Abstract

Oral drug delivery is the preferred route of administration, due to patient compliance and low manufacturing costs. New drug candidates for oral drug delivery tend to have poor aqueous solubility and early pharmaceutical profiling is needed in drug discovery and drug development of these candidates. *In vitro* screening saves time, money and animal lives if the models are efficient and predictive. In current thesis, the general aim was to perform, investigate and evaluate preclinical *in vivo, in situ* and *in vitro* studies for evaluating oral drug delivery systems in order to assess the importance of supersaturation in the intestinal tract and further to investigate microcontainers as an oral drug delivery.

In the first part of the thesis, the aim was to develop a simulated rat gastric and intestinal media for predictive *in vitro* dissolution studies. The rat gastrointestinal (GI) fluids were characterized in terms of pH, osmolality, bile salt concentration and phospholipid concentration. MALDI-MSI was used for visualizing bile salts and phospholipids, and additionally investigated for mapping the spatial distribution of fenofibrate throughout the rat GI tract (GIT). A two-step *in vitro* dissolution model was developed based on the characterization of the rat GI fluids and the MALDI-MSI. The dissolution of crystalline and amorphous sodium salt furosemide (ASSF) was investigated in the two-step dissolution model. This was performed in order to investigate if a better *in vitro-in vivo* correlation could be seen between the dissolution profile and earlier animal studies. The results from characterizing the rat GIT confirmed, in accordance with existing literature, an increasing pH after the stomach, and constant pH in the small intestine. Bile salts and phospholipids were found at high concentrations in the proximal small intestine and the concentration doubled in the distal small intestine. MALDI-MSI confirmed cholic acid, glycocholic acid and taurocholic acid in the lumen of the small intestine. Phosphatidylcholine was present in the intestinal wall and/or mucus and lyso-phosphatidylcholine was present in the entire cross-section. When investigating fenofibrate distribution throughout the rat GIT with MALDI-MSI, it was detected in the stomach, together with fenofibric acid, indicating hydrolysis of fenofibrate in the stomach.

In the second part of the thesis, the effect of the degree of supersaturation (DS) on drug absorption was elucidated with and without the precipitation inhibitor hydroxypropyl methylcellulose (HPMC) in the perfusate medium. *In vivo* elucidation of apparent DS (aDS) of indomethacin and tadalafil in a single pass intestinal perfusion (SPIP) model, showed that indomethacin was absorbed despite precipitation during a supersaturated state. A higher aDS resulted in a higher

absorption of indomethacin. Adding HPMC to FaSSIF significantly lowered area under the curve ($AUC_{0\text{-}60\ min}$) of plasma concentrations *versus* time of indomethacin. For tadalafil, despite a higher aDS when perfusing with $FaSSIF_{HPMC}$, absorption was not improved.

The third part of the thesis evaluated and compared SU-8 microcontainers with different coatings, which were evaluated *in vitro* and *in vivo* and further compared to microspheres with the same coatings. The two-step *in vitro* dissolution model, developed in part 1 of the project, provided a prediction of the rank order of drug release between the microcontainer formulations with the different coating. Further, the two-step *in vitro* dissolution model predicted release profiles of paracetamol of the microcontainers and microspheres, which correlated to the time (T_{max}) for max concentration (C_{max}) of the *in vivo* pharmacokinetic studies. The SU-8 microcontainers were comparatively assessed as a drug delivery vehicle with microspheres as a control formulation, showing a significantly delayed release both, *in vitro* and *in vivo*, of paracetamol compared to the microspheres.

The fourth part of the thesis studied the *in vivo* performance of biodegradable polycaprolactone (PCL) microcontainers in rats. Biodegradable PCL microcontainers were produced and investigated *in vivo* in rats as an oral drug delivery system, and showed a higher $AUC_{0\text{-}24h}$ compared to the control and a relative bioavailability of 166±116%, suggesting that the PCL microcontainers might exert a mucoadhesive effect, leading to a longer retention time at the absorptive site. Further, the study presented a tendency to a delayed T_{max} compared to the control, indicating a sustained release of the PCL microcontainers.

In conclusion, a two-step *in vitro* dissolution model was developed in order to improve *in vitro-in vivo* prediction. The model is advantageous, since it allows less animal studies and a better understanding of the *in vivo* process. This project has considerably contributed to deepened knowledge of *in vivo* circumstances of the GIT in rats, which is are frequently used laboratory animals, and further lead to development of a better *in vitro* prediction of *in vivo* performance of potential drugs and formulations for oral use. Further, the project has led to more insight in the use of MALDI-MSI as a qualitative method for visualization of spatial distribution of prodrugs and endogenous substances, and laid foundation for further studies on following drugs throughout the GIT. The project has also evaluated drug saturation in the intestinal lumen and gained insight in the mechanisms of absorption of two model drugs. Lastly, the project has contributed to a deepened and improved understanding of *in vivo* performance of SU-8 and PCL microcontainers as an oral drug delivery system, as the first to study biodegradable PCL microcontainers in an *in vivo* model.

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