

High Volume Intradermal Delivery in Humans using a Fully-Integrated Hollow Microneedle Device

Scott A. Burton, Nicole Sullivan, Patrick Young, David Wirtanen, **Kris J. Hansen** 3M Drug Delivery Systems, 3M Center, St. Paul, MN 55144

Abstract

PURPOSE: This clinical study compared the discomfort and skin tolerability of intradermal and subcutaneous fluid injections.

METHODS: Three 1 mL injections (5% dextrose) were administered to the anterior thigh through two different 3M prototype hollow microneedle devices (hMTS-D1 and hMTS-D2; insertion depth 600-650 μm) and through a commercial syringe autoinjector (Autoject 2; 1.2 cm insertion depth). Both hollow microneedle devices utilized a polymeric microneedle array with 18 structures shaped like mini-hypodermic needles. hMTS-D1 is a single module containing an applicator, API cartridge and a means of delivering the fluid into the skin. hMTS-D2 utilizes a separate applicator to apply the API cartridge and a standalone delivery pod that provides a means of delivering the fluid into the skin. The syringe autoinjector contained a tuberculin syringe with 27 gauge needle, filled with sterile formulation and then fit into the device, as prescribed in the package insert. Subjects rated pain and described sensations at needle/microneedle insertion (application), during and after delivery, and device removal. Following fluid delivery, the application site was inspected and scored with respect to surface fluid, bleeding, blanching, bruising, erythema and edema.

RESULTS : The pain scores associated with various stages of administration were uniformly low. Within each event, the pain scores were not significantly different between the three devices. Erythema and edema scores were low and resolved quickly. No hMTS delivery sites evidenced bruising. Leakage was minimal for all devices, although each device had one confirmed outlier (higher leakage). The subcutaneous average delivery time associated with the Autoject-2 was 4 seconds; and intradermal delivery time with the hMTS-D1 was 76+/-44 seconds and hMTS-D2 device was 41+/- 19 seconds.

CONCLUSION: The results demonstrate the usability and tolerability of high volume intradermal fluid delivery using 3M's hollow microneedle delivery devices. The devices enable fast, efficient, high volume intradermal delivery with minimal site reactions. These devices offer a viable delivery alternative to subcutaneous autoinjectors.

Results: Delivery Performance and Pain Perception, hMTS vs SC injection

| | Avg Delivery Time | # with fluid post device removal | Avg. Leakage | Adhesion |
|--------------------|-------------------|----------------------------------|--------------|------------|
| hMTS-1 | 76+/-44 sec | 4 | <1μL* | All – good |
| hMTS-2 (PT) | 41+/-19 sec | 9 | <1μL** | All – good |
| Autoject 2 | 4 sec (est) | 9 | <1μL* | NA |

NA = not applicable

* One outlier (statistically verified) was removed; in both cases, outlier was < 10μLs

** One outlier (statistically verified) was removed; volume was not measured but > 10μLs

No missing, fractured or broken microneedles were observed in either hMTS device.

No irritation associated with hMTS adhesive

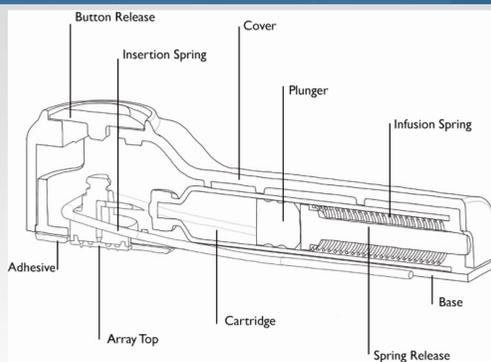
- Non-needle-phobic subjects referenced an 11-point analog pain scale*: 0 = No Pain; 5 = Moderate Pain; 10 = Worst Pain Imaginable

*From: Management of Cancer Pain, Clinical Guideline Number 9, AHCPR Publication 94-0592, March 1994

- All pain scores low
- No statistical differences in patient experience scores

| | Application | End of Delivery | Device Removal | 10min Post | 4 Hrs Post |
|--------------------|-------------|-----------------|----------------|------------|------------|
| hMTS-1 | 2.1 (1.2) | 0.5 (0.8) | 0.4 (0.6) | 0.2 (0.4) | 0 |
| hMTS-2 (PT) | 1.6 (1.6) | 0.4 (0.5) | 0.2 (0.4) | 0.2 (0.4) | 0 |
| Autoinjector | 1.5 (0.8) | 0.9 (1.2) | 0.6 (1.2) | 0.3 (0.6) | 0 |

Materials: hMTS-D1 (shown), hMTS-D2, Autoject-2®; 1mL of 5% Dextrose in Water



The hMTS array is 1.27cm in diameter and has 18 mini-hypodermic needles, each about 950μm long.



Subjects self-administered a 1mL injection of D5W using two different hMTS devices (hMTS-D1 is shown here) and the Autoject 2® - and autoinjector with a 1.75 cm long, 27Ga needle. Administrations were to the upper thigh and injection order was randomized.

Results: Skin Tolerability, hMTS vs SC injection

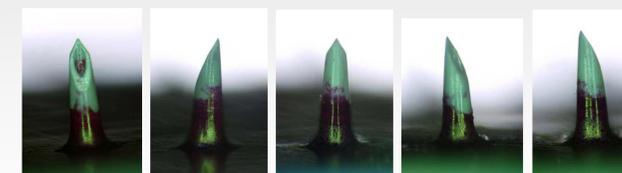
| | Erythema, 0 Minutes | Erythema, 24 Hours | Edema, 0 Minutes | Edema, 4 Hours |
|--------------------|---------------------|--------------------|------------------|----------------|
| hMTS-1 | 1.0 (0.6) | 0.6 (0.5) | 1.1 (0.4) | 0 |
| hMTS-2 (PT) | 0.6 (0.5) | 0.6 (0.5) | 1.1 (0.5) | 0 |
| Autoject 2 | 0.3 (0.6) | 0.1 (0.4) | 0.1 (0.3) | 0 |

Erythema/Edema (0-4) : 1= Slight, barely perceptible; 4 = Severe

| | Bruising | Skin Stripping | Skin Cuts |
|--------------------|----------|----------------|-------------------------|
| hMTS-1 | 0 | 0 | 0 |
| hMTS-2 (PT) | 0 | 0 | 2 (from edge of device) |
| Autoject 2 | 1 | NA | 0 |

NA = not applicable

- Thru 2 hours, higher edema/erythema scores for ID delivery
- Depth of penetration for hMTS devices ~ 0.07 cm versus 1.2 cm for autoinjector



POST-INSERTION (red is residual dye)

Comparison: Autoinjector versus hMTS devices

| | Autoinjector | hMTS |
|-----------------------------|-----------------------|-------------------------|
| Delivery Compartment | Subcutaneous | Intradermal |
| Injection depth | ~ 1.2 cm | ~ 0.07 cm |
| Delivery Mechanism | 1 needles | 18 needles |
| Admin Surface Area | 0.03mm²/0.03mm² | 0.14mm²/1cm² |
| Needle OD | 27 Gauge (~415μm) | 31 Gauge (~280μm) |
| Delivery Time, 1mL | 4-10 secs (estimated) | 40-180 secs (estimated) |
| Max Delivery Volume | 1-1.5mL | 2mL |

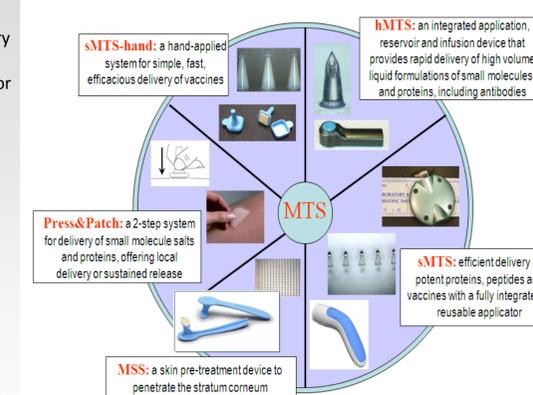


Conclusions

3M's hMTS device is a fully integrated intradermal delivery system designed for high volume (up to 2mL) intradermal delivery that provides a means of achieving intradermal delivery of a therapeutic dose of a biologic therapy. The device is designed for self-administration and includes an adhesive patch so that it can be worn during the brief administration time.

Despite the high delivery volume, subjects in the placebo clinical trial reported low levels of discomfort associated with delivery. Although, predictably, erythema and edema scores were higher for hMTS delivery, overall, skin tolerability to high volume intradermal delivery was very good.

Previous work has demonstrated the potential to achieve faster absorption and higher bioavailability for some molecules with hMTS delivery versus subcutaneous injection. Given the good tolerability of high volume ID delivery seen in this study, there is great interest in pursuing hMTS as an alternative delivery system for some biologic compounds currently administered by subcutaneous injection.



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