INVERSE PROBLEM BY RANDOM RESTRICTED WINDOW (R2W) IN THE PARAMETERS ESTIMATION OF INSULIN ADSORPTION

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Abstract. *The estimation of parameters by agitated batch process is the initial step in the characterization of separation chromatographic system. The inverse techniques are necessary tools for the determination of the important parameters involved in the design and performance of the industrial processes of chromatography. The application of methods that utilize stochastic strategies has increased in recent years, demonstrating its potential in the study and analysis of different systems in engineering applications. The stochastic routines are interesting as they are able to optimize the solution in a wide range of the variables domain, being possible the determination of multiple parameters at the same time. In this work the inverse method R2W (Random Restricted Window Method) was applied in the parameters estimation of insulin adsorption over the adsorbent Accel Plus QMA. The chromatographic models studied are related to kinetic mechanism of adsorption and desorption in agitated batch processes. The R2W method showed to be effective in the determination of parameters of the adsorption process studied, being observed the good performance for multiple estimations.*

Keywords*: Adsorption, Chromatography, Inverse Problem, Kinetic Modeling, Stochastic Routine*

1. INTRODUCTION

The preoccupation with the economical and envinonmental factors around the industrial processes has taken to the increasing use of chromatographic techniques. Such techniques are applied to different functions and objectives, for example: separation of chemical compounds (Câmara and Silva Neto, 2006a), purification of biomolecules (Costa *et al.* and Câmara *et al.,* 2007), decontamination in hazardous materials (Mathialagan and Viraraghavan, 2002), and others (Biasse *et al*., 2007). These applications are seen mainly in pharmaceutical industry, fine chemical, petrochemical and biotechnology.

In recent years, different systems of chromatographic separation have been studied (Cruz 1997, Silva 2000, Vasconcellos and Silva Neto 2003), demonstrating a high interest to the development of more efficient adsorption systems such as equipments of separation of greater productivity and lesser production cost.

Many approaches have been used to describe the phenomena and mechanisms involved in chromatographic separation processes. In the context, the methodology of inverse problem (Silva Neto and Moura Neto 2005) has contributed to the estimation of essential parameters, which can be applied to the characterization and design of separation equipments projects. Some results of these researches can be found in Câmara and Silva Neto (2006b, 2008), Vasconcellos and Silva Neto (2003).

The sucess of kinetic modeling applied to the parameters estimation of adsorption is directly related to the choice of the adequate mathematical model that describes the satisfatory form of the adsorption phenomenon studied. Thus, the first step is the determination of the direct models that will represent adequately the adsorption system of interest. Many important contribuitions of adsorption models to solid-liquid can be seen in Adriano *et al.* (2005), Câmara *et al*. 2007, Câmara and Silva Neto (2008), Hashim and Chu (2007), and Thomas (1944).

In this work, the inverse method R2W was applied to the parameters estimation of insulin purification (Brobeck 1976) through the adsorption models in agitated tank utilizing the experimental data of Cruz (1997).

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2. MODELING

2.1. Inverse problem by random restricted window (R2W) algorithm

The R2W is a basic random algorithm of search that follows the flowchart of Fig. 1A. The Fig. 1B shows a schematic representation of the R2W algorithm. The objective of the algorithm is the optimization of the following function *Z* (Eq. 1) from the determination of the best solution of parameters (ζ_i).

$$Z = f(\zeta_1,\ \zeta_2,\ \zeta_3, ...) \tag{1}$$

Initially, there is a random estimation of *S* random seeds related to the parameters above as following the procedure below,

$$\zeta_i = \zeta_{iL} + R.(\zeta_{iH} - \zeta_{iL}) \tag{2}$$

in which ζ_{iL}, ζ_{iH} and *R* represents the lowest value of the parameter, the highest value and the random number, respectively. The procedure from Eq. 2 is repeated for each parameter in the function *Z* of Eq.1, i.e for each seed *S* there is the random estimation for each parameter of the function *Z* (Eq.1). The random numbers are generated from a uniform random distribution.

After the initial procedure of random estimative of the parameters (Step 1 in the flowchart), we have the determination of the profile of function *Z*. In this work the function of Eq.1 was represented by one adsorption system of batch chromatography.

The step 2 in the flowchart corresponds to the comparison between the simulation results from the adsorption batch chromatography model (Function *Z*) and the experimental data. This comparison was carried out from the squared residues function *Q* (Eq. 3).

$$Q = \sum_{i=1}^{np} (C_{\exp} - C_{sim})^2 \tag{3}$$

with the terms C_{exp}, C_{sim} and *np* corresponding to, respectively, the experimental concentrations of adsorption, the concentrations from the simulations and the number of points for the same event (number of experimental points in the range of time). In the step 2 we have a vector of residues from the number of seeds generated. For each seed we have a comparison between the model (Eq.1) and the experimental data, having the determination of the square residue *Q*.

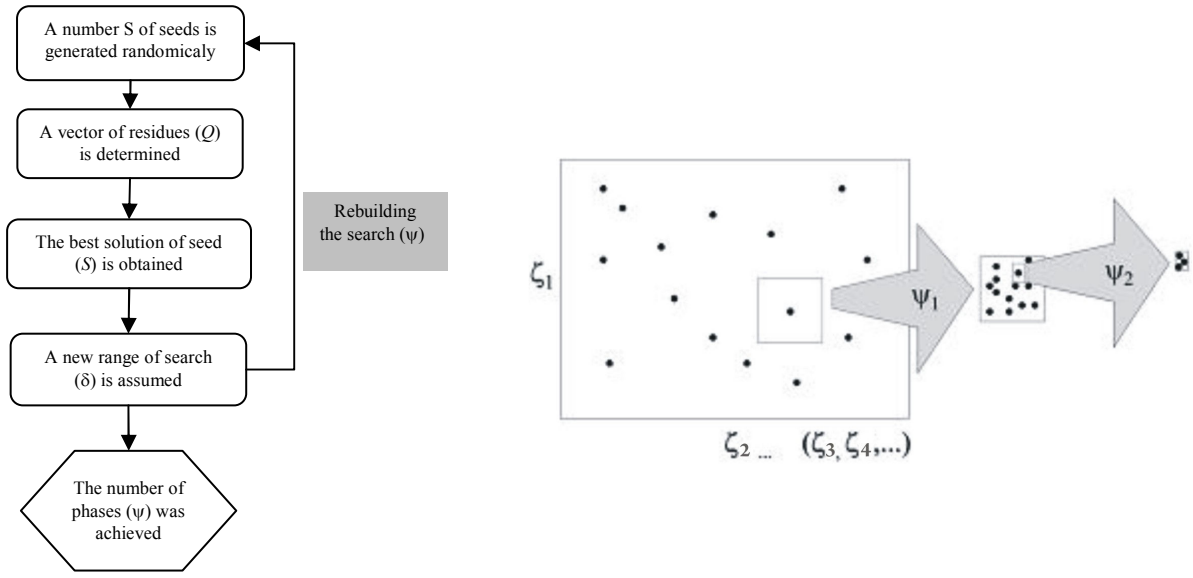
The step 3 corresponds to the determination of the seed *S* that leads to the lowest function of residue *Q* , i.e that solution that provide the best fit between the experimental data and the simulation results. The best solution of seed *S* is utilized in the step 4.

In the step 4 there is a restriction of the search around the solutions of the parameters encountered for the seed with the lowest residue. The search restriction is determined by the factor range of search (δ) which establishes the domain of search near the best solutions of parameters of Eq.1. The new range of search is determined by Eq. 4.

$$\zeta_{iL} = \zeta_i^* - \delta.(\zeta_i^*) \qquad \zeta_{iH} = \zeta_i^* + \delta.(\zeta_i^*) \tag{4}$$

in which ζ_i^* corresponds to the best solution of the parameter *i* encountered in the previous step. For each parameter ζ_i^* of the seed there is the determination of a new range of search utilizing the same range of search (δ).

The final step 5 is reached for the cases which is not assumed a new phase of search (ψ = 0) or the number of phases is achieved. For the cases which is assumed a number of phases (ψ), the algorithm returns to the step 1 with the range of search restricted, i.e the same number of random seeds are generated in the new restricted domain for each of the parameters. This procedure leads to a high concentration of estimations over a small range, which the chance to obtain the best solution is high.



(A) (B)

Figure 1. Flowchart of the R2W algorithm (A) with the schematic representation (B)

2.2. Formulation of the direct modeling

This step shows, through the kinetic concept, the stoichiometry to adsorption phenomenon dicussed (Fig. 2). It is related to a reversible mechanism of adsorption. The parameters k_1 and k_2 correspond the kinetic constant of adsorption and the kinetic constant of desorption, respectively. Which 1 (one) mol of insulin (Solute A) is adsorbed or dessorbed in 1 (one) mol of active site into adsorbent (s).

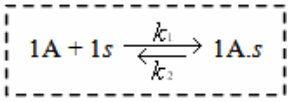


Figure 2. Representation of the adsorption stoichiometry

From the Fig. 2, the rate of consumption of insulin (Solute A), represented by r_A, is determined by Eq. 5.

$$-r_A = k_1.C_A.C_s - k_2.q_A \tag{5}$$

in which C_A, C_s and q_A represent the concentration of insulin in the liquid phase, the concentration of actives sites of the adsorbent Accel Plus QMA® and the concentration of insulin adsorbed in the solid phase (adsorbent), respectively.

The active sites concentration is obtained by the mass balance in the adsorbent (Eq. 6).

$$C_s = (q_m - q_A) \tag{6}$$

in which q_m represents the maximum capacity of insulin adsorption on adsorbent Accel Plus QMA® or the maximum concentration of active sites in solid phase.

After such considerations, the model of chromatography studied in this work is derived from rate of variation of insulin concentration into the agitaded tank (Eqs. 7 and 8).

$$\frac{dC_A}{dt} = -k_1.C_A(q_m - q_A) + k_2.q_A \tag{7}$$

$$\frac{dq_A}{dt} = k_1.C_A(q_m - q) - k_2.q_A \tag{8}$$

The negative terms that are present in the agitated batch model are directly related to the migration of insulin molecules into the solid adsorbent phase (adsorption) or the migration of insulin molecules out of the adsorbent (dessorption).

Which C_A, C_{A0}, q_A and q_m represent the concentration of insulin in the liquid phase, the initial concentration of insulin in the liquid phase, the concentration of insulin in the solid phase (rate of adsorption) and maximum capacity of the insulin adsorption in the solid phase, respectively. The constant kinetic dissociation (k_d) can be obtained from Eq. 9.

$$k_d = \frac{k_2}{k_1} \tag{9}$$

The solution of the system of ordinary equations from the batch model (Eqs. 7 and 8), was carried out applying the Runge-Kutta method of 4^{th} order, with a step size of 1.10^{-4}.

3. RESULTS AND DISCUSSION

The behavior of the experimental points (Cruz, 1997) of insulin adsorption is shown in Fig. 3, in which three different initial concentrations were considered.

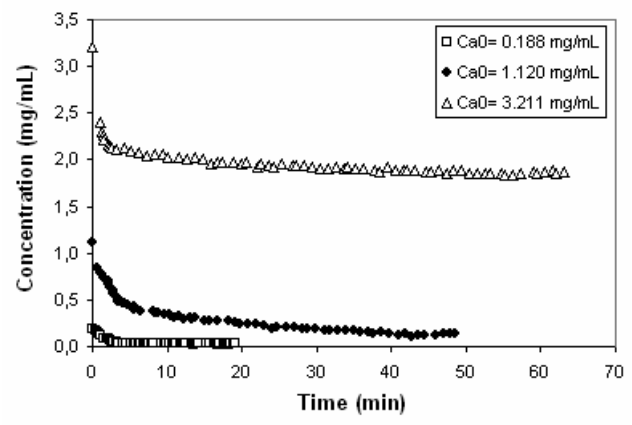


Figure 3. Kinetic behavior of the experimental data of the insulin adsorption

From Fig. 3 can be observed that each initial concentration of insulin goes to the equilibrium after a period of time. The final concentration of insulin or the equilibrium concentration of insulin is a parameter of great relevancy, which determines the moles balance between the equilibrium concentration (C_{eq}) and the initial concentration (C_{A0}). It is possible from the moles balance to estimate the maximum capacity of adsorption (q_m), since there is a finite number of adsorption sites.

The validation of modeling was carried out through the correlation between the agitated batch model and the experimental data (Fig. 3) of three different initial concentrations of insulin (Figs. 4-6).

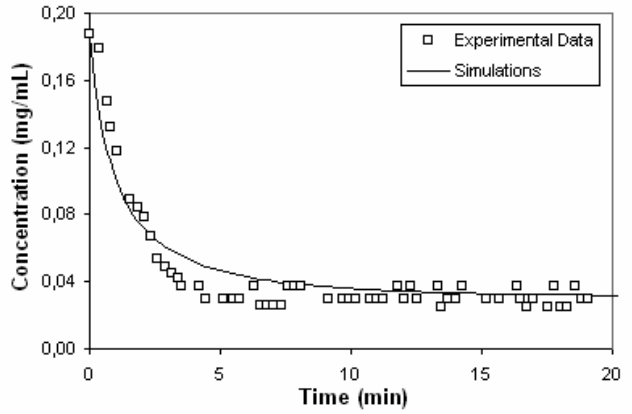


Figure 4. Correlation between the R2W inverse method (lines) and the experimental adsorption data (points) of the insulin on Accel Plus QMA®. Where C_{A0} = 0,188 mg/mL

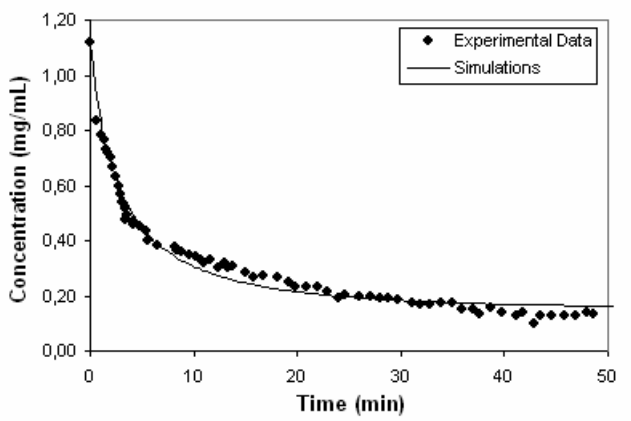


Figure 5. Correlation between the R2W inverse method (lines) and the experimental adsorption data (points) of the insulin onto Accel Plus QMA®. Where C_{A0} = 1,120 mg/mL

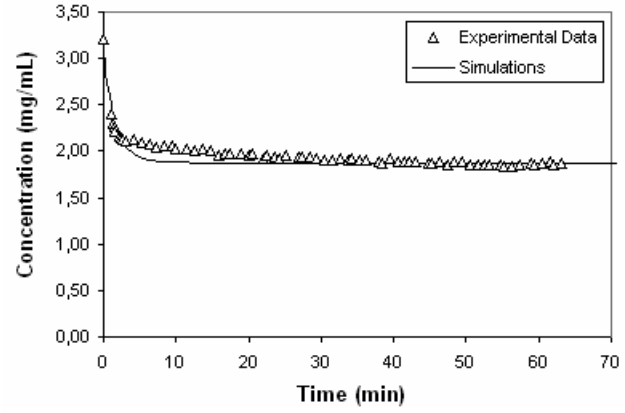


Figure 6. Correlation between the R2W inverse method (lines) and the experimental adsorption data (points) of the insulin onto Accel Plus QMA®. Where C_{A0} = 3,211 mg/mL

After observing the Figs. 4-6 it is possible to see that the simulations carried out show an excellent adjustment for all the initial concentrations studied. More satisfactory fit can be seen in the Fig. 4, for C_{A0} = 0,188 mg/mL. The correlations with the kinetic models is a factor of great importance, as the accuracy of estimation depends on the fit between the model and the experiments (more confiability of the results).

Therefore, the kinetic parameters estimated in simulations of the R2W method are show in the Table 1.

Table 1. kinetic parameters estimated in the simulations of the R2W method with experimental data

C_{A0} (mg/mL)	k_1 (mL/mg.min)	k_2 (min^{-1})	k_d (mg/mL)
0,188	2,982	$1{,}92.10^{-4}$	$6{,}40.10^{-5}$
1,120	0,171	$6{,}40.10^{-4}$	$3{,}74.10^{-3}$
3,211	0,136	$4{,}37.10^{-5}$	$3{,}20.10^{-4}$

In Table 1 an important phenomenology associated with experiments can be observed, that is the kinetic constant of adsorption decreases with the increasing of the initial concentration (Fig. 7).

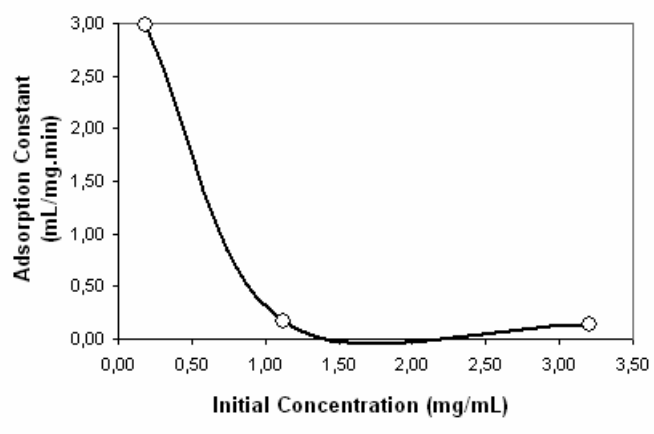


Figure 7. Values of kinetic constants of adsorption (k_1) with the initial concentration (C_{A0})

Such fact is associated with the competition of insulin molecules into adsorbent, since there is a finite number of adsorption sites in the adsorbent. It was also observed that the kinetic constant of desorption (k_2) is smaller than the kinetic constant of adsorption (k_1). Therefore, the mechanism of desorption in such cases can be ignored due to the kinetic constants of adsorption that is greater than the kinetic constants of dessorption. So, the mechanism of adsorption assumed in this work could be considered as an irreversible mechanism of adsorption. Some experimental studies lead to such hypothesis (Silva and Pereira, 1999). Therefore, washing and eluition steps must be used to return the initial property of adsorbent.

The dissociation constant is plotted into Fig. 8.

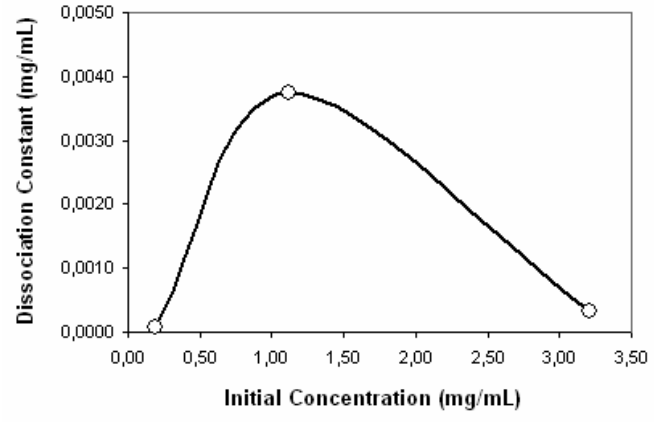


Figure 8. Kinetic scheme associate between the dissociation constant (k_d) with initial concentration (C_{A0})

The dissociation constant represents the ratio between the kinetic constant of adsorption and the kinetic constant of dessorption. So, it is possible to observe that the great value was related to the initial concentration of 1,120 mg/mL. Such fact demonstrates a big difference between k_1 and k_2 for this concentration.

In the Table 2, the maximum capacity of adsortion (q_m) is shown to each initial concentration. Also, the cost function (Q) is introduced as quantitative form of calculated residues in the simulations.

Table 2. Maximum capacity of adsortpion (q_m) and cost function (Q) associated

C_{A0} (mg/mL)	q_m (mg/mL)	Q
0,188	0,157	$6{,}79.10^{-3}$
1,120	0,987	$6{,}80.10^{-2}$
3,211	1,340	$4{,}26.10^{-1}$

The Table 2 shows the direct relation between the C_{A0} and q_m (Fig. 9).

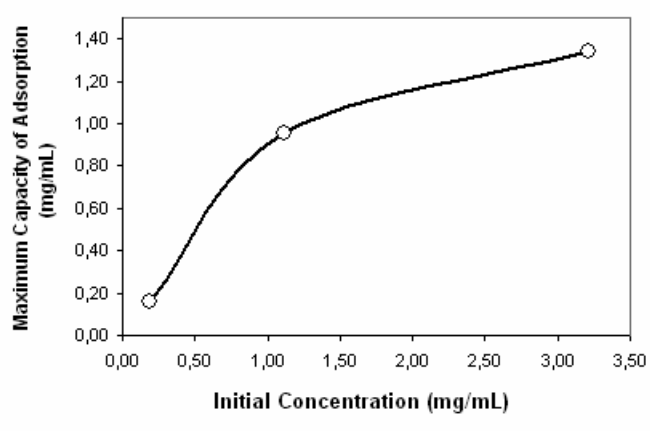


Figure 9. Relation between the maximum capacity of adsorption (q_m) and each initial concentration (C_{A0})

From these results can be concluded that the maximum capacity increase with the increase of the initial concentration of solutes, showing the proportional relation between these parameters. Also, an increase of the initial concentration causes a decrease of the cost function (Q). Thus it can be stated that increasing the initial concentration leads to more accurate estimations of the parameters of adsorption.

4. CONCLUSIONS

The inverse method R2W showed to be efficienty in the estimation of kinetic parameters of insulin adsorption. Its great advantage is related to many aspects. The first one is related to the excellent adjustment between the experimental data and the simulations. Other aspects are that the inverse algorithm is so simple to be implemented and the possibility to estimate multiple parameters at the same time. The R2W routine permitted to estimate the kinetic parameters of insulin adsorption with high accuracy; such observation was confirmed from the excellent adjustment between the experimental data and simulations.

5. ACKNOWLEDGEMENTS

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