Potential of Microdialysis in Evaluation of Topical Drug Products

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45 minutes – what to do?
Today’s talk

- Microdialysis: the principle
- Microdialysis for use in the skin
  - All research areas
  - Skin penetration
  - Impact of disturbed skin barrier function on penetration
  - Bioequivalence of topicals
- Which skin penetration situations are suitable for microdialysis methodology – and which aren’t
- Recent developments
  - Topically applied corticosteroids (revisited)
  - Probe depth matters!
- Conclusion
Microdialysis technique

Inlet: perfusate

Outlet: dialysate
Microdialysis principle

Perfusate flow

Nylon tube

3 cm accessible microdialysis fibre
0.22 mm OD
Probe material: an example
Probe types: Linear and concentric
Probe types for use in the skin and subcutaneous tissue

- **Linear or concentric design**
- **Linear (laboratory made)**
  - Low flux 2-10 kDa
  - High flux 40-70 kDa
  - Plasmapheresis membranes 3000 kDa
- **Concentric design (fixed area)**
  - Commercially available 20 and 100 kDa
Analysis of microdialysates

separation techniques

HPLC
gas chromatography
electrophoresis

direct assays

RIA
REA
enzyme methodology
LC-MS, LC-MS/MS
Topical drug administration
Factors affecting recovery I

- **Substance specific**
  - MW
  - Configuration
  - Lipophilicity
  - Protein binding
  
  \[ \text{inverse relation } MW \sim RR \]

- **Related to choice of instrumentation**
  - Probe design: linear, concentric
  - Probe material: cut-off; “pore size”
  - Probe surface area
  - Perfusate: protein content, lipids
  - Perfusate flow rate: inverse relation flow \sim RR
Factors affecting recovery II

• *In vitro* recovery $>>$ *in vivo* recovery
  • Tortuosity factor
  • Blood flow
  • Tissue metabolism
  • Temperature

• Important to standardize all parameters accessible to standardization!
Calculations of absolute ("true") tissue concentrations

- Limited to situations where tissue levels are at steady state
  - No net flux
  - Stop flow / low flow
  - Retrodialysis by drug*
  - Retrodialysis by calibrator

- Relative values (study design with multiple probes in each animal/person) will often suffice

- The *in vitro* performance of the probe and the *in vivo* loss (retrodialysis) should be established prior to a human study
Research areas employing microdialysis sampling in the skin

- **Allergy, inflammation**
  - Histamine
  - Substance P
  - IL 6
  - IL 8
  - Bradykinin
  - Prostaglandin E2
  - Protein extravasation

- **Metabolism**
  - glucose (up to 3 w)

- **Plastic surgery**
  - Flap survival

- **Pharmacokinetics**
  - **Systemic drugs**
    - Antibiotics
    - Corticosteroids
    - Transdermal drug delivery
    - Effect of ischaemia, diabetes
    - Drug penetration in tumour processes

- **Pharmacokinetics**
  - **Topical drugs**
    - Effect of formulation
    - Effect of iontophoresis
    - Effect of alterations in blood supply
    - Effect of barrier perturbation
    - Comparison in vitro-in vivo
    - Ex vivo-in vivo
Microdialysis in the skin: Issues!

- The impact of the probe depth in the skin
  - Low variability (e.g. $0.98 \pm 0.16 \text{ mm}$)
  - Intended variation in probe depth if impact to be demonstrated

- The invasiveness of microdialysis
  - Insertion trauma – lasts 60 minutes (Groth, 1998)
  - Bruising at the site of insertion, infections very rare

- Sources of variability

- The feasibility of sampling very lipophilic, low concentration drugs in a formulation
  - The competent skin barrier and more

Later...
Variability: Systemic administration study

- Investigation of dermal drug levels by MD technique
  - 10 healthy volunteers
  - 4 MD probes in volar forearm
  - 2 g. acetyl salicylic acid (ASA) p.o.
  - Sampling every 20 min for 4 h

(Benfeldt et al. Acta Derm-Venereol 1999)
Variability I: Systemic administration study
Variability II: Where variability occurs

Retrodialysis by calibrator: Recovery of $^3$H-salicylic acid added to the perfusate.

Concentration of $^{14}$C-Salicylate in dialysates sampled after topical application of $^{14}$C-Butyl salicylate.

(L Simonsen et al., Eur J Pharm Sci 2004)
Topical drug administration

= drug molecule
Barrier perturbation study

18 healthy human volunteers

- Barrier perturbation
- Quantification by non-invasive methods
- Local anesthesia
- 8-10 MD probes in the dermis
- Topical salicylic acid 5% w/v in ethanol
- Sampling every 20 min for 4 h

(Benfeldt, Serup and Menné. Br J Derm 1999; 140: 739)
Old school microdialysis...
The effect of barrier perturbation on cutaneous drug penetration

Eva Benfeldt

PQRI Workshop March 2013
Bioequivalence of topicals

Topical formulations are considered bioequivalent when

- the active ingredient and its strength is the same in both formulations
- the inactive ingredients in the generic topical product are the same as the innovator product
- the new product is labelled for the same condition of use as the existing product
- both formulations produce comparable drug concentration-time curves

(AAPS report 1998)
Dermal Pharmacokinetics of Microemulsion Formulations Determined by In Vivo Microdialysis

Mads Kreilgaard¹,²

Received November 7, 2000; accepted December 11, 2000

Purpose. To investigate the potential of improving dermal drug delivery of hydrophilic and lipophilic substances by formulation in microemulsion vehicles and to establish a reliable pharmacokinetic model to analyze cutaneous microdialysis data.

Methods. After a topical application of microemulsions, commercially available creams, and a hydrogel, unbound cutaneous concentrations of lidocaine and prilocaine were determined by in vivo microdialysis in rats. Recovery was monitored during the experiments via retrodialysis by calibrator.

Results. The presented pharmacokinetic model provided an excellent fit of the microdialysis concentration-time curves with reliable estimation of absorption coefficient and lag time. The microemulsion formulations were shown to increase the absorption coefficient of lidocaine more than eight times (753 μg/l/min) compared with a conventional oil-in-water emulsion-based cream (89 μg/l/min) and prilocaine hydrochloride almost two times (8.9 μg/l/min) compared with hydrogel (5.2 μg/l/min).

Conclusions. The microemulsion formulations can be applied to increase dermal drug delivery of both the hydrophilic and lipophilic model drug. The pharmacokinetic model presented in this report is, to the author's knowledge, the first example in the literature, providing reliable estimation of cutaneous absorption coefficient and lag time from microdialysis data of topically applied substances.

Influence of a Microemulsion Vehicle on Cutaneous Bioequivalence of a Lipophilic Model Drug Assessed by Microdialysis and Pharmacodynamics

Mads Kreilgaard¹,³ Michiel J. B. Kemme², Jacobus Burggraaf², Rik C. Schoemaker², and Adam F. Cohen⁷

Received January 2, 2001; accepted February 12, 2001

Purpose. The aim of the study was to investigate the cutaneous bioequivalence of a lipophilic model drug (lidocaine) applied in a novel topical microemulsion vehicle, compared to a conventional oil-in-water (O/W) emulsion, assessed by a pharmacokinetic microdialysis model and a pharmacodynamic method.

Methods. Dermal delivery of lidocaine was estimated by microdialysis in 8 volunteers. Absorption coefficients and lag times were determined by pharmacokinetic modelling of the microdialysis data. Subsequently, the anaesthetic effect of the treatments was assessed by mechanical stimuli using von Frey hairs in 12 volunteers.

Results. The microemulsion formulation increased the cutaneous absorption coefficient of lidocaine 2.9 times (95% confidence interval: 1.9/4.6) compared with the O/W emulsion-based cream. Also, lag time decreased from 110 ± 43 min to 87 ± 32 min (P = 0.02). The compartmental pharmacokinetic model provided an excellent fit of the concentration-time curves with reliable estimation of absorption coefficient and lag time. A significant anaesthetic effect was found for both active treatments compared to placebo (P < 0.02), but the effect did not diverge significantly between the two formulations.

Conclusions. The microemulsion vehicle can be applied to increase dermal drug delivery of lipophilic drugs in humans. The microdialysis technique combined with an appropriate pharmacokinetic model provides a high sensitivity in bioequivalence studies of topically applied substances.
MD in bioequivalence studies

SC
EP
D
SCF

= drug molecule
The penetration of lidocaine 5% cream vs. ointment formulation, evaluated by microdialysis

Lidocaine study

- 8 healthy volunteers (4 male, 4 female)
- Participation on 2 separate study days
- DAY 1: Lidocaine 5% cream
- DAY 2: Lidocaine 5% ointment
  - Left: 2 probes in 2 areas (duplicate)
  - Probe insertion without local anesthesia
  - Sampling every 20 min for 5 h
  - Right: 3 areas, strip at 30 min, 2 h, control

...to formulation applied 2-5 mg/cm²
Ultrasound scanning measuring skin thickness and probe depth
RESULTS FROM ONE VOLUNTEER
Lidocaine concentration in dialysates
Lidocaine penetration from the 2 formulations

![Graph showing lidocaine penetration over time for cream and ointment formulations.](image)

![Bar graph showing AUC lidocaine 0-300 min for cream and ointment formulations.](image)
## MD: Pharmacokinetic comparison

<table>
<thead>
<tr>
<th></th>
<th>AUC&lt;sub&gt;t-5&lt;/sub&gt; ng/ml*min</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; ng/ml</th>
<th>Lag time min</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lidocaine 5% cream</strong></td>
<td>15983 6317-444835</td>
<td>112 44-3132</td>
<td>18 12.7-23.6</td>
<td>243 214-272</td>
</tr>
<tr>
<td><strong>Lidocaine 5% ointment</strong></td>
<td>3309 1271-8612</td>
<td>27.5 11-71</td>
<td>40.6 15.1-66.1</td>
<td>275 260-290</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>0.018</td>
<td>0.030</td>
<td>0.08</td>
<td>0.0058</td>
</tr>
</tbody>
</table>
Analysis of MD variables
Where is the variability introduced: Relative size of coefficients of variation

- Between probes
- Between areas
- Between subjects

Parameters:
- **AUC**
- **C_max**
- **Rate**
Sources of variability: conclusion

- The following factors did not significantly increase variability (MD):
  - Age
  - Gender
  - Room temperature and humidity
  - Dose applied
  - Probe depth in the skin
  - Skin thickness

- Main source of variability identified as individual skin barrier properties
## Study size estimates for BE studies of topical formulations

### BE study with two formulations in each subject

<table>
<thead>
<tr>
<th>Probability (%)</th>
<th>Limits of variation (%)&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Two probes per area</th>
<th>Three probes per area</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>&lt;25 (80–125%)</td>
<td>20</td>
<td>14</td>
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<tr>
<td>80</td>
<td>&lt;33</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>80</td>
<td>&lt;50</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>90</td>
<td>&lt;25</td>
<td>27</td>
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<td>90</td>
<td>&lt;33</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>90</td>
<td>&lt;50</td>
<td>10</td>
<td>7</td>
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<td>95</td>
<td>&lt;25</td>
<td>33</td>
<td>23</td>
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<td>95</td>
<td>&lt;33</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td>95</td>
<td>&lt;50</td>
<td>12</td>
<td>8</td>
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</tbody>
</table>

<sup>1</sup> Limits of variation for BE studies of topical formulations.
<table>
<thead>
<tr>
<th>BE study with one formulation in each subject</th>
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<tbody>
<tr>
<td>80</td>
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BE, bioequivalence.
Number of subjects required for BE determination of topical formulations in healthy human volunteers, based on intraindividual (upper) and interindividual (lower) variabilities.
Conclusion from lidocaine study

- Different pharmacokinetics depending on formulation
- Intersubject (skin barrier associated) variability dominated overall variability
- BE studies feasible in 18 subjects (best case)
Metronidazole study

- 14 healthy volunteers (7♀ & 7♂)
- 3 metronidazole cream formulations:
  - Flagyl® 1%, Metronidazole® 1%, Rozex® 0.75%

- Non-invasive measuring methods:
  - TEWL
  - Erythema

- Ultrasound:
  - Probe depth
  - Skin thickness

Study I: Set up

Left forearm

Dermal microdialysis

3 penetration areas

3 probes/area = 9 probes

Flow rate: 1.173 µl/min

Sampling every 20 min for 5 hours
Metronidazole in dialysates

![Graph showing metronidazole concentration over time for different creams.](image)
BE evaluation by DMD: variability issue
Conclusions from metronidazole study

- Variability was higher than anticipated
- May depend on formulation?
- Composition of formulations as well as concentration of active was not the same
- Methodology still relevant
  - But mid-study analysis for correction of no of subjects needed
  - Or in vivo pilot study
Ketoprofen gel study

Figure 4 Mean dialysate concentration-time profiles (± SD) (n=18)

Experimental: Four probe insertions, 4 application sites, 1 probe per site, probes were 3 cm apart, probes covered approximately 2 quarters of the volar aspect of the forearm of each volunteer, 18 subjects, Formulation: Fastum® gel.

Conclusion from ketoprofen study

- Gel formulation applied in excess gave very low variability
- Perhaps “infinite dose” is better than finite?
The effect of a disturbed skin barrier function

(Ortiz PG, Hansen SH, Shah VP, Menne T, Benfeldt E. Contact dermatitis 2008;59:23-30)


Using the same probe, perfusate and topical MTZ formulation (Flagyl 1%)
Study II: Set up

Left forearm
Dermal microdialysis
2 penetration areas
2 probes/area = 4 probes
Flow rate: 1.173 µl/min
Sampling every 20 min for 3 h
Study III: Set up

Left forearm
Dermal microdialysis
2 penetration areas
2 probes/area = 4 probes
Flow rate: 1.173 µl/min
Sampling every 20 min for 3 hours
Study II and III: Dermal concentration of MTZ

Dermal Concentration of Metronidazole sampled by Microdialysis

Results from study II and III

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Concentration (ng/µl)</th>
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<tbody>
<tr>
<td>0</td>
<td>Healthy skin</td>
</tr>
<tr>
<td>10</td>
<td>Irritant Dermatitis</td>
</tr>
<tr>
<td>30</td>
<td>Uninvolved skin</td>
</tr>
<tr>
<td>50</td>
<td>Atopic Dermatitis</td>
</tr>
</tbody>
</table>

Eva Benfeldt
PQRI Workshop March 2013
Study II and III: AUC sampled by microdialysis

Results from Study II and III

Dermal concentration of metronidazole sampled by Microdialysis

Concentration (ng/µl*min)

Healthy skin

Irritant Dermatitis

Uninvolved skin

Atopic Dermatitis

p= 0.0002

p=0.004
Study II and III: Conclusion

- Microdialysis sampling in irritant dermatitis as well as atopic dermatitis was perfectly feasible
- Variability even decreased in irritant dermatitis
- The location of endogenous skin disease may add extra variability due to variability between anatomical regions
Figure 1. Aciclovir \((n = 8)\) and penciclovir \((n = 29)\) dialysis following absorption through normal (vasoconstricted) skin over time. Time 0 is the time of application of topical penciclovir (Vectavit\textsuperscript{®}) or aciclovir (Zovirax\textsuperscript{®}). Results are presented as mean concentrations ± SEM. (Morgan, Renwick and Friedmann, Br J Derm 2003;148:434)
...the competent skin barrier...

**Figure 4.** Dialysis of aciclovir \((n = 5)\) and penciclovir \((n = 7)\) following absorption through skin tape stripped to glistening over time. Results are presented as log mean concentration ± SEM with time.

*(Morgan, Renwick and Friedmann, Br J Derm 2003;148:434)*
..still something to worry about!

Fig. 1. Individual concentration–time curves of acyclovir in the skin (cutaneous microdialysate) after topical application of 5% acyclovir cream on 2 cm² areas of skin with stratum corneum partially removed in eight healthy male volunteers.

(Klimowicz, Farfal and Bielecka-Grzela, J Clin Pharm Ther 2007; 32: 143)
..but there is good news

Figure 3. The concentration-time profiles of ACV topically applied on pig skin. Three ACV topical formulations (3%) were applied on the dorsa of pigs at a dosage of 0.2 g/cm² for 2 h. Consecutive microdialysate samples were collected every 30 min in a period of 4 h. Real-time ACV concentration was measured by HPLC. Data are presented mean ± SD (n = 12).

(Wei HL et al, Drug Dev and Industrial Pharm 2012;38(7):785-91)
Microdialysis and topical formulations II

- Many topically active drugs are
  - Very lipophilic (corticosteroids) (log P 3.5-4.5)
  - Very very lipophilic (tacrolimus, pimecrolimus) (log P 6.8+)

- Some of them are
  - Very potent and/or hormones - thus present in low (0.25%, 0.1%, 0.03%) concentration in the formulation

- So if a formulation contains a very very lipophilic drug of interest at a low concentration...
Mission Impossible
Recent developments

Remakes of... challenging studies and unfinished business
CP sampled by DMD in humans in vivo

**Figure 3.** Mean concentration of CP in dermal microdialysates following application of the CP solution at t=0 (n= 10).

Ex vivo microdialysis
Feasibility study: ex vivo microdialysis
Impact of probe depth

Impact of probe depth

**Fig. 3.** Concentration of BA (mean ± SD) in dialysates, sampled hourly by DMD during 12 h (n = 22). The concentrations are shown separately for the 3 different probe depths.

**Fig. 5.** The relationship between the probe depth and the AUC of BA sampled over 12 h. A linear regression analysis shows a negative correlation ($r^2 = 0.5$) and a statistically significant difference in mean depth of the three probe levels (p value <0.001).

Overall conclusion: Microdialysis for in vivo (human) studies of topicals

- The methodology is not suitable for all drugs
- Study design should acknowledge intersubject variability
- Variability may be different between studies due to drug or formulation characteristics
- A thorough pre-study work-up and modifications of the set-up can overcome “partial unsuitability”
- Variability and validation are still important issues
Regulatory outlook on microdialysis methodology
Regulatory outlook I

- FDA has actively sought information, presentations and co-operation with MD researchers
- Little is known about how much MD is used in pre-application work in industry
- Submission of MD studies is encouraged by the FDA
- European counterpart slower to act
Regulatory outlook II

21 CFR 320. Bioavailability definition:
...and becomes available at the site of action...

- Approval of topical drug products
  - Clinical study
  - Surrogate markers
    - HPA axis
    - Vasoconstriction
  - DPK method rejected as FDA standard for BE
Regulatory outlook III

• Microdialysis has been used as a part of a formulation optimization programme

• MD cannot replace clinical trial as yet

• FDA has requested both pre- and post approval MD data to support in vivo bioavailability trials

• MD is in line with the Critical Path Initiative (FDA 2004)
• Microdialysis, which does measure drug in solution in skin, can supply in vivo data in terms of absorption and, should there be sufficient absorption, pharmacokinetic studies may also be performed.
• The usefulness of data produced in this manner will be evaluated on a case by case basis by the relevant regulatory authority.
• The sponsor developing a topical formulation using these techniques should seek scientific advice from the concerned regulatory authority before conducting such trials.

(Mugglestone C, Mariz S and Lane ME. The development and registration of topical pharmaceuticals. Int J Pharm 2012:435;22–26)
AAPS-FDA Workshop White Paper: Microdialysis Principles, Application, and Regulatory Perspectives

Chandra S. Chaurasia, PhD, RPh, Markus Müller, MD, Edward D. Bashaw, PharmD, Eva Benfeldt, MD, PhD, Jan Bolinder, MD, PhD, Ross Bullock, MD, PhD, Peter M. Bungay, PhD, Elizabeth C. M. DeLange, PhD, Hartmut Derendorf, PhD, William F. Elmquist, PhD, Margareta Hammarlund-Udénæs, PhD, Christian Joukhadar, MD, Dean L. Kellogg Jr, MD, PhD, Craig E. Lunte, PhD, Carl Henrik Nordström, MD, Hans Rollema, PhD, Ronald J. Sawchuk, PhD, Belinda W. Y. Cheung, PhD, Vinod P. Shah, PhD, Lars Stahle, MD, PhD, Urban Ungerstedt, MD, PhD, Devin F. Welty, PhD, and Helen Yeo, PhD

Keywords: Microdialysis; regulatory aspects; tissue pharmacokinetics

Journal of Clinical Pharmacology, 2007;47:589-603
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Key papers II


Review

Application of Microdialysis in Pharmacokinetic Studies

William F. Elmquist\textsuperscript{1,3} and Ronald J. Sawchuk\textsuperscript{2}

The AAPS Journal 2006; 8 (2) Article 30 (http://www.aapsj.org).

Themed Issue: The Role of Microdialysis in Pharmacokinetics and Pharmacodynamics
Guest Editors - Markus Mueller and Ronald J. Sawchuk

Microdialysis Versus Other Techniques for the Clinical Assessment of In Vivo Tissue Drug Distribution
Submitted: November 21, 2005; Accepted: March 1, 2006; Published: April 14, 2006

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Microdialysis sampling and the clinical determination of topical dermal bioequivalence

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Bioequivalence of Topical Formulations in Humans: Evaluation by Dermal Microdialysis Sampling and the Dermatopharmacokinetic Method

Eva Benfeldt¹, Steen H. Hansen², Aage Vølund³, Torkil Menné¹ and Vinod P. Shah⁴,⁵,⁶

The aim of this study was to evaluate the relationship between dermal microdialysis (DMD) sampling and the dermatopharmacokinetic method when employed simultaneously for bioequivalence (BE) investigations of topical formulations. Topical lidocaine cream and ointment (both 5%) was investigated in eight healthy human volunteers (four male, four female). On one forearm, four microdialysis probes in two penetration areas sampled for 5 hours, and on the other arm, tape stripping was performed 30 and 120 minutes after product application. Lidocaine content in samples was analyzed by HPLC-mass spectrometry. The two methods were in agreement showing 3- to 5-fold higher lidocaine penetration from cream formulation than from ointment. A rank-order correlation between the two methods was demonstrated for lidocaine contents in microdialysates versus tape strip at 120 minutes, significant for the ointment formulation and for both formulations analyzed together. Analysis of variance demonstrated reproducible lidocaine concentrations in microdialysates with an intra-subject variability of 19% between probes and 20% between the two penetration areas. Thus, intersubject variability accounted for 61% of the variance. DMD sampling proved effective and variability analyses demonstrated the feasibility of BE studies in as little as 18 subjects.

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Journal of Investigative Dermatology advance online publication, 27 July 2006; doi:10.1038/jid.2004.495
Clinical Microdialysis in Skin and Soft Tissues: An Update

Stephan Schmidt, BS, Rebecca Banks, BS, Vipul Kumar, PhD, Kenneth H. Rand, MD, and Hartmut Derendorf, PhD, FCP

Traditionally, plasma or serum drug concentrations have been used for the assessment of bioavailability and bioequivalence. Since in the majority of cases the site of drug action is in the tissue rather than the blood, the use of corresponding free, unbound concentrations in the tissue is a much more meaningful approach. This can become especially important for topical drug administrations, where locally active drug concentrations can significantly exceed free concentrations in plasma. The ability to measure these free concentrations at the site of drug action over time makes microdialysis a very valuable tool for the assessment of bioavailability and bioequivalence. This has been recognized by industry and regulatory authorities, resulting in a recommendation of the microdialysis technique as a tool for bioequivalence determination of topical dermatologic products. The aim of this article is to provide an updated review of the microdialysis technique, its applications in skin and soft tissues, and the resulting impact on clinical drug development.

Keywords: Microdialysis; skin; soft tissues; pharmacokinetics

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Microdialysis Sampling for Investigations of Bioavailability and Bioequivalence of Topically Administered Drugs: Current State and Future Perspectives

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\textsuperscript{a}Department of Environmental Medicine, University of Southern Denmark, Odense, and
\textsuperscript{b}Department of Dermato-allergology, University of Copenhagen, Gentofte Hospital, Hellerup, Denmark

and bioequivalence of topical formulations is concluded by the current regulatory point of view. The future perspective includes further expansion and validation of the use of MD in the experimental and clinical setting as well as in the optimization of the method for regulatory purposes, i.e. the commercialization of bioequivalent, generic drug products.
Thank you for your attention