In vitro / ex vivo analyses

Orientating in in vitro/ex vivo analyses are the first steps to develop an optimised drug delivery system. Parameters such as solubility, logD, logP, stability and membrane permeability are the basis for first crucial strategic decisions in order to define the route of administration and the type of delivery system. In addition, orientating bioavailability calculations rely on these data.

ThioMatrix performs for you the following analyses:

**Physicochemical characterisation**
- Solubility studies
- Stability in solution
- Moisture
- logP, logD and pKa
- Isoelectric point and tendency to aggregate
- Protein binding studies

**Stability studies**

*Enzymatic stability studies*

ThioMatrix is well-versed in the performance of enzymatic stability studies. The degradation profile of your drug by various enzymes such as plasmatic enzymes [1], mucosal membrane bound enzymes or secreted intestinal enzymes [2] can be determined within a few weeks. The major cleavage sites within your drug are identified. Such enzymatic stability studies are additionally supported by software, which has been generated within the company, identifying the most likely cleavage sites of your drug. In Fig. 1 the cleavage sites of a peptide drug are shown and in Fig. 2 the degradation of this peptide by elastase as a function of time is illustrated [3]. The gained information represents the basis for:
- first PK estimations
- slightly chemical modifications of the molecule in order to improve its enzymatic stability (e.g. substitution or modification of certain amino acids in case of therapeutic peptides)
- choice of enzyme inhibitors as auxiliary agents if needed

**Snapshot:**

*Physicochemical Characterisations*
*Stability Studies*
*Drug Permeation Studies*
*Formulation Development*
*Bioavailability Studies*
*Common Technical Documents*

- design and development of delivery systems protecting towards an enzymatic attack

**Storage stability studies**

ThioMatrix designs and performs storage stability studies of new dosage forms. Stability studies usually include long-term, intermediate and accelerated testing according to ICH guidelines. Analyses include physical, chemical, biological and microbiological tests. An overview on available storage stability studies is provided in Table 1. Quality is assured by an SMS and E-mail alarm system overnight and during weekends, frequent calibrations, backup climate exposure chambers and a backup generator.

<table>
<thead>
<tr>
<th>Table 1. Overview on storage stability studies</th>
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</thead>
<tbody>
<tr>
<td><strong>Test type</strong></td>
</tr>
<tr>
<td>Storage stability studies</td>
</tr>
<tr>
<td>Stress testing</td>
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</tbody>
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**Drug permeation studies**

In vitro/ex vivo permeation studies allow the reduction of many cost-intensive and time-consuming in vivo studies. In Fig. 3 the accuracy of various prediction models is illustrated. In particular, utilizing freshly excised mucosal membranes under appropriate conditions a very high in vitro – in vivo correlation such as illustrated in Fig. 4 is provided.

The screening of numerous drug candidates can be completed by ThioMatrix within a few weeks. ThioMatrix is specialized on:
- Permeation studies with freshly excised gastric, intestinal, nasal, pulmonary, ocular, buccal and vaginal mucosal membranes

![Fig. 1. Chemical structure of antide and identified cleavage sites for gastrointestinal peptidases. Adapted from Bernkop-Schnürch et al. [3].](image1)

![Fig. 2. Enzymatic degradation of antide caused by elastase applied in physiological concentration at 37 ± 0.5°C. Adapted from Bernkop-Schnürch et al. [3].](image2)

![ThioMatrix Process](image3)
Transdermal permeation studies with porcine skin
Blood-brain-barrier permeability studies utilizing various monolayers
Based on results gained substantial information about the permeation behaviour is provided. This information includes:
- Apparent permeability coefficient (Papp)
- Mechanism of drug uptake
  - transcellular vs. paracellular
  - active vs. passive
  - receptor-mediated vs. receptor-independent
  - involvement of efflux pumps, etc.
- Degree of presystemic metabolism of the drug
- Membrane toxicity
- Impact of permeation enhancers on drug uptake
- Impact of ion pairing on drug uptake
- Impact of efflux pump inhibitors

Formulation development
Formulation development is always an important step in the drug development process. We support our clients’ projects from initial feasibility studies, to highly efficient, optimised drug delivery systems and product development. With our extensive experience, flexible services, and innovative technologies we are well-positioned to put you ahead of your competitors.

ThioMatrix provides clients with the experience, science, and know-how necessary to take their pharmaceutical products to the market. Drug delivery systems developed by ThioMatrix allow you to:
- Improve the bioavailability of your drug
- Improve stability
- Reduce side effects
- Achieve demanded delivery profiles that meet specific therapy requirements
- Select release kinetics
- Sustained drug release
- Targeted drug release
- Improve patient compliance

Mucoadhesion studies
The use of mucoadhesive drug delivery systems allows the improvement in bioavailability of your drug and to prolong its therapeutic action. ThioMatrix is capable of performing mucoadhesion studies via various test systems such as tensile studies or the rotating cylinder method [5]. The gained information shows you:
- The mucoadhesive properties of your delivery system on various mucosal membranes
- The influence of certain excipients on the mucoadhesive properties of the dosage form
- How long your delivery system will likely adhere on a certain mucosa in vivo

In vivo studies
Development of quantification methods
For in vivo studies with a new drug it is essential to establish an accurate and reliable quantification method in order to be able to determine drug concentrations in compartments such as plasma or cerebrospinal fluid even in the picogram per ml range. Based on such quantification methods ADME and PK/PD studies can be performed. ThioMatrix develops validated quantification methods and/or can assist you thereby.

In vivo studies
ThioMatrix designs and performs in vivo studies in various rodent and non-rodent animal models with all types of formulations. Based on the results of such studies drug delivery systems can be further optimised. In particular we are specialised on the in vivo comparison of different formulations. All work performed at ThioMatrix complies with international guidelines such as GLP and ICH guidelines. In addition, all laboratory instruments and test apparatus are permanently in a validated state. Our employees undergo extensive external and internal GLP instruction and training programs.

References

For more information
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