

Development of lidocaine coated microneedle product for rapid local analgesic action

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Ying Zhang, Ken Brown, Kris Siebenaler, Amy Determan, Daniel Dohmeier, Kris Hansen, 3M Drug Delivery Systems Division, 3M Center, St. Paul, MN, 55144

Abstract

The purpose of this study was to demonstrate rapid (~1 min) lidocaine delivery from coated microneedles using 3M's solid microstructured transdermal system (sMTS) for prolonged, local analgesic action. Formulations comprising lidocaine and dextran were developed for uniform and thick coating on the microneedles. The amount of lidocaine coated onto the microneedles was determined by high performance liquid chromatography (HPLC). To assess drug delivery and dermal pharmacokinetics, the lidocaine-coated microneedles were inserted into domestic swine. Skin punch biopsies were collected and analyzed to determine the lidocaine concentration in the skin using HPLC-mass spectrometry (LC-MS). The lidocaine dissolves rapidly off of the microneedles and into the skin such that a 1 min wear time associated with microneedle patch achieves or exceeds the estimated therapeutic threshold in the skin (100 ng/mg, obtained by measuring the total amount of lidocaine and prilocaine in the skin following 1 hr application of EMLA (Eutectic Mixture of Local Anesthetic) cream). When co-formulated with 0.03 wt% of the vasoconstrictor-epinephrine, the concentration of lidocaine in the tissue was maintained above 100 ng/mg for approximately 90 minutes.

Experimental methods

Arrays: The sMTS arrays were injection molded from a medical grade polymer and were of a surface area of approximately 1.27cm². 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.

Coating: The lidocaine was coated onto microneedle arrays using a dip-coating process with formulations listed in Table 1. The coated microneedles were allowed to dry for 1 hr at 35°C and examined microscopically to assess coating uniformity. For in-vivo application, each array was attached to a 5 cm² adhesive patch with double-sided medical adhesive, and configured within a proof-of-concept applicator system.

In Vivo study: Female Yorkshire swine, weighing between 10-45 kg, were anesthetized with isoflurane gas. The hair was first clipped using an electric shaver followed by shaving with a wet multi-blade disposable razor and shaving cream. Arrays were applied to the swine with a spring-loaded applicator that provides an impact velocity of ~8m/s; the arrays remained in contact with the skin for 1 to 5 minutes. The patches were removed and a cotton ball moistened with phosphate buffered saline (PBS) 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 was collected from the site of array application at the designated time following removal of the array. The used arrays were examined using an optical microscope to observe any remaining drug on the arrays which was also assayed by HPLC.

EMLA applications were completed using two different iterations. In iteration 1, EMLA was applied on the swine ribs and covered with an occlusive dressing for a pre-determined application time of 15, 30 or 60 min. At the appropriate time, the cream was cleaned from the skin prior to collection of a 4 mm skin biopsy. In the second iteration, EMLA was applied to the ribs for 60 min. Then a 4 mm skin biopsy was collected following a 15, 30 or 60 min delay after patch was removed and skin was cleaned.

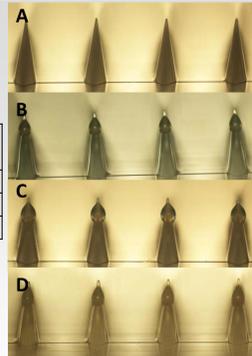
Analytical method: To assay drug content of the arrays, coatings of microneedles were desorbed into an appropriate volume of diluent (0.1% TFA in H₂O) and analyzed using HPLC.

Lidocaine was extracted from skin biopsy punches using enzymatic digestion. Protein precipitation was used to prepare the digested skin samples for analysis using a liquid chromatograph coupled to a triple quadrupole mass spectrometer.

Lidocaine coated arrays

Table 1 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



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).

- The formulation appears to be uniformly located on the upper 30-50% of the needles.
- The number of dips increased both the thickness of the coating and the drug amount coated onto the microneedles.
- The arrays showed very good stability in coating appearance and initial loading either at 4 weeks at elevated temperature (45°C/75%RH, 90.1±8.3 μg/array) or 28 weeks at room temperature (25°C/60%RH, 95.6±5.4 μg/array) vs day 0 (94.0±9.0 μg/array).

Dissolution and release of coated lidocaine: 1, 2 or 4 min

Microscope imaging of Formulation A, 2dips 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).

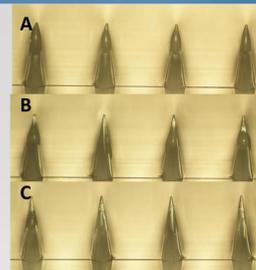
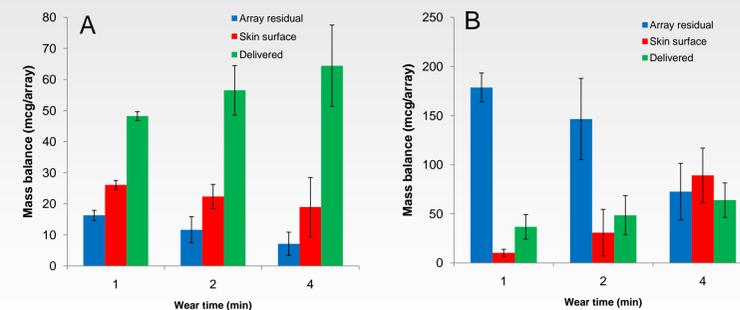


Table 2 Summary of delivery efficiency following in vivo testing

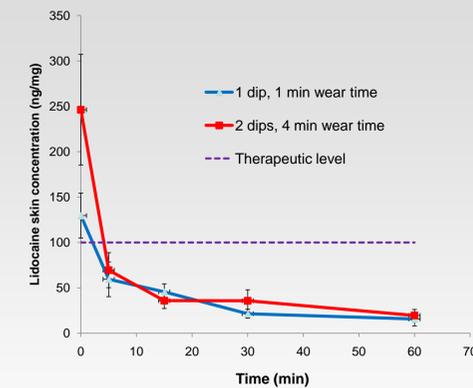
Number of dips	Wear time	Initial loading (mcg/array)	Delivery efficiency (%)
1	1	90.5±14.5	53.3±1.6
1	2	90.5±14.5	62.4±8.8
1	4	90.5±14.5	71.1±1.4
2	1	225.7±13.4	16.3±5.5
2	2	225.7±13.4	21.5±8.8
2	4	225.7±13.4	28.3±7.8



- Lidocaine delivery efficiency via microneedles was increased with patch wear time.
- The delivery efficiency of lidocaine was decreased with increased number of dips.

Dermal pharmacokinetics of lidocaine-sMTS

Dermal pharmacokinetics of lidocaine delivered via microneedle arrays



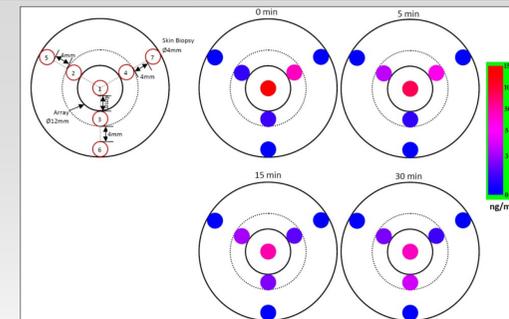
- The estimated therapeutic concentration providing analgesia was 100 ng/mg based on 1 hr application of EMLA.

- The targeted skin concentration was achieved from lidocaine-coated arrays after 1-5 minutes of wear time.

- 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.

Distribution and spread of lidocaine in the skin tissue

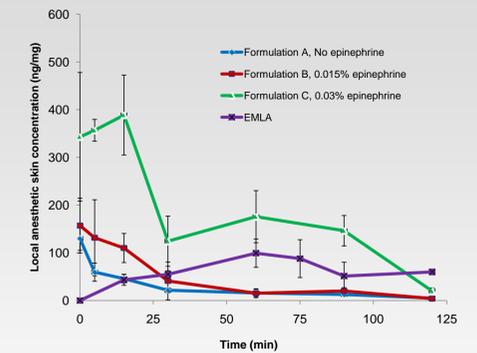
Lidocaine skin concentrations in three regions 0, 5, 15, 30 minutes after patch removal.
Lidocaine loading: 94mcg/array, patch application time: 1min



- There is very little lateral transport of the lidocaine through the skin once the array is removed.
- No significant amount of lidocaine was detected in the underlying tissues.
- Lidocaine is rapidly absorbed into the capillaries around the site of administration and cleared from the skin.

Addition of epinephrine as a local anesthetic adjuvant

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



- The epinephrine did not change the lidocaine loading and the amount of lidocaine delivered to the skin.

- Addition of epinephrine significantly slowed down the lidocaine transport from the patch application site, presumably by decreasing local blood flow.

- When 0.03% epinephrine was formulated and delivered with lidocaine, lidocaine levels in the skin were maintained above 100 ng/mg for approximately 90 minutes much longer than when lidocaine was delivered alone.

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 minute) 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 while maintaining the rapid onset of action associated with lidocaine. Altogether, this study shows that the lidocaine-sMTS product produces comparable duration of analgesia and provides substantial improvements over conventional creams with respect to the rate of onset.

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