Prediction of intra-articular drug clearance through synovium from slow-release carriers using a two-compartment finite element model

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INTRODUCTION: Musculoskeletal joint diseases, such as osteoarthritis (OA), are associated with significant burdens to human health and the economy in the USA and globally. Intra-articular (IA) injection of disease-modifying drugs is an important approach for treating single joints affected by OA and presents advantages of reduced side effects and enhanced effectiveness compared to systemic drug delivery. However, therapeutic drugs may be rapidly cleared from the joint space if not delivered with a depot of sustained release carrier. Currently, there is no robust model to predict drug residence times *in vivo* from in vitro data for drug release from a wide range of slow-release carriers. A computational model predicting drug residence time and concentration over time in the joint will help bring a paradigm shift in treating joint diseases effectively. Here, we developed a two-compartment finite element (FE) model of drug clearance from the joint through synovium based on in vitro drug release kinetics from sustained-release carriers. We demonstrated that in vitro kinetics of drug release, together with the known properties for molecular weight-dependent drug transport through joint synovium, can be used to predict prolonged drug residence times and concentration in the intra-articular joint space.

METHODS: An FE model of 1D solute diffusion after bolus or sustained release in joint space was created in FEBio (Fig. 1A). The joint synovium was modeled as a porous and hydrated solid matrix represented by Neo-Hookean model using experimentally measured properties for fluid permeability, stiffness, and diffusivities as measured previously [1, 2]. This study predicted the residence times for drugs and polymeric carriers developed in collaborator groups. We first utilized release kinetics of zoledronic acid (Zol) bound to Ca^{2+} in a nanoparticle complex (NP) and NP loaded in microparticles (MP) [3]. The kinetics of drug release from in vitro data were fitted with Peppas power law (NP)/two-phase decay equation (MP) to predict 100% cumulative release. Following this, the fitted release kinetics were used to calculate adjusted release kinetics by applying exponential decay for each incremental release in the fitted kinetics (for example, nth and $(n+1)_{th}$ release, Fig. 1A), with a half-life of the drug's diffusion into synovium from the joint space dictated by the drug's molecular weight (MW) (Fig. 1A-D). This adjusted release kinetics, reflecting the amount of remaining solute in the joint space at any timepoint, was used as a boundary condition in the joint space of FE model. Similarly, we studied the clearance of the compound RS504393 (RS), a CCR2 chemokine receptor antagonist, from a sustained-release PVA carrier and predicted joint residence times compared with a bolus release of RS as a free drug [4]. The effective diffusivity of Zol and RS was matched to the diffusivity of mannitol (180 Da) based on similarity of molecular weight. A zero concentration boundary condition was applied at the outermost layer of tissue to mimic the sink bath, or the systemic circulation in a joint model. Solute residence in the joint space and synovium over time was determined by concentration values in the mid-layer element of the synovium tissue.

RESULTS: Zol NP exhibited a higher peak concentration (10% of total concentration) compared to Zol released from MP (3% of total concentration), while Zol from MP had approximately a 9-fold longer residence time (half-life ~ 40-45 days) compared to NP (half-life ~ 5 days) (Fig. 2A-C). The concentration map on day 4 exhibited lower concentration of Zol released from MP compared to NP. For the model of RS, RS from the bolus release attained a higher peak concentration (40% of total) compared to that released from the PVA carrier (10%). However, the time to 50% clearance was ~9 hours for the free drug, compared to ~6 days for the drug released from the PVA carrier (Fig. D-F). The concentration map on day 2 demonstrated the evidence of RS being cleared mostly from the tissue when released as a free drug. The results successfully confirmed higher predicted residence time and lower peak concentration in the joint space and synovium tissue than for drugs injected in a bolus, free formulation.

DISCUSSION: Our work has demonstrated that the FE model can predict drug concentration profiles following intra-articular delivery of drugs in sustained-release carriers. This work suggests that quantitative predictions of FE models, together with in vitro experimental data, can be used to predict the peak concentration of a drug as well as total residence time following intra-articular delivery, both of which are crucial to design an in vivo preclinical study. Following validation with data from a preclinical model, this approach will enable us to utilize this model as an in vitro screening assay for in vivo drug behavior, thereby supporting the design of carriers and drug dosing to achieve a therapeutic effect in the treatment of joint disease.

SIGNIFICANCE/CLINICAL RELEVANCE: Optimal therapeutic effects in both preclinical and clinical models depend on multiple factors, including drug carriers, drug transport properties, and tissue properties, and achieving such effects requires extensive animal studies. Our model will be utilized as a rapid simulator of in vivo drug behavior, reducing the need for animal studies to a great extent.

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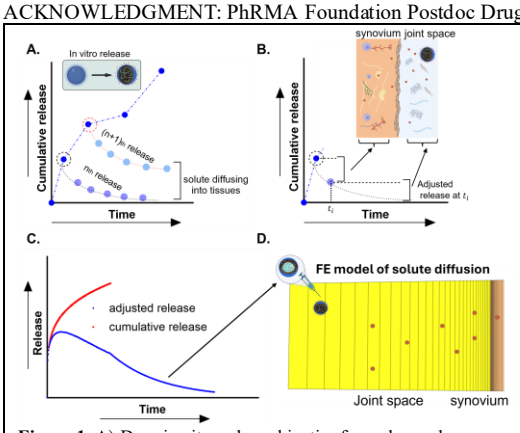

Figure 1: A) Drug in vitro release kinetics from slow-release carrier diffuses into tissue exponentially dictated by MW of the drug. B) & C) Adjusted release kinetics are computed reflecting the amount of drug remaining in the joint space, and D) utilized as a boundary condition in the joint space of the FE model.

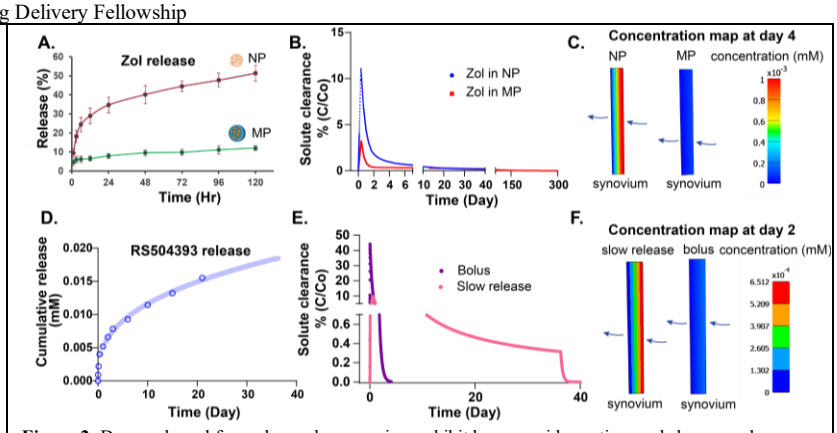

Figure 2: Drugs released from slow-release carriers exhibit longer residence time and slower peak concentration in the joint. A) Zol from NP and MP adapted from [3], and D) RS from PVA. B) Clearance kinetics and C) concentration maps of Zol in synovium. E) Clearance kinetics and F) concentration maps of RS in synovium