MALDI imaging a new quantitative methodology approach for understanding drug distribution in skin

Delphine MAUX
delphine.maux@galderma.com
Dermatology

• In dermatology the efficacy of a topical drug may be related to its concentration and distribution within the skin.

• 1- Stratum corneum
• 2- Epidermis (100-280μm)
• 3- Dermis (1200μm)
• 4- Deep dermis (1200μm)
• 5- Hypodermis
Dermatology

• In dermatology the efficacy of a topical drug may be related to its concentration and distribution within the skin.

• Key questions:
  – Does the drug reach the target in the skin?
  – To what extent does the drug reach the target?
  – How long does it stay there?

• Approach:
  – Up to now LC-MS-MS analysis (gold standard method) was used to determine the concentration of drug in the different compartments of the skin (stratum corneum, epidermis, dermis, ....)
Bioanalytical support

• Bioanalytical support, a continuous improvement journey

question: how quantitative is quantitation using imaging technology?

» Few examples of one technology, MALDI-FT-ICR

note: Image performed in collaboration with Imabiotec
Skin samples analysed by MALDI-FT-ICR MS
Calibration curve approach

- Few approaches regarding calibration (calibration curve)

On tissue dilution range

- Ion suppression
- Skin area specific (normalised by pseudo IS)

Mimetic tissue dilution range

- Ion suppression
- Skin compartment specific

Mixed, spiked & reconstituted tissue

Tissue Extinction Coefficient calculation

In-solution dilution range

- Ion suppression
- Multi organ analysis

Patent FR1154731
US Patent pending

Patent FR1152334
US Patent pending
Example: formulation choice

- **Context**

  - **Formulation 2**
    - 0.2% solution

  - **Formulation 3**
    - 0.5% gel

- **Study**
  - In vitro skin penetration study performed (Franz cell)
    - Area treatment = 2 cm²
    - Biopsy punch size = 3.5 mm
  - Quantification performed by:
    - LC-MS-MS
    - MALDI FT-ICR-MS

Which is the best formulation?

Deep Dermis

*After 2 strips remove excess*
Example: formulation choice

- LC-MS-MS analysis results

Formulation 2 appears to be better than 3
Example: formulation choice

- MALDI-FT-ICR MS results

Quantification results: MALDI-FT-ICR MS similar to LC-MS-MS
Example: formulation choice

• Added value of image

- Formulation 3 is able to reach the deep target
- The best formulation is number 3

Deep Dermis

Which is the best formulation?
Example: exposure at site of action

• Context

• Study
  – Treatment:
    • Area = large surface
    • Repeated application (3 weeks, one application per day)
    • Biopsy punch size = 3.5 mm
  – Quantification performed by:
    • LC-MS-MS
    • MALDI FT-ICR-MS

Does the formulation provide the right exposure at the target?
Example: exposure at site of action

- LC-MS-MS analysis results

- High level of exposure using LC-MS-MS, but highly variable !!!
- Quantification level seems enough regarding EC$_{50}$
Example: exposure at site of action

- MALDI-FT-ICR MS results

- Similar level of exposure using MALDI-FT-ICR MS
- Exposure highly variable too !!!!
Example: exposure at site of action

- Added value of image

- Dermis

Does the formulation provide the right exposure at the target?

- Localized “only” in the hair follicle area
- Exposure is directly linked to the number of hair follicles in the biopsy
- Not enough exposure at the target !!!!
Quantification by MALDI FT-ICR-MS versus LC-MS-MS

- Overview of internal correlation
  - $200 < \text{compound MW} < 700$
  - Skin samples

Quantification by LC-MS-MS (3 sections per biopsy)

Quantification by MALDI FT-ICR-MS

Works on all compounds tested / all skin matrix tested
Quantification using MALDI FT-ICR-MS versus LC-MS-MS

- Overview of internal correlation
  - $200 < \text{compound MW} < 700$
  - Skin samples

Should we use MALDI-FT-ICR to quantify compounds in tissue? Can we validate the analytical method and workflow?

Quantification by MALDI FT-ICR-MS

(3 sections per biopsy)
Scientific “validation” approach using MALDI FT-ICR-MS

• Based on previous results: Why not?
  – Key points should be verified:
    • Specificity regarding compound response
    • Matrix effect (calibration approach)
    • Reproducibility
    • Accuracy
    • Drug stability in tissue during sampling, storage, and analytical workflow
Summary of using MALDI FT-ICR-MS

• MALDI FT-ICR-MS shows similar quantitation compared to the “gold standard” LC-MS-MS approach
• The added value of using this technique is the image produced
• The image shows the extent of exposure at the target site (e.g. dermis)
• By using MALDI FT-ICR-MS we can answer the key questions:
  – Does the drug reach the target in the skin?
  – To what extent does the drug reach the target?
  – How long does it stay there?
And …..???

MALDI Matrix Assisted Laser Desorption Ionization, (Imabiotech, Lille)

SIMS Secondary Ion Mass Spectrometry Imaging

DESI Desorption Electrospray Ionization Imaging

Infra-red spectroscopy : Quantum cascade lasers imaging (QLR-IR with Daylight solution, US) Coherent Anti-Stokes Raman Scattering (CARS) microscopy imaging. (Fresnel Institute, Marseille).

Laser Micro Dissection Liquid Vortex Capture ESI-MS (Oak Ridge National Laboratory)
Thanks

DMPK team

MALDI imaging: collaboration with Imabiotech
contact@imabiotech.com

Sylvain.ghilini@galderma.com