The Transdermal Delivery of Human Growth Hormone (hGH)

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Introduction

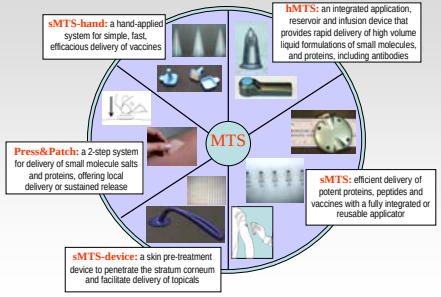
The stratum corneum is the outermost layer of the human skin. It is composed of a horned layer of dead cells that act as the primary defense against foreign matter entering the body. This layer of skin prohibits the transdermal delivery of molecules larger than 500 Daltons and most salt forms of small molecules. The molecules capable of passing thru the skin usually do so as a result of a concentration gradient and the rate is limited by passive diffusion.

3M has developed a solid microstructured transdermal system (sMTS) composed of 300-1250 microstructures capable of delivering salts of small molecules, and macromolecules such as proteins, transdermally. The work herein describes the transdermal delivery of hGH, a macromolecule, to the systemic circulation and the rapid transdermal delivery of lidocaine-HCl resulting in local skin concentrations associated with an anesthetic effect within a minute of application.

sMTS array prior to coating

sMTS "proof-of-concept" system adhesive patch

3M"s Microneedle Technology



Experimental methods

Arrays

The sMTS arrays were injected molded from a medical grade polymer. The arrays were composed of 366 square pyramid microstructures with a height of 500 microns.

Coating

The API was coated onto the arrays using a dip coating process. The amount of API loaded onto the arrays was controlled by the API concentration in the formulation and by the processing conditions.

Animal methods (hGH)

Male Yorkshire swine, weighing between 10-45 kg, were anesthetized with isoflurane gas. Oesterich blade #50 clippers were used to remove the coarse hair from the ham of the animals. The skin was further shaved with a straight razor and shaving cream. The skin was wiped with IPA prior to patch application. Three patches were applied to the animal. After 10 minutes the patches were removed. Blood was drawn (1mL) at the specified time points.

Animal methods (lidocaine-HCl)

Osterich blade #50 clippers were used to remove the coarse hair from the ribs of the animal. The ribs were further shaved with a straight razor and shaving cream. The skin was wiped with IPA prior to patch application. After the specified wear time the patches were removed. A moist cotton ball was used to swab the application site and then a 4 mm skin biopsy was completed.

Analytical methods

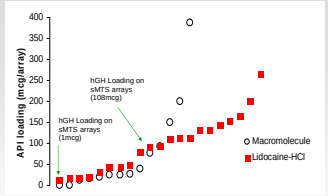
Initial Patch Content: The initial API loading was determined by extracting the API off of the array in 0.5mL to 1mL of buffer. The extraction solution was then analyzed using HPLC-UV. The hGH was quantified on a Zorbax 300SB-C8, 2.1 X 150 mm 5 micron particle size column using a gradient A (0.1% TFA aqueous): B (0.15 TFA in acetonitrile) from 95:5 to 10:90 at a flow rate of 1 mL/min. The lidocaine-HCl was quantified using a Zorbax SB-C18, 3.0 x 150mm, 3.5 micron particle size column using an A:B gradient of 80:20 to 40:60 at a flow rate of 0.5 mL/min.

In-vivo Assays: The concentration of hGH in the blood was quantified using ELISA, R&D Systems (Minneapolis, MN). For lidocaine-HCl, the amount of lidocaine-HCl in the skin biopsy was quantified by first digesting the skin with proteinase K. The digested skin was then analyzed by liquid chromatography coupled to mass spectrometry to quantify the amount of lidocaine-HCl in the sample.

Abbreviations

API – active pharmaceutical ingredient
BSA – bovine serum albumin
ELISA – Enzyme linked immunosorbent assay
EMLA – Eutectic mixture of local anesthetics
sMTS – solid microsturctured transdermal system
Tmax – Time of maximum API concentration in body after dosing
AUC – area under the curve
Cmax – Maximum API concentration in body after dosing
hGH – human growth hormone
SC – subcutaneous injection
TFA – Trifluoroacetic acid

API loading capabilities



•Due to limited availability of hGH, the majority of formulation work with macromolecules was done using BSA as a surrogate protein

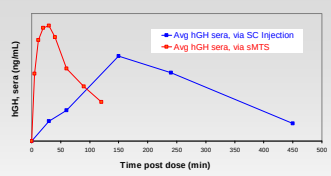
•The therapeutic dose of macromolecules such as hGH can vary from 150 to 800mcg a day

•This graph demonstrates the range of API amounts that can be loaded onto sMTS arrays.

- •Macromolecule loadings of 400 mcg/array have been achieved with sMTS arrays
- •Small molecule loadings of up to 250 mcg/array have been achieved with sMTS arrays

•hGH has been loaded onto sMTS arrays at two different levels, 1mcg and 108mcg per array

Systemic delivery of hGH using sMTS arrays



10X optical microscopy images of hGH coated sMTS arrays prior to application to swine

10X optical microscopy images of hGH coated arrays after application to swine

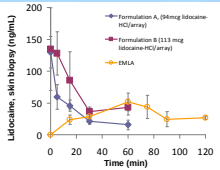
•The delivery of hGH by sMTS provided a higher Cmax than hGH delivered by SC

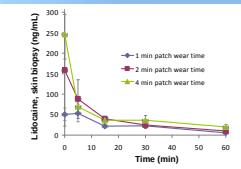
•The delivery of hGH by sMTS provided an earlier Tmax than hGH delivered by SC

•The delivery of hGH by sMTS provided a similar AUC as the hGH delivered by SC

•>80% of the hGH was released from the sMTS arrays

Lidocaine-HCl local anesthetic affect





•Goal of delivering lidocaine-HCl with sMTS arrays is to provide anesthetic effect faster than can be achieved by the commercially available lidocaine cream, EMLA

•Lidocaine can cause cardiac arrest at high levels if taken up systemically by the body, want to provide anesthetic effect with low doses of lidocaine-HCl

•Initial drug loading on the sMTS arrays was not high enough to result in a lethal systemic dose

•Faster transdermal delivery of lidocaine-HCl was achieved when delivered by sMTS as compared to passive transdermal delivery.

•Local skin concentration associated with anesthetic effect occurs within 1 minute of application with sMTS arrays, as compared to 1 hour for EMLA.

Discussion and Conclusions

•Therapeutic levels of macromolecules, such as hGH, have been loaded onto sMTS arrays

•Maximum macromolecule loading achieved to date ~400 mcg/array

•Delivery of hGH by sMTS provides an earlier Tmax and higher Cmax than hGH delivered by SC

•sMTS provides an alternative pharmacokinetic profile for macromolecules, as seen with hGH. This alternative delivery profile may reduce the risk of side effects for certain API's.

•sMTS can be used to deliver small molecule salts that are not capable of passive transdermal delivery, such as lidocaine-HCl.

•sMTS arrays coated with lidocaine-HCl can provide local skin concentrations associated with an anesthetic effect within 1 minute of application