

Hollow Microneedle Delivery of a therapeutic dose of Methotrexate and Humira® advantages of intradermal delivery over conventional routes

Kris J. Hansen, Leonard Chu, Simmon Schaefer, Scott A. Burton 3M Drug Delivery Systems, 3M Center, St. Paul, MN 55144

Abstract

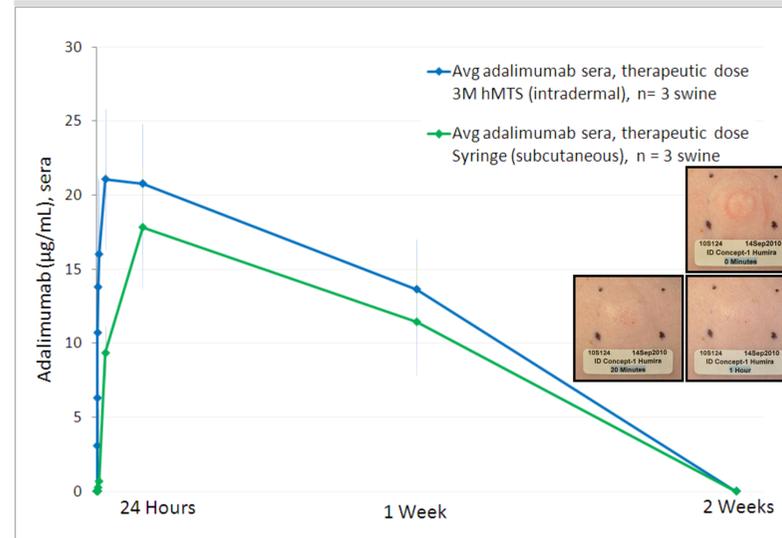
Purpose: Microneedles provide a means of delivering proteins, peptides, vaccines, nanoparticles, and liposomes into the skin which cannot be accomplished using traditional transdermal delivery technologies. Development of this technology for the delivery of therapeutic doses of many drugs provides the opportunity to evaluate intradermal delivery against more traditional routes such as subcutaneous injection or oral delivery. 3M is developing a family of hollow microneedles devices (hollow Microstructured Transdermal System (hMTS)) that provide intradermal delivery of 0.5-2mL of liquid formulation into the dermis. The hMTS devices were evaluated for delivery of therapeutic doses of methotrexate and of Humira® in to swine. In this work, we quantitatively compare the PK associated with delivery of a therapeutic dose of methotrexate via oral, IV and hMTS delivery and of Humira® via hMTS and subcutaneous injection. Mapping of the local lymphatic bed via high volume delivery of methylene blue is also demonstrated.

Methods: Therapeutic doses of select APIs were administered to swine with the hMTS device or via a conventional delivery route. Blood samples were collected from all animals and analyzed to determine blood levels of the drug. A dilute solution of methylene blue is delivered via hMTS. Lymphatic capillaries and local lymph nodes, selectively stained following delivery were excised from the swine following sacrifice.

Results: The hMTS delivery of methotrexate resulted in a PK profile statistically identical to that achieved via IV injection and a greater than 40% increase in AUC versus oral delivery. The intradermal delivery of the Humira® via the hMTS device resulted in an increase in the average AUC by 20% and a shift in observed Tmax from 24hr (SC injection) to 4hr (hMTS). Methylene blue delivery via hMTS shows rapid and selective uptake of the dye by lymphatic capillaries with transport to the local lymph node.

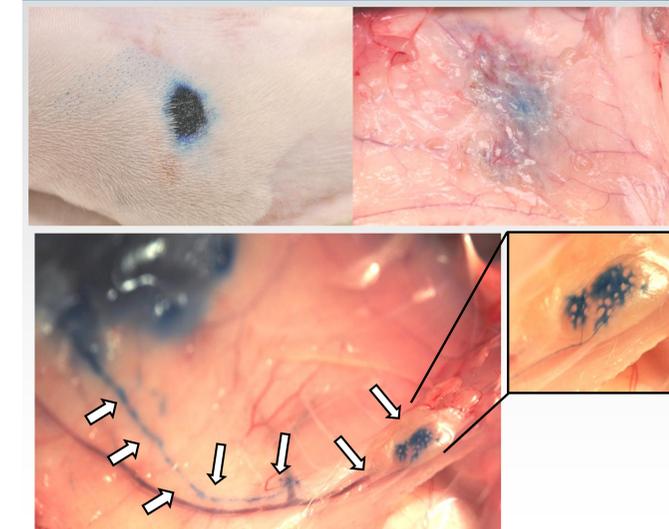
Conclusions: Intradermal delivery via 3M's hMTS enables the evaluation of alternate delivery route for certain drugs that may suffer from limits associated with traditional delivery forms such as poor gastric tolerability or low AUC. Intradermal delivery provides fast and efficient access into the lymphatic system, the main portal to systemic delivery for injectable drugs.

Results: PK Profiles of Humira® via hMTS and via subcutaneous injection in swine



- 1) Cmax:** Through 4.5 hours, blood levels associated with hMTS delivery were significantly higher than those associated with SC injection.
 - 2) Tmax:** Blood levels for hMTS subjects reached a plateau between 4.5 and 24 hours; all SC injection Profiles evidenced a Tmax at 24 hours.
 - 3) AUC:** Although not statistically significant, the AUC associated with the hMTS delivery was 20% higher than the average AUC associated with injection.
- These differences likely result from faster, more complete lymphatic uptake of this large protein in the dermis versus the subcutaneous tissue. The dermis is a very dynamic environment with a high rate of fluid exchange and a high density of lymphatic and circulatory capillaries.

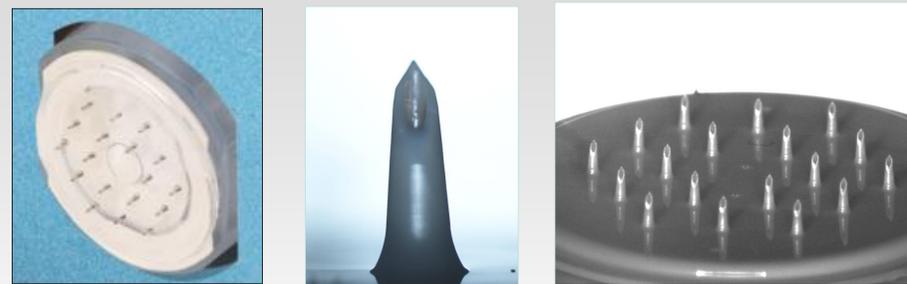
Results: Sentinel Lymph Node Staining in rats



A 1mL volume of 0.1% methylene blues was delivered intradermally to rats. The top figures show the delivery (exterior and interior) confirming that the staining agent stayed in the dermis. Upon sacrifice and dissection, it is possible to observe the methylene blue in the lymphatic capillaries and, ultimately in the draining (subiliac) lymph node. Analysis of the non-draining lymph node, which occurred at the same time post-delivery, showed no evidence of methylene blue staining.

When performed in humans using conventional staining technique, multiple intradermal injections of a higher concentration of methylene blue may be required for sentinel lymph node staining.

hMTS Fully Integrated Device High volume (up to 2mL) Intradermal Delivery



The standard hMTS device uses a cartridge for injection and can deliver up to 2mL of fluid into the skin, typically in less 5 minutes. Delivery is accomplished via the hMTS array (above) that is characterized by 16-18 hypodermic-shaped microneedles. The microneedle array is injection molded out of medical grade plastic. The hMTS device is designed to be easy to use and, given the potential therapeutic advantages associated with ID delivery, may be ideal for administration of biologics.

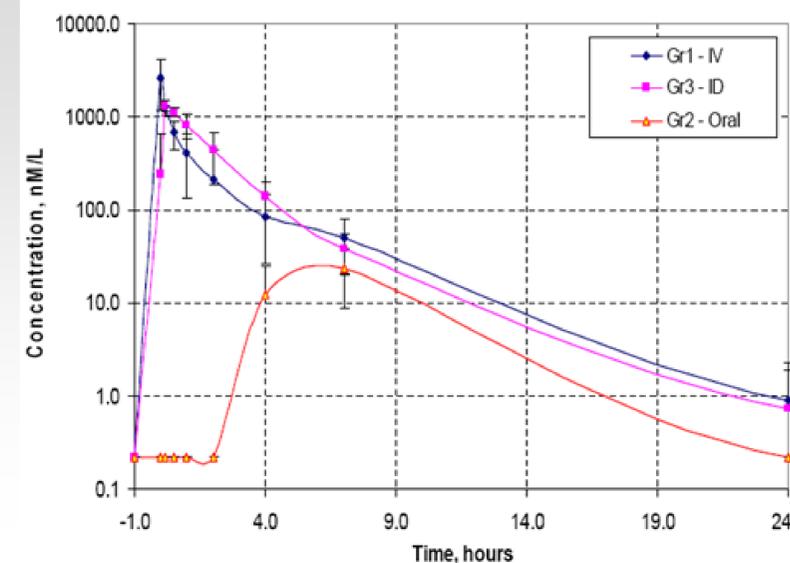
Results: PK Profiles of Methotrexate via hMTS, IV, and oral in swine

When taken in relatively high doses as prescribed as part of a chemo therapy regiment to treat cancer, methotrexate has adverse side effects including severe nausea and hair loss.

In humans, methotrexate has a dose-dependent bioavailability, ranging from about 17-40%.

The Cmax and Tmax for hMTS delivery of methotrexate are closely matched with those observed for IV delivery. Measured bioavailability relative to IV administration is 101%, indicating complete and rapid absorption of the drug. By comparison, the relative oral bioavailability for the methotrexate is about 40%, a close match to values measured by others in humans.

Following hMTS delivery, the site of administration had a yellowish tint that faded after a few hours. Other than that, skin tolerability to the hMTS administration was very good.



Looking Ahead: User and Human Factor Trials are On-going thru Development Summary of US/UK Trial, Aug 2012

Trial Design: RA patients, rheumatologists, and rheumatoid nurses were interviewed, 1:1, for about 1 hour each. They were questioned about RA as a disease state, treatment regimes and preferences. Subjects were shown microneedle arrays and prototype hMTS devices to handle in a simulated use environment. They were asked about their preferences and impressions of the devices.



General impressions (direct quotes):

- "Just think it's so much easier and the concept of not having a big syringe that you press in"
- "It is so simple and I don't think there would be any pain involved in it"
- "this is a lot more simple than doing an injection... easy to give yourself or someone else"
- "the needle array is much less scary than a single needle... I don't want to see it, I don't want think about it"
- "would feel better than if I had to inject myself with a needle... this is less intimidating"
- "if it reduced pain or gave me better quality of life I would jump through hoops"

Acknowledgments

The authors wish to thank Ryan Simmers, David Wirtanen, Ron Krienke, Allan Bohlke, Jim Christensen, Joann Oesterich, Chris Webb, Mary Hopp, Tom Fenn and Tonya Grunwald.

