Lidocaine-Ibuprofen Ionic Liquid for Dermal Anesthesia

Han Jung Park
School of Chemical and Biomolecular Engineering, Georgia Institute of Technology, Atlanta, GA 30332

Dept. of Chemistry, University of Tennessee at Chattanooga, Chattanooga, TN 37403

Mark R. Prausnitz
School of Chemical and Biomolecular Engineering, Georgia Institute of Technology, Atlanta, GA 30332

DOI 10.1002/aic.14941
Published online August 7, 2015 in Wiley Online Library (wileyonlinelibrary.com)

Local anesthesia in the skin occurs approximately 1 h after application of a commercial topical formulation of lidocaine and prilocaine prepared as a eutectic mixture. A number of lidocaine salts was screened and lidocaine-ibuprofen was found to form a room-temperature ionic liquid. When applied to the skin of rats, local anesthesia of skin was achieved within 10–20 min in the rats' paws and tails with no apparent adverse effects to the skin as determined by histological analysis. We believe that the lidocaine-ibuprofen ionic liquid increased lidocaine absorption into the skin due to the high lidocaine concentration in the ionic liquid and due to possible interactions between the ionic liquid and the skin to increase skin permeability. These findings suggest that lidocaine-ibuprofen ionic liquid may provide a more rapid method of drug delivery to the skin for local anesthesia. © 2015 American Institute of Chemical Engineers *AIChE J*, 61: 2732–2738, 2015

Keywords: ibuprofen, ionic liquid, lidocaine, local anesthesia, transdermal drug delivery

Introduction

Transdermal drug delivery is a safe and noninvasive drug administration method that is used both for systemic delivery across the skin and for local delivery within the skin. When used for local drug delivery, the transdermal route provides a targeted delivery method that can increase efficacy and decrease side effects compared to systemic delivery strategies (e.g., oral route and injections) that expose the whole body to the drug.[1] Transdermal drug formulations can be prepared in different forms, such as patches, that are more expensive and often used for sustained, systemic delivery over 1 or more days, and creams/ointments that are less expensive and typically used for local delivery to the skin for shorter times. Active pharmaceutical ingredients (APIs) are often in a solid form at ambient conditions, but are prepared as pharmaceutical products in a liquid or semisolid form for topical administration to the skin.[2] This is typically done by dissolving the API in a solvent (e.g., water) in a suitable form (e.g., gel, ointment, or cream).[3]

A limitation of preparing an API as a solute in a liquid solvent is that the concentration of the API is limited by its solubility in the solvent. Due to this limitation, the pharmaceutical product is largely solvent and only a small portion is API. Another limitation is that relatively few solvents are safe for use in patients, which limits the range of possible physicochemical properties that the pharmaceutical product can have.[4] To address these limitations, we and others are developing APIs that are in the form of room-temperature ionic liquids or liquid salts, which allows us to prepare liquid drug products without the need for a solvent.[5–7]

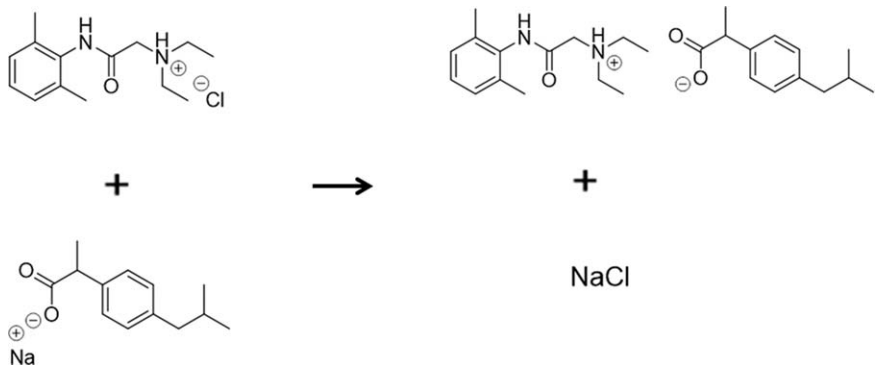
Ionic liquids are salts that are in the liquid state at atmospheric or body temperature and pressure.[8] Unlike API salts that use conventional counterions like Na^+ and Cl^-, ionic liquids involve larger counterions with properties that inhibit the fusion process and maintain the salts in a liquid state at relatively high temperatures and pressures. Preparing an API as an ionic liquid has a number of expected advantages. By eliminating the need to dissolve the API in a solvent, the API concentration can be high; the vapor pressure of the ionic liquid is almost zero, which essentially eliminates problems associated with evaporation; and the stability of the API is often increased because interactions with a solvent are eliminated.[6,7,9] In addition, ionic liquids have different physicochemical properties compared with liquid solutions, which has been widely studied for industrial applications outside of pharmaceuticals[8] and has received limited attention in pharmaceutical scenarios.[7,10,11]

An ionic liquid is typically composed of a cation and an anion. The cation could be an API, the anion could be an API or both could be APIs.[7,10,11] Absorption of an API across a keratinized (e.g., skin) or nonkeratinized (e.g., cornea, oral, and gastrointestinal mucosa) epithelial barrier depends on the concentration (i.e., chemical activity) of that API at the surface of that barrier.[1] Because an ionic liquid often has a concentration of an API ion that is 50% on a molar basis (e.g., the ionic liquid is composed of 50% cation and 50% anion, with no solvent), this provides a very high API concentration that typically exceeds the concentration that could be achieved by dissolving the API in a solvent.

Additional Supporting Information may be found in the online version of this article.

Correspondence concerning this article should be addressed to M. R. Prausnitz at prausnitz@gatech.edu.

© 2015 American Institute of Chemical Engineers



Scheme 1. Synthesis of lidocaine-ibuprofen ionic liquid.

Lidocaine hydrochloride (upper left) and sodium ibuprofen (lower left) were reacted in aqueous medium and the resulting lidocaine-ibuprofen ionic liquid (upper right) was extracted into chloroform.

Ionic liquids are known to have unusual physicochemical properties because they have the fluid properties and densities of a liquid (often including high viscosity) and the ionic properties of a salt.[8] As a result, the absorption into a tissue of an API in an ionic liquid form can occur differently from the absorption of an API in a solution form. For example, ionic liquids are often more lipophilic than dissociated salts (i.e., that carry a charge) in aqueous solution. This increase in lipophilicity should increase API permeation across the skin by increasing partitioning into the lipophilic environment of the skin's barrier layer.[1] It is also well known that the use of different solvents in transdermal drug delivery affects the partitioning of drugs into the skin and the diffusion of drugs through the skin.[1] There is evidence that the use of ionic liquids can likewise alter the drug delivery process in skin. Some prior work has taken the approach of converting the API into an ionic liquid, as we propose in the study too, whereas other prior work has dissolved API (i.e., not as an ionic liquid) into an ionic liquid solvent.[10,12,13]

Conversion of an API to an ionic liquid form may also have drawbacks. For example, ionic liquids have increased molecular mass relative to dissociated salts, which should decrease API permeation due to reduced diffusivity.[1] In addition, the increased viscosity characteristic of many ionic liquids compared with conventional pharmaceutical solutions would also decrease API permeation due to reduced diffusivity.

If the API itself is an ionic liquid, it may be important to know if and when the ionic liquid may dissociate after administration to the body and become dissolved in the body's (aqueous) fluids as ions, thereby losing the properties of an ionic liquid. Moreover, it is not known if an API will have the same biological activity in the body when in the form of an ionic liquid (either miscible or immiscible in the body's fluids) as when in the form of a solute in aqueous solution.

Many minor surgical procedures performed on the skin cause patient pain. This pain and associated stress are significant clinical concerns that can be reduced with local anesthesia. Lidocaine is the most widely used local anesthetic, and local anesthesia using lidocaine can be achieved rapidly by intradermal injection.[14] However, most patients find the injection procedure painful or uncomfortable and, in addition, intradermal injections cannot be easily self-administered. An alternative is the use of a topical formulation called EMLA (an abbreviation for eutectic mixture of local anesthetics), which is a eutectic mixture of equal quantities of lidocaine and prilocaine and is marketed as a 5% oil-in-water emulsion incorporated in a cream base.[15] EMLA must be applied at least 1 h before local anesthesia is needed, which typically precludes its use in the busy clinical environment. Given these inadequate options for local anesthesia, many procedures are performed without anesthetic and the ones that must have anesthesia usually employ intradermal injection.

In this study, we hypothesized that preparation of lidocaine as an ionic liquid would increase lidocaine absorption into the skin and thereby shorten the time to achieve local anesthesia. After screening a number of candidate counterions, we showed that a lidocaine-based ionic liquid could be synthesized using ibuprofen as the counterion. Following physicochemical characterization of the lidocaine-ibuprofen ionic liquid, we applied it to the skin of rats to assess its absorption, as determined by two different measures of local anesthesia.

Materials and Methods

To prepare lidocaine-ibuprofen ionic liquid, lidocaine hydrochloride (10 mmol, Sigma Aldrich, St. Louis, MO) and sodium ibuprofen (10 mmol, Sigma Aldrich) were dissolved in deionized (DI) water (100 mL) with stirring and heating (80°C) for 1 h to drive the reaction (Scheme 1). The products were extracted with chloroform (100 mL, Sigma Aldrich). The chloroform phase was then washed with water to remove inorganic salt (NaCl) and the solvent was removed. The resulting product was placed in a chemical hood for 1 day and subsequently in a low-pressure chamber ($<$400 mm Hg) for 10 min to remove residual solvent. A silver nitrate test was performed to confirm that chloride ions associated with the inorganic salt were removed.[16] A similar method was used to prepare other salts by combining the hydrochloride salts of bupivacaine, dibucaine, lidocaine, prilocaine, procaine, and tetracaine with the sodium salts of ampicillin, diclofenac, ibuprofen, naproxen, saccharin, sulfacetamide, and valproic acid and the potassium salt of acesulfame (Sigma Aldrich).

The synthesis of lidocaine-ibuprofen ionic liquid was verified in four ways. First, the product was examined visually to determine if it was in a liquid or solid state. Second, ^{1}H NMR spectra were recorded at 300 MHz on a Bruker DSX-300 spectrometer (Bruker, Coventry, UK) in deuterated chloroform (Sigma-Aldrich). Third, electrical conductivity (σ) was calculated from electrical resistance measurements (R) as $\sigma = L/RA$, where L is distance between the two electrodes (0.2 cm) and A is cross-sectional area (0.07 cm^2) of the electrode (EVOM2, World Precision Instruments, Sarasota, FL). Lastly,

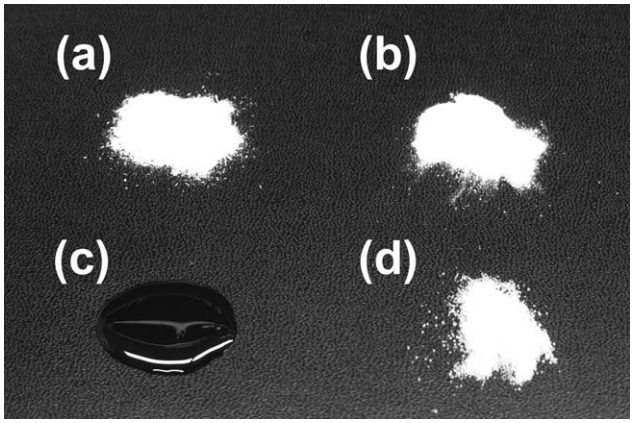


Figure 1. Photographic images of reactants and products of the lidocaine-ibuprofen synthesis reaction.

(a) Lidocaine hydrochloride powder, (b) sodium ibuprofen powder, (c) lidocaine-ibuprofen ionic liquid, and (d) NaCl powder.

thermogravimetric analysis (TGA; STA 449 F1 Jupiter, Netzsch, Germany) was performed at a ramp rate of 2 K min^{-1}.

Delivery of lidocaine into the skin was assessed by measuring local anesthesia *in vivo* in male hairless rats (280–340 g, CD hairless rats, Charles River, Wilmington, MA) using two different tests. All experiments were performed with approval from the Georgia Tech Institutional Animal Care and Use Committee.

In the first test (i.e., thermal test), rats were acclimated to the test cubicles for 30 min prior to testing. Either EMLA cream or lidocaine-ibuprofen ionic liquid was administered topically to cover the plantar surface of a hind-paw using a Q-tip. Excess cream or ionic liquid was removed after 5 min. Local anesthesia was measured periodically after topical drug administration using the hot-plate test as described previously.[17,18] The apparatus was equipped with a timer and a thermocouple to maintain a constant temperature of 55°C. At each test exposure, the left and right paws were tested 1 min apart in random order. The time required for paw licking or lifting from the heated surface was taken as the response latency time. If an animal did not remove its paw within 20 s, the heat stimulus was automatically stopped to prevent injury to the animal. Each animal served as its own negative control first to get baseline latency and the same animal was used to measure the effect of EMLA or ionic liquid anesthetic. The response latency of the rat for a given test represents the average of the time to paw withdrawal.

In the second test (i.e., tactile test), approximately 1 mL of lidocaine-ibuprofen or EMLA cream was applied to the middle of the tail of an animal. At various times, dermal anesthesia was assessed using the Von Frey Hair test, which assesses the threshold for touch sensation.[19] To conduct this test, Von Frey hairs of progressively larger diameters were applied to the tail at the site of local anesthetic application until the tactile threshold was identified. Each hair is designed to produce a given force precisely upon buckling. Thus, the minimum force to evoke a tail flicking threshold was determined. Each hair was applied 10 times with 5 s intervals. The tactile threshold was defined as a tail flicking response in 8 of the 10 trials of a given stimulus intensity.

In a set of experiments to assess safety, lidocaine-ibuprofen was applied to the dorsal skin of hairless rats for 5 min and then wiped off. Animals were later euthanized by carbon dioxide gas asphyxiation and the treated skin was collected using an 8-mm biopsy punch. After fixation in formalin, the skin was prepared for histopathological analysis by sectioning and staining with hematoxylin and eosin followed by microscopic examination by a dermatopathologist at Emory University School of Medicine.

Results and Discussion

Ionic liquid screening and characterization

The first step in this project was to identify candidate ionic liquids that could be used for dermal anesthesia. As local anesthetics, we considered hydrochloride salts of six different topical anesthetics: bupivacaine, dibucaine, lidocaine, prilocaine, procaine, and tetracaine.[14] As anionic counterions, we considered the sodium and potassium salts of acesulfame, ampicillin, diclofenac, ibuprofen, naproxen, saccharin, sulfacetamide, and valproic acid, all of which are either drugs or excipients that are safely used in pharmaceutical products.[2] To determine if combinations of these ions would form ionic liquids, pairs of a cation and an anion in their salt forms were added to water

Table 1. Ion Pairs that did not Appear to Form Ionic Liquids

Cation	Anion	Observation[a]
Bupivacaine	Acesulfame	NP
Bupivacaine	Ampicillin	NP
Bupivacaine	Diclofenac	NP
Bupivacaine	Naproxen	SP
Bupivacaine	Ibuprofen	SP
Bupivacaine	Saccharin	NP
Bupivacaine	Valproic acid	SP
Dibucaine	Acesulfame	SP
Dibucaine	Ampicillin	NP
Dibucaine	Diclofenac	NP
Dibucaine	Ibuprofen	SP
Dibucaine	Naproxen	SP
Dibucaine	Saccharin	SP
Dibucaine	Sulfacetamide	NP
Dibucaine	Valproic acid	SP
Lidocaine	Ampicillin	SP
Lidocaine	Diclofenac	NP
Lidocaine	Naproxen	SP
Lidocaine	Sulfacetamide	SP
Prilocane	Acesulfame	NP
Prilocane	Ampicillin	NP
Prilocane	Ibuprofen	NP
Prilocane	Saccharin	NP
Prilocane	Sulfacetamide	NP
Prilocane	Valproic acid	NP
Procaine	Acesulfame	SP
Procaine	Ampicillin	SP
Procaine	Diclofenac	SP
Procaine	Ibuprofen	SP
Procaine	Naproxen	SP
Procaine	Saccharin	SP
Procaine	Valproic acid	SP
Tetracaine	Acesulfame	NP
Tetracaine	Ampicillin	NP
Tetracaine	Diclofenac	NP
Tetracaine	Ibuprofen	SP
Tetracaine	Naproxen	SP
Tetracaine	Saccharin	SP
Tetracaine	Sulfacetamide	NP
Tetracaine	Valproic acid	SP

[a]NP, no product; SP, solid product formed after synthesis reaction and extraction.

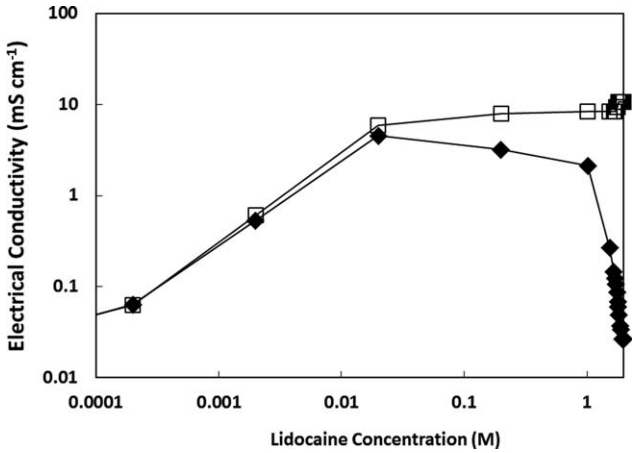


Figure 2. Electrical conductivity of aqueous solutions as a function of lidocaine-ibuprofen ionic liquid (diamonds) and lidocaine hydrochloride (squares) concentration.

Measurements were carried out at room temperature (23°C) and pressure (1 atm) and represent the average of 10 replicate measurements. Positive error bars are contained within the data points.

and allowed to react. Products were extracted with chloroform and dried.

Eighteen of the combinations did not appear to make an ionic liquid, because no residual material was observed after evaporating off the chloroform (Table 1). Twenty-two other combinations appeared to undergo a chemical reaction, but did not produce an ionic liquid at room temperature, because only a solid material was observed after evaporating off the chloroform (Table 1). Only the combination of lidocaine hydrochloride and sodium ibuprofen produced a liquid at room temperature after evaporating off the choloroform, which is believed to be the ionic liquid lidocaine-ibuprofen (Figure 1).

The synthesis of lidocaine-ibuprofen ionic liquid was verified in a number of ways. First, a liquid product was formed at the end of the reaction-purification process, as noted above. The only species present during the reaction were lidocaine hydrochloride, sodium ibuprofen, and the solvents water and chloroform. Because there is no reason to expect reaction with the solvents, the only expected reaction products are lidocaine-ibuprofen and NaCl. Because the reactants and NaCl are solids at room temperature and the solvents should have evaporated off during the drying step, the only candidate liquid to be present at the end of the process would be the ionic liquid lidocaine-ibuprofen.

Second, ^{1}H NMR spectroscopy showed peaks at 1.01 and 7.24 ppm, which correspond to the methyl groups of lidocaine[20] and the aromatic ring of ibuprofen,[21] respectively (Supporting Information Figure S1). The integral numbers show that molecular ratio of each compound is 1:1, which is the expected ratio for lidocaine-ibuprofen ionic liquid. The other peaks on the NMR spectrum correspond to other groups found on the lidocaine and ibuprofen molecules. None of the peaks correspond to chloroform or water.

Third, TGA gave a single-step decomposition ($T_{\text{onset5\%}} = 181$°C), which is consistent with the presence of a single chemical species with relatively high thermal stability (Supporting Information Figure S2). Finally, electrical conductivity analysis is also consistent with the formation of an ionic liquid, as discussed immediately below.

Electrical conductivity

The electrical conductivity of ionic liquids is known to be different from that of, for example, nonpolar liquids or dissociated ions in solution.[22,23] We, therefore, measured the electrical conductivity of lidocaine-ibuprofen ionic liquid at various concentrations in water and compared it with solutions of lidocaine hydrochloride in water. Lidocaine hydrochloride shows the expected behavior of a salt dissolved in water, where the conductivity increases with increasing salt concentration (Figure 2).

In contrast, lidocaine-ibuprofen shows different behavior. At low concentrations, conductivity increases with increasing lidocaine-ibuprofen concentration in water, suggesting that the ionic liquid has dissociated and the free ions are carrying charge in a manner similar to lidocaine hydrochloride. At a concentration of 0.02 M, the conductivity peaks and then decreases as a weak function of increasing concentration up to 1 M. At higher ionic liquid concentrations, the conductivity drops sharply as a function of concentration, ultimately achieving a conductivity of 10^{-2} mS cm^{-1} for pure lidocaine-ibuprofen (i.e., with no water). The electrical conductivity at the peak is approximately 100 times higher than the value of pure ionic liquid. This nonlinear behavior of ionic liquids has been seen before, where conductivity peaks at an intermediate concentration of ionic liquid in water.[22,23]

Altogether, these data suggest that (1) at high lidocaine-ibuprofen concentration, the lidocaine and ibuprofen ions are in the form of an ionic liquid with low conductivity due to reduced ionic mobility attributed to cation-anion interactions and increased viscosity, (2) at low lidocaine-ibuprofen concentration the ionic liquid dissociates into free lidocaine and ibuprofen ions in solution, such that conductivity increases with lidocaine-ibuprofen concentration due to increased charge density, and (3) at intermediate concentrations, the lidocaine and ibuprofen ions may have different degrees of cation-anion interactions distributed among the ionic liquid state, the free ion state and possible intermediate states.[24]

Local anesthesia: Thermal test

We next assessed the hypothesis that lidocaine in the form of an ionic liquid would be absorbed more efficiently into the skin and therefore be more effective at inducing local anesthesia. The kinetics and extent of local anesthesia induced by the lidocaine-ibuprofen ionic liquid was compared with the commercial lidocaine product EMLA in rats by measuring the paw withdrawal latency time after applying heat to the paw.

In all three experimental groups, at the beginning of the experiment (time = 0), the mean paw withdrawal latency was 9.0 ± 2.0 s. In the negative control group, which received no lidocaine, there was on average a small decrease in latency time, but this change was not statistically significant (one-way analysis of variance (ANOVA), $P = 0.67$, Figure 3a). In the positive control group, which received EMLA, there was essentially no change in latency time for the first 40 min (Figure 3a). After 1 h, the latency time increased (one-way ANOVA, $P = 0.18$) and then slowly decreased over time, indicating that it took 1 h for EMLA to induce significant local anesthesia in the skin, which is consistent with prior findings.[25]

When the lidocaine-ibuprofen ionic liquid was applied to the skin, there was a significant increase in latency time at the

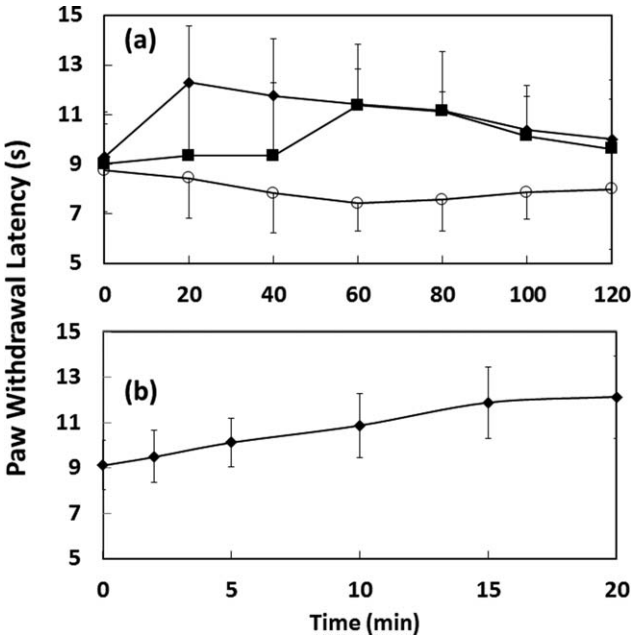


Figure 3. Effect of lidocaine-ibuprofen ionic liquid on rat paw withdrawal latency response.

(a) Comparison of pharmacodynamic response to lidocaine-ibuprofen (diamonds), EMLA (squares), and no local anesthetic (circles). (b) Pharmacodynamics of lidocaine-ibuprofen with greater time resolution. Data represent the average of 8 replicates ± standard deviation.

first data point at 20 min (one-way ANOVA, $P = 0.018$, Figure 3a). A closer examination of the paw withdrawal response after application of the ionic liquid revealed that there was a steady increase in latency time over the course of the first 20 min (one-way ANOVA, $P = 0.00015$, Figure 3b). After just 10 min, the latency time was significantly longer than the value at time = 0 (one-way ANOVA, $P = 0.0009$) and not significantly different from the latency value 1 h after EMLA application (one-way ANOVA, $P = 0.25$). We, therefore, conclude that the time for onset of action by lidocaine-ibuprofen is 10 min, which is significantly faster than the 1 h onset time for EMLA.

Local anesthesia: Tactile test

As an additional test, the Von Frey Hair test was performed to measure local anesthesia in the skin to tactile sensation on the rat's tail. In this test, nylon filaments of varying diameter (i.e., Von Frey hairs) were pressed against the skin with a controlled force to identify the threshold of sensation, as indicated by a flick of the rat's tail. In negative control animals (receiving no local anesthetic), the tail flick sensation threshold was constant over time at 5.3 g (Figure 4). When EMLA was applied to the skin, the sensation threshold increased over the first hour, indicting the onset of local anesthesia, and then decreased over the second hour, indicating a reduced local anesthesia (one-way ANOVA, $P < 0.05$). The sensation threshold was not significantly changed relative to the time = 0 value until 30 min after EMLA application (one-way ANOVA, $P = 0.33$).

When lidocaine-ibuprofen was applied to the skin, the sensation threshold also increased during the first hour and decreased during the second hour (one-way ANOVA, $P < 0.05$, Figure 4). However, the threshold was significantly higher in the animals receiving the ionic liquid compared with those receiving EMLA (two-way ANOVA, $P < 0.05$). In addition, the sensation threshold was significantly higher than the initial value 20 min after ionic liquid application (one-way ANOVA, $P = 0.00027$). Altogether, these results indicate that lidocaine-ibuprofen induced a faster and stronger local anesthetic effect compared with EMLA.

Histopathological analysis

We assessed the safety of lidocaine-ibuprofen ionic liquid applied to the skin through histopathological analysis of skin biopsies 10 min, 4 h, and 1 day after exposure to lidocaine-ibuprofen on the skin (Figure 5). Examination by a board-certified dermatopathologist revealed no significant damage to the epidermis or any marked inflammatory infiltrate within the dermis or subcutis. Visual observation of the skin on the rat paws and tails after treatment showed no evidence of erythema, edema, or other adverse effects. We conclude that the ionic liquid was well tolerated by the skin.

Discussion

Although ionic liquids have received extensive attention for their potential use in industrial applications,[8] there has been only limited research on developing ionic liquids composed of drug molecules to serve as novel pharmaceuticals.[5,6] Here, we screened salts of local anesthetics and showed that lidocaine-ibuprofen forms a room-temperature ionic liquid. Lidocaine was selected as the cation for its use as a local anesthetic.[2] Ibuprofen was selected as the anion because of its excellent safety record in medical use.[2] While ibuprofen has anti-inflammatory properties and is sold as a topical gel to reduce local inflammation (e.g., Ibugel, Dermal Laboratories), we did not specifically seek to use its anti-inflammatory properties in this study.

This study showed that application of lidocaine-ibuprofen to the skin of rats had significant local anesthetic effects as determined by two different tests, and that this effect was significantly greater and with faster onset compared with the commercial product, EMLA. In addition, there were no adverse side effects observed in the rats or their skin. The greater efficacy could be due to a number of reasons. First, the ionic liquid formulation required no solvent and therefore was 50% lidocaine on a molar basis. In contrast, EMLA is only 5%

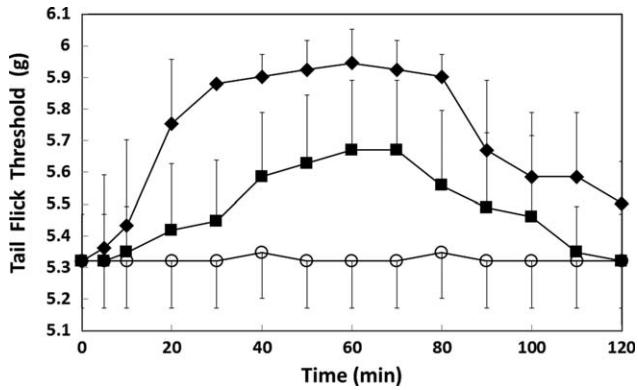


Figure 4. Effects of lidocaine-ibuprofen ionic liquid on the rat tail flick threshold determined by the Von Frey Hair test.

The pharmacodynamic response is compared among lidocaine-ibuprofen (diamonds), EMLA (squares), and no local anesthetic (circles). Data represent the average of 10 replicates ± standard deviation.

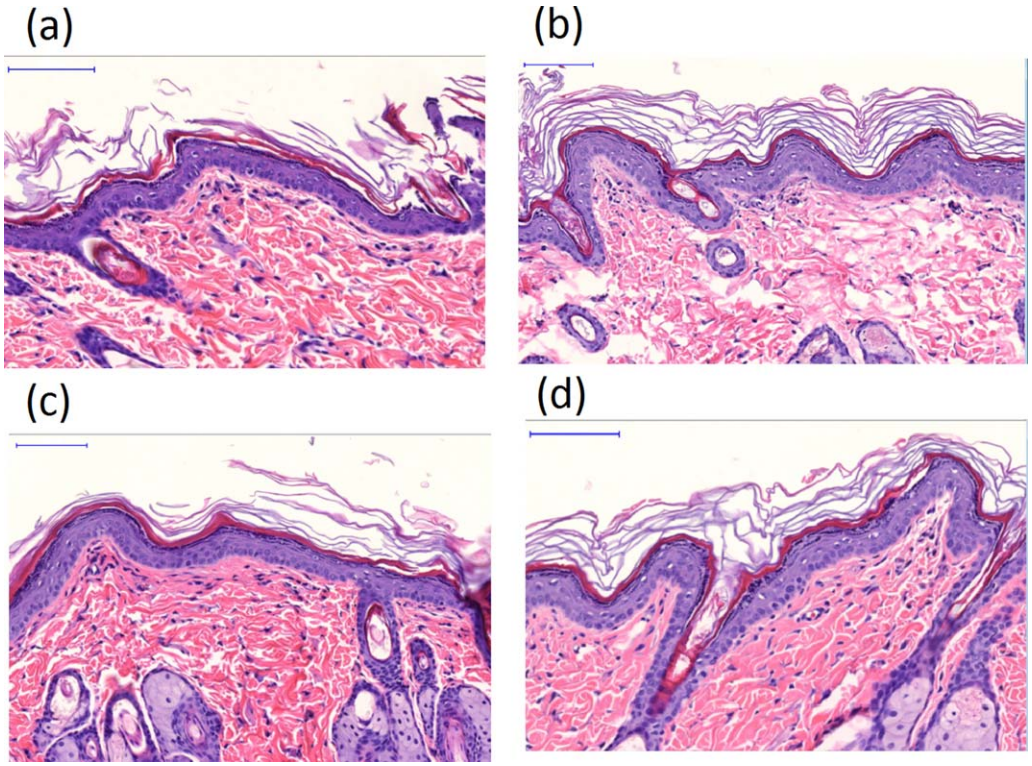


Figure 5. Representative histopathology images of skin sections taken from the dorsal region of the hairless rat.

Skin was either (a) not treated (i.e., negative control) or exposed to lidocaine-ibuprofen for 10 min and then excised (b) 10 min, (c) 4 h, or (d) 1 day later. Skin sections were stained with hemotoxylin and eosin. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

API (i.e., 2.5% lidocaine and 2.5% prilocaine, which is also a local anesthetic). This high concentration of lidocaine in the ionic liquid formulation should increase the rate of drug delivery into the skin due to an increased driving force.

Second, the skin almost certainly has a different permeability to the ionic liquid form of lidocaine-ibuprofen than the lidocaine base or cation. Skin permeability depends largely on oil-water partition coefficient and molecular weight. Although we did not determine a partition coefficient for lidocaine-ibuprofen, the ionic liquid is likely to partition differently from the lidocaine base or cation, given the different physicochemical properties of ionic liquids, which would favor increased skin permeability if the ionic liquid has a greater oil-water partition coefficient. Given that the ionic liquid was isolated by extraction from water into chloroform indicates that its oil-water partition coefficient was much larger than unity. In contrast, lidocaine-ibuprofen (440 Da) has a significantly larger molecular weight than lidocaine (234 Da), which suggests decreased skin permeability for the ionic liquid. However, a molecular weight of 440 Da is still small enough to enable good skin permeability, based on prior observations.[1]

Third, lidocaine-ibuprofen may alter the microanatomical structure of skin due to its solvation properties. Solvents, such as ethanol and dimethyl sulfoxide are often applied to the skin to increase skin permeability by a mechanism that often involves fluidization and/or extraction of the lipid bilayers found in the skin's stratum corneum barrier.[1] Given the unusual solvation properties of ionic liquids,[8] it is possible that lidocaine-ibuprofen could alter skin permeability due to these effects.

Finally, this study assessed the pharmacological effect of lidocaine-ibuprofen on local anesthesia and did not directly measure transdermal transport. However, we expect that this increased pharmacological effect can be best explained by increased lidocaine delivery into the skin. It is also possible that the increased local anesthesia was not (completely) due to increased dermal absorption, but was due to more potent pharmacological properties of lidocaine in the ionic liquid form. However, we do not suspect that this is the correct explanation, because our electrical conductivity measurements suggest that when lidocaine-ibuprofen is significantly diluted into water (as it would be in the aqueous environment of the skin), the lidocaine and ibuprofen dissociate and become separate ions in solution, thereby losing their ionic liquid properties. It is also possible that the increased effectiveness of the ionic liquid could be explained by increased systemic delivery of the drug, but we do not expect this to be the case, because other evidence of systemic exposure (e.g., lethargy) was not observed in the animals.

Considering possible medical applications, there is a large need for local anesthesia of the skin to carry out procedures including excising tumors, collecting tissue biopsies, or just giving injections or drawing blood. Locally anesthetizing the skin by injection of lidocaine is painful for patients and administering EMLA takes too long. Products have been developed using iontophoresis (e.g., LidoSite, Vyteris and Iontocaine, Iomed), ultrasound (e.g., SonoPrep, Sontra Medical), or jet injectors (e.g., Zingo, Powder Pharmaceuticals) to drive lidocaine into the skin faster, but these products have either been discontinued or otherwise have had little impact on medical practice in large part because of the complexity of using sophisticated delivery devices and the associated expense. Administration of lidocaine-ibuprofen ionic liquid involves rubbing a viscous liquid onto the skin, which should be

inexpensive and simple. For this reason, lidocaine-ibuprofen may provide an easy, cost-effective, and relatively rapid method of local anesthesia for medical procedures.

Conclusions

This study supports the hypothesis that lidocaine salt prepared as an ionic liquid results in faster and more potent local anesthesia than the commercial product EMLA, which is believed to be due to increased lidocaine absorption into the skin. We achieved this result by screening lidocaine salts and identifying that lidocaine forms a room-temperature ionic liquid when combined with ibuprofen as a safe counterion. Lidocaine-ibuprofen was found to have a thermal decomposition temperature of 181°C and an electrical conductivity that reached a maximum when diluted in water at a concentration of 0.02 M, suggesting that in the presence of little or no water, lidocaine-ibuprofen is largely in the ionic liquid form, but in the presence of more water, the ions dissociate.

When applied to the skin of hairless rats, lidocaine-ibuprofen caused significant local anesthesia within 10–20 min according to two different sensory tests with no adverse side effects, which was much faster than after the application of EMLA, which had an onset time of up to 60 min. These faster onset kinetics suggest that lidocaine-ibuprofen ionic liquid may be well suited for providing local anesthesia rapidly in time-constrained clinical settings. Overall, this study suggests that drug salts prepared as ionic liquids may provide a novel approach to enabling transdermal delivery of lidocaine, as well as other drugs in the future.

Acknowledgments

The authors thank Dr. Brian P. Pollack at Emory University for helpful discussions and technical expertise in histopathology and Donna Bondy for administrative support. Financial support from the National Institutes of Health is gratefully acknowledged. This work was carried out at the Center for Drug Design, Delivery and Development and the Institute for Bioengineering and Bioscience at Georgia Tech.

Literature Cited

1. Prausnitz MR, Langer R. Transdermal drug delivery. *Nat Biotechnol*. 2008;26:1261–1268.
2. Brunton L, Chabner B, Knollman B. *Goodman and Gilman's the Pharmacological Basis of Therapeutics*, 12th ed. New York: McGraw-Hill Professional, 2011.
3. de Araújo DR, da Silva DC, Barbosa RM, Franz-Montan M, Cereda CM, Padula C, Santi P, de Paula E. Strategies for delivering local anesthetics to the skin: focus on liposomes, solid lipid nanoparticles, hydrogels and patches. *Expert Opin Drug Deliv*. 2013;11:1551–1563.
4. Florence A. *Physicochemical Principles of Pharmacy*, 5th ed. London: Pharmaceutical Press, 2011.
5. Hough WL, Smiglak M, Rodrıguez H, Swatloski RP, Spear SK, Daly DT, Pernak J, Grisek JE, Carliss RD, Soutullo MD, Davis JH, Rogers RD. The third evolution of ionic liquids: active pharmaceutical ingredients. *New J Chem*. 2007;31:1429–1436.
6. Ferraz R, Branco LC, Prudêncio C, Noronha JP, Petrovski Z. Ionic liquids as active pharmaceutical ingredients. *ChemMedChem*. 2011;6:975–985.
7. Shamshina JL, Barber PS, Rogers RD. Ionic liquids in drug delivery. *Expert Opin Drug Deliv*. 2013;10:1367–1381.
8. Seddon K, Plechkova N. *Ionic Liquids UnCOILed: Critical Expert Overviews*, 1st ed. Hoboken, NJ: Wiley, 2012.
9. Stoimenovski J, MacFarlane DR, Bica K, Rogers RD. Crystalline vs. ionic liquid salt forms of active pharmaceutical ingredients: a position paper. *Pharm Res*. 2010;4:521–526.
10. Dobler D, Schmidts T, Klingenhöfer I, Runkel F. Ionic liquids as ingredients in topical drug delivery systems. *Int J Pharm*. 2013;441:620–627.
11. Marrucho IM, Branco LC, Rebelo LP. Ionic liquids in pharmaceutical applications. *Annu Rev Chem Biomol Eng*. 2014;5:527–546.
12. Bica K, Shamshina J, Hough WL, MacFarlane DR, Rogers RD. Liquid forms of pharmaceutical co-crystals: exploring the boundaries of salt formation. *Chem Commun (Camb)*. 2011;47:2267–2269.
13. Zakrewsky M, Lovejoy KS, Kern TL, Miller TE, Le V, Nagy A, Goumas AM, Iyer RS, Del Sesto RE, Koppisch AT, Fox DT, Mitragotri S. Ionic liquids as a class of materials for transdermal delivery and pathogen neutralization. *Proc Natl Acad Sci USA*. 2014;111:13313–13318.
14. McCleane G. Topical analgesics. *Anesthesiol Clin*. 2007;25:825–839.
15. Nyqvist-Mayer AA, Brodin AF, Frank SG. Drug release studies on an oil-water emulsion based on a eutectic mixture of lidocaine and prilocaine as the dispersed phase. *J Pharm Sci*. 1986;75:365–373.
16. Maines L, Bruch M. Identification of unknown chloride salts using a combination of qualitative analysis and titration with silver nitrate: a general chemistry laboratory. *J Chem Educ*. 2012;89:933–935.
17. Hargreaves K, Dubner R, Broun F, Flores C, Joris J. A new and sensitive method for measuring thermal nociception in cutaneous hyperalgesia. *Pain*. 1988;32:77–78.
18. Vitale G, Sandrini M, Pini LA. Lack of activity of ketorolac in hotplate test and serotonin binding capacity of brain membranes in rats. *Agents Actions*. 1994;41:184–187.
19. Pitcher GM, Ritchie J, Henry JL. Paw withdrawal threshold in the von Frey hair test is influenced by the surface on which the rat stands. *J Neurosci Methods*. 1999;87:185–193.
20. Laplanche L, Vanderkooi G, Jasmani H, Suki M. The solution structure of lidocaine: conformational analysis and NMR lanthanide-induced shifts. *Magn Reson Chem*. 1985;23:945–951.
21. Sen S, Anliker K. 1H NMR analysis of R/S ibuprofen by the formation of diasteriomeric pairs: microscale stereochemistry experiment for the undergraduate organic laboratory. *J Chem Educ*. 1996;73:569–572.
22. Vila J, Gines P, Rilo E, Cabeza O, Varela LM. Great increase of the electrical conductivity of ionic liquids in aqueous solutions. *Fluid Phase Equilib*. 2006;247:32–39.
23. Torriero A. *Electrochemistry in Ionic Liquids. Volume 1: Fundamentals*. Berlin: Springer, 2015.
24. Molenat J. Étude systématique de la conductivité a 25 °C dans des solutions concentrées des halogenures alcalins. *J Chim Phys*. 1969;66:825–833.
25. Lidocaine and Prilocaine Cream, 2.5%/2.5% [Package Insert]. Melville, NY: E. Fougera & Co., September 2007.

Manuscript received Jan. 27, 2015, and revision received May 19, 2015.