Absorption, Bioavailability, and Immunogenicity after Subcutaneous Administration: Evaluation of a Subcutaneous Platform within the Open Systems Pharmacology framework

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Objective

- Expand the evaluation of the SC platform's performance in terms of capturing absorption, bioavailability and immunogenicity towards collated reference data for small molecules and TPs.
- Identify key processes for investigated applications and to propose recommendations of use given specific drug characteristics.
- Explore whether and how nonclinical data can increase predictability of clinical SC processes.

Conclusions

As the SC route of drug administration gains popularity there is an increased need for means to support SC specific decisions at different stages of the drug development process. Conducted model evaluations illustrate how predictions, analyses and learn-and-confirm strategies related to drug absorption, bioavailability, exposure, and immunogenic response after SC drug administration can be accomplished.

The outcome of this work illustrates that the proposed open-source platform could serve as a valuable tool across drug classes, including new modalities of treatment, and applications of use.

Background

Subcutaneous (SC) injection is a common route of drug administration for both small molecules and biologics. To support the development of new SC administered drugs, we have previously described a physiologically based model for predictions of SC absorption and bioavailability of small molecules and therapeutic proteins (TPs) including local immunogenicity [1,2].

Given drug program stage and needs, the SC model can be informed by different data sources, and either be linked to a systemic disposition model applying conventional compartmental pharmacokinetics or a whole body physiologically based pharmacokinetic (WB-PBPK) model.

With an aim to provide a general open-source platform applicable across drug characteristics and development phases, we have evaluated the model in respect of pre-clinical to clinical translations, IV-to-SC switch, and immunogenicity.

Data and methods

The evaluation of species translations was based on 7 drugs exhibiting different physicochemical properties with reference data originating from 6 different species. A data set of 31 TPs was used to evaluate model performance of predicting clinical absorption rate and bioavailability of TPs. Implication of local immunogenicity after SC delivery was evaluated using pre-clinical and clinical reference data for 5 biologics. Model sensitivity was performed to identify critical processes given drug characteristics and the specific application. Evaluations included naïve and informed predictions to assess model application at different levels of knowledge and to what level such information could be leveraged to improve results. The results were summarized to establish context driven extrapolation strategies.

All activities were performed within MoBi® aligning to the PBPK implementation in PK-Sim® to allow for full integration in the Open Systems Pharmacology framework [3]. Previously described models for local distribution and absorption after SC administration as well as systemic and local immunogenicity were adopted [1,2,4]. Implementation of the generic distribution model of TPs accommodates for local endosomal uptake, degradation, endothelial trafficking, and FcRn-salvaging [5].

Results

Local unspecific tissue distribution and absorption of small molecules could be informed by systemic disposition and translated across species. SC absorption was influenced by drug properties, response to the injected formulation as well as drug administration factors. Pre-clinical data were superior to standard in vitro measurements for high lipophilic and low soluble compounds.

Based on systemic disposition information, the default implementation predicted AUC and Cmax after SC delivery within 0.80-1.25-fold difference for 60% of investigated TPs. An increased residence time in the local interstitial space was identified as a key attribute for bioavailability, indicating the relevance of processes related to drug mobility. Standard physicochemical properties did not correlate with bioavailability, highlighting a need to better understand and inform the distribution dynamics of TPs in the interstitial space.

The local immunogenicity model successfully captured the correlation between immune response following IV and SC administration. The effects were driven by changes in immune cell differentiation and the memory cell pool, occurring both locally and downstream. In addition to epitope potency this highlighted drug property-dependent dynamics in plasma and SC tissue as a primary driving factor for immunogenic response.

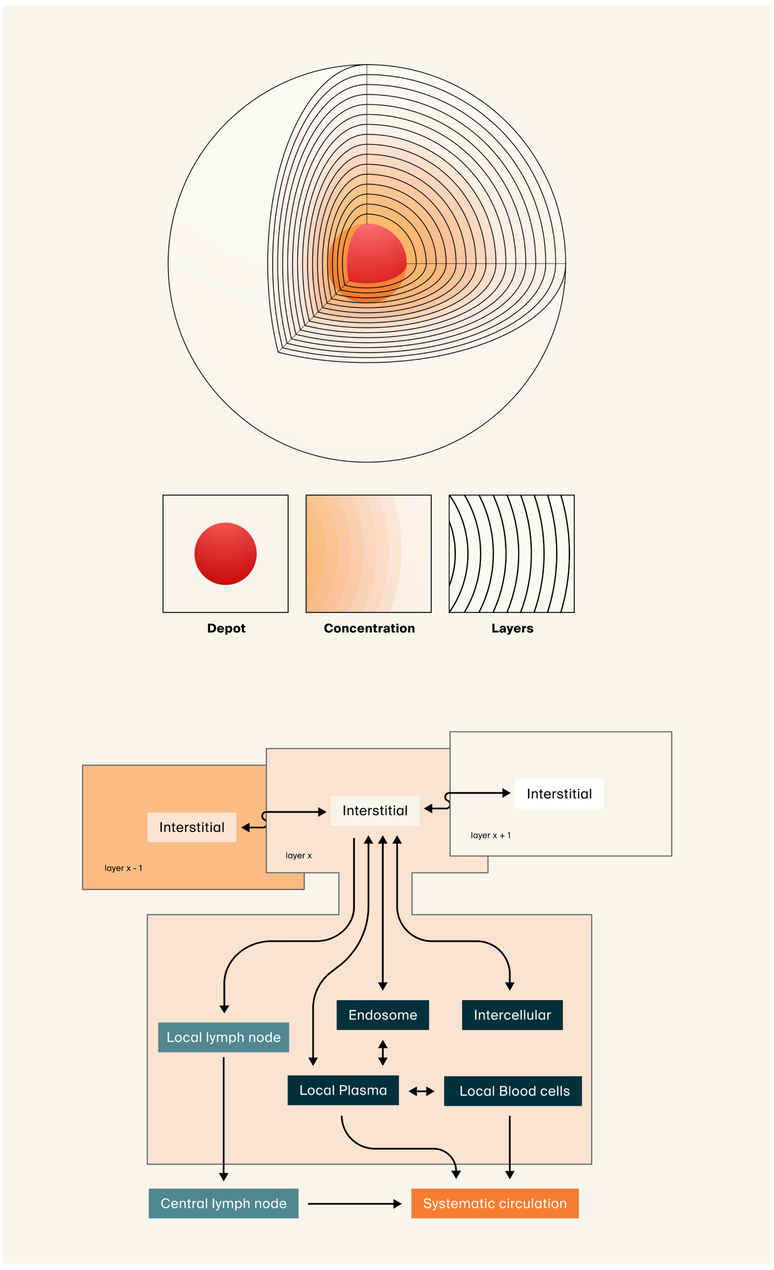

Figure 1. Schematic representation of the subcutaneous absorption and disposition model.

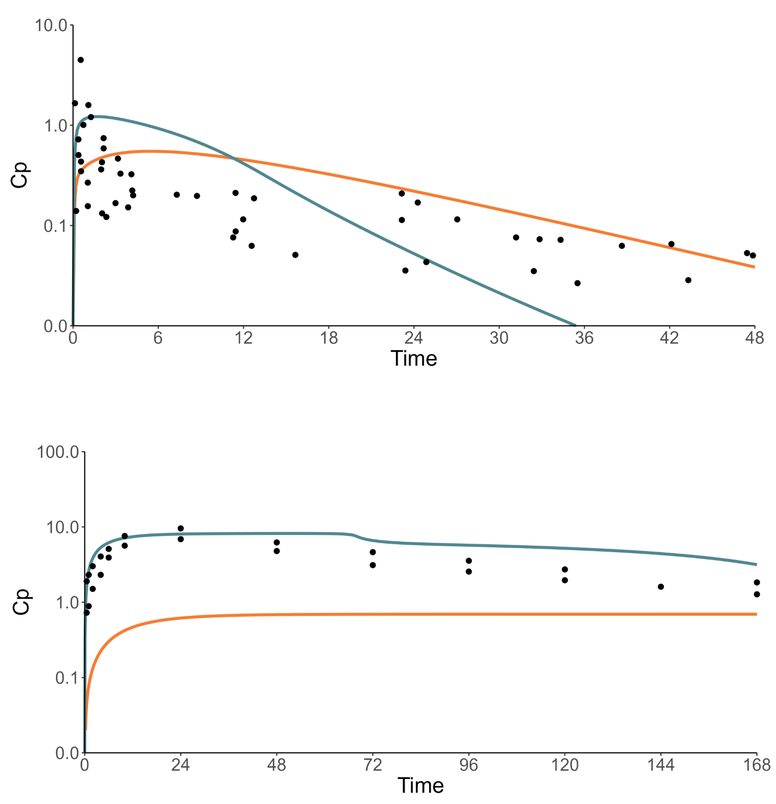

Figure 2. Observed (dots) and model predicted (lines) clinical plasma concentration (Cp) time profiles after subcutaneous administration of a lipophilic small molecule either as a solution (top) or as a long acting injectable (bottom). Subcutaneous absorption predictions were informed by IV disposition analysis and in vitro measurements alone (orange) or both in vitro measurements and pre-clinical data (blue).

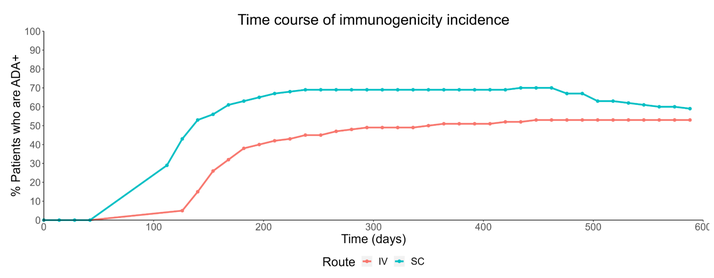

Figure 3. Model simulations for ADA response and drug concentration in 100 virtual patients according to intravenous(IV) or subcutaneous (SC) route of administration for Adalimumab. (Top) Time course of the percentage of ADA+ patients. (Bottom) Comparison of the median through concentration in ADA+ and ADA- populations along the duration of the treatment when administered IV or SC.

References

1. Pellowe. M., Eriksson. J., Chenel. M., Sjögren. E., (2022) A platform for mechanistic modelling of subcutaneous administration with the effect of immunogenicity within the Open Systems Pharmacology framework. PAGE meeting, Ljubljana, Slovenia
2. Pellowe. M., Selvaggio. G., Chenel. M., Sjögren. E., (2023) Mechanistic modelling of bioavailability and local immunogenicity after subcutaneous administration within the Open Systems Pharmacology framework. PAGE meeting, A Coruña, Spain
3. Lippert, J., Burghaus, R., Edginton, A., Frechen, S., Karlsson, M., Kovar, A., ... & Teutonico, D. (2019). Open systems pharmacology community—an open access, open source, open science approach to modeling and simulation in pharmaceutical sciences. CPT: pharmacometrics & systems pharmacology, 8(12), 878.
4. Chen, X., Hickling, T. P., & Vicini, P. (2014). A mechanistic, multiscale mathematical model of immunogenicity for therapeutic proteins: part 1—theoretical model. CPT: pharmacometrics & systems pharmacology, 3(9), 1-9.
5. Niederalt. C., Kuepfer. L., Solodenko. J., Eissing. T., Siegmund. HU., Block. M., Willmann. S., Lippert. J. (2018) A generic whole body physiologically based pharmacokinetic model for therapeutic proteins in PK-Sim. J Pharmacokinet Pharmacodyn 45(2):235-257

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