Drug release from ion-exchange microspheres: Mathematical modeling and experimental verification

Mohammad J. Abdekhodaie [a,b], Xiao Yu Wu [a,*]

[a] *Faculty of Pharmacy, University of Toronto, 44 College Street, Toronto, ON, Canada M5S 2S2*
[b] *Department of Chemical Engineering, Sharif University of Technology, Tehran, Iran*

Abstract

This paper presents for the first time a mathematical model for a mechanism of controlled drug release involving both ion exchange and transient counter diffusion of a drug and counterions. Numerical analysis was conducted to study the effect of different factors on drug release kinetics including environmental condition, material properties, and design parameters. The concentration profiles of counterions and drug species, the moving front of ion exchange, and three distinct regions inside a microsphere, namely unextracted region, ion-exchange region and drug diffusion region, were revealed by model prediction. The numerical results indicated that the rate of drug release increased with an increase in the initial drug concentration in the microspheres, the salt concentration in the external solution, or the valence of the counterions, whereas it decreased with increasing Langmuir isotherm constant. The mathematical and experimental procedures for determination of the equilibrium constant and the usefulness of the model were demonstrated using verapamil hydrochloride and sulfopropyl dextran microsphere system as an example. This work has provided a very useful mathematical tool for predicting kinetics and equilibrium of drug release and for optimizing the design of ion-exchange drug delivery systems.
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1. Introduction

Ion-exchange polymers and microspheres have long been used in pharmacy for masking taste of bitter drugs, delivering anticancer drugs and chemosensitizer to solid tumors, controlled drug release, and for diagnosis [1–13]. Ion-exchange microspheres contain charged functional groups that have high affinity for oppositely charged ions. Therefore, ionic drugs can be readily loaded onto them without the use of organic solvents which are normally employed for the preparation of drug-loaded microspheres. Because of the easy loading process, high drug loading capacity, and prolonged drug release at a specific site through exchange with counterions in the release medium, ion-exchange microspheres are more attractive in certain applications than other microsphere systems [6,8].

An ion-exchange process can be described as a series of reaction and mass transfer, including stoichiometric exchange of a counterion with a bound solute [14]. Prior to ion exchange, diffusion of a counterion and thereafter diffusion of a solute may take place in two regions: (1) the solution outside the particle, normally the stagnant film surrounding the particle, and (2) within the particle. The mass transfer resistance outside the particle can be neglected when rigorous stirring is applied. Often the reaction at the ion-exchange site is assumed to be fast compared to mass transfer [14–19], that is, the reaction is considered to be instantaneous. Moreover, local equilibrium is assumed to exist between the free and the bound solute, which leads to the Langmuir isotherm. Langmuir isotherm has been shown to give a good representation of binding between

* Corresponding author. Tel.: +1 416 978 5272; fax: +1 416 978 8511.
E-mail address: xywu@phm.utoronto.ca (X.Y. Wu).

Nomenclature

C_i	concentration of species i in the microsphere
C_i^0	initial concentration of species i
C_m	maximum solute binding capacity of the ion-exchange microsphere
C_{RS}^0	initial drug loading in the microsphere
$C_{Na^+}^{b,0}$	initial sodium-ion concentration in the external solution
$C_{Na^+}^{b,\infty}$	sodium-ion concentration in the external solution at the equilibrium
$C_{S^+}^{b,\infty}$	drug concentration in the external solution at the equilibrium
$\widehat{D}$	drug-cation diffusion coefficient ratio
D_i	diffusion coefficient of species i
K	Langmuir isotherm constant
K_a	association rate constant
K_d	dissociation rate constant
M_0	total amount of solute in the microsphere
M_t	amount of solute release into the external volume at any time
M_∞	releasable total amount of solute at the equilibrium
r	position variable
R	position of the surface of microsphere
x	dimensionless spatial coordinate defined by Eq. (13)
β	effective charge of the counterion
λ	volume ratio defined by Eq. (28)
θ_i	dimensionless concentration defined by Eq. (13)
θ_i^0	dimensionless initial concentration
τ	dimensionless time defined by Eq. (13)

Subscripts

Ca^{++}	calcium ion
I^+	counter ion
Na^+	sodium ion
R	cation exchanger
RS	bound drug with cation exchanger
S^+	solute or drug ion

some drugs (such as polypeptides and proteins) and polymeric substrate [16,17].

So far, several models, such as homogeneous, heterogeneous, pore, surface and combined diffusion models, have been developed to predict the behavior of ion-exchange polymers in fixed bed columns [20–28]. Although ion-exchange processes have been widely studied in chemistry and chemical engineering, only a few mathematical descriptions have been applied to analyze the behavior of ion-exchange systems in pharmaceutics [14,15,18,19]. Singh and coworkers developed a mathematical model for drug release from hydrogel matrices with slab geometry *via* a mechanism of diffusion coupled with desorption [15]. In their model, a desorption term was

considered based on Langmuir kinetics. Carrere et al. and Li and coworkers presented models for protein extraction by adsorption [18,19]. Their models also incorporated both kinetic terms, based on Langmuir isotherm, and a transient Fickian diffusion. Carrere and coworkers assumed that the solute adsorption took place on the solid surface only and Li et al. considered an inert core for a spherical geometry. Boudy and coworkers developed a model for adsorption of an ionizable drug onto microspheres [14]. In their model, Langmuir isotherm was considered but a concentration gradient in the microsphere was neglected.

Following our previous work in which a mathematical model was developed to predict the behavior of drug loading onto ion-exchange microspheres [1], this study was intended to provide a framework to predict drug release kinetics involving ion exchange and diffusion. The kinetics of counterion diffusion into and drug diffusion out of a microsphere were described by the governing equations of Fick's second law of diffusion coupled with an ion-exchange rate term. The latter was a non-linear function of time and concentration calculated from the rate of adsorption and desorption. Similar to previous work, it was assumed that the binding interaction between drug and polymer could be described by Langmuir isotherm due to an ion-exchange process. The concentration distribution of counterions and drug inside the microsphere and the drug release profiles were computed in relation to external conditions, material properties and design parameters. To verify the model and the computational programs, equilibrium drug loading and drug release experiments were carried out using a cationic drug, verapamil HCl, loaded in the microspheres of sulfopropyl dextran.

2. Theoretical analysis

2.1. Mathematical modeling

The principal property of ion-exchange polymers is their ability to exchange bound ions with those in the solution. Since the majority of drugs possesses an ionic site in each molecule, the charges of the polymer provide a means to bind such drugs by ionic complexation. The bound drug ions may be freed to the solution through exchange with counterions that are absorbed on the ionic polymer. The following formula illustrates such an ion-exchange process involving a cationic drug and an anionic polymer:

$$\beta RS + I^{+\beta} \overset{K_a, K_d}{\longleftrightarrow} R_\beta I + \beta S^+ \tag{1}$$

where R is the binding site of a cation exchanger, S^+ is the free solute or a drug ion with a single positive charge, RS is the solute bound with the polymer binding site, I is the counterion, β is the effective charge of the counterion, $R_\beta I$ is the counterion bound with the binding site of the ion exchanger, and K_a and K_d are the adsorption and desorption rate constants, respectively. At the equilibrium, the rates of adsorption and desorption are equal resulting in Langmuir isotherm:

$$K = \frac{K_a}{K_d} = \frac{C_{RS}^\beta C_{I^{+\beta}}}{C_{R_\beta I} C_{S^+}^\beta} \tag{2}$$

where K is the ratio of K_a and K_d, and will be referred to the Langmuir isotherm constant or equilibrium constant; C_{RS}, $C_{I^{+\beta}}$, $C_{R_\beta I}$, and C_{S^+} are, respectively, the concentrations of various species described above.

Drug release from an ion-exchange microsphere involves three steps: (1) counterion diffusion from the external medium to the binding sites within