

Services for the pharmaceutical industry

Tissue specific pharmacokinetic and pharmacodynamic studies



We investigate the actions of drugs, nanoparticles and various delivery systems at the target tissue level – in vivo and ex vivo. We perform tissue-specific pre-clinical and clinical pharmacokinetic (PK) and pharmacodynamic (PD) studies of new drugs as well as mechanistic studies of diseases. We can also investigate bioavailability / bioequivalence and perform metabolomic studies in vivo and ex vivo. For these investigations, we use microdialysis and our patented technique – open flow microperfusion (OFM).

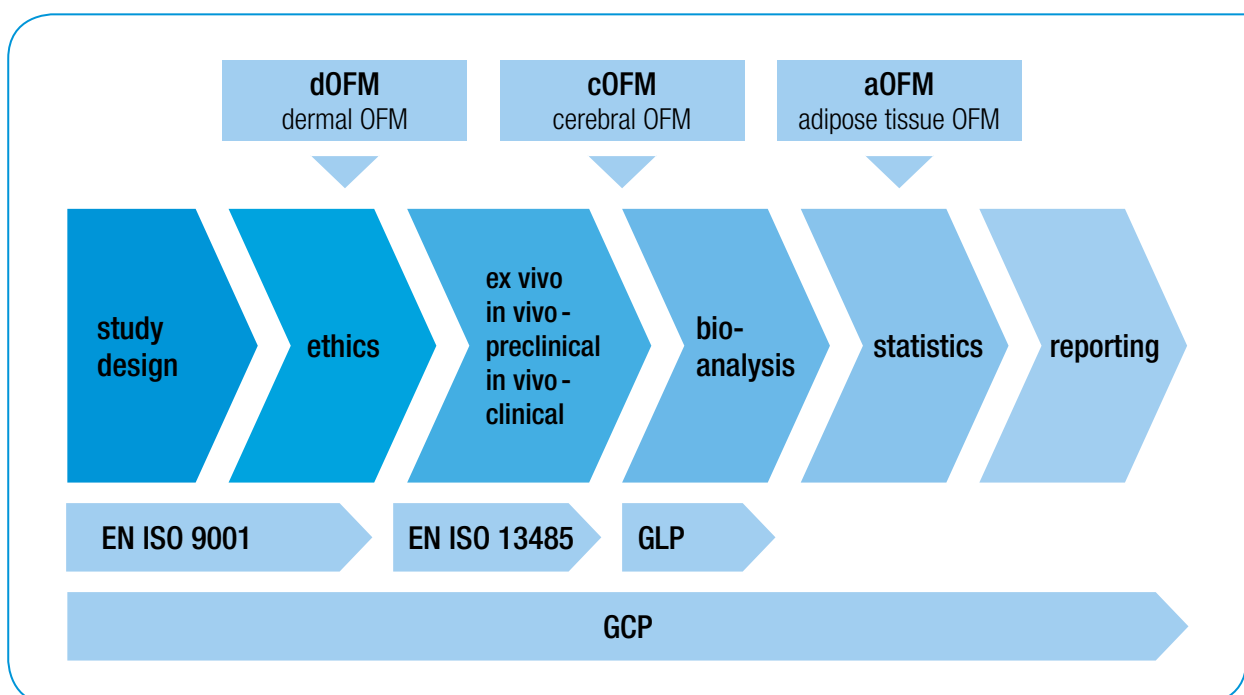
Tissue specific pharmacokinetic and pharmacodynamic studies

Open flow microperfusion - OFM

- OFM is a continuous tissue sampling technique based on minimally invasive, membrane-free probes.
- OFM enables direct contact with the interstitial fluid compartment.
- Interstitial fluid can be collected continuously in vivo and used for simultaneous analysis of multiple substances (e.g. biomarkers) – without any limitation in molecular size (up to cells), lipophilicity or protein binding.
- OFM enables access to the entire biochemical information of the interstitial fluid compartment in vivo, and thus opens up new horizons in pre-clinical and clinical drug testing.

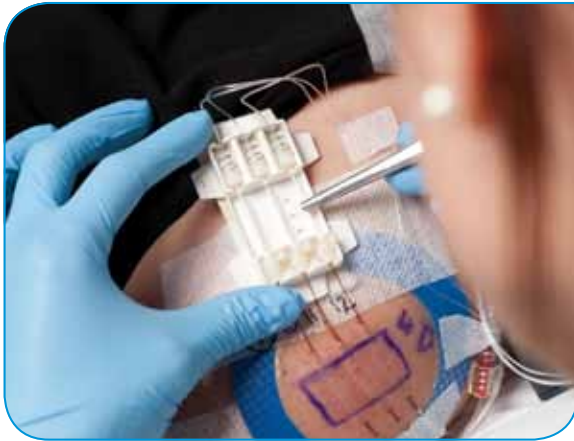
Your One-Stop-Shop for tissue specific PK and PD

- preparing study protocols
- submitting ethical applications
- conducting pre-clinical and clinical trials
- performing and validating bioanalytical procedures
- statistically analyzing the data
- reporting



Tissue specific pharmacokinetic and pharmacodynamic studies

We focus on the target tissue level



- **dermal OFM – dOFM:** transport and effects of drugs in the dermis after topical or systemical application; e.g. topical glucocorticoids and systemic antibodies with psoriasis



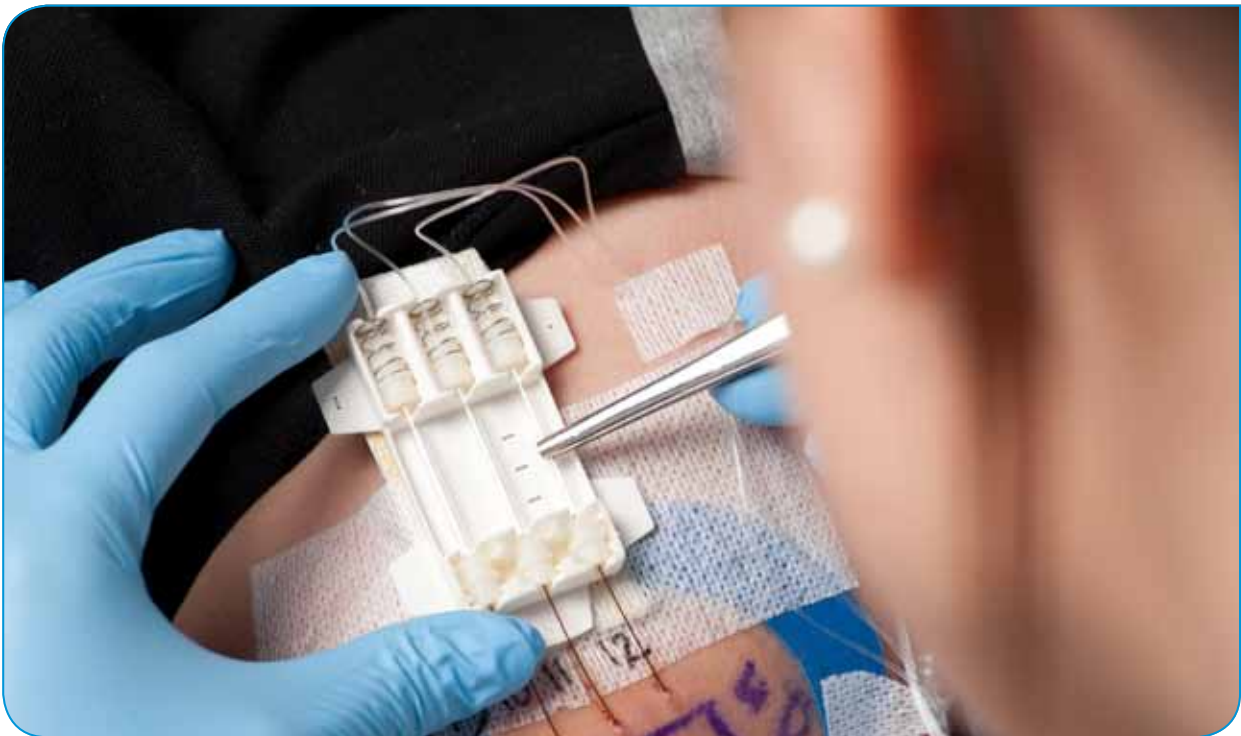
- **cerebral OFM – cOFM:** transport over blood–brain–barrier (BBB), dose-response with bypassing BBB, monitoring of BBB function; e.g. highly lipophilic neuropharmaceuticals



- **adipose tissue OFM – aOFM:** transport and effects of drugs in adipose tissue; e.g. insulins

Tissue specific pharmacokinetic and pharmacodynamic studies

dermal OFM – dOFM



dOFM provides PK / PD information for dermatological substances directly from the site of action. dOFM can thus provide valuable information very early in preclinical and clinical phases.

dOFM/aOFM material

- CE-certified dOFM/aOFM probes, pump and accessories for preclinical and clinical use
- minimally invasive membrane free probe with a 0.36 x 15 mm sampling mesh and a 0.5 mm insertion needle
- wearable pump (0.1-10 μ l/min) allowing delta push-pull operation
- 3 OFM probes per pump
- patent for pump and probes pending



dermal OFM – dOFM



Your advantages

- PK and PD of systemically or topically applied drugs can be measured continuously for more than 48 hours at the target site.
- We can tell if a dermatological agent passes the stratum corneum and actually arrives in the target tissue (dermis) at an early stage in a drug's development.
- Testing new formulations in low-dose experiments by topically applying a dermatological agent to very small application area reduces the patient's risk.
- PK data in skin are available much earlier in the drug development process – as early as exploratory clinical phase 1 studies. Highly relevant PK / PD data are available about two years earlier than in the standard drug development process.
- By using several dOFM probes simultaneously in lesional as well as non-lesional sites in a single subject, intersubject variability is reduced and statistical power is raised. Thus, dOFM reduces the required number of study participants, because sufficient data are available at phase 1 of a clinical study, which lowers the risk of having to redesign a drug after a phase 3 clinical trial, where hundreds of study participants have already been assessed.
- Costs and development time can be reduced because the pharmacological profile of a drug is known at an earlier phase in drug development. Companies therefore already learn at a very early stage whether a dermatological agent is a potential therapeutic agent.

Complementary methods

- ultrasound, for verification of probe position and measurement of skin thickness
- skin biopsies, for validation purposes only
- tape stripping, for proteomics
- suction blister, for validation purposes only

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cerebral OFM – cOFM



The blood–brain barrier (BBB) is the natural protective shield of the brain. It restricts the exchange between blood and brain tissue and prevents harmful substances from accessing the brain. But it may also prevent potential neuroactive drugs from reaching the brain. cOFM can be used to learn if, and to what extent, a pharmaceutical agent crosses the BBB.

cOFM material

- cOFM material only available for preclinical use
- FEP material: 0.8 mm diameter, 5 mm length
- high precision stereotactic implantation
- probe using a removable healing dummy allows tissue regeneration after insertion
- no tissue trauma
- no tissue ingrowth in guide cannula
- patent pending

cerebral OFM – cOFM



Your advantages

- cOFM allows us to see beyond the blood–brain barrier, and to investigate the concentrations and action of a neurological agent directly at the target site – in brain tissue.
- cOFM allows continuous monitoring of PK in intact brain tissue. Our experiments show that 15 days after probe implantation, the BBB has healed and has re-established its function. Thus, cOFM facilitates the continuous measurement of substance transport over the intact BBB.
- BBB function can be simultaneously monitored in any animal to demonstrate the intactness of the BBB.
- cOFM provides daily time-resolved measurements in each subject for up to eight hours at a time, reducing the number of subjects required.
- Costs and development time can be reduced because cOFM provides the pharmacological profile of a drug at an earlier phase in drug development. Companies thus learn at a very early stage whether a neurological agent is a potential therapeutic agent.

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adipose tissue OFM – aOFM



The interstitial fluid of peripheral tissues is now the preferred site for sampling because it can provide a direct picture of what is happening in the tissue. aOFM enables direct access to the interstitial fluid of the subcutaneous tissue milieu.

Your advantages

- Glucose-clamp techniques in combination with aOFM allow investigation of insulin sensitivity as well as concentration of insulin and its effect in the subcutaneous tissue. This advances our understanding of diseases like diabetes mellitus.
- aOFM can be used for reliable PK/PD studies. Such studies are invaluable for pharmaceuticals with a site of action in the subcutaneous adipose tissue as well as for basic research; e.g. in fat metabolism and insulin resistance.
- aOFM can provide valuable information very early in preclinical and clinical phases of drug testing. It can reveal, for example, whether the drug reaches its target after oral, subcutaneous, topical, intravenous or inhaled administration, and allows calculation of C_{max} and T_{max} .

General OFM study portfolio

Clinical in vivo testing

OFM is minimally invasive and enables multiple and prolonged OFM sampling in patients or volunteers with no scar formation or pigment changes. OFM streamlined study designs for PK/PD and bioavailability that can deliver powerful data in a relatively small number of subjects.

Clinical trials are conducted according to ICH-GCP-standards at the local Clinical Research Centre of the Medical University of Graz.



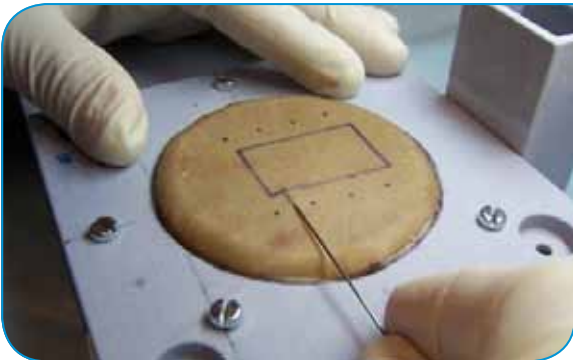
Pre-clinical in vivo studies

In pre-clinical in vivo studies we perform metabolic tests to investigate the pharmacokinetics of active pharmaceutical ingredients (APIs). We examine how the API is absorbed, metabolized and excreted by the body when introduced transdermally, intravenously, intraperitoneally or in other ways. Studies can be carried out on conscious or anaesthetized animals for up to 12 hours.

Our animal studies are performed in cooperation with the Institute for Biomedical Research at the Medical University of Graz.

Animal models: pig/minipig, rat, mouse

General OFM study portfolio



Pre-clinical ex vivo testing in explanted human skin

The skin is obtained from donors undergoing plastic surgery (abdomen, breast). After preparation and cultivation, ex vivo experiments are performed under controlled conditions. We can investigate the absorption and liberation of topically applied active pharmaceutical ingredients (API). Human explanted skin is provided by the Biobank at the Medical University of Graz.



In vitro evaluation / validation / verification

In vitro testing precedes any in vivo or ex vivo study, to ensure reliability of quantitative sampling.

We investigate compound stability in the sample matrices, including freeze-thaw cycles, followed by tests for stability of compound recoveries; i.e., we verify the adsorption-free passage of the compounds from sampling probe to sampling vial by analysing simulated perfusates and test solutions. The obtained data can help prevent misinterpretation of in vivo or ex vivo results.



Bioanalysis

In our GLP certified OFM lab bioanalysis is performed with highly sensitive methods allowing us to analyze microliter sample volumes and low concentrations with state-of-the-art bioanalytical methods.

We develop, optimize, qualify, validate and automate innovative bioanalytical methods for high-throughput analysis.

We have vast experience with various biological matrices (serum, plasma, interstitial fluid, tissue, cell culture).



Quality standards

We set high quality standards for our services and products. As our partner, you can rely on the application of international quality standards right from placing your orders up to delivery of the final product/service. We operate and are certified according to the following guidelines:

- EN ISO 9001
- EN ISO 13485
- GLP – Good Laboratory Practice

Our partnerships for your benefit

We enjoy a synergistic partnership with the Medical University of Graz. Because of our collaboration with the Evidence-Based Medicine Review Center and with the Center for Medical Research (with its first-class laboratories, equipment and trained technical staff), we can provide excellent research services for your benefit.

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