T4056

Development of *In Vitro-In Vivo* Correlation for Long Acting Injectable Microsphere Formulations

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PURPOSE

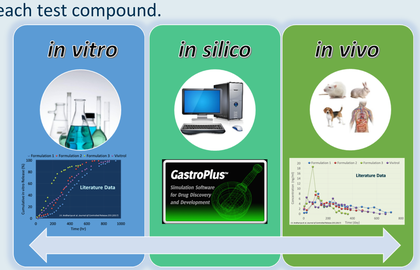
The concept of *in vitro-in vivo* correlations (IVIVCs) for long-acting injectable (LAI) microsphere formulations has gained more significance in the past decade. However, this problem is challenging due to the multiphase release characteristics of compositionally equivalent formulations, the lack of a mechanistic deconvolution method, and the lack of compendial *in vitro* release testing methods. This study aims to (1) determine whether an IVIVC can be established for long-acting injectable microsphere formulations with different release profiles; (2) assess the role of mechanistic deconvolutions in determining the *in vivo* release profiles; and (3) explore the potential for using a triphasic Weibull function on improving results of the deconvolution process.

OBJECTIVE(S)

The Objectives of this study are to investigate the feasibility of establishing IVIVC for long acting injectable microsphere formulations and to discover important aspects of this process.

METHOD(S)

We attempted to establish validated Level A IVIVCs using GastroPlus™ 9.6 (Simulations Plus, Inc.) for several drugs formulated as long-acting injectable microspheres. Literature data for several poly (d,l- lactide-co-glycolide) (PLGA) or poly(d,l-lactide) (PLA) formulations administered subcutaneously in Sprague-Dawley rats for olanzapine [1], intramuscularly in beagle dogs for huperzine A [2], and subcutaneously in rats for orntide [3] were used in this study. For each case study, the PK was established based on plasma concentration-time (Cp-time) profiles after intravenous (IV) (huperzine A), intraperitoneal (IP) (olanzapine), or subcutaneous (SC) (orntide) injection. The PK model was subsequently linked to the intramuscular or subcutaneous controlled release model in the Additional Dosage Routes Module (ADRM) in GastroPlus, and the complete model was used to deconvolute the *in vivo* release profile for each formulation. Finally, level A IVIVCs between the deconvoluted *in vivo* release and *in vitro* dissolution profiles were established and evaluated across different formulations for each test compound.

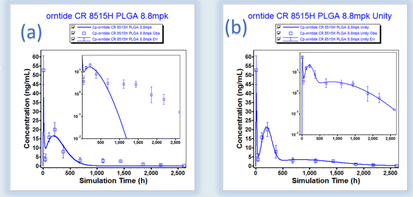


RESULT(S)

A level A IVIVC was established for each of the test compounds and formulations and several important aspects were discovered in the process.

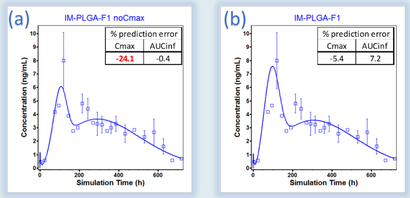
(1) Complex *in vivo* Profile: The *in vivo* release profiles for these long-acting injectable microspheres may be complex and cannot be always accurately described by a single- or double-Weibull function. A triple-Weibull function was required to accurately describe the *in vivo* release profiles for orntide formulations.

*Simulated Cp-time profiles after SC injection of one orntide LAI formulation in rat. The in vivo release profile was fitted as **(a)** double-Weibull and **(b)** triple-Weibull function.*

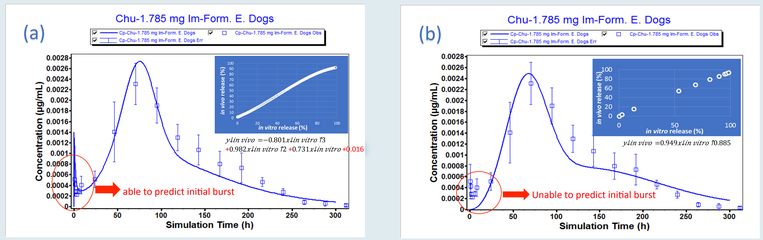


(2) Optimization Target Criteria: When fitting the *in vivo* release profile against the entire observed Cp-time profile, the error on Cmax is often higher than allowed by the IVIVC criteria due to the number of other concentration points outweighing the contribution of the single Cmax value. This issue can be addressed by including additional weight on Cmax during the deconvolution/optimization process.

*Simulated Cp-time profiles for a naltrexone LAI microsphere formulation considering **(a)** target observed Cp-time profile and **(b)** additional weight added to Cmax in the optimization function.*



(3) Insufficient *in vitro* Sampling: The density of *in vitro* sampling points is also important for prediction of the correct shape of the Cp-time profile. In the case of huperzine A, the IVIVC was able to predict the Cmax and AUC for new formulations, but a smaller initial peak was not captured due to the lack of *in vitro* data points representing the initial release of the drug. This limitation was addressed by using interpolated data points in the *in vitro* dissolution profile.



*Predicted Cp-time profiles for a huperzine A LAI microsphere formulation based on IVIVC built **(a)** with and **(b)** without using the interpolated in vitro data*

CONCLUSION(S)

The possibility of establishing IVIVCs for long-acting injectable microsphere formulations was investigated. The results show promise, but the desired success is yet to be achieved. Several important aspects have been discovered, including:

- The significance of using a triple-Weibull function in the mechanistic deconvolution and describing the more complex *in vivo* release of some long-acting injectable microspheres
- The role of the selected optimization objective function in the mechanistic deconvolution, specifically in the case of lacking sufficient *in vivo* sampling points
- The effect of using interpolated *in vitro* data in establishing an IVIVC and predicting the correct shape of the Cp-time profile

We aim to continue our study on the pharmacokinetics of LAI microspheres with the goal of better characterizing the *in vivo* environmental parameters that affect polymer degradation, microsphere dispersion, and API pharmacokinetics after *in vivo* injection of these formulations.

FUNDING / GRANTS / ENCORE / REFERENCE OR OTHER USE

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