current increases with increases in electrolyte
concentration since there are more ions present in a unit volume to carry the current. The
observed decreases in conductivity are consistent with decreases in the water content of the
systems, and to an increased resistance to ion transport due to the characteristic structures
of the liquid crystals. The conductivity is dependent on the mobility of ions as given by Equation 4.2 below (205, 216):

$$\Lambda_i = F u_i |z_i|$$  \hfill [4.2]

where, $F$ is the Faraday constant; $\Lambda$ is the equivalent conductivity; $u$ is the mobility; and, $z$ is the charge of ionic species $i$.

The mobility of ions decreases with increases in the viscosity of a medium. It is also dependent on the structure of the liquid crystalline phase. The more difficult the barrier to ion transport is through aqueous channels, the smaller will be the mobility of the ion. The barrier for ionic transport in liquid crystalline phases is a hydrophobic domain of poloxamer micelles consisting of the propyleneoxide units. This was discussed previously for the effect of liquid crystalline structure on the flux of lidocaine H' (see pages 29-30).

As shown in Figure 4.19, conductivities and passive diffusional fluxes of lidocaine H' from all of these mesophase formulations and from a solution were proportional to their water contents. The passive flux depends on the diffusion coefficient of the drug as given in Equation 4.1. The conductivity of the ions is proportional to their diffusion coefficients as given by Equation 4.3 below:

$$\Lambda_i = \frac{D Z_i^2 e^2}{RT}$$  \hfill [4.3]
where, \( k \) is the Boltzman constant; \( T \) the absolute temperature; and \( e \) an electronic charge. The diffusion of ions depends on the water content since it determines the microviscosity in the aqueous channels through which ions are transported. The higher the water content in the system, the faster will be the diffusion of drug ions.

### 4.3.3.7 Drug concentration

Although conductivity increases with increases in lidocaine HCl concentration, iontophoretic flux increases minimally for the solution and cubic liquid crystalline formulations. No significant changes in the fluxes were found for the hexagonal and lamellar liquid crystalline formulations over the range of concentrations studied.

The thermodynamic activity gradient of a drug is enhanced by an increase in drug concentration which leads to subsequent enhancement in passive diffusional drug release. In iontophoresis, however, an electric potential gradient is the primary driving force for flux across a membrane. Increasing drug concentration leads to increases in flux up to a maximum value after which it attains an essentially constant value, and in fact, may sometimes decrease \( (33) \). This nonlinear dependency of iontophoretic flux on concentration appears to occur due to aggregation of drug molecules, alteration in electroosmosis, ion-pairing/complexing and/or to saturation of ion-conducting pathways in a membrane \( (32, 34, 35) \). Lidocaine H\(^+\), being surface active, has a tendency to aggregate at high concentrations to form dimers, thereby reducing its effective concentration. The iontophoretic flux at moderate currents is mainly determined by the diffusivity of the drug and of the counter-ions on the opposite side of the
membrane in the receiver compartment. If drug diffusivity is relatively smaller than that of
the counter-ions in the receiver compartment, then iontophoretic drug delivery becomes less
dependent on drug concentration (36).

At the higher currents, fluxes from hexagonal and lamellar liquid crystalline formulations
containing 2.5 and 5.0% w/w lidocaine HCl were greater than the corresponding fluxes from
an aqueous solutions at the same concentrations of drug, but similar to those from solutions
at the high concentrations of drug. This appears to be due to an increase in the effective
aqueous concentrations of lidocaine HCl in these formulations resulting from proportionate
decreases in water content.

4.3.3.8 Transport number

In iontophoresis, drug flux is characterized by transport numbers, i.e., the fraction of the
current carried by drug ions. Figure 4.20 shows the transition in transport behavior of
lidocaine H\(^+\) from diffusion controlled to ionic transference controlled processes. The slope
of the straight line portions of a plot of the cumulative amounts of lidocaine H\(^+\) transported
(\(\mu\)g) as functions of time (minute) was used to calculate the transport number. In passive
diffusion, molecules move at random velocities depending on a concentration gradient,
whereas in ionic transference controlled processes, molecules move rapidly at their terminal
velocities. The significance of this figure is that it establishes the range of currents that can
be used for comparing current induced fluxes for a given experimental configuration. As
Figure 4.20 shows, transport numbers become independent of current at about 0.75 mA DC
and above, and are therefore ionic-transference controlled. This can be explained as follows:

The total iontophoretic flux is given as,

\[ J_i = J_p + J_e + J_c \]  \[4.4\]

where, \( J_i \) is the total flux; \( J_p \) the passive diffusional flux; \( J_e \) the electrophoretic flux; and \( J_c \) the electroosmotic flux. \( J_e \) and \( J_c \) are proportional to current and can be written as,

\[ J_e + J_c = kI \]  \[4.5\]

where, \( k \) is a proportionality constant and \( I \) is the current. Substituting Equation 4.5 into Equation 4.4 gives:

\[ J_i = J_p + kI \]  \[4.6\]

Transport numbers, calculated on the basis of the total fluxes rather than the iontophoretic fluxes, are given by:

\[ t_D = \frac{(ZFJ_p)}{I} + ZFk \]  \[4.7\]

where \( t_D \) is the transport number of the drug. As current increases, the contribution of passive
diffusional flux decreases and becomes less significant. Under these conditions, transport numbers finally attain values independent of voltage. This asymptotic value of the transport number is given by (36):

\[ t_D = \frac{D_D}{D_{\text{Counterions}} + D_D} \]  \[ \text{[4.8]} \]

where, \( D_D \) and \( D_{\text{Counterions}} \) are the diffusion coefficients of lidocaine \( H^+ \), and the counter-ions, respectively. In this work chloride and phosphate ions are the counter-ions. The limiting value of the transport number of lidocaine \( H^+ \) from the solution formulation can be calculated from the diffusion coefficient of lidocaine \( H^+ \) and \( Cl^- \) if one ignores the transport of phosphate ions. The diffusion coefficient of lidocaine \( H^+ \) can be calculated from conductivity data as explained in the following discussions.

The specific conductivity of an electrolyte solution increases with increases in the concentration of electrolytes. For electrolytes, the molar conductivity, \( \Lambda \), which represents the conducting power of all the ions produced by one mole of an electrolyte in a given solution, is a convenient measure, and is calculated from specific conductivities as follows:

\[ \Lambda = \frac{1000 \kappa}{C} \]  \[ \text{[4.9]} \]

where \( C \) is the concentration in moles per liter and the units of \( \Lambda \) are \( S \text{ cm}^2 \text{ mol}^{-1} \). Similarly, the equivalent conductivity, \( \mu \), the conducting power associated with one mole of unit
charges, is given by,

\[ \mu = \frac{1000\kappa}{zC} = \frac{1000\kappa}{N} \]  \hspace{1cm} [4.10]

where, \( N \) is the concentration of electrolyte in equivalents per liter and \( z \) is the number of equivalents per mole. The units of \( \mu \) are S cm\(^2\) equiv\(^{-1}\). For lidocaine HCl, the equivalent conductivity is the same as the molar conductivity. At infinite dilution, if electrolytes are completely ionized, the conductivity of an electrolyte is the sum of the ionic conductivities of the individual ions. The ability of an electrolyte to conduct a current is determined by the total charge and the actual velocities of the ions. For an equivalent solution at high dilution, the total charge is constant; therefore, conductivity is determined by the ionic velocities. The velocity of an ion per unit electric field strength is the ionic mobility, \( \mu \).

Figure 4.21 is a Kohlrausch's plot of molar conductances as functions of the square roots of the molar concentrations of lidocaine HCl at 32 °C. The plot for the solution is a straight line with the intercept (molar conductance at infinite dilution) of 109.07 S cm\(^2\) equiv\(^{-1}\) at 32 °C. The molar conductance of lidocaine HCl \((^0\Lambda_{\text{lidocaine HCl}})\) at infinite dilution is the sum of the molar ionic conductances of lidocaine \(H^+ \) \((^0\Lambda_{\text{lidocaine H}^+})\) and \(Cl^- \) \((^0\Lambda_{\text{Cl}^-})\) ions (Kohlrausch’s law of independent migration of ions) as follows (205, 216, 217):

\[ ^0\Lambda_{\text{lidocaine HCl}} = ^0\Lambda_{\text{lidocaine H}^+} + ^0\Lambda_{\text{Cl}^-} \]  \hspace{1cm} [4.11]
The molar ionic conductance of chloride ions at infinite dilution at 25 °C is 76.34 S cm² mol⁻¹ (218, 219). The ionic conductance at infinite dilution at temperature $t$ with fair accuracy calculated from the ionic conductance value at 25 °C is given by (220),

$$^{0}\Lambda_t = ^{0}\Lambda_{25} \left[ 1 + \alpha (t-25) + \beta (t-25)^2 \right]$$  \hspace{1cm} [4.12]

The factors $\alpha$ and $\beta$ are constant for a given ion in the particular solvent. For a narrow temperature range, e.g., 25 °C ± 10 °C, $\beta$ may be omitted and the value of $\alpha$ for chloride ions is $1.88 \times 10^{-2}$. Therefore, the molar ionic conductance of chloride ions at infinite dilution at 32 °C is 86.39 S cm² equiv⁻¹. Subtracting the molar ionic conductance of chloride ions at infinite dilution from the molar conductance of lidocaine HCl at 32 °C gives the molar ionic conductance of lidocaine H⁺ at infinite dilution at 32 °C of 22.68 S cm² mol⁻¹. Therefore, the mobility of lidocaine H⁺ calculated by dividing its molar ionic conductance by the Faraday constant is $2.35 \times 10^{-4}$ cm² V⁻¹ s⁻¹. The diffusion coefficient, $D$, of lidocaine H⁺ can be obtained from the Einstein relationship between the diffusion coefficient and the electric mobility (205, 216, 217),

$$D = \frac{RTu_i}{|z_i|F}$$ \hspace{1cm} [4.13]

where, $R$, is the gas constant. Using this equation, the calculated value of the diffusion coefficient of lidocaine H⁺ is $6.18 \times 10^{-6}$ cm² s⁻¹. Unfortunately, there is no reported value for the diffusion coefficient of lidocaine H⁺ in the literature, but the value calculated from
equation 4.13 can be confirmed by calculating the diffusion coefficient using the Wilke-Chang equation (221),

\[ 0.0 D_{AB} = \frac{7.4 \times 10^{-8} (\phi M_B)^{1/2} T}{\eta B V_A^{0.6}} \]  

[4.14]

where,

\( 0.0 D_{AB} \) = mutual diffusion coefficient of solute A at very low concentrations in solvent B, \( \text{cm}^2 \text{s}^{-1} \)

\( \phi \) = association factor of solvent B (dimensionless)

\( M_B \) = molecular weight of solvent B, \( \text{g/mol} \)

\( T \) = temperature, K

\( \eta_B \) = viscosity of solvent B, \( \text{cP} \)

\( V_A \) = molar volume of solute A at its normal boiling temperature, \( \text{cm}^3/\text{mol} \)

For water, the recommended value of \( \phi \) is 2.6, and the viscosity of water at 32 °C is 0.784 cP (221). The molar volume of lidocaine at 32 °C can then be estimated using the Le Bas additive volume method as shown in Table 4.4 (221).

Substituting the value of the molar volume of lidocaine \( \text{H}^+ \) in the Wilke-Chang equation gives the value for the diffusion coefficient of \( 6.3 \times 10^{-6} \text{ cm}^2 \text{s}^{-1} \), which is in excellent agreement with the value found from conductivity data. This indicates the accuracy of the conductivity data, in addition to providing the diffusion coefficient of lidocaine \( \text{H}^+ \) in water.
The diffusion coefficient of Cl⁻, calculated from its mobility at 32 °C, is $2.35 \times 10^{-3}$ cm²s⁻¹. Substituting the values of the diffusion coefficient of lidocaine H⁺ and Cl⁻ ions into the Equation 4.8 gives the value for the transport number of lidocaine H⁺ of $2.11 \times 10^{-1}$, which is in agreement with the value calculated from the iontophoretic fluxes. As mentioned previously, this is the limiting value of the transport efficiency of lidocaine H⁺. The observed transport of lidocaine H⁺ would be smaller than this value since other ions such as phosphate ions compete for current transport, thereby reducing the efficiency of lidocaine H⁺ which has been ignored in the calculation.

4.3.3.9 Constant current

The average steady state fluxes at higher currents were similar from all the formulations, although conductivity decreased with decreases in their water content. This happens because the mobility of drug ions as well as counter-ions in the formulation is lower than in water. The potential difference across the membrane is of course the primary driving force for iontophoretic flux. In iontophoresis, the current, and therefore the ions in a formulation, would be transported through paths of least resistance, i.e., the aqueous channels. In this context, the apparently greater resistances to transport through the aqueous channels in the poloxamer formulations, compared with those of the solution, appear to be compensated for by the higher voltages. The use of constant current appears to equalize the drug delivery rate at higher currents. This result is consistent with Phipps, et al, who observed fluxes of similar magnitudes through different types of skins at constant moderate currents (222).
Correlations of steady state fluxes and currents for the solution and poloxamer liquid crystalline formulations containing 10% w/w lidocaine HCl are given in Table 4.5. The intercept of the regression line is a hypothetical drug transport rate at zero current, the slope of which represents the rate of drug transport per current unit, i.e., \( \mu g \ \text{min}^{-1} \ \text{mA}^{-1} \). High correlation coefficients indicate no apparent interference on drug release due to electrorheologic, electromorphologic and/or electrohydrodynamic effects or to other physical instabilities within the range of currents used. These electrical effects generally occur above a certain threshold voltage. In these cases, however, the applied voltages may be lower than the threshold voltage.

4.3.3.10 Enhancement factors

The enhancement factors, the ratios of the iontophoretic fluxes at particular currents to the passive diffusional fluxes, increase in the order: solution, cubic, hexagonal, lamellar, due to the decreasing passive diffusional fluxes and to the similar iontophoretic fluxes from these systems at the higher currents (Figure 4.22). It can be seen that the enhancement factors decrease as the concentration of lidocaine H\(^+\) increases. Such would be seen if an electroneutrality approximation to the Nernst-Planck equation was used without considerations of electroosmotic effects, which would be possible considering the small magnitude of charge on the Nuclepore\(^*\) membranes (36). Although enhancement factors are decreased, total drug delivery still increases with increases in drug concentration.
4.4. **Summary**

Because of their unique physico-chemical properties, liquid crystalline systems are appealing as donor formulations in iontophoresis to make this mode of drug administration more convenient and efficient. In transdermal drug delivery systems, liquid crystalline vehicles can modulate drug flux by influencing the physical-chemical properties of the drug. Two types of materials, which form liquid crystalline phases, have been evaluated as donor media for iontophoresis.

Initially, a lamellar liquid crystalline formulation consisting of monoolein, water and lidocaine HCl was studied. Drug delivery from this system was enhanced over that by passive diffusion upon the application of an electrical current. Unlike that from a simple solution, the iontophoretic fluxes from the monoolein mesophase were found to be non-linear with respect to the magnitude of the current. This non-linearity in drug flux could be due to electrically induced phenomena such as electrorheological and electrohydrodynamic effects along with the anisotropicity of conductivity in lamellar liquid crystals. At low currents (0.1 mA DC), both the passive diffusional flux and the electrically facilitated flux contribute to the total flux. On the other hand, at higher currents, the contribution of passive diffusional flux toward the total iontophoretic flux becomes smaller due to increases in viscosity. Electrohydrodynamic effects occur in liquid crystalline phases above certain threshold voltages and would influence drug transport depending on the magnitude of currents applied. In addition, the formulation
was electrically less conductive due to the lipid nature of monoolein. Overall, the delivery rate of lidocaine H⁺ was significantly lower when compared with that from an aqueous solution.

Poloxamers liquid crystalline systems have several advantages over that of monoolein as an iontophoretic drug delivery medium including their simple preparation, ease of application, retention at the site of application and ease of removal because of their reversible thermogelation properties. In addition, poloxamers have been reported to increase the stability of various peptides. These poly(ethyleneoxide)-poly(propyleneoxide)-poly(ethyleneoxide) surface-active block copolymers are water soluble/dispersible and form several types of mesophases in water. The poloxamer liquid crystalline systems are also reasonably electrically conductive which helps to minimize power requirements without the necessity to add extraneous ions.

Cubic, hexagonal and lamellar liquid crystalline systems of two poloxamers were studied. The mesophases were identified by polarized light microscopy and ²H-NMR. The passive and iontophoretic release of lidocaine H⁺ from these formulations and that from an aqueous solution across an artificial membrane have been studied as functions of current and lidocaine HCl concentration. The passive diffusional flux of lidocaine H⁺ from such formulations appeared to decrease in the order: solution; cubic, hexagonal, lamellar liquid crystalline phase. The water contents of the systems also decreased in the same order. Drug delivery from the liquid crystalline formulations upon application of current was enhanced over that by passive
diffusion and were highly correlated with the magnitude of the current. Thus, iontophoretic drug release appeared to be independent of any electrically induced effects in the liquid crystalline phases.

The passive diffusional fluxes from three types of poloxamer systems were proportional to the concentration of lidocaine HCl; whereas, iontophoretic fluxes were changed little, if any, over the range of concentrations of lidocaine HCl studied. Drug delivery was similar from all the formulations at the higher currents, i.e., ionic transference controlled drug release was not dependent on the structure of the liquid crystalline phase. Enhancement factors, the ratios of the iontophoretic fluxes at particular currents to the passive diffusional fluxes, decreased with increases in lidocaine HCl concentration. The enhancement factors also decreased with increases in water content, i.e., in the order: lamellar, hexagonal, cubic liquid crystal; solution, due to the increasing passive diffusional fluxes and to the similar iontophoretic fluxes from these systems at the higher currents.

The specific conductivities of the mesophase formulations were highly dependent on the water contents of the systems. The value of the diffusion coefficient of lidocaine H⁺ at 32 °C estimated from the conductivity of the solution was $6.18 \times 10^{-6}$ cm$^2$ s$^{-1}$. This value was confirmed by calculating the diffusion coefficient of lidocaine H⁺ using the Wilke-Chang equation ($6.3 \times 10^{-6}$ cm$^2$ s$^{-1}$). The limiting value of the transport efficiency ($2.11 \times 10^0$) of lidocaine H⁺ estimated using this diffusion coefficient value was in agreement with the values calculated from the iontophoretic fluxes.

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This study also demonstrated clearly that the choice of a vehicle can significantly affect the
drug release efficiency of these types of transdermal drug delivery systems. The potential
benefits of using poloxamer liquid crystalline formulations as donor media in iontophoresis
include the formation of drug reservoirs free of materials commonly used for polymerization
which can reduce drug delivery efficiency, the absence of seepage problems, the ease of
replacement of the poloxamer-drug reservoir in an iontophoretic device, the stabilization of
the drug, and the control of passive diffusional fluxes for periods of time between
iontophoretic drug release.
<table>
<thead>
<tr>
<th>Materials</th>
<th>Supplier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine HCl</td>
<td>Astra Pain Control AB Södertälje, Sweden</td>
</tr>
<tr>
<td>Sodium phosphate, dibasic, 12-hydrate</td>
<td>J. T. Baker Phillipsburg, NJ</td>
</tr>
<tr>
<td>Potassium phosphate, monobasic</td>
<td>J. T. Baker Phillipsburg, NJ</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>Fisher Scientific Pittsburgh, PA</td>
</tr>
<tr>
<td>Sodium formate</td>
<td>Sigma Chemical Company St. Louis, MO</td>
</tr>
<tr>
<td>Formic acid</td>
<td>Sigma Chemical Company St. Louis, MO</td>
</tr>
<tr>
<td>Potassium chloride</td>
<td>Mallinckrodt, Inc. Paris, KY</td>
</tr>
<tr>
<td>Methanol HPLC grade</td>
<td>Fisher Scientific Pittsburgh, PA</td>
</tr>
<tr>
<td>Nuclepore® polycarbonate membrane</td>
<td>Corning Inc. Acton, MA</td>
</tr>
<tr>
<td>$^2$H$_2$O (99.99 atom% $^2$H)</td>
<td>Aldrich Chemicals Milwaukee, WI</td>
</tr>
<tr>
<td>(99.0 atom% $^2$H)</td>
<td></td>
</tr>
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</table>

Table 4.1 Materials.

(continued)
Table 4.1 Materials (continued).

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Monoolein</td>
<td>Chem Service</td>
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<td>Pluronic® Polyol P 104 (Poloxamer 334)</td>
<td>BASF Corporation</td>
</tr>
<tr>
<td></td>
<td>Wyandotte, MI</td>
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<tr>
<td>Pluronic® Polyol L 64 (Poloxamer 184)</td>
<td>BASF Corporation</td>
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<td></td>
<td>Wyandotte, MI</td>
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<td>Equipment</td>
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<td>------------------------------------------</td>
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<td>Iontophoretic cells</td>
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<td>Riegelsville, PA</td>
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<tr>
<td>Ag/AgCl embedded electrodes</td>
<td>AMIE Systems</td>
</tr>
<tr>
<td></td>
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<td>Scepter™ 12 channel programmable power supply</td>
<td>Keltronic Corp.</td>
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<tr>
<td></td>
<td>Oklahoma City, OK</td>
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<td>Multimeter, Model 2001</td>
<td>Keithley Instruments, Inc.</td>
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<tr>
<td></td>
<td>Cleveland, OH</td>
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<tr>
<td>Multi-channel peristaltic cassette pump, Model IPN</td>
<td>ISMATEC SA</td>
</tr>
<tr>
<td></td>
<td>Zürich, Switzerland</td>
</tr>
<tr>
<td></td>
<td>Karlsruhe, Germany</td>
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<tr>
<td>Fraction collector, Retriever IV</td>
<td>ISCO, Inc.</td>
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<tr>
<td></td>
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<td>Refrigerated circulating bath, Model RTE-90D</td>
<td>Neslab Instruments</td>
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<td>Portsmouth, NH</td>
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<td>Cooling jacket</td>
<td>Spectra-Tech, Inc.</td>
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<tr>
<td></td>
<td>Stanford, CT</td>
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<td>Magnetic stirrer, IKAMAG Model RET with revolution counter, IKA-TRON Model DZM 1</td>
<td>IKA-Works, Inc.</td>
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<tr>
<td>Temperature indicator and controller IKA-TRON Model ETS-D2</td>
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**Table 4.2** Equipment.

(continued)
Table 4.2 Equipment (continued).

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<th>Equipment</th>
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<td>Microbalance,</td>
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<td>Model UM-3, sensitivity 0.1 µg</td>
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<tr>
<td>Model AE 240, sensitivity 1.0 µg</td>
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<td>$^2$H-NMR, Avance 500 Model DRX 500</td>
<td>Bruker Instruments, Inc.</td>
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<td></td>
<td>Lisle, IL</td>
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<td>Conductivity</td>
<td>Extech</td>
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<td>Meter, Model 480</td>
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<td>Standard electrode</td>
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<td>Microelectrode, series MI-900</td>
<td>Microelectrodes</td>
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<td>Londonderry, NH</td>
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<tr>
<td>pH</td>
<td>Beckman</td>
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<tr>
<td>Meter, Model Φ 72</td>
<td>San Ramon, CA</td>
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<tr>
<td>Electrode, semimicro ROSS combination, glass</td>
<td>Orion</td>
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<tr>
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<td>Boston, MA</td>
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<td>Optical microscope</td>
<td>Leitz</td>
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<td>Microscope, Laborlux</td>
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<td>Video camera, Model DXC-151</td>
<td>Sony Corporation</td>
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<td>Model UP-3000</td>
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<td>Temperature controller, Model FP2 and FP21</td>
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(continued)
Table 4.2 Equipment (continued).

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<th>Equipment</th>
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<td>Beckman</td>
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<td>San Ramon, CA</td>
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<td>Injector, (250µL loop)</td>
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<td>Detector, Model 607</td>
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<tr>
<td>Analog interface, Model 406</td>
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</tr>
<tr>
<td>Software, System Gold™</td>
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<tr>
<td>Column, reverse phase, PRP-1,</td>
<td>Hamilton,</td>
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<tr>
<td>4.1 mm × 25 cm, 10 µm part.</td>
<td>Reno, NV</td>
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<td>Computer, PS/2, Model 30</td>
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<td></td>
<td>Armonk, NY</td>
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<tr>
<td>Formulation</td>
<td>I (% w/w)</td>
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<tr>
<td>-----------------------------</td>
<td>-----------</td>
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<tr>
<td>Solution</td>
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<tr>
<td>Lidocaine HCl</td>
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Table 4.3  Composition of formulations.
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<th>Atom</th>
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<td>H</td>
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<td>O (amide)</td>
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<td>13.5</td>
<td>13.5</td>
</tr>
<tr>
<td>N (2°)</td>
<td>1</td>
<td>12.0</td>
<td>12.0</td>
</tr>
<tr>
<td>6-membered ring</td>
<td>1</td>
<td>-15.0</td>
<td>-15.0</td>
</tr>
</tbody>
</table>

Total molar volume of lidocaine $H^+ = 310.2$ (cm³/mol)

Structural formula of lidocaine HCl: $C_{14}H_{23}ClN_2O$

Table 4.4 Calculation of the molar volume of lidocaine $H^+$ by the Le Bas volume incremental method.
<table>
<thead>
<tr>
<th>Formulation</th>
<th>Lidocaine HCl (% w/w)</th>
<th>Correlation coefficient ($r^2$)</th>
<th>Slope ($\mu g \text{ min}^{-1} \text{ mA}^{-1}$)</th>
<th>Intercept ($\mu g \text{ min}^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solution</td>
<td>2.5</td>
<td>0.990</td>
<td>20.5</td>
<td>6.05</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>0.993</td>
<td>11.9</td>
<td>20.1</td>
</tr>
<tr>
<td>Cubic liquid crystal</td>
<td>2.5</td>
<td>0.991</td>
<td>26.6</td>
<td>-1.47</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>0.999</td>
<td>22.9</td>
<td>8.73</td>
</tr>
<tr>
<td>Hexagonal liquid crystal</td>
<td>2.5</td>
<td>0.995</td>
<td>31.8</td>
<td>-3.49</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>0.994</td>
<td>27.9</td>
<td>1.56</td>
</tr>
<tr>
<td>Lamellar liquid crystal</td>
<td>2.5</td>
<td>0.999</td>
<td>34.1</td>
<td>-3.91</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>0.997</td>
<td>31.7</td>
<td>-0.78</td>
</tr>
</tbody>
</table>

**Table 4.5**  Linear regression of the transport of lidocaine H+ as functions of current from various formulations containing 2.5 and 10% w/w lidocaine HCl.
Figure 4.1  Polarized light microscopy of the lamellar liquid crystalline formulation containing 15% w/w lidocaine HCl, 2% w/w NaCl, 35% w/w water and 50% w/w monoolein.
Figure 4.2  Transport of lidocaine H⁺ from the lamellar liquid crystalline formulation containing 15% w/w lidocaine HCl, 2% w/w NaCl, 35% w/w water and 50% w/w monoolein as functions of current.
Figure 4.3 Transport of lidocaine H⁺ from the lamellar liquid crystalline formulation containing 15% w/w lidocaine HCl, 2% w/w NaCl, 35% w/w water and 50% w/w monoolein at 0.4 mA DC.
Figure 4.4  Linear regression of the steady state fluxes of lidocaine H⁺ from the lamellar liquid crystalline formulation containing 15% w/w lidocaine HCl, 2% w/w NaCl, 35% w/w water and 50% w/w monoolein as functions of current density.
Figure 4.5  Polarized light microscopy of hexagonal liquid crystalline systems consisting of 2.50-10.0% w/w lidocaine HCl, 45.0-48.7% w/w poloxamer 184 and 45.0-48.8% w/w water.
Figure 4.6  Polarized light microscopy of lamellar liquid crystalline systems consisting of 2.50-10.0% w/w lidocaine HCl, 63.0-68.2% w/w poloxamer 184 and 27.0-29.3% w/w water.
Figure 4.7  Deuteron NMR spectra of cubic liquid crystalline formulations at 32 °C.

A 2.5% w/w lidocaine HCl, 32.5% w/w poloxamer 334 and 65% w/w water.
B 10% w/w lidocaine HCl, 30% w/w poloxamer 334 and 60% w/w water.
Figure 4.8  Deuteron NMR spectra of hexagonal liquid crystalline formulations at 32 °C.

\(^A\) 2.5% w/w lidocaine HCl, 48.7% w/w poloxamer 184 and 48.8% w/w water.
\(^B\) 10% w/w lidocaine HCl, 45% w/w poloxamer 184 and 45% w/w water.
Figure 4.9  Deuteron NMR spectra of lamellar liquid crystalline formulations at 32 °C.

^2.5% w/w lidocaine HCl, 29.2% w/w poloxamer 184 and 68.3% w/w water.

^B 10% w/w lidocaine HCl, 63% w/w poloxamer 184 and 27% w/w water.
Figure 4.10 Transport of lidocaine $\text{H}^+$ from aqueous solutions as functions of lidocaine HCl concentration and current.
Figure 4.11  Transport of lidocaine H⁺ from cubic liquid crystalline formulations of poloxamer 334 and water (1:2) as functions of lidocaine HCl concentration and current.
Figure 4.12  Transport of lidocaine H⁺ from hexagonal liquid crystalline formulations of poloxamer 184 and water (1:1) as functions of lidocaine HCl concentration and current.
Figure 4.13  Transport of lidocaine $H^+$ from lamellar liquid crystalline formulations of poloxamer 184 and water (2.3:1) as functions of lidocaine HCl concentration and current.
Figure 4.14  Formation of a cubic liquid crystalline phase in poloxamer/water systems as functions of poloxamer concentration.
Monomers → Micelles → Cubic liquid crystal

↓

Hexagonal liquid crystal

**Figure 4.15** Formation of a hexagonal liquid crystalline phase in poloxamer/water systems as functions of poloxamer concentration.
Monomers $\rightarrow$ Micelles $\rightarrow$ Cubic $\rightarrow$ Hexagonal liquid crystal

$\downarrow$

Lamellar liquid crystal

Figure 4.16 Formation of a lamellar liquid crystalline phase in poloxamer/water systems as functions of poloxamer concentration.
Figure 4.17 Release of lidocaine H\(^+\) from a cubic liquid crystalline formulation containing 10% w/w lidocaine HCl, 30% w/w poloxamer 334 and 60% w/w water as functions of programmed currents.
Figure 4.18 Specific conductivities of various formulations of lidocaine HCl at 32 °C as functions of lidocaine HCl concentration.
Figure 4.19  Passive diffusional fluxes and conductivities at 32 °C as functions of water contents in various formulations containing 2.5% w/w lidocaine HCl.
Figure 4.20  Transport behavior of lidocaine H⁺ from various formulations containing 10% w/w lidocaine HCl as functions of current.
Figure 4.21  Molar conductivities of various formulations of lidocaine HCl at 32 °C as functions of the square roots of lidocaine HCl concentration.
Figure 4.22  Enhancement factors as functions of lidocaine HCl concentration and current for an aqueous solution; and cubic, hexagonal and lamellar liquid crystalline formulations.
CHAPTER 5

AN EFFICIENT GEL FORMULATION FOR IONTOPHORESIS

5.1 Introduction

5.1.1 The use of gels in electrically modulated drug delivery systems

In recent years, much attention has been given to the development of electrically modulated drug delivery systems using hydrogels and gels (223-226). Electrically modulated drug delivery from such gels is based on several electroresponsive mechanisms, including, solubilization of a polymer complex, modification of polymer swelling and the control of drug transport through a polymer membrane (227-229). Gels have several advantages over conventional solution formulations, such as their ease of handling and application, minimal skin hydration resulting from their application and increased skin compliance due to the absorption of sweat gland secretions (223). These gels are substantially rigid despite having high water content and can be designed as drug delivery systems consisting of multiple doses of drugs for extended periods of treatment.
Electrically controlled drug delivery of charged and uncharged drugs from gels consisting of sodium alginate, polyacrylic acid and polyallylamine has been determined (230-233). Hsu, et al. studied the effect of current on hydrophilic gels consisting of the anionic polymers, carbomer and agarose, as will be discussed below (234). In iontophoresis, gels have been used as electrodes in addition to their role as the donor media (119, 235, 236). Chien, et al. have quantified iontophoretic drug release kinetics from various hydrogels (118).

Gels sensitive to an electric field usually consist of polyelectrolytes. The ionizable fixed charge groups of polyelectrolytes give rise to important electromechanical and swelling phenomena that can significantly affect drug transport. Transport rates through these materials can be altered by manipulating electrostatic forces arising from the fixed charge groups of the polyelectrolytes which cause significant changes in the physical and chemical properties of the gels (237).

This chapter is concerned with iontophoretic drug release from agarose gels. Agarose gel formulations were modified by the addition of a negatively charged polymer, called 'efficient' gels for the purposes of this study, to achieve a higher iontophoretic drug delivery rate.

5.1.2 Agarose

Agarose is a biostuctural polysaccharide obtained from the cell walls of marine red algae (Rhodophyceae). It is an alternating copolymer of 1,3-linked β-D-galactose and 1,4-linked 3,6-anhydro-α-L-galactose substituted at irregular intervals with neutral and charged groups.
such as sulfate esters, methyl ethers, and/or pyruvate residues to varying degrees, and has a molecular weight of approximately 120,000 (238). It has a very low content of sulfate (0.30% w/w) and carboxylate groups. Agarose dissolves as a colloidal sol in water when heated to about 80-90 °C, and forms solid gels upon cooling below its gelling point of 35-45 °C. This gelation is thermoreversible and involves the transition of random coils in solution to bundles of double helixes in the gel (239). It is widely used for fractionating macromolecules by gel electrophoresis. It has been investigated also for the sustained delivery of ibuprofen or indomethacin to avoid stomach irritation (240-242).

The charged residues, mentioned above, are responsible for many agarose properties. Endoelectroosmosis (EEO) or the electroosmosis which occurs during electrophoresis because of the fixed negative charge on agarose polymers, is a functional measure of the number of the sulfate and pyruvate residues present on the agarose polysaccharide. Endoelectroosmosis is quantitated by subjecting a mixture of dextran and albumin to electrophoresis, then visualizing them and measuring their respective distances from the origin. High EEO agarose has more charged substituents than low EEO agarose (243).

5.1.3 Carbomers

Carbomers (Carbopol® resins) are synthetic high molecular weight polymers of acrylic acid crosslinked with allyl sucrose or allylpentaerythritols (244). A number of carbomer grades are commercially available which vary in molecular weight, degree of cross-linking and polymer structure. The carboxyl groups of the acrylic acid backbone of the polymer are
responsible for many of the properties. Carbomer polymers contain 56-68% of carboxylic acid groups. These crosslinked polymers swell in water up to 1000 times their original volumes to form gels when exposed to a specific pH environment. Carbomers when dispersed in water begin to hydrate and uncoil slightly to form acidic colloidal dispersions of low viscosity. The polymers must be completely uncoiled to form a gel. This can be accomplished by neutralizing the polymers with a suitable base such as sodium hydroxide or triethanolamine. Neutralization ionizes the carbomer resin, generating negative charges along the polymer backbone. Repulsion between the negatively charged polymers then causes swelling of the polymer.

These readily water-swellable polymers are used in various pharmaceutical applications to provide thickening in topical lotions, creams, oral suspensions and transdermal gel drug delivery systems; bioadhesion in buccal, ophthalmic, intestinal, nasal, vaginal and rectal applications; controlled release in tablets and for the formulation of gels (245-251).

5.1.4 Objectives

Hydrogels/gels have been used in electrically modulated drug delivery systems for various purposes. The fixed charges of these gels give rise to several important phenomena in an electrical field which could influence drug transport. This study was conducted therefore with the following objectives:

- To develop gel formulations, i.e., ‘efficient’ gels, for enhanced iontophoretic drug delivery which are free of extraneous ions such as polymerization
initiators, crosslinkers and buffer ions commonly used for forming gels.

- To examine the effects of the ionic charges of gel formulations on passive diffusional and iontophoretic drug fluxes.
- To investigate the effects of parameters such as drug concentration and electrical current on passive diffusional and iontophoretic drug release from the 'efficient' gel systems.

5.2 **Experimental**

5.2.1 **Materials**

All materials obtained commercially are listed in Table 5.1 and were used as received. Carbomer 934P was stored in light protective vials. Hereafter, "carbomer" will refer to carbomer 934P. All other materials were stored at ambient temperature according to the recommendations of the manufacturers. Distilled/Deionized water with a specific resistance of no less than 18 MΩ cm was obtained from a Millipore® Milli-Q® (Bedford, MA) system.

5.2.2 **Equipment**

Equipment used is listed in Table 5.2.
5.2.3 Methods

5.2.3.1 Preparation of carbomer-agarose gels
Lidocaine HCl was dissolved in water contained in a glass vial (~20 mL) after which agarose was added. The mixture was heated to 80 °C for about 20 minutes in a waterbath under continuous stirring. The carbomer was dispersed in water in a light protective vial under continuous stirring with a magnetic stirrer. Preheated agarose mixtures were then slowly added to the carbomer dispersions under continuous stirring to obtain the desired compositions. Agarose systems in which pH was adjusted to 2.5 were prepared by the addition of 1N HCl to preheated lidocaine-agarose dispersions. Care was taken to ensure that the mixtures were homogenous, yet free of air bubbles. Fresh gels were prepared before each iontophoresis experiment.

5.2.3.2 Composition of carbomer-agarose gels
Lidocaine HCl was added to the gel systems at concentrations of 0.1, 0.5 and 1.0% w/w while agarose was used at concentrations of 0.5, 2.0 and 3.0% w/w either, alone or in combination with 0.5 and 1.0% w/w carbomer 934P (Table 5.3).

5.2.3.3 Preparation of carbomer gels
Carbomer (0.5% w/w) was dispersed in water in a light protective vial under continuous stirring with a magnetic stirrer. A neutralizing agent (1 N NaOH or triethylamine) was added to the dispersions under moderate continuous stirring to obtain the desired pH (~6.8).
Carbomer gels neutralized by lidocaine base were prepared in a similar manner by slowly adding a sufficient amount of a methanol solution of lidocaine base (67.0% w/w) to the aqueous carbomer dispersion to give 1.0% w/w lidocaine. The pH of this system was 6.9.

5.2.3.4 pH measurement
The pH values of the agarose gels were measured after cooling the heated solubilized agarose mixtures to about 50 °C before loading into the donor compartment of an iontophoretic cell (Table 5.3). This was accomplished by placing the formulations in a jacketed beaker heated by circulating warm water.

5.2.3.5 Iontophoresis
The anode (donor) compartment was filled with 0.8 mL of a hot (~45 °C) gel dispersion and the same volume of isotonic phosphate buffer saline was placed in the cathode compartment. The gel dispersions underwent gelation immediately upon cooling to form a gel matrix in the donor compartments. Since the volume of the anode and cathode compartments is actually 0.32 mL, the remainder of the sample added to these compartments moved into the overflow chambers of the cell when the electrode was inserted. All experiments were conducted with ten stacked layers of Nuclepore® membranes (Media Separations, Inc., Lake Geneva, WI) that had been presoaked in isotonic phosphate buffer saline (PBS). Fresh membranes were used for each experiment. The temperature of the cell and eluant was maintained at 32 °C.
and the flow rate of isotonic phosphate buffer saline was controlled at 0.2 mL min\(^{-1}\). The flow of eluant was started as soon as the donor compartment was filled, following which it was collected at 15 minute intervals and assayed for lidocaine H\(^+\) by HPLC.

5.2.3.6 Electrical factors

Iontophoretic drug release was studied as functions of current to investigate the effects of current on drug release. In addition, passive diffusional release was also studied. Currents of 0.1, 0.2 and 0.3 mA DC, which corresponded to current densities of 0.16, 0.32 and 0.48 mA cm\(^{-2}\), respectively, were used. A continuous constant current was provided by a computerized power source with Scepter\textsuperscript{®} software. In all experiments, after an initial 1.5 hour period of passive diffusion, current was applied for another 1.5 hours and samples of the eluant were collected for up to 1 hour after the current had been turned off (Protocol 1). In addition to this, a programmed on:off incremental current was used as follows in Protocol 2.

Protocol 2: 0-45 min at 0 mA DC, 45-90 min at 0.3 mA DC, 90-135 min at 0 mA DC, 135-180 min at 0.1 mA DC, 180-225 min at 0 mA DC, 225-270 min at 0.2 mA DC, 270-315 min at 0 mA DC.

5.2.4 Data analysis

Steady state fluxes were determined by linear regression of the straight line portions of plots of the cumulative amounts of lidocaine H\(^+\) transported (\(\mu g\)) as functions of time (minute). The data from three experiments is presented as the mean ± standard deviation.
5.3 Results and Discussion

5.3.1 Drug transport barrier

Instead of five layers that had been used previously in studies of the liquid crystalline systems (see Chapter 4), ten layers of Nuclepore® membranes were used in these experiments in order to increase resistance to drug transport. This along with a decrease in lidocaine HCl concentration would facilitate achieving ionic transference controlled drug transport at low current densities. The low current density protocol has a primary advantage, an extended durability of the Ag/AgCl electrodes. A flow rate of 0.2 mL/min was selected in order to obtain drug concentrations in the eluant within detection limits, while at the same time maintaining sink conditions in the receiver compartments.

5.3.2 Agarose gels

Agarose was selected because of its ability to form rigid gel structures at low polymer concentrations. Agarose gels are simple in nature and easy to prepare. Agarose hydrogels are useful as iontophoretic drug delivery media in that they provide a rigid high conductivity matrix which is pliable and easily handled, but at the same time behaves as a fluid for drug transport because of the presence of microscopic water channels in its gel structure. Unlike gels consisting of synthetic polymers such as polyacrylamides, which are swollen networks of chemically cross-linked chains produced by reverse osmosis, agarose gels consist of randomly branched fibrous networks. The chemically cross linked polyacrylamide gels have more uniform internal gel structures compared with those of agarose gels (252). Unlike the
polyacrylamide gels, however, agarose gels can be oriented extensively in low electric fields (1-20 V cm\(^{-1}\)) due to metastable hydrogen bonded junction zones and to the absence of covalent bonding in their structure (253). This structural rearrangement of an agarose matrix requires very little external energy, and these orientations of domains in the agarose gels may affect drug transport significantly. It also has small net negative charges which facilitate cationic drug transport by electrical phenomena. For example, Hsu, et al, studied the effect of electrical current on anionic gels consisting of agarose, in conjunction with carbomer and xanthum gum, rather than drug transport which is a focus of the present investigation. Platinum electrodes were used in their study which produced very large changes in pH (3 orders of magnitude). These pH changes might be responsible for most of the observations they made regarding the effect of current on the gels. In the present study, reversible Ag/AgCl electrodes are used, and increased transmembrane drug delivery from agarose-carbomer formulations will be shown, contrary to observations made by Hsu, et al.

5.3.3 Drug release

5.3.3.1 Agarose gels

The cumulative release of lidocaine H\(^+\) and its release rate profile from an agarose gel system containing 2.0% w/w agarose are shown in Figure 5.1. It can be seen that upon the application of current, the steady state flux of lidocaine H\(^+\) is enhanced over that achieved by passive diffusion. The steady state passive diffusional and iontophoretic fluxes from various agarose gels are shown in Figure 5.2. The steady state passive diffusional flux from agarose
gels is not affected significantly by the concentration of agarose. This is in agreement with Sundelof, et al, who observed similar diffusion coefficients of chlorpheniramine maleate in 1 and 4% w/w agarose gels (254). This anomaly can be explained by examining the structure of an agarose gel matrix.

In a sol phase, agarose molecules aggregate and form large fiber bundles which are held together by hydrogen bonds. The size of the fiber bundle depends on the agarose concentration and the ionic strength of the solution (239, 255, 256). In the gel state, agarose exists in double helical states which are extensively aggregated and contain many agarose chains in a side-by-side assembly involving an unspecified degree of order. The diameter of these fiber bundles ranges from 2-30 nm to 60-100 nm. The gel matrix contains “junction zones” of these fibrous bundles which are mainly responsible for the rigidity of a gel matrix. It is reasonable to expect large voids in such a structure because of the aggregation of agarose chains into separate filamentous networks in a gel which contains large amounts of water. Electron micrographs reveal that the heterogenous structures of agarose gels consist of large interstitial voids occupied by solvent molecules bounded by irregularly branched fibrous networks of varying density (256). These microvoids are relatively independent of agarose concentration in the gels, whereas the fibrous regions become denser with increases in agarose concentration. In contrast, gels consisting of chemically crosslinked soluble random polymer chains will have much smaller pore sizes. Thus, the agarose gel matrix will have internal channels through which drug molecules can be transported (see Figure 5.3) (239).
Viscosity is defined as the resistance of a fluid to flow. In the presence of a polymer, the viscosity of water increases dramatically and the system becomes non-Newtonian in behavior. The Stokes-Einstein equation states that diffusion of a solute would be slower in a viscous medium, as follows (257, 258):

\[ D = \frac{kT}{6\pi\eta r} \]

where,

- \( D \) = Diffusion coefficient
- \( k \) = Boltzman constant
- \( T \) = Absolute temperature
- \( \eta \) = Viscosity of medium
- \( r \) = Radius of a diffusant

However, an anomalous diffusion in gels has been reported which could be explained by taking into consideration the microviscosity of the systems (259). Microviscosity is an operational term that describes the rheological properties of microscopic fluid regions, and which allows their evaluation in terms of classical hydrodynamics expressions (260). The viscosity or more specifically, macroviscosity, does not necessarily reflect the resistance experienced by the solute in its molecular environment, since it actually diffuses through the microscopic interstitial spaces filled with solvent between the polymer segments. Therefore, the viscosity of this microenvironment, i.e., its microviscosity, determines the diffusion of solute and not the bulk rheological characteristics of the gels (261). In this context, the
diffusion of solute depends upon the volume fraction occupied by polymer in the system as
does the macroviscosity of the system (262). The similar steady state fluxes from agarose
gels containing various concentrations of agarose may indicate a similar microviscosity in the
interstitial channels of these systems.

The steady state iontophoretic fluxes from agarose gels decrease as the concentration of
agarose increases from 0.5 to 2.0% w/w. The small but significant reductions in
iontophoretic flux may be due to different ionic transference controlled processes, due to
increases in agarose content, since steady state passive diffusional fluxes are independent of
agarose content. Agarose is slightly negatively charged and has few ionic species present due
to inefficient fractionation. Further increases in agarose content do not seem to affect the
steady state iontophoretic flux, since as explained previously (see Section 4.3.3.7),
iontophoretic fluxes are non linear with respect to the concentration of ionic ingredients.
Iontophoretic fluxes of drug have been observed to decrease with increases in the
concentration of co-ions up to a limit, beyond which they plateau or increase with further
increases in co-ion concentration (30).

5.3.3.2 Agarose-carbomer gels

Figure 5.4 shows the steady state passive diffusional and iontophoretic fluxes from various
agarose formulations containing 0.5% w/w carbomer. It can be seen that the presence of
carbomer in the agarose gels increases steady state iontophoretic fluxes up to 40%, while
passive diffusional fluxes remain relatively constant (see Figure 5.5).
The distribution of agarose fibers, and consequently the structure of the gels, is strongly dependent on ionic strength. Agarose gels formed in the presence of salts give rise to greater mobilities for drug molecules due to larger effective pore sizes compared with gels formed in salt-free environments (256). Thus, an agarose gel formed in the presence of a carbomer could have a different gel structure due to negative charges on the carbomer polymers. These differing structures of the gels may lead to substantial differences in the mobilities of drug ions depending on their molecular weight (256, 263). The presence of carbomer polymers could affect the microviscosity in the aqueous channels of the agarose gel matrices. Transport through a gel matrix depends upon the proportions of free water and bound water which could be affected by the presence of carbomer polymers in the agarose gels. However, all these effects might be insignificant, given the similar passive diffusional fluxes from the agarose gels and agarose-carbomer gels containing 0.5% w/w carbomer. Hsu, et al, found the microviscosities of agarose and agarose gels containing 0.5% w/w carbomer were the same as that of pure water (234). These increases in iontophoretic fluxes in these anionic gel systems can be explained by differences in electrokinetic transport phenomena.

Anionic gels undergo electrochemomechanical deformation which is largely due to changes in pH resulting from hydronium and hydroxyl ions generated by electrostatic interactions of the charged medium with polarizable electrodes such as those of platinum. Hydrogen ions generated near the anode due to hydrolysis of water will protonate the anionic groups of anionic gels and cause these groups to become less hydrated or dissociated, resulting in increased polymer-polymer interactions and subsequent gel collapse (230, 233). Tanaka, et
suggested that the uniaxial stress developed along the gel axis due to negatively charged groups was responsible for contraction of the gel (264, 265). This electrochemomechanical deformation, if significant, is accompanied by permeability changes. It is reasonable to expect therefore that agarose gels containing a negatively charged carbomer would exhibit deformations different from those of pure agarose gels. Since Ag/AgCl electrodes, which do not cause significant pH changes, and a low magnitude of current (0.2 mA DC) were employed in this study, gel deformation would not occur to such a significant extent that it would in turn affect drug transport. Also, separation of fluid from the gel phase due to contraction of the gel and the migration of polymers under the influence of an electrical field will not be sufficient to influence drug flux.

It could be expected that agarose will form a gel matrix and that carbomer polymer chains would be entangled throughout the matrix, resulting in semi-interpenetrating networks. The agarose keeps the added carbomer polymer spatially arranged and thereby maintains the volume of the gel constant. The agarose is slightly negatively charged, whereas carbomer contains up to 70% carboxylic acid groups (calculated on dry weight basis) which renders it highly negatively charged. Thus, the whole agarose-carbomer gel matrix could be seen as a negatively charged multiple layered network. It could be conceived therefore that endoelectroosmotic flux through the agarose gel is enhanced in the presence of the carbomer. As such, electroosmotic flux would contribute to syneresis, the separation of a fluid from a gel phase. This solvent flow is positive, i.e., in the same direction as current, and therefore, will assist lidocaine H+ transport.
The efficiency of iontophoretic drug delivery is predominantly determined by the mobility of drug ions and counterions (chloride and phosphate ions in the present example) when a formulation does not contain co-ions. Non specific electrostatic interactions will affect the equilibrium partitioning of charged solutes across each interface of a charged matrix. Thus, carbomer polymers, because of the presence of dissociated carboxylic acids, will hinder the transport of negatively charged counterions by raising an electrostatic barrier. The consequence of this decrease in counterions transport is an increase in lidocaine $H^+$ flux, since the sum of all ionic transport numbers is always unity.

Lidocaine $H^+$, being positively charged, would interact with negatively charged carbomer polymers. These electrostatic interactions do not seem to affect passive diffusional and iontophoretic fluxes significantly (see Figure 5.6). This could be due more to a high concentration of lidocaine hydrochloride than the site of interactions on the carbomer chain.

The steady state passive diffusional and iontophoretic fluxes from agarose gel systems as functions of carbomer concentration are shown in Figure 5.7. Passive diffusional flux decreases as the concentration of carbomer in the gel systems increases. This could be due to an increased matrix effect, i.e., an increased obstruction effect, increased microviscosity and most importantly, to increased interactions between the negatively charged polymer and the positively charged drug ions. As shown previously, iontophoretic flux increases significantly with increases in carbomer content of the agarose gel systems. The increases in iontophoretic fluxes are due to the effect of carbomer on the structure of the agarose gel,
increased electrokinetic transport phenomena and to enhanced electrostatic partitioning due
to the presence of more negatively charged polymers in system. But it is predominantly due
to the latter two effects since passive flux decreases in the presence of the carbomer.

5.3.3.3 pH adjusted agarose gels

The addition of the carbomer lowers the pH of the agarose gels by three orders of magnitude.
In this context, the pH of a donor formulation can affect drug delivery in several ways. These
may include competitive ion transport of hydronium and hydroxyl ions, effects on the charged
state of weak basic or weak acidic drugs such as lidocaine HCl, and influences on the
membrane such as membrane damage and/or changes in permselectivity due to very low or
high pH values (122, 145, 266). The latter effect would be negligible in this study considering
the chemical nature (polycarbonate) of the Nuclepore* membranes.

The fraction of lidocaine in the ionized form increases as pH decreases below its pKa (7.9).
In this context, electromigration, a major contributor to the iontophoresic flux of lidocaine
H\(^+\), is dependent upon the concentration of the ionized form of a drug, in contrast to passive
flux which is not as sensitive to pH.

Agarose molecules are substituted with charged groups such as sulfate esters and pyruvate
residues and the ionization of these charged groups is dependent on the pH of a formulation.
The charged residues are responsible for many agarose properties such as gelling strength and
endoelectroosmosis, which would modify drug release. The agarose matrix structure is
maintained by noncovalent bonds such as hydrogen bonds and junction zones which are influenced by changes in pH. Therefore, changes in pH could affect gel porosity and subsequently, drug flux.

The release profile of lidocaine H\(^+\) from agarose systems in which pH was adjusted to 2.5 with HCl is shown in Figure 5.8. The steady state passive diffusional flux is similar to that from unadjusted agarose systems (pH = 5.1). This indicates that passive diffusional flux is not significantly affected by the amount of drug in its charged state. The iontophoretic flux shown in Figure 5.8 (3.4 ± 0.28 μg min\(^{-1}\)) is higher than that from the unadjusted agarose system (2.97 ± 0.04 μg min\(^{-1}\)). This difference would be expected since a greater amount of lidocaine is present in the charged state. However, iontophoretic flux from the pH adjusted agarose systems is lower than that from carbomer-agarose systems (4.58 ± 0.13 μg min\(^{-1}\)) of similar pH values. Therefore, the higher iontophoretic fluxes from the agarose-carbomer systems are not entirely accountable for by pH changes. This then suggests that additional processes may be operative, i.e., those which are new in nature and/or modifications of those already existing, on drug release due to the fixed negative charges of the agarose-carbomer systems which were responsible for the enhanced drug flux. As mentioned previously, the fixed negative charges can result in differential electrostatic partitioning and electrokinetic transport phenomena which enhance drug transport.
5.3.3.4 Carbomer gels

The carbomer molecules form a rigid gel structure upon neutralization. Figure 5.9 shows passive diffusional and iontophoretic drug release from carbomer gels formed upon the addition of various neutralizing agents. The final pH of all of these formulations was about 6.8. The figure shows that the passive diffusional fluxes of lidocaine H\(^+\) were similar, irrespective of the neutralizing agent employed. However, the lower iontophoretic fluxes found for gels neutralized by NaOH and triethylamine were due to competitive co-ion transport. The transport of a drug across the membrane is dependent on the applied electric current, and the concentration and mobility of other ions. The co-ions, ions having the same charge as the drug ions, when present in the donor formulations carry a certain fraction of the total applied current. As they increase in concentration, the fraction of current carried by the drug ions decreases as does the resulting drug flux. Furthermore, the iontophoretic fluxes from these two carbomer gels were similar despite the fact that Na\(^+\) ions have greater mobility than do triethylammonium cations. This might be due to a complex relationship between drug fluxes, and the mobilities and concentrations of the co-ions. The lower mobilities of the triethylammonium cations may be compensated for by their higher concentrations in the system than the Na\(^+\) ions. As such, the iontophoretic flux from a carbomer gel neutralized by lidocaine base is higher because of the absence of extraneous co-ions in the donor system.

The iontophoretic flux from a gel containing 0.5% w/w carbomer neutralized by lidocaine base is higher than the corresponding flux from a “plain” agarose system. Furthermore, the iontophoretic flux from this carbomer system is similar to that from an agarose system.
containing 0.5% w/w carbomer. This similarity in fluxes bolsters the proposal that carbomer molecules are responsible for the enhanced fluxes when they were added to the agarose systems. The pH of the carbomer-lidocaine base system was 6.8, whereas the pH of the carbomer-agarose system was 3.0. At higher pH values a greater number of carboxyl groups are ionized and therefore more negative charges are present. The similar fluxes from carbomer-lidocaine base and carbomer-agarose systems despite the pH difference of four orders of magnitude, suggests a saturation or a limit on the effect of the anionic charges on drug delivery.

5.3.3.5 ‘Efficient’ gels

5.3.3.5.1 Constant current

Agarose matrices in electric fields are composed of numerous, independently oriented domains, each consisting of bundles of agarose fibers (253). The inherent alignment of agarose molecular helices within the domains is irregular and differs from one site to another. The size of the orienting domains depends on the duration and nature of the electric field, in addition to its magnitude. The size of these orienting domains in agarose gels has been reported to decrease with increases in electric field strength. The overall degree of orientation in agarose gels is also dependent on the electric field strength and increases as the electric field increases. In order to undergo orientation, gel fibers must detach from at least one of their junction zones. The initial direction of orientation of the gel fibers in an electric field is determined by its degree of spatial freedom in its local vicinity. The agarose fiber partially
detached from its first junction zone by the electric field enters new junction zones in its newly oriented position. These changes in junction zones modify the microscopic structure of the agarose gel matrix.

The electrophoretic mobilities of drug ions depending on their molecular size could be influenced by the orientations of agarose fibers and domains which therefore could have a significant impact on drug transport. The orientation of agarose fibers and domains in unidirectional electric fields, those of less than 20 V cm\(^{-1}\), depend on field strength. This was a prime reason for studying iontophoretic drug release at different, but clinically acceptable current densities. The transition or trends in the transport behavior of lidocaine H\(^+\) as functions of current are shown in Figure 5.9. The slope of the straight line portions of the plot of cumulative amounts of lidocaine H\(^+\) transported (\(\mu \text{g}\)) as functions of time (minute) was used to calculate the transport number. As this figure shows, the transport number becomes independent of current at 0.2 mA DC and above, and is therefore ionic-transference controlled.

Figure 5.10 also shows correlations between steady state iontophoretic fluxes and currents for an 'efficient' gel. The intercept of the regression line, a hypothetical drug transport rate at zero current, is similar to release by passive diffusion. The high correlation coefficient indicates no apparent interference on drug release due to orientation of the agarose fibers or domains within the range of currents evaluated. This could be due to orientations occurring
to a lesser extent under the voltages used in this study. Another more likely explanation may be an insignificant effect due to orientation of agarose fibers and domains on the electrophoretic mobilities of lidocaine H⁺ resulting from its relatively smaller size.

5.3.3.5.2 Programmed current

The release of lidocaine H⁺ from an ‘efficient’ gel is shown in Figure 5.11, in which the effect of the programmed current should be noted. After turning off the electric field, the oriented gel fibers and domains apparently relax back to a disordered state in their new local environments. Memory effects, i.e., metastable changes activated by an electric field which remain for some time after the current has been turned off, have been reported in the literature (267). The magnitude of the post-iontophoretic passive diffusional fluxes indicates in general that no significant changes were taking place in the formulations due to the passage of the current. As shown in the figure, post-iontophoretic passive diffusional fluxes eventually attain the value of that of the pre-iontophoretic passive flux, some time after the current had been turned off. This increased drug release during the off period may be due to the release of entrapped drug in the membrane and/or to accumulated drug in the receptor compartment.

5.3.3.5.3 Drug concentration

The junction zones in the agarose matrix which maintain their three-dimensional structure are altered by changes in ionic strength leading to modified transport of solutes through the gels (256). The effect of lidocaine HCl concentration on passive and iontophoretic drug release from an ‘efficient’ gel is shown in Figure 5.12. As expected, increases in drug concentration
lead to proportionate increases in passive diffusional drug release. Steady state iontophoretic fluxes also have been found to increase with increases in drug concentration. The iontophoretic fluxes are not proportional to drug concentration due to a nonlinearity between drug transport and mobility, and the concentration of all ionic species present in the system.

5.4 Summary

To minimize drag on drug flux, gels free of external agents such as polymerization initiators, cross-linkers, and buffer ions were prepared by utilizing the thermogelation properties of agarose. Agarose based gel formulations provide biomedically acceptable conductive solid structures with transport environments similar to fluids.

Enhanced iontophoretic fluxes of lidocaine H⁺ were obtained from agarose-carbomer systems, called 'efficient' gels in this study, compared with those from agarose systems only. This is in contrary to Hsu, et al, who reported reduced gel mass loss and consequently decreased drug flux from agarose-carbomer gel systems compared with those from agarose gels alone. This could be due to higher levels of current, lower concentrations of drug and to larger pH changes in the gel matrices due to electrochemical reactions. The observed increases in iontophoretic fluxes in the present study may be the result of differences in electrostatic partitioning and electrokinetic transport phenomena.
Enhanced iontophoretic fluxes were obtained from agarose systems in which pH had been adjusted to 2.5. However, these enhanced fluxes were lower than those from carbomer-agarose systems. Therefore, pH changes were not entirely responsible for the higher fluxes of lidocaine H$^+$ from the carbomer-agarose systems.

Iontophoretic fluxes from carbomer gels formed in the presence of external neutralizing agents such as NaOH and triethylamine were found to be lower due to competitive co-ions transport. The carbomer gel neutralized by lidocaine base gave higher iontophoretic fluxes, however, passive diffusional fluxes were similar from all of the carbomer gels. The iontophoretic fluxes from carbomer gels neutralized by lidocaine base were similar to those from agarose systems containing carbomer. This indicates that the enhanced iontophoretic fluxes from the carbomer-agarose systems were due to the presence of the negatively charged carbomer molecules.

The linear iontophoretic fluxes from the ‘efficient’ gels as functions of current indicate that no apparent interferences on drug release occur due to the orientation of agarose fibers and domains within the range of electric currents used (upto 0.3 mA DC). Furthermore, a programmed, stepwise on:off application of current showed no interference on drug release due to ‘memory’ effects in the gels. Lastly, iontophoretic fluxes were increased by, but not proportionate to, increases in drug concentration.
Finally, the data suggests that manipulating the ionic charges of the donor formulations provides a means of enhancing iontophoretic fluxes, and thereby, reducing the currents required for iontophoresis with the possibility of minimizing current induced effects on the skin.
<table>
<thead>
<tr>
<th>Materials</th>
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<tr>
<td>Lidocaine HCl monohydrate</td>
<td>Astra Pain Control AB</td>
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<td>Sodium phosphate, dibasic, 12-hydrate</td>
<td>J. T. Baker</td>
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<td>Phillipsburg, NJ</td>
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<td>St. Louis, MO</td>
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<td>Formic acid</td>
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<td></td>
<td>St. Louis, MO</td>
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<td>Methanol HPLC grade</td>
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<td>Sodium hydroxide</td>
<td>Aldrich Chemical Company</td>
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<td></td>
<td>Milwaukee, WI</td>
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<td>Hydrochloric acid</td>
<td>EM Science</td>
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<td>Gibbstown, NJ</td>
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<td>Triethylamine</td>
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Table 5.1 Materials.

(continued)
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<td>BF Goodrich</td>
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<td>(Carbopol 934P-NF)</td>
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Table 5.1 Materials (continued).
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<td>Riegelsville, PA</td>
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<td>IKA-TRON Model ETS-D2</td>
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Table 5.2 Equipment.

(continued)
### Table 5.2  Equipment (continued).

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| Microbalance,  
Model UM-3, sensitivity 0.1 mg  
Model AE 240, sensitivity 1.0 mg | Mettler  
Hightstown, NJ |
| pH  
Meter, Model Φ 72  
Electrode, semimicro ROSS combination, glass | Beckman  
San Ramon, CA  
Orion  
Boston, MA |
| HPLC  
Solvent pumps, Model 110B  
Injector, (250μL loop)  
Detector, Model 607 | Beckman  
San Ramon, CA  
"  
" |
| HPLC  
Analog interface, Model 406  
Software, System Gold™  
Column, reverse phase, PRP-1,  
4.1 mm × 25 cm, 10 μm part.  
Computer, PS/2, Model 30 | Beckman  
San Ramon, CA  
"  
Hamilton,  
Reno, NV  
IBM  
Armonk, NY |
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<tr>
<th>Formulation</th>
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<th>Water (%) w/w</th>
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<tr>
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<td>0.5</td>
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<td></td>
<td>98.5</td>
<td>6.9</td>
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pH was adjusted with: \(a\), 1N HCl; \(b\), 1N NaOH; \(c\), triethylamine.
\(d\), lidocaine base used instead of lidocaine HCl.

Table 5.3  Composition and pH of the gels.
Figure 5.1  Release of lidocaine $H^+$ from gels containing 1.0% w/w lidocaine HCl, 2.0% w/w agar and 97.0% w/w water under a current of 0.2 mA DC.
Figure 5.2  Transport of lidocaine H⁺ from agarose gels containing 1.0% w/w lidocaine HCl as functions of agarose content.
Figure 5.3  Schematic diagram of agarose gel structure.
Figure 5.4  Transport of lidocaine $H^+$ from agarose gels containing 1.0% w/w lidocaine HCl and 0.5% w/w carbomer as functions of agarose content.
Figure 5.5 Drug delivery efficiency of agarose-carbomer gel systems compared with that from agarose gels as functions of agarose content.
Figure 5.6  Release profiles of lidocaine H⁺ from carbomer dispersion containing 0.5% w/w carbomer and an aqueous solution. Initial concentration of lidocaine HCl was 1% w/w.
Figure 5.7  Transport of lidocaine H⁺ from agarose-carbomer gels containing 1% w/w lidocaine HCl and 2.0% w/w agarose as functions of carbomer content.
Figure 5.8 Release of lidocaine H⁺ from a gel (pH adjusted to 2.5 with HCl) containing 1% w/w lidocaine HCl, 2.0% w/w agarose and 97.0% w/w water under a current of 0.2 mA DC.
Figure 5.9 Transitory transport of lidocaine H⁺ from gels containing 0.5% w/w carbomer and 1% w/w lidocaine HCl or lidocaine formed by various neutralizing agents.
Figure 5.10 Transport behavior and linear regression of iontophoretic fluxes of lidocaine $\text{H}^+$ from 'efficient' gels containing 1% w/w lidocaine HCl, 0.5% w/w carbomer, 2.0% w/w agarose and 96.5% w/w water as functions of current.
Figure 5.11  Release of lidocaine $\text{H}^+$ from ‘efficient’ gels containing 1% w/w lidocaine HCl, 0.5% w/w carboxer, 2.0% w/w agarose and 96.5% w/w water as functions of programmed currents.
Figure 5.12  Transport of lidocaine H⁺ from 'efficient' gels containing 0.5% w/w carbomer and 2.0% w/w agarose under a current of 0.2 mA DC as functions of lidocaine HCl concentrations.
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