Chemical Engineering Science 139 (2016) 163–172

Contents lists available at ScienceDirect

Chemical Engineering Science

journal homepage: www.elsevier.com/locate/ces

Dynamic binary protein adsorption in ion-exchange media depicted with a parallel diffusion model derived from Maxwell–Stefan theory

Kun Yang *

Department of Pharmaceutical & Biological Engineering, College of Chemical Engineering, Sichuan University, Chengdu 610065, China

HIGHLIGHTS

- A binary parallel diffusion model based on the Maxwell–Stefan theory was established.
- The model parameters were independently determined.
- The model offered good prediction to the dynamics of binary protein adsorption.

ARTICLE INFO

Article history:
Received 2 July 2015
Received in revised form
6 September 2015
Accepted 22 September 2015
Available online 8 October 2015

Keywords:
Chromatography
Binary protein adsorption
Mass transfer
diffusion
Maxwell–Stefan equation
Mathematical modeling

ABSTRACT

A parallel diffusion model based on the Maxwell–Stefan (MS) theory that was ever used to depict single protein adsorption kinetics was extended to a binary protein adsorption system, leading to the establishment of a binary parallel diffusion model based on the MS theory (BiMS-ParDM). Dynamic adsorption behaviors of two proteins (bovine serum albumin, BSA, and bovine hemoglobin, BHb) in a commercial chromatographic ion-exchange medium, SP Sepharose FF, were analyzed with the comprehensive model. Effective diffusion coefficients (lumped diffusion flux including the pore and surface diffusions) of the two proteins were determined via dynamic single protein adsorption experiments. By incorporating with a binary Langmuir isotherm, the BiMS-ParDM was applied to predict the binary protein (BSA and BHb) adsorption. The results fitted reasonablely well with experimental data. This study demonstrated that the Maxwell–Stefan theory offered an advanced framework for constructing kinetic models for protein adsorption, especially when the surface diffusion of adsorbed protein was significant. Moreover, it revealed that more acurate isotherm models that can precisely depict multi-protein adsorption equilibria need to be developed to further improve the performance of the recent diffusion model.

1. Introduction

Protein adsorption kinetics in chromatographic media is one of the important research areas of bioseparation. Normally, the rate-limiting step of such an adsorption process is the intraparticle molecular diffusion, which has already become the core event of the kinetics research. Adsorption kinetics of single protein has been extensively studied from either experimental (Dziennik et al., 2003, 2005; Lewus and Carta, 1999b, 2001; Ljunglof et al., 2007; Russell et al., 2003) or theoretical aspects (Chen et al., 2002; Gutenwik et al., 2004b; Sun and Yang, 2008; Yang and Sun, 2007). However, similar researches on the protein adsorption system of two or more components are rare. Recent improvements in experimental detection methods have brought it into the opportunities to understand the kinetics of multi-component protein adsorption in depth. Confocal laser scaning microscopy realized in-situ obsevation of dynamic protein adsorption at single absorbent particle level (Hubbuch et al., 2003a, 2002, 2003b; Linden et al., 1999). In virtue of a specially desigined micro-equipment, multicomponent protein adsorption in hydrogel was also observed and analyzed via fluorescence microscopy (Russell and Carta, 2005). On the other hand, the mathematically modeling of multicomponent protein adsorption which can depict and predict such a process remains underdeveloped. In order to accurately describe the kinetics of binary or multicomponent protein adsorption with *mathematical language*, several prerequisites need to be fulfilled (Gallant, 2004; Lewus and Carta, 1999a):

1. An accurate adsorption isotherm which reflects the competitive adsorption equilibrium of two or more proteins;
2. Accurate description of the mass transfer of each components in binary or multicomponent adsorption system;
3. Sometimes, electrokinetic mechanism may be concerned.

* Tel.: +86 28 8540 5221; fax: +86 28 8540 3397.
E-mail address: cookyoung@scu.edu.cn

http://dx.doi.org/10.1016/j.ces.2015.09.027
0009-2509/

Accordingly, the difficulties for the kinetics research of binary or multicomponent protein adsorption are as follows. First of all, the process of multicomponent competitive adsorption is more complicated, which thwarts the adequacy of traditional adsorption equilibrium model. Second, the intraparticle mass transfer of two or more components is more complicated than that in the single component system. The mathematical methodology involved in the kinetics model also becomes more sophisticated. Furthermore, from the aspect of experimental design, getting accurate concentration of each component in the mixture sets a higher standard on the employed analytical methods.

Although there are so many difficulties in the research of binary or multicomponent protein adsorption kinetics, this work cannot be ignored, since in engineering practices, the systems to be separated are often multicomponent. In order to realize rational design of such a multicomponent protein adsorption, it is necessary to thoroughly understand the kinetics of such a process.

As stated by Lewus and Carta (Lewus and Carta, 1999a), before 1999, studies on mass transfer process during protein adsorption only considered the situation of non-adsorption or non-competitive weak adsorption, or were just limited to the single protein adsorption and desorption kinetics. In their study, Maxwell–Stefan theory was first introduced to the mass transfer model of protein adsorption and was compared with Fick's law. Although the mathematic model based on mass transfer theory gave poor prediction of the experimental results, Maxwell–Stefan theory was still believed to give the better model framework, in consideration of the coupling interactions between two diffusion components. The poor prediction was attributed to the inaccuracy of adsorption equilibrium models (Langmuir and Steric mass action models, SMA). Moreover, it can be found that the intraparticle diffusion flux was considered as a whole without discriminating the pore and surface diffusion in that work. In 2005, Martin et al. analyzed binary protein adsorption by using pore diffusion model with Langmuir adsorption equilibrium, which gave fairly good results. Furthermore, an analytical solution of this model under rectangular adsorption condition was given (Martin et al., 2005). By using a pore diffusion model with SMA equilibrium, Gallant theoretically calculated the binary protein adsorption kinetics of α-Chymotrypsinogen A and Cytochrome c (Gallant, 2004). The results predicted a negligible salt gradient induced during the adsorption process. Besides, they did not verify the model with experimental results. Gutenwik et al. developed a mathematic model to describe the hindered diffusion and competitive adsorption of two proteins in an agarose gel (Gutenwik et al., 2004a). The model took into account of the hindered diffusion, competitive adsorption, pore size distribution of the gel, and a shrinking effective pore radius attributed to protein binding, which explained the competitive adsorption and the phenomenon of displacement as combining effects of hindered diffusion, adsorption kinetics and binding capacity. As this model considers almost all factors involved in chromatographic adsorption kinetics, the complexity of the resulted model construction may to some extent confine its practical application.

In a previous report, we had analyzed the parallel diffusion, ***which included both pore and surface diffusion***, of single protein in a porous anion exchanger with a mass transfer model derived from Maxwell–Stefan theory in comparison with its counterpart based on Fick's law (Sun and Yang, 2008). It was found that the MS diffusion coefficient was less dependent on the protein concentration. We were convinced that Maxwell–Stefan theory gives better framework of mass transfer model for protein adsorption. In this recent work, we will extend the model to the condition of binary protein adsorption. The dynamic data of a binary protein adsorption system, the adsorption of bovine serum albumin (BSA) and bovine hemoglobin (BHb) onto a cation exchanger, SP Sepharose FF, were used to validate the model.

2. Theory

2.1. Maxwell–Stefan diffusion of single component

The most widely used intraparticle mass transfer models are in general based on Fick's law, but there are actually restrictions on their applicability due to the limitations of the theoretical assumption of Fick's law. Fick's law was a derivation based on ideal solution prerequisite, so it is strictly compliant to the following conditions: (1) plain binary mixture or (2) diffusion of diluted constituent in multi-component system, (3) without extra electric or centrifuge field.

Maxwell–Stefan theory, as an independent diffusion theory other than Fick's law, considers the gradient of chemical potential as the driving force of mass transfer. It shows more extensive applicability than Fick's law does (Krishna and Wesselingh, 1997). It has been widely used in describing the diffusive mass transfer in gas adsorption, gas chromatography (Vandenbroeke and Krishna, 1995), and liquid chromatography for small molecules (Kaczmarski et al., 2002), and in recent years it has also been gradually used in the mass transfer analysis of single (Wesselingh and Bosma, 2001) and multicomponent (Lewus and Carta, 1999a) protein adsorption.

In a plain binary mixture system (as shown in Fig. 1), molecule 1 makes uniform motion in the bulk phase 2. The gradient of chemical potential is considered as the driving force, which is balanced by intermolecular friction. Maxwell–Stefan equation can be derived as follows (Krishna and Wesselingh, 1997). The force balance equation was written as:

$$-\frac{d\mu_1}{dz}=\frac{RT}{D}x_2(u_1-u_2) \tag{1}$$

where μ_1 means the chemical potential of molecule 1 (J mol^{-1}), R the universal gas constant (8.314 J mol^{-1} K^{-1}), T the absolute temperature (K), x_2 the molar fraction of molecule 2, u_1 and u_2 the velocities of molecule 1 and 2, respectively. The right side of the equation indicates the driving force acting on unit molar of molecule 1, and the term RT/D on the right side of the equation was interpreted as drag coefficient. It can be imagined that drag force is proportional to the relative velocity (u_1-u_2) between molecules 1 and 2. Based on such a depiction, the diffusion coefficient D in the Maxwell–Stefan equation exhibits the dimension of

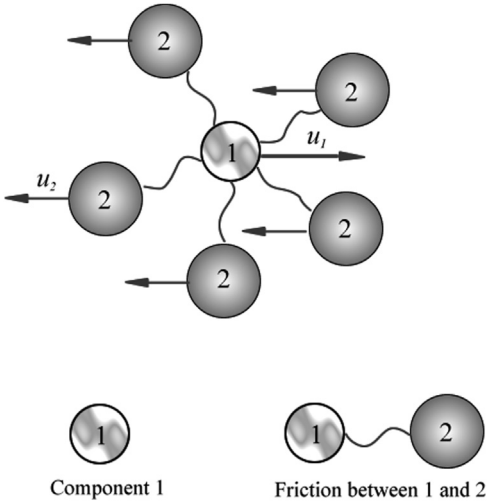

Fig. 1. Illustration of Maxwell–Stefan molecular diffusion theory with a mended figure from (Krishna and Wesselingh, 1997).