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RESEARCH PAPER

Development of Lidocaine-Coated Microneedle Product for Rapid, Safe, and Prolonged Local Analgesic Action

Ying Zhang • Ken Brown • Kris Siebenaler • Amy Determan • Daniel Dohmeier • Kris Hansen

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ABSTRACT

Purpose To demonstrate rapid (~1 min) lidocaine delivery using 3M's solid microstructured transdermal system (sMTS) for prolonged, local analgesic action.

Methods Polymeric microneedles were fabricated via injection molding and then dip-coated using an aqueous lidocaine formulation. The amount of lidocaine coated onto the microneedles was determined by high performance liquid chromatography (HPLC). To assess drug delivery and dermal pharmacokinetics, lidocaine-coated microneedles were inserted into domestic swine. Skin punch biopsies were collected and analyzed to determine lidocaine concentration in skin using HPLC-mass spectrometry (LC-MS). Commercial lidocaine/prilocaine EMLA (Eutectic Mixture of Local Anesthetic) cream was used as comparative control.

Results Lidocaine dissolves rapidly off the microneedles and into skin such that the 1-min wear time achieves or exceeds lidocaine tissue levels needed to cause analgesia. This therapeutic threshold (100 ng/mg) was estimated by measuring the total amount of lidocaine and prilocaine in skin following a 1 h EMLA application. When co-formulated with 0.03 wt% vasoconstrictor-epinephrine, the concentration of lidocaine in tissue was maintained above 100 ng/mg for approximately 90 min.

Conclusions 3M's sMTS can be used to provide rapid delivery of lidocaine for local analgesia up to 90 min.

KEY WORDS epinephrine · Lidocaine · microneedles · skin biopsy · transdermal delivery

Y. Zhang · K. Brown · K. Siebenaler · A. Determan · D. Dohmeier · K. Hansen (✉)
3M Drug Delivery Systems Division
St. Paul, Minnesota 55144, USA
e-mail: kjhansen@mmm.com

INTRODUCTION

Many clinical procedures, including venipuncture, introduction of an intravenous catheter, and minor dermatological surgeries, may be associated with patient pain, discomfort or anxiety. The procedural pain and associated stress represent a significant clinical concern which may be addressed by pre-treatment of the site with topical anesthesia. Lidocaine, the most widely used local anesthetic, is routinely applied via topical formulation as a means of diminishing the discomfort associated with the procedures mentioned above (1). EMLA™, the eutectic mixture of 2.5% lidocaine and 2.5% prilocaine, is a common topical agent providing anesthesia of the superficial and deep skin layers to mitigate pain associated with procedures such as hemodialysis or vascular access. EMLA requires a minimum application time of 60 min to provide analgesia sufficient for minor intervention and 2 h for larger skin grafting. Upon achieving the application time, the cream provides an average duration of action of 30–60 min (2). Although effective, the application time associated with EMLA can be impractical in a clinical setting (3). The application time also limits the use of EMLA in emergency settings where fast onset of anesthesia is required. In addition, systemic absorption of large amounts of the component local anesthetics can potentially result in systemic toxicity.

The clinical utility of conventional transdermal technologies, such as creams or patches, is limited to those drugs that can passively cross the stratum corneum, the outermost, protective layer of the skin. This barrier effectively excludes or minimizes delivery of most water-soluble drugs (4–6). 3M's solid microstructured transdermal system (sMTS) is composed of small microneedles that painlessly penetrate the stratum corneum and enter the epidermis,

increasing the permeability of the skin to water-soluble drugs while avoiding nerve endings that reside in the deeper dermis. Upon application of the sMTS array, drug coated on the microneedles rapidly dissolves, releasing the drug into the skin. Coated microneedles have been shown to deliver water-soluble, polar and ionic molecules, as well as peptides and proteins *in-vivo* (7,8).

This work describes the performance of a lidocaine-coated sMTS system for targeted and rapid dermal delivery of lidocaine in comparison with that of EMLA cream. Tissue levels of the active pharmaceutical agents were evaluated via quantitative analysis of drug levels in punch biopsy samples collected after *in-vivo* exposure in swine. Delivery time associated with lidocaine-coated sMTS was targeted at 1–5 min, while the recommended 60 min application time was used for EMLA.

MATERIALS AND METHODS

Materials

Lidocaine hydrochloride and epinephrine bitartrate were obtained from Sigma (St. Louis, MO), and mepivacaine hydrochloride was purchased from Spectrum Chemical & Laboratory Products (New Brunswick, NJ). Dextran was obtained from Pharmacosmos (Holbaek, Denmark), and proteinase K was purchased from EMD Biosciences, Inc (San Diego, CA). The 70% isopropyl alcohol was ordered from BDH (West Chester, PA). All reagents were of USP grade and used without further purification.

Coating Solution Formulations

Aqueous coating solution formulations (wt/wt%) were prepared using DI water and are listed in Table I. Epinephrine bitartrate was used as an adjuvant in some of the formulations. The total solids content of the formulations was maintained at 60% wt/wt.

Array Dip-Coating

All microneedle arrays were injection molded (3M, St. Paul, MN) from Class VI, Medical Grade liquid crystalline polymer (LCP) (Vectra® MT1300, Ticona Plastics, Auburn Hills, Michigan) with a surface area of approximately 1.27 cm^2. All needles were square pyramids with an aspect ratio of 3:1. The arrays were composed of approximately 316 microneedles with a needle height of approximately 500 μm and a tip-to-tip needle spacing of approximately 550 μm.

Table I Lidocaine Coating Formulation for sMTS

Formulation ID	Lidocaine (wt%)	Dextran (wt%)	Water (wt%)	Epinephrine (wt%)
A	30.0	30.0	40.0	NA
B	30.0	30.0	39.99	0.015
C	30.0	30.0	39.97	0.03

The lidocaine was coated onto microneedle arrays using a dip-coating process with formulations comprised of 30% dextran and 30% lidocaine with and without the local anesthetic adjuvant, epinephrine bitartrate. Prior to coating, the microneedle arrays were cleaned with 70% isopropyl alcohol and dried in a 35°C oven for 1 h. Microneedle arrays were then dipped into the coating solution once or twice. The delay between each dip was 6 s. The coated microneedles were allowed to dry for 1 h at 35°C and then examined using a Nikon Eclipse LV100 or a Nikon Eclipse ME 600 microscope (Melville, NY) to assess coating uniformity. For *in-vivo* application, each array was attached to a 5 cm^2 adhesive patch with 1513 double-sided medical adhesive (3M Company, St. Paul, MN) that was configured within a proof-of-concept applicator system. The arrays were stored in a light- and moisture-proof pouch (Oliver-Tolas Healthcare packaging, Feasterville, PA) at room temperature until *in-vivo* application.

In Vivo Study

Naïve young adult female mixed-breed agricultural swine (Yorkshire X from Midwest Research Swine, Gibbon, MN) with minimal skin pigmentation and weighing 10–40 kg were used for *in-vivo* delivery studies. The animals were initially sedated with ketamine (10 mg/kg). Glycopyrrolate (0.011 mg/kg) was intramuscularly administered to reduce salivary, tracheobronchial, and pharyngeal secretions. Skin test sites were selected based on lack of skin pigmentation and skin damage. To minimize complications, hair and dirt on the swine skin at the intended application sites were removed prior to application of the microneedle array. The hair was first clipped using an electric shaver followed by shaving with a wet multi-blade disposable razor (Schick Xtreme3) and shaving cream (Gillette Foamy Regular) while the animal was under anesthesia.

A light surgical plane of anesthesia was achieved by administering 1.5%–5% Isoflurane in 1.5–4 L of oxygen by mask. Anesthetized animals were placed in lateral recumbency on insulated table pads. During the experiment, the animals were placed on a heated table to control body temperature at approximately 38°C. Animals were observed continuously until normal recovery was attained. Arrays were applied to the swine with a spring-loaded applicator that provides an impact velocity of ~8 m/s; the arrays remained in contact with the skin for 1–5 min. The

patches were removed, and a cotton ball (Walgreen Co, Deerfield, IL) moistened with phosphate-buffered saline (PBS) (EMD Chemicals Inc., Gibbstown, NJ) was used to swab the application site. Following this swabbing, a dry cotton ball was used to remove any residual PBS. A 4-mm skin biopsy (Disposable Biopsy Punch from Miltex Inc. York, PA) was collected from the site of array application at the designated time following removal of the array. The used arrays were examined using a Nikon Eclipse LV100 or a Nikon Eclipse ME600 optical microscope to observe any remaining drug; the residual drug on the arrays was quantitatively assayed by HPLC.

After preparing the swine as described above, the EMLA applications were completed using two different iterations. In iteration 1, EMLA was applied on the swine ribs and covered with an occlusive dressing (Tegaderm, 3M, St. Paul, MN) for a pre-determined application time of 15, 30 or 60 min. At the appropriate time, the backing was removed, and the cream was cleaned from the skin with soap and DI water prior to collection of a 4-mm skin biopsy. In the second iteration, EMLA was applied to the ribs and covered with occlusive dressing for 60 min. Then the backing was removed, and the cream was cleaned from the skin with soap and DI water. A 4-mm skin biopsy was collected following 15, 30 or 60 min delay. For both iterations, each time point was repeated in triplicate. Skin biopsy samples were to a depth of 3–4 mm.

The animal facility used was accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC, Frederick, Maryland), and all procedures were in accordance with an approved Institutional Animal Care and Use Committee (IACUC) protocol.

Determination of Lidocaine Content in Coatings and Swab Solutions

Analyses of the lidocaine content were conducted using an Agilent 1100 HPLC (Agilent Technologies, Wilmington, DE) equipped with a quaternary pump, well-plated thermostatted autosampler, thermostatted column compartment, and diode array UV detector. Coatings of the microneedles were desorbed into an appropriate volume of diluent, (0.1% trifluoroacetic acid (TFA, J T. Baker, Phillpsburg, NJ) in water), and injected into the HPLC system. PBS skin swab solution was injected directly into the HPLC system. Results were quantified against an external standard of lidocaine (free base) at a similar concentration to the coating amount. A Zorbax SB-C18 column, 3.5 μm particle size, 150×3.0 mm I.D. (Agilent Technologies, Wilmington, DE) was used for the separation. The mobile phase consisted of two eluents: eluent A was 100% water with 0.1% TFA and eluent B was 100% Acetonitrile (Spectrum Chemical & Laboratory Products, New Brunswick, NJ) with 0.1% TFA. A linear gradient from 80/20 to 0/100 (A/B) was applied over 5 min. The flow rate was 0.5 ml/min, and the UV detection wavelength was 230 nm. The total run time was 8 min.

Determination of Lidocaine Concentration in Skin Tissue

Lidocaine was extracted from each swine skin biopsy punch using enzymatic digestion. The skin tissue was weighed into a glass vial, then tissue digestion buffer containing 0.1 U proteinase K per mg skin was added to the vial. The tissue was digested at 55°C for 5 h. The digestion process produced a homogenous digested skin sample solution.

Protein precipitation was used to prepare the digested skin samples for analysis by LC/MS/MS. Protein was removed from the digested skin samples by adding 2 volumes of methanol containing mepivacaine as the internal standard, followed by centrifugation at 14,000 RPM for 10 min. The resulting sample was quantitatively analyzed with a Sciex API3000 triple quadrupole mass spectrometer (Applied Biosystems, Foster City, CA) running in positive ion mode using Turbo IonSpray interface to monitor the product ions resulting from the m/z transitions: 235→86.2 and 247→97.5. The linear range for lidocaine was 50.0–20,000 ng/ml evaluated using $1/x^2$ curve weighting.

Stability Study

The lidocaine-coated arrays were individually placed into a foil pouch (Oliver-Tolas, Grand Rapid, MI) and heat sealed. The pouches were then stored at 40°C/75% relative humidity (RH) for 4 weeks or 25°C/60% RH for 28 weeks. After 4 weeks or 28 weeks, the samples were pulled from the stability chambers. Five samples were used for appearance evaluation and lidocaine content, and five samples were used for *in-vivo* release for each set of the study.

RESULTS AND DISCUSSION

Coated Arrays

The physical properties of the coating formulation significantly impact the drug loading on the microneedles, so initially a number of excipients were screened to modify the formulation properties and obtain satisfactory drug loading on the arrays. After excipient and formulation screening, the formulation comprising of 30% lidocaine and 30% dextran was selected.

As can be seen from the array images (Fig. 1a–c), following dip-coating, the formulation appears to be

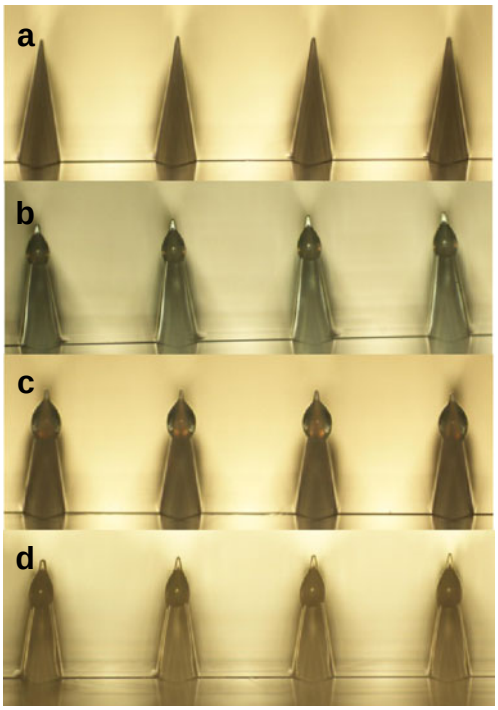

Fig. 1 Microscope imaging of blank array (**a**), Formulation A, 1 dip (**b**), Formulation A, 2 dips (**c**), Formulation A, 1 dip following 28 weeks at 25°C and 60%RH (**d**).

uniformly located on the upper 30%–50% of the needles. The coatings of double-dipped coated arrays stretch lower on the structures than the coating on the single-dipped arrays, but both processes confine the drug to the top half of the needle with no formulation present on the base of the array. The number of dips increased both the thickness of the coating and the drug amount coated onto the microneedles. In most cases, arrays dipped twice had more than two times the amount of drug as the single-dipped arrays. It is likely that the surface area available for coating increases after the first dip and there is a favorable interaction between the formulation and the coating.

The arrays showed very good stability in coating appearance and initial loading either at elevated temperature (45°C/75%RH) or at room temperature (25°C/60% RH). After 4 weeks under accelerated stability conditions or 28 weeks under 25°C, neither the appearance (as shown in Fig. 1d) nor the lidocaine content had changed. On day 0, the lidocaine content of each array was 94.0±9.0 μg/array, not statistically different from the level measured after 4 weeks at 45°C and 75%RH (90.1±8.3 μg/array) or after 28 weeks at 25°C and 60% RH (95.6±5.4 μg/array). The stability of the drug on the array is not surprising, as the formulation on the array is dried immediately following coating. It is also worth mentioning that this study was conducted on laboratory-scale equipment to demonstrate proof-of-concept for the lidocaine-sMTS concept, so the standard deviation in the lidocaine loading is higher than 10%. During scale-up of the concept, we anticipate that the manufacturing process would develop to incorporate automation and other manufacturing scale processes that would help to minimize variation.

Dissolution and Release of Coated Lidocaine

To investigate the delivery and release of the lidocaine-coated microneedle arrays, the patched arrays were applied to the rib area of domestic swine. The amount of lidocaine delivered from the microneedle arrays was determined for different wear times. To differentiate between lidocaine that was delivered into (*versus* onto) the skin, after patch removal, the application site was swabbed with a moist and then a dry cotton ball. Lidocaine delivered into the skin was calculated by difference upon measuring the initial lidocaine loading, minus the amount deposited on the skin surface (determined upon analysis of the moist skin swab), and minus the amount of lidocaine remaining on the array after patch removal from the swine. These results are shown in Table II.

Lidocaine delivery efficiency via microneedles was increased with patch wear time. An application time of 1 min resulted in 53.3% delivery efficiency when the microneedles were prepared by dipping them once into the formulation solution. As the wear time increased to 4 min, more drug was released, and 71.1% delivery efficiency was obtained.

Conversely, 1-min wear time was not sufficient to deliver lidocaine from needles dipped twice in the formulation (Fig. 1c); the delivery efficiency was only 16.3%. The reduced delivery efficiency might be due to a reduction in penetration depth with increased number of dips or due to the limited availability of interstitial fluids to dissolve the coating (9). More of the coated formulation was delivered as the wear time increased (Fig. 2a–c). This increase in drug delivery with increased wear time is paralleled by an increase in residual drug found on the skin surface and a decrease in residual array content, as shown in Fig. 3. The lidocaine

Table II Summary of Delivery Efficiency Following *In Vivo* Testing

Number of dips	Wear time	Initial loading (mcg/array)	Delivery efficiency (%)
1	1	90.5±14.5	53.3±1.6
1	2	90.5±14.5	62.4±8.8
1	4	90.5±14.5	71.1±1.4
2	1	225.7±13.4	16.3±5.5
2	2	225.7±13.4	21.5±8.8
2	4	225.7±13.4	28.3±7.8

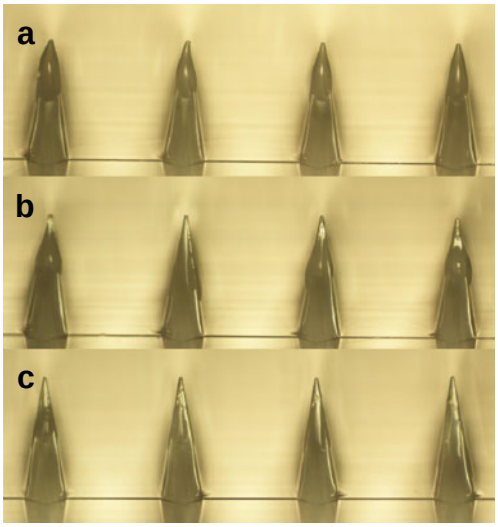

Fig. 2 Microscope imaging of Formulation A, 2 dips following 1-min wear time *in-vivo* (**a**), Formulation A, 2 dips following 2-min wear time *in-vivo* (**b**) Formulation A, 2 dips following 4-min wear time *in-vivo* (**c**).

delivery associated with 2 dip-coated microneedle arrays with a 4 min patch wear time was still less than 30%. Further increasing wear time would likely improve the delivery efficiency; however, the purpose of this study was to demonstrate rapid delivery of the local anesthetic through skin and achieve the therapeutic concentration causing analgesia immediately for potential use in the emergency department or a time-constrained setting. With this in mind, we did not pursue the *in-vivo* study beyond the 4 min patch wear time reported here. These results demonstrated rapid release and delivery of drug into the skin.

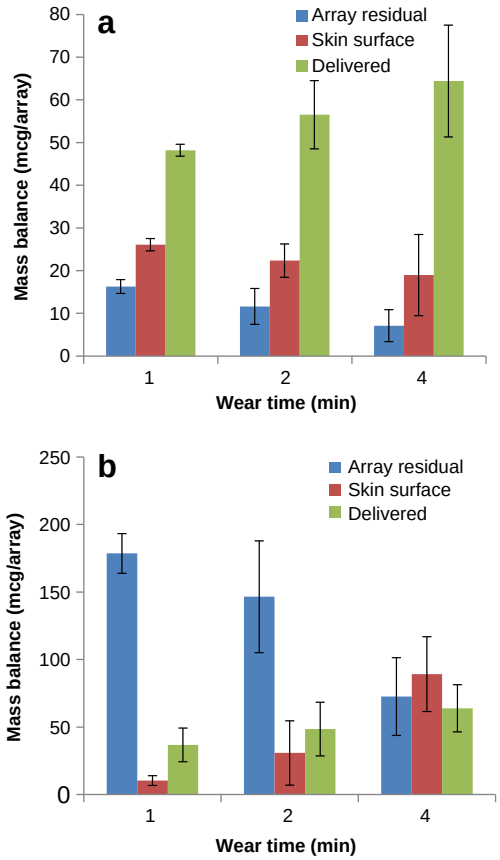

Fig. 3 Mass balance of lidocaine delivered from microneedles dipped 1 time (**a**) and 2 times (**b**) in the coating formulation.

Dermal Pharmacokinetics of Lidocaine-sMTS

A few studies that measured tissue concentration of lidocaine over time have been reported in the literature. Most of those studies used microdialysis to determine the local pharmacokinetic profile of cutaneous drug penetration from the sampling site (10). Quantitative analysis of skin biopsy samples was used in this study to assess the tissue concentration of lidocaine and prilocaine following delivery. The top 3–4 mm of the skin layer was sampled and analyzed. This method provides a direct measurement of the drug present in the skin.

EMLA is a topical formulation based on an eutectic mixture of lidocaine and prilocaine, which forms a liquid oil with a melting point lower than room temperature; EMLA is the most commonly used topical anesthetic commercially available for intact skin (11,12). Directions for use indicate that EMLA should be applied at least 60 min before the clinical procedure in order to achieve the desired level of anesthesia. For comparison to the delivery profile via sMTS, EMLA was applied to swine according to the directions in the package insert. After 1 h application of EMLA, the cream was wiped off, and a 4-mm skin biopsy sample was collected. The tissue concentrations of lidocaine and prilocaine were approximately 50 ng/mg each; thus, we considered 100 ng/mg to be the estimated therapeutic concentration providing analgesia.

Lidocaine-sMTS patches were applied to the swine with 1–5-min wear times. The skin biopsies were collected after patch removal and extensive cleaning of the skin surfaces. The targeted skin concentration was achieved from lidocaine-coated arrays after 1–5 min of wear time, as shown in Fig. 4. The results suggested that the lidocaine-sMTS delivered the drug into the epidermis and dermis almost instantaneously. Assuming tissue concentration is a viable indicator of analgesia, the lidocaine-sMTS provides a dramatically faster onset of local anesthesia than is possible with EMLA cream.

Following removal of the sMTS array, tissue levels of lidocaine decreased quickly, suggesting that either lidocaine was removed by the systemic blood supply or that the lidocaine diffused away from the application site into deeper tissues. Lidocaine may bypass the dermal microcirculation to accumulate in underlying tissues (13).

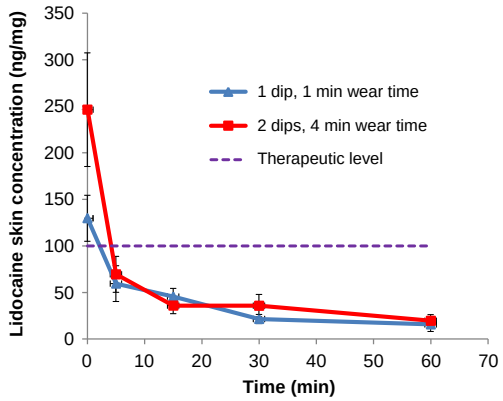

Fig. 4 Dermal pharmacokinetics of lidocaine delivered via microneedle arrays.

Distribution and Spread of Lidocaine in the Skin Tissue

When a local anesthetic is administered by injection, it moves toward its neural target by mass movement. The spread is dependent on the volume, injection speed, site of injection and whether physical or enzymatic enhancement is utilized (14–16). It is not known if lidocaine delivered via microneedles will diffuse away from the application site laterally or into deeper tissues. To better understand the movement of lidocaine post-delivery, dip-coated arrays with 94 mcg lidocaine/array were applied to the swine for 1 min. The lidocaine concentrations in three regions of skin were examined at 0, 5, 15 and 30 min after patch removal. The first region covered the array application site, where one 4-mm biopsy was taken in the center point of the array application site; this biopsy concentration represents the lidocaine concentration of the array application site; the second region included the areas immediately surrounding the array. Three skin biopsies were taken in the second region. The third region was sampled 14 mm from the center point of the applied patch. Fig. 5 illustrates the three regions that were examined, as well as the lidocaine measured in these regions at different times following delivery.

The lidocaine concentration measured at the array site decreased over time. A small concentration of lidocaine was detected in the skin located in the second region, and no lidocaine was detected in the third region, furthest from the application site. These data indicate that there is very little lateral transport of the lidocaine through the skin once the array is removed.

The concentration of lidocaine in underlying tissues 4–8 mm below the patch application site following array removal was also measured. No significant amount of lidocaine was detected in the underlying tissues. These data indicate that lidocaine is rapidly absorbed into the capillaries around the site of administration and cleared from the skin. Characterization of the distribution of lidocaine was not completed for EMLA.

Addition of Epinephrine as a Local Anesthetic Adjuvant

Although these data indicate that the lidocaine-sMTS product can provide rapid delivery of local analgesic, the effect may only be sustained for ~15 min. While this may be sufficient for many surgical or dermatological procedures, there may be instances when a longer duration anesthesia is needed. To prolong the duration of peripheral and central neuraxial blocks, epinephrine is often added to the local anesthetic. It has been proposed that the prolonging effect epinephrine provides results from local vasoconstriction and, consequently, a decrease in the rate of absorption and clearance of local anesthetic from the injection site (17,18).

To investigate whether a similar prolonging effect would be observed with microneedle-based delivery, epinephrine was co-formulated at 0.015% and 0.03 wt% with lidocaine and coated onto the sMTS arrays. The epinephrine did not increase the amount of lidocaine delivered to the skin, but it did have profound effects on the dermal pharmacokinetics associated with the lidocaine. The lidocaine skin concentration-time profiles resulting from three separate lidocaine/epinephrine-sMTS configurations are shown in Fig. 6; a 1-min patch application was used for all iterations.

The results suggested addition of epinephrine significantly slowed down the lidocaine transport from the patch application site, presumably by decreasing local blood flow. Visual indications of vasoconstriction, slight blanching of the skin, were observed in this study, though it is notable that the blanching resolved almost immediately following removal of the array. Slight discoloration of the tissue was observed when a high level of epinephrine was coated on the arrays. The rate of clearance of lidocaine from the biopsied skin was dependent on the amount of epinephrine in the formulation. When 0.03% epinephrine was formulated and delivered with lidocaine, lidocaine levels in the skin were maintained above 100 ng/mg for approximately 90 min much longer than when lidocaine was delivered alone. This prolonged maintenance of lidocaine suggests that the sMTS product may have utility for more extensive analgesic needs.

These results support other findings associated with injectable formulations that indicate the effect of epinephrine on pharmacokinetics (19). Epinephrine causes a temporary restriction of local blood flow in the tissue, thereby delaying the removal of lidocaine from the application site. The result is a prolonged residence of the locally administered lidocaine. Distribution and spread of lidocaine delivered via sMTS containing epinephrine was

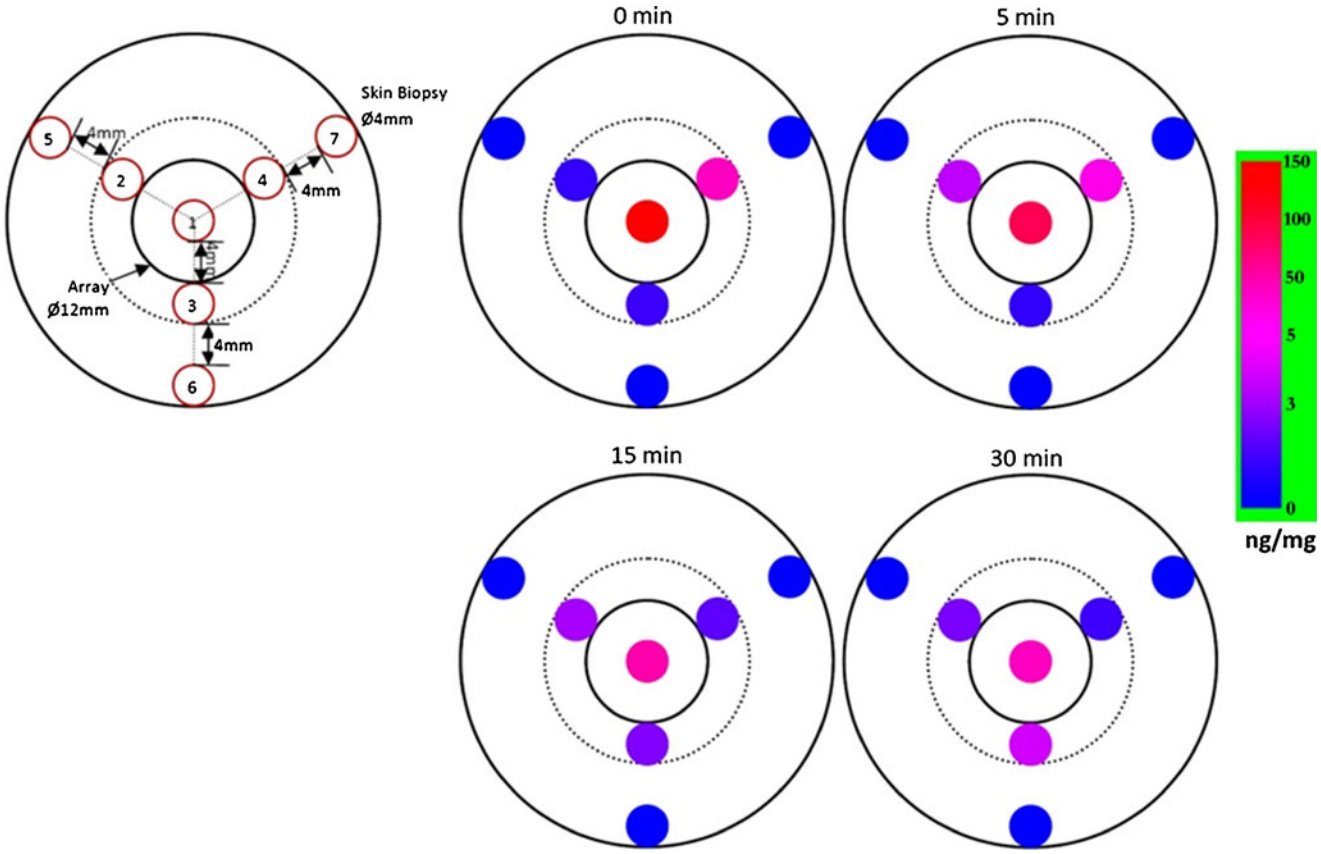

Fig. 5 Lidocaine skin concentrations in three regions 0, 5, 15, 30 min after patch removal.

also evaluated, as illustrated in Fig. 5. We did not observe that epinephrine increased the lateral distribution of lidocaine, as reported in another study (20).

EMLA has been used very widely across dermal and mucous membrane topical applications in the last 20 years and so is a viable comparative control in this study. Two experiments using EMLA were conducted. In the first experiment, EMLA was applied on the ribs of swine for 15, 30 or 60 min. Skin biopsies were collected and analyzed in order to study the absorption of lidocaine and prilocaine. In the second experiment, EMLA was applied for 60 min. Skin biopsies were taken at 15, 30 and 60 min after application in order to study the clearance of the lidocaine and prilocaine from the skin. The results obtained show that the free base of both lidocaine and prilocaine have very similar pharmacokinetic profiles (data not shown). Lidocaine and prilocaine slowly penetrated into the skin after topical application, increasing with application time. After removal of the cream at 60 min, both lidocaine and prilocaine were cleared much more slowly than the lidocaine delivered by the epinephrine-free (Formulation A) sMTS array. This slow clearance following removal of the EMLA is likely due to the reservoir of anesthetic that accumulates in the stratum corneum during occlusion (21).

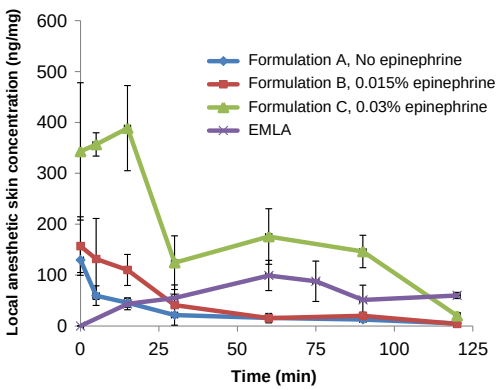

Fig. 6 Skin concentrations of lidocaine (sMTS) and lidocaine+prilocaine (EMLA) over time.

Lidocaine-sMTS has no any safety risk to patients, since the total lidocaine amount delivered via sMTS to the skin is approximately 50 mcg/application only, which is far below the maximum recommended dose of lidocaine injection with or without epinephrine, 300 mg (22). Lidocaine-sMTS arrays were well tolerated on the swine. There was no observable erythema or skin irritation on any of the treatment sites after administration. The lidocaine-sMTS arrays were configured as a single-unit dosing device that quickly delivers a known amount of lidocaine onto a clearly defined area of skin. The lidocaine-sMTS arrays demon-

strated potential for substantial improvement over conventional practices, especially with respect to speed of onset. The rapid onset and the duration of lidocaine residency in the skin would be suitable for many clinical and dermatological procedures such as blood sampling, mole removal, skin sample collection for diagnostic test, and vaccination or venous cannulation for pediatric patients. Longer duration can be achieved by including epinephrine in the formulation, increasing further the utility of this concept.

CONCLUSIONS

These results demonstrate the capability of 3M's sMTS to successfully deliver drugs to the skin within seconds and provide rapid onset of local analgesia (~1 min) to facilitate routine or emergency procedures. A coating formulation was developed to achieve uniform lidocaine loading at target levels. Upon *in-vivo* application, the coating was readily released into intradermal space, and the estimated therapeutic tissue concentration necessary to provide analgesia was achieved. Using epinephrine bitartrate as an adjuvant slowed the clearance of lidocaine from the skin and prolonged the local residence of lidocaine, but the rapid onset of action associated with lidocaine was maintained. Altogether, this study shows that the lidocaine-sMTS produced comparable duration of analgesia but provided substantial improvements over conventional creams with respect to the rate of onset.

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