Microneedle Integrated Transdermal Patch for Fast Onset and Sustained Delivery of Lidocaine

Jaspreet Singh Kochhar,† Wan Xuan Selina Lim,† Shui Zou,† Wei Yan Foo,† Jing Pan,† and Lifeng Kang*,†

†Department of Pharmacy, National University of Singapore, 18 Science Drive 4, Singapore 117543, Singapore
‡Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543, Singapore

ABSTRACT: Lidocaine as an analgesic is of particular interest in both acute and chronic pain conditions and is used via injections or transdermal patches. While injections are associated with problems such as patient incompliance, topical administration of lidocaine using patches is less efficient due to variability of drug absorption among individuals, slower drug permeation through the skin, and hence a resultant undesirable delay in analgesic effects. To address this clinical problem, we developed a microneedle integrated transdermal patch (MITP), using a photolithography based process, in which microneedles create micrometer-sized channels in the skin to deliver lidocaine rapidly, while the reservoir patch holding the bulk of the drug enables higher drug loading and carries on to release the drug for prolonged periods. We demonstrated a new approach of drug delivery using microneedles, where drugs diffuse out of microneedles through the porous channels left by dissolving drug particles. MITP was shown to be able to encapsulate up to 70 mg of lidocaine. In vitro permeation through rat skin demonstrated that MITP delivered a significantly higher amount of lidocaine than a commercial patch and with a faster onset of drug permeation.

KEYWORDS: microneedles, transdermal patch, transdermal drug delivery, lidocaine, acute pain, peripheral neuropathic pain

■ INTRODUCTION

The occurrence of pain is common among all age groups, with about 1.5 billion people suffering from it around the globe. On the basis of duration, pain may be classified as acute or chronic pain. Acute pain is defined as "pain of recent onset and probable limited duration". It usually has an identifiable temporal and causal relationship to injury or disease.† On the other hand, chronic pain is a "pain without apparent biological value that has persisted beyond the normal tissue healing time".‡ Chronic pain is the most prevalent disorder in the United States, with more people affected by it than diabetes, coronary heart disease, and cancer combined.§ Chronic pain of moderate to severe intensity affects 19% of adult Europeans as well.§ Approximately 3–4.5% of world’s population suffers from chronic neuropathic pain, with incidence commensurating with increasing age.¶

Lidocaine, also known as lignocaine or xylocaine, has been of special interest for its analgesic properties apart from its known role as a local anesthetic, being used in the management of both acute and chronic pain conditions. For the management of acute pain, perioperative infusion of lidocaine has been used to prevent dose escalation of opioids, reducing pain scores, nausea, vomiting, and other related symptoms associated with abdominal surgery.¶ In addition, topical formulations of lidocaine and its combination with prilocaine and tetracaine have been widely used to provide superficial skin anesthesia in prophylactic pain management, especially in children before intravenous administration.¶ It has also been used in minor dermatological surgery procedures.¶ On the other hand, for chronic pain management, lidocaine finds its most prominent analgesic application in the management of peripheral neuropathic pain, being recommended as a first line therapy. Lidocaine 5% transdermal patch is licensed in many countries for the management of postherpetic neuralgia; it is used off-label in most cases of neuropathic pain.¶ Many randomized controlled trials support the use of transdermal lidocaine patches in the management of peripheral neuropathic pain.¶

Despite their regnant use, their lack of efficacy and rapid action, primarily due to skin’s barrier properties, is a major concern with patch-wear times up to 60 min required, which may be unacceptable to some pediatric patients.¶ In
randomized controlled trials, a maximum of 420 cm² of patch area was applied to the skin for 4 h before any significant reduction in pain could be observed.¹³,¹⁴ For chronic pain, a maximum of 3−4 patches/day are recommended for a period of 12−18 h a day. Such a long patch wear time has been reported with incidents of skin rash, erythema, and discomfort.¹⁵

To address these problems, iontophoresis and ultrasound have been employed to reduce the lag time to be less than 10 min, and iontophoretic lidocaine administration has been approved as an anesthetic prior to venipuncture.¹⁶,¹⁷ Nonetheless, considerable skin irritation and pain have been reported due to significant inflammation of underlying nerve innervated tissues.¹⁸ Complicated fabrication methods and device design accrue the cost of therapy for the end user, resulting in poor patient acceptance and physician willingness.¹⁹

Recently, microneedle arrays have been shown to enhance delivery of drugs like naltrexone,²⁰,²¹ lidocaine,²² and insulin²³ in humans. Lidocaine delivery using microneedles has been demonstrated using hollow microneedles coupled to liquid formulation containing syringe to deliver large amounts of lidocaine. However, the complicated multicomponent application systems are not ideal for self-administration and long wear times.²² Coated microneedles were reported to deliver lidocaine tissue concentrations comparable to commercial EMLA cream (applied for 1 h) in 1−5 min of wear time. However, the drug loading on these microneedles was limited due to small surface area, and only 225 μg of lidocaine could be coated.²⁴ While these hollow and solid microneedles pose the additional risk of breakage in the skin, polymeric microneedles present a viable alternative.

Drugs could be encapsulated within the polymeric matrix in higher doses than surface coating of solid microneedles and do not require an additional source of drug delivery as needed with hollow microneedles. Lee et al. first demonstrated the utility of polymeric microneedle backings as drug reservoirs for higher drug loading and sustained release of small molecular weight drugs.²⁵ Drug amounts in the range of 1−3 mg have been encapsulated at the maximum using polymeric microneedles. Ito et al. recently demonstrated the attachment of drug loaded chip fabricated by pouring a drug-polymer glue in the molds of a tabletting machine, to a microneedle array fabricated by conventional mold based process to achieve a drug encapsulation of 12 mg.²⁶

In this study, we fabricate a microneedle integrated transdermal patch (MITP), which could be tuned in size to encapsulate drugs several times higher than the previously reported methods, using a simple process. Mechanical properties of the microneedles attached to the MITP were studied to gain an insight into axial loading properties of the newly developed integrated patch system. In vitro permeation from MITP was compared to a commercial lidocaine patch, namely, Lignopad. The integrated patch system is intended to provide a reservoir system with high drug loading, to deliver the initial drug load rapidly and also sustaining the release of the active

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**Figure 1.** Schematic showing fabrication of microneedle integrated transdermal patch (MITP) using ultraviolet curing. (A) Fabrication of thick transdermal patch using low intensity UV irradiation, (B) conjugation of prefabricated microneedle array from²⁷ to the thick patch by ultraviolet curing forming interpenetrating polymer networks, and (C) rapid release (within 5 min) of lidocaine from MITP, potentially providing rapid pain relief.

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ingredient, with potential applications for management of both acute and chronic pain conditions.

In addition, we demonstrate a novel approach to deliver drugs by keeping microneedles inside skin, providing the opportunity for longer application time of microneedles, where microneedle shafts act as channels for drugs encapsulated in backing layers. This circumvents the premature closure of miniaturized pores created by microneedles, possibly due to removal of microneedles, aiding in continued drug permeation.

## EXPERIMENTAL SECTION

### Materials.
Poly(ethylene glycol) diacrylate, PEGDA ($M_n = 258$), 2-hydroxy-2-methyl-propiophenone (HMP), trypan blue, and lidocaine were purchased from Sigma-Aldrich (St. Louis, MO, USA). Rhodamine B and sodium azide were purchased from Alfa Aesar (Lancaster, UK). HPLC-grade acetonitrile was supplied by Tedia, USA. Phosphate-buffered saline (PBS) ultra pure grade was obtained from Vivantis, Malaysia. Water used in these studies was purified using Millipore Direct-Q (Molsheim, France). All other materials were reagent grade and used as received.

### Fabrication of the Microneedle Integrated Transdermal Patch (MITP).
Fabrication of MITP consists of two phases. In the phase one, a microneedle array was fabricated as described previously by our group. Briefly, PEGDA containing 0.5% (w/v) of HMP (called “prepolymer” solution) was filled into a 190 μm thick preformed cavity made from glass slides and coverslips. The solution was then exposed to a high power (12.9 W/cm$^2$) ultra violet (UV) light source (Exfo, Canada) for 2 s. This resulted in the formation of a thin film (microneedle backing) that acts as a support for subsequently fabricated microneedle shafts. Following this, the thin film was removed from the fabrication setup and placed on another similar setup scaffold, 950 μm in height. The cavity formed was filled with prepolymer solution and exposed to UV (12.9 W/cm$^2$) through a specially patterned photomask, for a duration of 4.3 s, forming the microneedle shafts. The remaining prepolymer solution was pipetted out, and microneedles were rinsed with water to remove any un-cross linked polymer and left to air dry.

In the second phase of fabrication, low power ultraviolet curing was used to fabricate a thick patch for enhanced drug loading capacity. A cavity measuring 1.2 mm in height was created using glass slides as base and spacers and a coverslip as a lid shown in Figure 1A. Prepolymer solution was wicked into a 190 μm thick prepolymer layer filled into a 190 μm thick preformed cavity made from glass slides and coverslips. The solution was then exposed to a high power (12.9 W/cm$^2$) ultra violet (UV) light source (Exfo, Canada) for 2 s. This resulted in the formation of a thin film (microneedle backing) that acts as a support for subsequently fabricated microneedle shafts. Following this, the thin film was removed from the fabrication setup and placed on another similar setup scaffold, 950 μm in height. The cavity formed was filled with prepolymer solution and exposed to UV (12.9 W/cm$^2$) through a specially patterned photomask, for a duration of 4.3 s, forming the microneedle shafts. The remaining prepolymer solution was pipetted out, and microneedles were rinsed with water to remove any un-cross linked polymer and left to air dry.

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## Drug Encapsulation and Imaging of MITP.
Incorporation of lidocaine in the MITP was achieved by dissolution of the drug in the prepolymer solution prior to UV curing. Various concentrations (2.2%, 15%, and 21% w/w) of lidocaine were dissolved in prepolymer solution followed by fabrication of MITT. As all of the liquid prepolymer was converted to solid polymer, the amount of lidocaine encapsulated in MITT was determined by weighing the MITT specimens and calculating the amount on weight by weight basis. Selective incorporation of drugs in a specific layer of MITT could be possible by using the drug containing prepolymer solutions to specifically fabricate that layer, while other components can be fabricated using drug free prepolymer solution. Figure 1C demonstrates a schematic showing rapid release of lidocaine from MITT and its subsequent diffusion through the skin’s layers upon application.

Rhodamine B was encapsulated at 0.075% (w/v) in the prepolymer solution to image the drug distribution using a Nikon AZ 100 microscope (Nikon, Japan).

### Mechanical Strength of MITP.
To determine the mechanical strength of the microneedles on the integrated patch, an electronic force gauge (Dillon model GL, USA) held on a test stand (Dillon CT manual test stand) was used. The fracture force of the microneedles was first determined by placing the microneedles on a flat block of aluminum and rotating the hand wheel of the test stand slowly until the force probe contacts the top of the patch. Successive increase in application force caused the microneedles to break, with a sudden decrease in the amount of force exerted. This point was taken to be the fracture force of the microneedle. As a comparative control, the force of a thumb was obtained from five individuals, males and females, aged 21–25, by pressing the thumb of the stronger hand against the force gauge probe.

The effect of varying the amount of force exerted on the microneedle patch was also investigated for studying the degree of skin penetration. Defatted rat skin was placed on top of 10 layers of Kimwipes to provide a tissue-like mechanical support. Varying forces (10N, 30N, 50N, 70N) were exerted on the microneedles placed on rat skin for 1 min. The extent of needle penetration into the rat skin was determined by the trypan blue staining method. Trypan blue was placed on the microneedle treated skin with a dropper for 5 min and removed gently using Kimwipes and 70% ethanol. Skin samples were then viewed under the hand-held microscope (Eikon Soft, China).

### In Vitro Release Test.
To ensure that lidocaine could diffuse out of the integrated patch, an in vitro release test was conducted. First, the upper surface of the integrated patch was covered with a waterproof vinyl tape (3 M Vinyl Tape) to prevent diffusion of lidocaine from the upper surface (which will be in contact with the air during in vivo application) of the integrated patch. After which, the integrated patch was immersed in 15 mL of 1× PBS in a falcon tube incubated at 37 °C and sampled at regular intervals. At each sampling point, all 15 mL of the release solution was withdrawn and replaced with fresh PBS. A positive control to determine the release of lidocaine from Lignepad was done as well. The amount of lidocaine released into PBS was determined by high-performance liquid chromatography (HPLC) method described previously.

To characterize the surface properties of microneedles before and after the release test, samples with different concentrations of lidocaine were imaged using a JSM-6701F field emission scanning electron microscope (JEOL, Japan) at an acceleration voltage of 5 kV. The microneedle samples were first platinum sputter-coated using a JFC-1600 autofine coater (JEOL, Japan) at a current of 20 mA for 30 s to provide a coating of 5 nm thickness.

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In Vitro Rat Skin Permeation Study. To determine the enhancement of rate of delivery of lidocaine by MITP, an in vitro skin permeation study was carried out. Cadaver rat skin was used to determine the comparative rate and extent of permeation of lidocaine through the skin between the fabricated MITP and commercial lidocaine patch, Lignopad. Hair on the rat skin was removed using a hair removal cream (Veet, Reckitt Benckiser, Poland). The subcutaneous fat was removed using a scalpel and skin was hydrated in 1x PBS for 30 min. The skin from the same rat was divided into six portions to minimize interanimal variation: three replicates with Lignopad placed on intact skin and three replicates using the fabricated MITP. For the application of MITP, 10 layers of Kimwipes which mimic underlying skin tissues was used to support the rat skin. The integrated patch was applied on the skin for 1 min with the force of a thumb. The array was then secured onto the skin using Scotch tape.

The rats skins with the patches were mounted on horizontal diffusion cells (TK-6H1, Shanghai Kai Kai Science and Technology Co., Ltd.) with an effective area of 1.131 cm². The diffusion cells were maintained at 37 °C by a circulating water jacket, and the solutions were continuously stirred at 250 rpm. The receptor cells were filled with 4.5 mL of PBS with 0.005% (w/v) sodium azide as an antimicrobial agent, and samples were taken at regular intervals. A sample of 4 mL of receptor solution was withdrawn at each time interval and replaced with the same amount of fresh receptor solution. The samples were stored at 4 °C upon collection, and they were centrifuged at 10 000 rpm for 5 min before the supernatant was withdrawn for HPLC analysis. All animal experiments were approved by Institutional Animal Care and Use Committee (IACUC), National University of Singapore.

Interaction between Polymer and Lidocaine: FTIR-ATR Spectroscopy. To verify the interactions between the PEGDA and lidocaine, Fourier transformed infrared attenuated total reflectance (FTIR-ATR) spectroscopy using a Spotlight 400 FTIR Imaging System (PerkinElmer, CT, USA) with an ATR accessory having a diamond crystal was carried out. The spectra of the prepolymer solution with and without lidocaine and that of the polymerized film with and without lidocaine were obtained. The films (190 μm thick) were fabricated under identical conditions as used for MITP fabrication, to expose the polymer and drug to same extent of UV radiation. To analyze liquid samples, a drop of liquid was placed on top of and covering the crystal. For solid samples, the solid was placed on top of the crystal, and a pressure arm was positioned over the sample to exert a force of ~80 N on the sample. No additional sample preparation was required for IR analysis.

Statistical Analysis. The data were computed using Microsoft Office Excel 2011 (Microsoft, Redmond, USA), and statistics were performed IBM SPSS Statistics 21.0 software. One-way analysis of variance (ANOVA) was performed to compare groups of data. The results were presented as the mean ± standard deviation unless otherwise stated, and p values of less than 0.05 were considered statistically significant.

RESULTS

Geometric Properties of MITP. Governed primarily by the photomask dimensions, an array of 8 × 8 microneedles covering an area of ~1.44 cm² was fabricated. The fabricated microneedles had an average length of 889 ± 48 μm, base diameter of 334 ± 43 μm, and center-to-center spacing of 1474 ± 39 μm. The thin backing layer fabricated in phase I was 212 ± 22 μm in height while the integrated patch fabricated in the phase II was 1054 ± 34 μm thick. An image of the fabricated MITP containing rhodamine B is shown in Figure 2A and various layers of MITP in Figure 2B.

Drug Encapsulation in MITP. As the integrated patch encapsulating lidocaine appeared colorless, rhodamine B (0.075% w/v in prepolymer solution) was encapsulated as a model drug into the array to observe the uniformity of drug distribution. Rhodamine B, a fluorescent dye, was dissolved in the prepolymer solution prior to UV exposure and was observed to be uniformly distributed in all layers of the fabricated MITP (Figure 2A). Lidocaine was encapsulated in different concentrations (2.2%, 15%, and 21% w/w), leading to fabrication of MITP containing 7.917 ± 0.739 mg, 50.592 ± 1.855 mg, and 70.940 ± 2.189 mg, respectively.

Mechanical Strength of MITP. Fracture force of the microneedles supported on the integrated patch was evaluated by application of axial force upon the microneedles held against a stationary aluminum block. The fracture force of the microneedles on the integrated patch against the block was recorded as 91.28 ± 9.2 N, as compared to the force of a thumb (10.72 ± 0.9 N) obtained from five individuals, which was significantly lower than the fracture force.

MITP application on excised cadaver skin was carried out at successively increasing forces to evaluate the extent of penetration and strength of microneedles when applied to a skin model. With a successive increase in the force applied between 10 and 70 N, an increasing amount of microneedles penetrated the skin (Figure 3A). Supporting Information (Figure SI 1) shows no apparent change in microneedle structures when applied to rat skin for a period of 1 min at different forces (10−70 N). An insignificant decrease in the average length of a microneedle was observed with length decreasing from 865 ± 22 μm at 10 N to 848 ± 23 μm at 70 N (p > 0.05) (Figure SI 2). The microneedle arrays appear sharp even after a single administration and removal from rat skin (Figure SI 2A−D). While microneedle shafts were robust enough to penetrate the skin, at higher forces beyond 50 N, 2−4 needles broke on the surface of the skin (Figure 3B). Even when lidocaine was encapsulated in different concentrations in the microneedles arrays, there was a minimal amount of microneedle breakage observed on the skin, indicating that drug encapsulation did not hamper the microneedle strength (Figure 3C−E).
An increased force of application also increased the percentage of microneedles penetrating through the skin as ascertained by increase in the number of spots stained by trypan blue. Even at the lowest penetration force of 10 N, which closely resembles force of a human thumb, more than 75% of microneedles penetrate, with this number increasing to nearly 95% at 70 N (Figure SI 3). However, since a force of a thumb would be more ideal and practical in microneedle applications in humans, a force of 10 N using a force gauge was used for application of MITP for subsequent in vitro permeation studies.

**In Vitro Release of Lidocaine from MITP.** It is interesting to note that, with a higher drug concentration, MITP surface exhibits a rougher and corrugated surface, as observed in Figure 4A, B, and C. With lower (2.2% w/w) lidocaine in MITP, a tightly packed polymer structure is observed as seen in Figure 4A, while with an increase in concentration to 15% polymer surface appears to be rougher (Figure 4B) and at highest drug loading of 21% (w/w), a highly rough and irregular structure is seen (Figure 4C). This rough surface morphology potentially allows for better interaction with the release medium and hence higher drug release. As observed from SEM images post drug release, most drug was released from the microneedle shafts, tightly packed polymer structure is observed as seen in Figure 4A, while with an increase in concentration to 15% polymer surface appears to be rougher (Figure 4B) and at highest drug loading of 21% (w/w), a highly rough and irregular structure is seen (Figure 4C). This rough surface morphology potentially allows for better interaction with the release medium and hence higher drug release. As observed from SEM images post drug release, most drug was released from the microneedle shafts,
resulting in smooth surface across all tested concentrations (Figure 4D, E, and F).

The release of lidocaine from the integrated patches encapsulating different concentrations of drug was studied over a period of 24 h. For all samples, lidocaine was released with an initial rapid burst followed by a gradual release after about 6 h (Figure 5A and B). A total of 0.20 ± 0.01 mg of lidocaine was released from the MITP containing 2.2% (w/w) lidocaine, which constituted 15.1% of total lidocaine encapsulated. A larger amount of lidocaine (86.24 ± 11.61 mg) was released from the MITP containing 21% (w/w) of lidocaine, which made up nearly 100% of lidocaine encapsulated in the patch (Figure 5A).

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In Vitro Skin Permeation of Lidocaine Test. With significant amounts of lidocaine released from the fabricated patch, an in vitro skin permeation test was conducted over a similar period of 24 h to determine the practical applications of MITP with respect to a commercial patch, in carrying a higher load of the drug and delivering it at a faster rate. The MITP was compared with Lignopad placed on intact rat skin to compare the permeation of lidocaine from both patches.

Figure 5. Results from in vitro release test of lidocaine encapsulated integrated patch (A) over 24 h and (B) over the first two hours. The cumulative amount of lidocaine released increased as encapsulation concentration increases, with higher concentration showing a sustained release over a period of 24 h, whereas the commercial patch showed an initial burst release followed by a plateau, due to possible drug depletion.

Figure 6A demonstrates a schematic for skin permeation studies using a microneedle array. Although a lower amount of lidocaine permeated when using a 2.2% (w/w) lidocaine MITP as compared to 5% lidocaine commercial patch, it was observed that when 21% (w/w) MITP was used more lidocaine permeated through the skin as compared to the commercially available patch (Figure 6B). For the MITP, a total of 25.21 ± 3.41 mg/cm² of lidocaine permeated through skin. In contrast, a total of 19.49 ± 8.01 mg/cm² of lidocaine from Lignopad permeated through skin over a period of 24 h. While a higher amount of drug permeation is desirable, in conditions such as pain, rapid absorption is equally essential. Using the MITP to create microchannels in the skin, lidocaine could be detected in the receptor solution within 5 min of placing the MITP on the skin, as compared to Lignopad in which lidocaine was first

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Figure 6. (A) A schematic of horizontal diffusion cell assembly for microneedle-based skin permeation studies. Permeation of lidocaine through rat skin was determined (B) over 24 h and (C) over the first two hours. The amount of lidocaine permeated from the 21% (w/w) lidocaine patch was higher than that of Lignopad. Higher initial rates of permeation were also observed for the 21% (w/w) patch, potentially providing rapid pain relief.

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detected in the receptor solution only after 45 min (Figure 6C). This faster initial rate of drug release could potentially allow for a more rapid rate of pain relief as lidocaine can be delivered to the pain sites faster.

Interaction between Polymer and Lidocaine: FTIR-ATR Spectroscopy. As observed in the in vitro release study, particularly for lower concentrations of lidocaine in MITP, a lower amount of lidocaine was released, prompting us to explore any possible chemical interaction between PEGDA and lidocaine. FTIR-ATR spectra revealed the N−H peak for shifted from ~3271 cm⁻¹ in pure lidocaine powder to ~3258 cm⁻¹ in lidocaine in polymerized PEGDA film, and broadening of the peak was observed. Also, there was an obvious broadening of the peak at ~1600 cm⁻¹, which could possibly indicate the amide C=O stretch (Figure 7). As these observations correlate to those reported in Cui et al.’s characterization of lidocaine in polymers, possible hydrogen bonding might be present in the lidocaine integrated patch, which limits the release of lidocaine from the polymer and some lidocaine to remain in the fabricated patch even after 24 h of application, necessitating a higher initial drug loading required in the MITP. In addition, the spectroscopic peaks at 1633, 1621, 1409, and 810 cm⁻¹, corresponding to the main C=C bond signals of acryl groups in liquid PEGDA (Figure 7A) are no longer present upon polymerization of PEGDA into the solid film (Figure 7D), indicating cross-linking between PEGDA molecules to form interpenetrating polymeric networks.

**DISCUSSION**

The microneedle integrated transdermal patch is a promising approach to improve lidocaine delivery across the skin, providing a suitable alternative to painful injections as well as passive, slow, and unreliable diffusion of transdermal creams and patches. Fabrication of the MITP by the photolithographic approach is rapid and simple as encapsulated drugs are not exposed to high heat or drastic temperature changes seen in the micromolding process where the molds are exposed to high heat or drastic temperature changes seen in the fabrication of transdermal creams.38

MITP containing a thicker backing is also amenable to an application of larger forces, aiding more efficient microneedle penetration and at the same time making microneedle shafts more resistant to breakage as compared to microneedles supported on a thin film. Although UV light has been shown to...
cause photodegradation of light sensitive drugs, our short exposure process did not cause lidocaine degradation, as was highlighted from the FTIR-ATR spectra as well (Figure 7).

Lidocaine was successfully shown to be released from the MITP and permeated through rat skin (Figures 5 and 6). We observed for PEGDA microneedles that drug only leached out in contact with an external fluid. For skin permeation studies, this only occurs in the case of microneedles entering the skin and not from the surface of the skin. However, as water diffuses into the whole microneedle patch, it is possible that drugs can also penetrate skin via passive diffusion through the intact skin. As a result, the measured permeation is a combination of drugs permeating through the passages created by the microneedles and those permeating through intact skin. The MITP can serve as a potential drug delivery system, which is able to overcome the limitations of a conventional transdermal patch. Even though Lignopad released more drug than the microneedle integrated patches, it showed an initial burst release profile followed by a plateau indicating drug depletion in the patch. On the other hand 21% (w/w) lidocaine MITP showed a consistent increase and sustained release of lidocaine over a period of 24 h. With a lower concentration (2.2% w/w) of drug loading, microneedle structures were formed with tight polymer structure packing as shown from SEM images in Figure 4A, while with higher concentrations (15 and 21% w/w), a more porous structure was observed, explaining the higher drug release from the microneedles containing higher amounts of lidocaine (Figure 4B and C). This potentially provides an useful delivery system, with a rapid release of drugs from the polymeric core and a sustained release due from the reservoir patch.

The permeation of lidocaine was greater from the integrated patch due to the presence of microneedles that penetrate the stratum corneum. This highlights the utility of having a combination of active and passive drug delivery system, integrated into one device to have benefits of both. The lag time for lidocaine permeation was reduced from 45 min in Lignopad to 5 min when the MITP was used. This is favorable to achieve almost instantaneous pain relief (within 0–15 min) from the use of microneedles, similar to the effects achieved by a hypodermic injection. Maximum pain relief from transdermal patch was shown to be obtained after 4 h of patch application with three transdermal patches were applied onto the skin, with the patch application requiring a larger area for drug absorption. This problem could be potentially alleviated with MITP application as the larger amount of drug could diffuse through a smaller area in a shorter period of time, providing higher patient compliance and quality of life. Hence, MITP could provide a more efficient delivery of lidocaine for faster pain relief in patients with peripheral neuropathic pain.

Although lidocaine delivery using microneedles has been studied previously, the MITP offers the advantage of having a simple fabrication process and high encapsulation efficiency of more than 70 mg of drug. This is particularly relevant as small molecular weight drugs are required in higher amounts to achieve clinically relevant concentrations. In addition, the use of MITP does not require any additional gel or lidocaine containing solution to be applied onto the skin, as lidocaine can be easily incorporated and released from the cross-linked polymer matrix. For hydrophilic drugs insoluble in PEGDA, they can be first dissolved in very small amounts of water and mixed with PEGDA to form a uniform dispersion. Preferential incorporation of drugs could be achieved in the MITP. Drugs incorporated into microneedle shafts allow for bolus and rapid release, while that in the backing layers allow for sustained release as it acts as a drug reservoir. Dissolving lidocaine in PEGDA assures a uniformed distribution of drug and retains the geometry of microneedle shafts, a feature largely lost during coating of microneedles.

Despite the higher permeability achieved with MITP as compared to Lignopad, a higher amount of drug loading was required to achieve this effect. This is probably due to chemical interactions between lidocaine and PEGDA, forming hydrogen bonds as was revealed in the FTIR-ATR spectrum (Figure 7), where enhanced affinity between lidocaine and the polymer matrix prevents drug release. A similar effect was also observed in the release test, where lower amounts of lidocaine were released from MITP as compared to Lignopad, where an MITP patch containing 2.2% (w/w) of lidocaine contains similar amounts of lidocaine as compared to the same area of Lignopad. However, the amount of lidocaine released and permeated from the 2.2% (w/w) lidocaine integrated patch is much lower than that from Lignopad. This effect was observed to a lower extent, with higher drug loading amounts of 15 and 21%, possibly due to the reason that more diffusion passages were created at higher drug-loading microneedles.

**CONCLUSION**

The lidocaine encapsulated microneedle integrated transdermal patch was shown to be a useful alternative to passive transdermal systems for the management of acute and chronic pains. It can deliver lidocaine at a faster initial rate than Lignopad, with lidocaine permeating skin within 5 min of MITP application, whereas Lignopad had a delay of 45 min before lidocaine permeated. This faster permeation enables a possibly faster rate of pain relief for patients. Having a larger amount of lidocaine permeating through the skin can also potentially reduce the patch application time which decreases the likelihood of developing skin irritation. Potentially, the integrated patch could be a good clinical tool for pediatric applications and management of perioperative pain and chronic pain in patients suffering from diabetes, cancer, and herpes zoster infection and can be used in home care settings due to its ease of application.

**ASSOCIATED CONTENT**

Supporting Information
Mechanical and penetration properties of microneedle integrated transdermal patch. This material is available free of charge via the Internet at http://pubs.acs.org.

**AUTHOR INFORMATION**

Corresponding Author
*Tel.: +65 6516 7519. Fax: +65 6779 1554. E-mail: lkang@nus.edu.sg.*

**Author Contributions**

**Notes**
The authors declare no competing financial interest.

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