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A unified multicomponent stress-diffusion model of drug release from non-biodegradable polymeric matrix tablets

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ABSTRACT

We propose a new transport model of drug release from hydrophilic polymeric matrices, based on Stefan-Maxwell flux laws for multicomponent transport. Polymer stress is incorporated in the total mixing free energy, which contributes directly to the diffusion driving force while leading to time-dependent boundary conditions at the tablet interface. Given that hydrated matrix tablets are dense multicomponent systems, extended Stefan-Maxwell (ESM) flux laws are adopted to ensure consistency with the Onsager reciprocity principle and the Gibbs-Duhem thermodynamic constraint. The ESM flux law for any given component takes into account the friction exerted by all other species and is invariant with respect to reference velocity, thus satisfying Galilean translational invariance. Our model demonstrates that penetrant-induced plasticization of polymer chains partially or even entirely offsets the steady decline of chemical potential gradients at the tablet-medium interface that drive drug release. Utilizing a Flory-Huggins thermodynamic model, a modified form of the upper convected Maxwell constitutive equation for polymer stress and a Fujita-type dependence of mutual diffusivities on composition, depending on parameters, Fickian, anomalous or case II drug transport arises naturally from the model, which are characterized by quasi-power-law release profiles with exponents ranging from 0.5 to 1, respectively. A necessary requirement for non-Fickian release in our model is that the matrix stress relaxation time is comparable to the time scale for water diffusion. Mutual diffusivities and their composition dependence are the most decisive factors in controlling drug release characteristics in our model. Regression of the experimental polymer dissolution and drug release profiles in a system of Theophylline/cellulose (K15M) demonstrate that API-water mutual diffusivity in the presence of excipient cannot generally be taken as a constant.

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1. Introduction

Polymer matrices have long been used in controlled drug delivery devices. The release kinetics is dictated by the physiochemical structure and characteristics of the polymer matrix (excipient), drug — i.e. the active pharmaceutical ingredient (API), and penetrant interactions. Mathematical modeling of drug release has been developed over the past two decades to help optimize the design of controlled release tablets and to minimize laborious in vitro drug release experiments.[1–4] Upon contact with water or a physiological buffer solution, penetrant molecules diffuse into the polymer matrix, leading to swelling and expansion. That, in turn, increase segmental mobility of polymer chains and effective diffusion of drug molecules into the surrounding release medium in typical in vitro studies. If the polymer is unstable to degradation by hydrolysis in water, chain scission and matrix degradation will follow in which case the API release rate is further sped up. Even for chemically stable matrices, if the polymer matrix is not chemically cross-linked, penetrant-induced disentanglements lead to chain detachment and surface erosion. As a result, API release is controlled by the net effects of API diffusion, matrix swelling and possibly chain erosion and/or degradation. Limited solubility of API can cause the released API to crystalize in the release medium, lowering the bioavailability of the API. Hydrophilic polymers such as poly (*N*-vinylpyrrolidone), cellulose and its derivatives such as hydroxypropyl methylcellulose (HPMC) are commonly used in controlled release tablets due to their high water uptake, drug loading capability and nontoxicity.

A considerable body of theoretical work at different levels of rigor has been dedicated to modeling transport of solutes from matrix tablets over the past two decades [1–4]. In principle, water swollen API/excipient is a multicomponent system and, as such, amenable to transport laws derived from irreversible thermodynamics. Weinstein et al. [5,6] and Lustig et al. [7] have proposed formal theoretical frameworks for modeling of fluid-polymer systems. Due partially to the complexity of these models, they have so far attracted little attention in the experimental community. As a result, much of the theoretical effort has been focused on formulation of relatively simple continuum transport models that can connect readily to experimental studies.

One of the early models is due to Lustig and Peppas [8] who developed a 1D description of solute transport using Fick's second law of

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diffusion with Fujita-type diffusivities. While Lustig and Peppas transformed their spatial coordinates globally to track the overall thickness of the polymer film as it swelled with solvent, they did not transform their equations locally into a proper Lagrangian polymer-fixed frame. Ju et al. [9] and Narasimhan and Peppas [10] incorporated matrix re-dissolution by appending a polymer diffusion boundary layer to the tablet–solvent interface where chain disentanglement dynamics dictate the polymer erosion rate. Siepmann and coworkers [11,12] solved 2D axisymmetric diffusion equations without advection terms in cylindrical coordinates (r and z) coupled to Fujita-type pseudo binary flux laws and accounted for swelling by following the overall content of individual area elements and zeroth order matrix re-dissolution kinetics. Borgquist et al. [13] also employed Fick's flux law but included the swelling-induced convective terms in their finite volume simulations explicitly. Hariharan and Peppas [14] and Brazel and Peppas [15] incorporated the matrix stress relaxation into the penetrant transport equation via a prescribed convective term that controls diffusion of drug molecules implicitly. Combining Darcy's law and a diffusion–advection equation for water and drug respectively, Xu et al. [16] predicted the drug release and swelling kinetics of linearly elastic cross-linked hydrogels with low initial drug loading. They did not consider matrix viscoelasticity. Recent 2D finite element simulations of Kaunisto et al. [17,18] using a generalized Fick's law and Caccavo et al. [19] employed a pseudo-binary flux law and dynamic re-meshing to keep track of the matrix re-dissolution and swelling-induced deformation of the computational domain using the Arbitrary Lagrangian–Eulerian (ALE) method. While mathematically elegant, the matrix viscoelasticity and thermodynamic non-idealities were lacking in both of these studies.

Solution of conventional models utilizing the pseudo binary Fick's law leads to Fickian drug release and penetrant sorption kinetics both characterized by a square root of time dependence. Numerous experimental investigations have long established that in addition to Fickian release, anomalous, linear (Case II) and even super linear (Sigmoidal or Super Case II) drug release profiles, collectively referred to as non-Fickian behavior hereafter, can also occur under certain conditions [20,21]. Non-Fickian diffusion has been originally investigated in the context of the closely related area of penetrant sorption into glassy polymers. A number of theories have been particularly proposed to elucidate Case II transport in glassy polymers that account for a sharp glassy–rubbery (swelling) front moving inwards, either explicitly by including a convective term into the penetrant conservation equation [15,22] or implicitly by coupling the glassy–rubbery transition kinetics to the conservation equations [23–25]. Both of the foregoing approaches require a prior knowledge of the experimentally-determined moving front velocity or empirical parameters describing kinetics of swelling.

Although there is an alternative explanation based on free volume theory [26], Case II diffusion is now widely attributed to a coupling between the viscoelastic stress response of the polymer matrix and Fickian diffusion as penetrant ingress and drug release lead to matrix deformation. In fact, a broadly accepted criterion for non-Fickian transport is that, in Case II diffusion, there is a steep moving composition front at which the diffusional Deborah number $= O(1)$ implying that at the moving front the chain relaxation time is comparable to the characteristic time for diffusion of solvent over the width of front region [27]. Coupling the polymer constitutive equation for stress with mass conservation and incorporating a history-dependent contribution of matrix deformation to the total free energy of mixing, Durning and Tabor [28] developed a model that obviated the need to know a priori the experimental front velocity or swelling dynamics at glassy–rubbery front. Peppas and coworkers [29,30] introduced polymer surface dissolution to the model of Durning and Tabor [28] but neglected the time dependence of the surface boundary conditions and deformation tensor in their Lagrangian [29] and Eulerian [30] approaches.

Despite the foregoing advances, some points have been largely overlooked in the literature. The time dependencies of boundary conditions at tablet outermost interface have either been completely neglected or included through a phenomenological exponential function whose rate is set by the chain relaxation time [15]. Due to sensitivity of water and API diffusivities to water concentration, use of static boundary conditions on water is not generally an accurate assumption.

More importantly, Fujita-type pseudo-binary flux laws are prevalent choices for transport of drug and penetrant molecules. The pseudo-binary flux law is accurate only for tablets with very low drug loading, since it does not account for diffusional friction between penetrant and drug molecules. Additionally, pseudo binary Fickian fluxes, being defined with respect to a reference velocity, do not properly account for diffusion-induced convection and therefore fail to satisfy Galilean invariance, a basic physical principle. Use of pseudo-binary flux laws in different reference frames can also render mutual diffusivities, a basic material property, frame-dependent. Lastly, in systems with more than three constituents, even a matrix-fixed frame may not be adequate except in very special cases. A more detailed comparison between ESM and pseudo-binary fluxes is provided in Supplementary material.

In what follows, we offer an extension of the two-component model of Durning and Tabor [28] to multi-component systems by employing frame-invariant ESM flux laws that explicitly account for diffusional drag between water and drug, thereby allowing arbitrary initial drug loading, and allowing simultaneous drug release and solvent sorption. Moreover, ESM flux laws establish a physically meaningful link between molecular scale simulations and continuum level transport models. In the subsequent sections, we first put forth a detailed description of our model followed by illustrative simulation results and discussion to demonstrate the salient features of the model. We compare our model predictions to experimentally determined drug and excipient dissolution profiles for Theophylline/K15M (HPMC) system. We shall conclude by conclusions and suggestions to overcome some remaining challenges.

2. Model development

We have made a number of fundamental assumptions listed below. We shall explain the rationale for these later in this section.

2.1. Assumptions

1. Upon exposure to a release medium, taken to be pure water hereafter, a matrix tablet is a ternary system composed of water, API (drug) and polymer matrix (excipient) denoted by *W*, *D* and *E*, respectively. (A detailed notation list is furnished at the end for quick reference.)
2. Ideal mixing. The excess volume of the system is identically zero irrespective of composition. In other words, partial molar volumes of all species are equal to those of respective pure components at the same pressure and temperature.
3. Polymer chains remain chemically stable in water throughout the duration of dissolution. This assumption applies to a broad range of hydrophilic polymers.
4. Tablet ingredients constitute a single continuous phase, i.e. tablet bulk porosity is not considered here.
5. Initially, ingredients are uniformly distributed across the tablet.
6. Phase change; i.e., crystallization or crystal dissolution, is not explicitly considered.
7. There is no resistance to mass transfer in the release medium up to the interface with the tablet. Consequently, a thermodynamic equilibrium between the tablet's outermost surface and bulk release medium is established instantaneously.

We restrict ourselves to one dimension in a planar geometry so as to underscore the main features as well as departures from previous models more readily. Generalization to higher dimensions and different coordinate systems will be straightforward, albeit with more computational and algebraic complexity. To begin with, consider a large slab of polymer matrix, two dimensions of which are vastly larger than the

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