Application of Modeling as a Tool for Early Derisking of Parenteral Delivery, from the Primary Container to the Tissue

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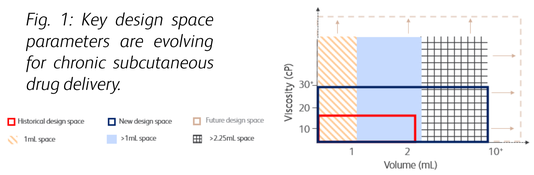
A trend to larger volumes and viscosities

Fig. 1: Key design space parameters are evolving for chronic subcutaneous drug delivery.



The trend to inject larger volumes and higher viscosity drug formulations in a home care setting brings the need to skillfully predict the drug injectability and tissue reactions to optimize acceptance [1] and ensure treatment efficiency. Characterizing the physics involved through conducting and modeling *in vivo* experiments [2,3] is emerging as a pre-requisite to develop *in vitro* and *in silico* tools to better analyze and control the key performance parameters of subcutaneous injections.

Modeling to enable faster time-to-market

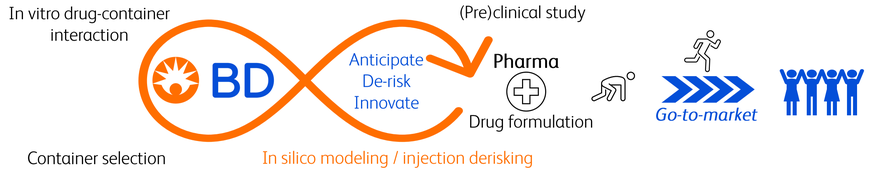
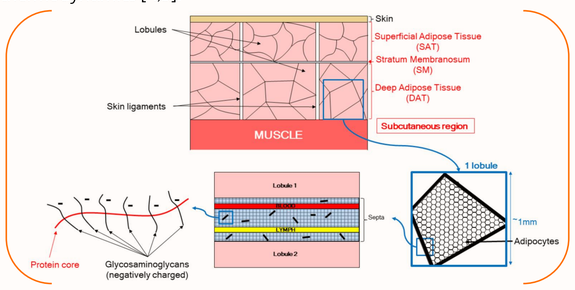


Fig. 2: Understand, Predict, Improve. The use of modeling to get a step ahead in the understanding of drug combination product performances. Make predictions of injection behavior for early de-risking, during product development and to improve system performance.

Leading concepts

Subcutaneous tissue modeling – The importance of a fully coupled electrochemical modeling

The underlying continuum mechanics of injections in subcutaneous tissue involves finite-strain poro-mechanics, where a viscous fluid containing different charged species is injected into an electrically-charged, porous, viscoelastic matrix and absorbed by blood and lymph vessels (Fig. 3). Accounting for these multiphysics couplings in a thermodynamically-consistent framework is a challenge by itself. The governing equations of the coupled problem are written by strictly applying the basic principles of nonequilibrium thermodynamics [4,5].



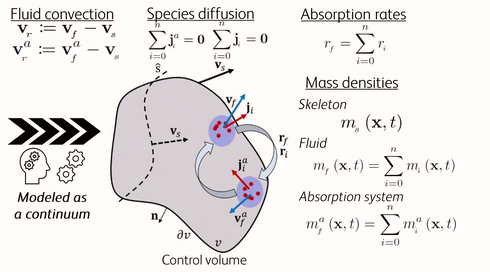


Fig. 3: Schematic of the subcutaneous tissue with different physics involved and its continuous representation [5].

Chemo-mechanical couplings are of high importance for the prediction of subcutaneous injections key performance indicators (pressures, deformations, fluid permeation), as shown in the illustrative case of Fig. 4 (linearized steady-state) [5].

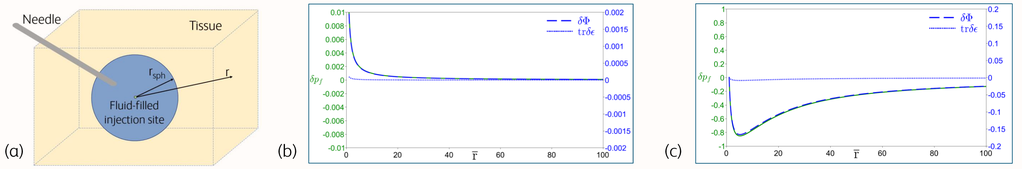
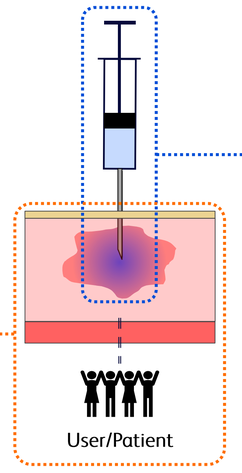


Fig. 4: Non-dimensional perturbations of pressure (δp_f), porosity ($\delta\Phi$) and tissue volume change ($\mathrm{tr}\delta\epsilon$) as function of the distance to injection point. (a) Axisymmetric infinite medium. (b) Without chemo-mechanical coupling: an injection pressure is applied. (c) With chemo-mechanical couplings: same injection pressure, one salt (NaCl), fixed charges, absorption. In this case, the applied pressure cannot overcome the osmotic pressure. Omitting the chemo-mechanical couplings in the modeling could lead to predicting a biased tissue response (e.g. swelling vs shrinking).

The model can then be calibrated against test data or values from literature and coupled to injection device models to simulate realistic subcutaneous injections.



Flow beyond limits

Predictive flow in Pre-Filled Syringes/Autoinjectors/Wearables Injectors – The importance of interfaces and deformation in fluid path

Predictive flow in rigid containers

The application of the governing laws of fluid mechanics and Newtonian equilibrium allows for accurate modeling of flow in a device, as illustrated with an example on a PFS (Fig. 5 and Fig.6).

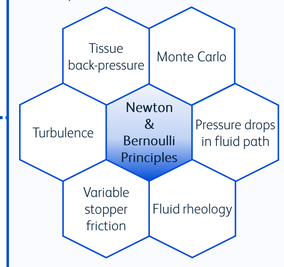


Fig. 5: Physics needed to model the flow in a fluid path.

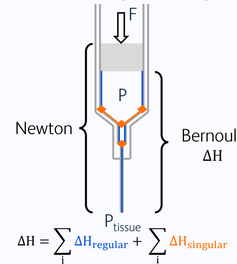


Fig. 6: Fluid path schematic of a PFS. Needle / Others = ~90% /~10%.

Turbulence, pressure drops at junctions in the fluid path, and variable stopper friction, bring valuable corrections to the predictions of injection time or injection force (contribution can be up to ~10%).

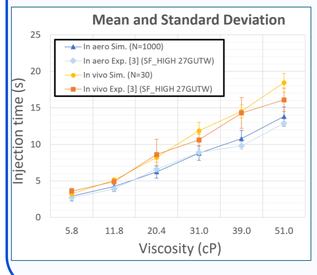


Fig. 7: Preliminary application of injection time prediction for a 2.25mL Pre-Filled Syringe + Autoinjector system. The system is coupled with a linearized version of the tissue model for a comparison with in vivo experimental data of injections in swine. The model shows good agreement with the preclinical data. More work is contemplated to fine-tune the calibration in nonlinear regime.

Predictive flow in a deformable fluid path

When the fluid path is made of deformable components, its transient deformation is modeled during the injection (Fig. 8).

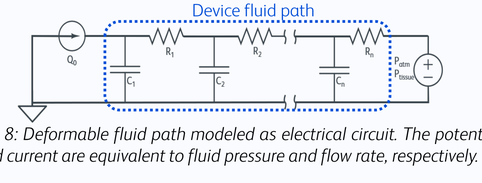


Fig. 8: Deformable fluid path modeled as electrical circuit. The potential and current are equivalent to fluid pressure and flow rate, respectively.

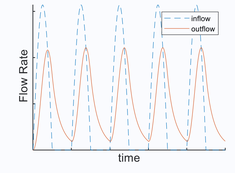


Fig. 9: Difference between inflow and outflow for a flexible fluid path.

Significant deformation of fluid path shifts the exit flow profile, especially in the case of an important transient regime, for example with pulsatile injection. Omitting this contribution can bias model calibrations and predictions relevance.

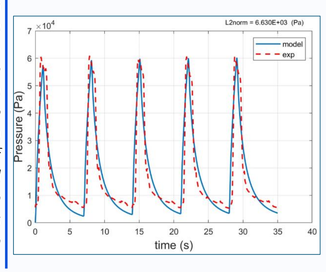


Fig. 10: Example of application of pressure prediction for a pulsatile injection profile in swine. The injection system is coupled with the tissue model, allowing for a comparison with in vivo experimental data of injection in swine. The preliminary calibrated model shows good agreement with the preclinical data.

Key take-away

In silico modeling of subcutaneous injections can be leveraged early in development, prior to pre-clinical studies, to reduce testing burden and predict aspects such as the time and forces required for full dose delivery into tissue and the tissue-injectate-device interactions. Such modeling is a promising tool to understand the injectability of drugs to support the development of injection systems, especially when pushing the design space boundaries of injectate volumes and viscosities.

References

[1] Mathias, N. et. al. (2024). "Towards more tolerable subcutaneous administration: Review of contributing factors for improving combination product design". Advanced Drug Delivery Reviews.
[2] Rini, C.J. et al. (2022). "Enabling Faster Subcutaneous Delivery of Larger Volume, High Viscosity Fluids". Expert Opinion on Drug Delivery.
[3] Woodley, W.D. et al. (2021). "Clinical Evaluation of Large Volume Subcutaneous Injection Tissue Effects, Pain, and Acceptability in Healthy Adults". Clinical and Translational Science.
[4] Gil, L. et al. (2022). "The Role of the Relative Fluid Velocity in an Objective Continuum Theory of Finite Strain Poroelasticity". Journal of Elasticity.
[5] Gil, L. et al. (2024). "The Importance of a Full Chemo-Poro-Mechanical Coupling for the Modeling of Subcutaneous Injections". Journal of the Mechanics and Physics of Solids.