A Drug Transport Model for Delivery Vectors Incorporating Chemical and Microstructure Properties

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ABSTRACT SUMMARY

The release of drugs by diffusion is affected by drug interactions with the vector matrix and material microstructure of drug vectors. Here we present our recently developed multiscale model for diffusion in materials with complex structure and physico-chemical properties showing superiority over classical approaches. The robustness of the method is demonstrated on validated examples with nanochannel-based drug vectors and diffusion through polymers.

INTRODUCTION

Drugs get confined in the matrix of drug delivery vectors after loading, and later are released by diffusion with kinetics that may strongly depend on drug vector microstructure and drug properties. The interactions between the diffusing substance and vector matrix become important and can profoundly affect the overall diffusion when the spatial dimensions bounding diffusion are comparable to the diffusing particles or molecules. This applies to many drug carriers based on polymers, nanopores or nanochannels. Under those circumstances Fick’s law alone cannot accurately describe diffusion and the surface interactions at the molecular level must be taken into account.

In order to meet the need for this accurate prediction, we have developed a novel physics-based deterministic method for drug diffusion in composite media that accounts for interactions within microstructure and material properties of the porous matrix.

METHODS

We have applied a method referenced in [1], which hierarchically bridges nanoscale interface effects on diffusivity with a Finite Element (FE) discretized continuum method, and was validated against experiments. This method relies on Molecular Dynamics (MD) simulations used for evaluation of a scaling function for diffusion that is derived from diffusion profiles at the solid interface. Concentration and interface effects are incorporated into the FE scheme through the diffusion scaling function S(h). Diffusivity D was adjusted using experimentally determined dependence D(c) in the bulk and the proximity to the drug vectors matrix (e.g. fibers, walls) solid phase, turning D(c) into D(c,h) as D(c,h)=D(c)·S(h); here the scaling function S(h) has values from zero to unity, and c is the concentration.

The basic equations rely on mass balance of diffusing drug molecules within the porous medium of the drug delivery vector, and also on phenomenological Fick’s law that mass flux is proportional to the concentration gradient. These fundamental equations of the partial differential form are transformed to the finite element equations of balance and integrated over time. An incremental-iterative procedure is applied, with an implicit integration scheme to suppress the error propagation during solution process. The FE solutions provide insight into the drug transport and concentration distribution during the course of the drug delivery.

RESULTS AND DISCUSSION

Using the diffusivity scaling scheme incorporated into a FE method approach, we modeled diffusion transport through nanochannels and through polymer fibers. Diffusivity corrections were calculated for channels and polymers fibers (Figure 1). Our method, where diffusivity depends on concentration and proximity to surface,
predicted 2.2 times slower mass release kinetics through 5 nm channels than predicted by Fick’s law. The results revealed that largest effects on interface will appear for small confined volumes, like nanopores or nanochannels. The model predicted experimental diffusion from implantable drug delivery capsule with a R = 0.99 (Figure 2), and showed interface effects to be crucial.

Figure 1. Diffusion coefficient as a function of distance from solid phase agarose fiber, and silica (inset)

Figure 2. Glucose release through nanochannel membrane may be predicted if interactions with membrane and concentrations are accounted using our model (without any fitting), as in [1].

The diffusion of rhodamine 6G as a drug model (antineoplastic, sharing similar molecular weight and logP) was examined through an agarose polymer gel by comparing our method and experiments (Figure 3). Both microstructural and continuum models (based on our original homogenization procedure – not described here) are used, giving the same total mass release. The excellent prediction of release kinetics was achieved by incorporating microstructure of polymer and molecular interactions of tracer with the polymer.

Figure 3. Rhodamine 6G penetration through hydrogel in using TEM data (A). Concentration distribution is shown in (B), with measured and predicted diffusion release (C).

CONCLUSION

The inclusion of drug interactions with drug carrier matrix is crucial for predicting drug release. The novel hierarchical model shows robust performance by accurately predicting diffusive mass transport, and flexibility to model drug transport in/from drug vectors of different structure, geometry, and materials. The model offers another tool for rational design of materials, micro- and nanoparticles, and devices.

REFERENCES


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