Kinetic Studies on the Controlled Release of Oral Antibiotics

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In recent years, the physicochemical and biological properties of silica materials make these solids interesting matrices for performing the controlled delivery of drugs. In particular, ordered mesoporous silica such SBA-15 have been widely investigated as potential drug carriers. This paper presents the results of a kinetic study regarding the controlled release of cephalexin, which belongs to the group of cephalosporins or β-lactams antibiotics, from silica matrices of amino-functionalized and sulfonic-functionalized SBA-15. The study used the experimental results reported by Basaldella and Legnoverde for the release of cephalexin from oral dosage forms. The results showed that the release mechanism of cephalexin depends on the structure of the silica material and on the the surface functionalization.

Keywords: cephalexin, SBA-15, controlled release, kinetics

Over the past three decades, there has been a rapid growth in the area of drug delivery, in searching of new drug delivery systems, which can maintain the concentration of the bioactive agent in the precise sites of the body within the optimum range and under the toxicity threshold.

As a main tool to control the oral drug release rate from the formulations, the pharmaceutical scientists often use polymeric matrices with specific properties which, so far, have not been attained by any other materials.

In recent years, the physicochemical and biological properties of silica materials, such as high surface areas, well-ordered structures, controllable mesoporosity, no toxicity and good biocompatibility make these solids interesting matrices for performing the controlled delivery of drugs. In particular, ordered mesoporous silica such MCM-41 and SBA-15 have been widely investigated as potential drug carriers [1].

SBA-15 presents large, controlled pore size and highly ordered hexagonal topology. For pure SBA-15 the channel walls there are only silanol groups which form weak intermolecular hydrogen bonds with the bioactive agents. The bonds are not strong enough to hold drugs and allow them to be released in a sustained manner. Therefore, introduction of functional groups on the surface of this mesoporous material, to induce specific host-guest interactions with drugs, is important and beneficial for the delivery process [2-7].

In the design of drug delivery systems, it is necessary to study and optimize the drug delivery dynamics specific for the release kinetics.

This paper presents the results of a kinetic study regarding the controlled release of cephalexin, which belongs to the group of cephalosporins or β-lactams antibiotics, from silica matrices of amino-functionalized and sulfonic-functionalized SBA-15.

Mathematical modeling of drug release

For many drug delivery systems, the release process can be modeled by using the classical unsteady state Fick's diffusion equation having appropriate boundary conditions or with the Higuchi expression [2]. The dosage forms represented by tablets can be considered as sheets. For the diffusion from a sheet and constant diffusivities, the equation [8] takes the form:

$$\frac{\partial C}{\partial t} = D \cdot \frac{\partial^2 C}{\partial x^2} \quad (1)$$

The initial and boundary conditions are written as follows:

$$t = 0; -L \le x \le +L; C = C_0$$
$$t > 0; -D\left(\frac{\partial C}{\partial x}\right)_L = h(C_s - C_\infty) \quad (2)$$

When the rate of stirring of the release medium is high enough, the value of the mass transfer coefficient is practically infinite, and the drug concentration on the surface reaches its value at equilibrium as soon as the dosage form is put in contact with the liquid.

In this case, the amount of drug released after a period of time *t*, as a fraction of the corresponding quantity after infinite time, is calculated from the equation [8]:

$$\frac{M_t}{M_\infty} = 1 - \frac{8}{\pi^2}\sum_{n=0}^{\infty}\frac{1}{(2n+1)^2}\cdot\exp\left(-\frac{(2n+1)^2\pi^2}{4L^2}D\cdot t\right) \quad (3)$$

The Higuchi equation describes the release of a drug from a porous system as the square root of a time dependent process based on a Fickian diffusion [2]

$$M_t = \sqrt{2D\cdot S\cdot\varepsilon(A - 0.55\cdot\varepsilon)\cdot t} = k_H\sqrt{t} \quad (4)$$

The parameter of the model is the release rate constant, k_H.

Most of work on the kinetics of the release of drugs from mesoporous carrier materials used Higuchi equation and showed a two step release profile, composed of an initial burst followed by slow release [2].

Because some release processes are dependent on the interaction between the drugs and the ionic components of the release medium, a kinetic interaction/reaction model can also be applied [9-10]. Considering a second order mechanism to describe the release process:

$$\frac{dC}{dt} = k(C_e - C)^2 \quad (5)$$

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Integration of equation (5) gives:

$$C = \frac{C_e^2 \cdot k \cdot t}{1 + C_e \cdot k \cdot t} \quad (6)$$

In terms of release percentage it becomes $\left(R = \frac{C}{C_0}\right)$:

$$R = \frac{R_e^2 \cdot k \cdot t}{\frac{1}{C_0} + R_e \cdot k \cdot t} \quad (7)$$

or

$$\frac{R}{R_e} = \frac{R_e \cdot k \cdot t}{\frac{1}{C_0} + R_e \cdot k \cdot t} \quad (8)$$

The parameters of the model are the percentage release in bulk liquid at equilibrium R_e and the kinetic constant k. The ratio between the current release percentage and percentage release in bulk liquid at equilibrium is equivalent with the amount of drug released after a period of time *t*, as a fraction of the corresponding quantity after infinite time.

Results and discussions

In our studies were considered the experimental results reported by Basaldella and Legnoverde for the release of cephalexin from oral dosage forms prepared with amino-functionalized and sulfonic-functionalized SBA-15, in water [1]. The release rate exhibits two steps, beginning with a fast delivery over the first 5h, followed by a slower desorption during the next 25h. Regarding this second stage, the time needed to attain a plateau is influenced by the surface functionalization.

The standard errors of all models were established by using the equation [11]:

$$e = \frac{\left\| \frac{M_{exp}}{M_\infty} - \frac{M_{calc}}{M_\infty} \right\|_2}{\sqrt{N - p}} \quad (9)$$

Based on the experimental data, we established the effective diffusivities of cephalexin and the drugs release was simulated by using equation (3).

Figure 1 shows the release behaviour of cephalexin from amino-functionalized SBA-15 matrices, using a value of $1.1 \cdot 10^{-11}$ m^2/s for the effective diffusivity.

In figure 2, the release profile of cephalexin from sulfonic-functionalized SBA-15 matrices is represented,

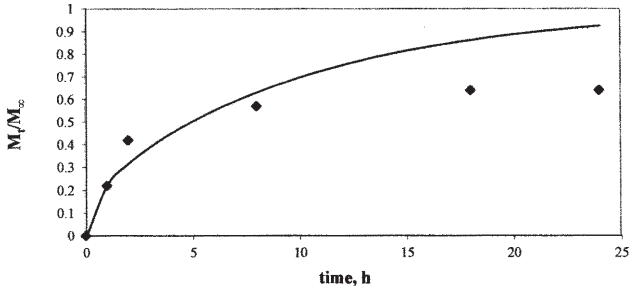

Fig.1 The release profiles of cephalexin from amino-functionalized SBA-15 matrices. ♦ Experimental profile; - Predictions of the diffusional model

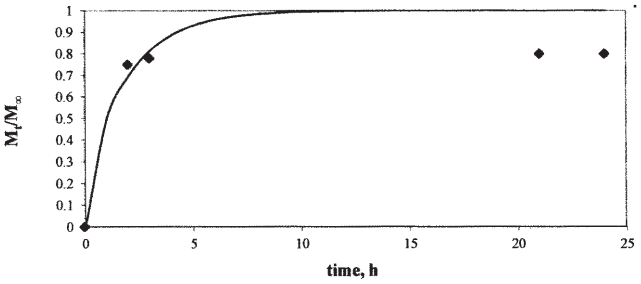

Fig. 2 The release profiles of cephalexin from sulfonic-functionalized SBA-15 matrices. ♦ Experimental profile; 6 Predictions of the diffusional model

considering a value of $5.6 \cdot 10^{-11}$ m^2/s for the effective diffusivity.

The predictions of the classical unsteady state Fick's diffusion equation were able to describe the release processes only for 60% of released drug from amino-functionalized SBA-15 matrices and respectively 80% of released drug from sulfonic -functionalized SBA-15 matrices. Over these values the simulation results show significant differences compared to the experimental data.

Applying the Higuchi model in two steps for the same experimental results, the established values of parameters are presented in tables 2-3.

Figures 3-4 indicate that the theoretical predictions with Higuchi equation serve as a reasonable estimate for the release processes of cephalexin from functionalized SBA-15 matrices.

For the kinetic interaction/reaction model, we also determined the values of the model parameters, presented in table 3.

Figures 5-6 shows the model fitting of eq. (8) to drug release experimental data.

	$D_{eff} \cdot 10^{11}$ (m^2/s)	e
Amino-functionalized SBA-15 matrices	1.1	0.06444
Sulfonic-functionalized SBA-15 matrices	5.6	0.04202

Table 1
THE VALUES OF THE PARAMETERS OF THE DIFFUSIONAL MODEL AND THE STANDARD ERROR FOR THE RELEASE OF CEPHALEXIN

T	k_h, % of $M_\infty/h^{0,5}$	e
t < 2h	27.135	0.00276
t >2h	6.3939	

Table 2
THE VALUES OF THE PARAMETERS OF HIGUCHI MODEL AND THE STANDARD ERROR FOR THE RELEASE OF CEPHALEXIN FROM AMINO-FUNCTIONALIZED SBA-15 MATRICES

T	k_h, % of $M_\infty/h^{0,5}$	e
t < 3h	48.237	0.00385
t >3h	0.6594	

Table 3
THE VALUES OF THE PARAMETERS OF HIGUCHI MODEL AND THE STANDARD ERROR FOR THE RELEASE OF CEPHALEXIN FROM SULFONIC-FUNCTIONALIZED SBA-15 MATRICES

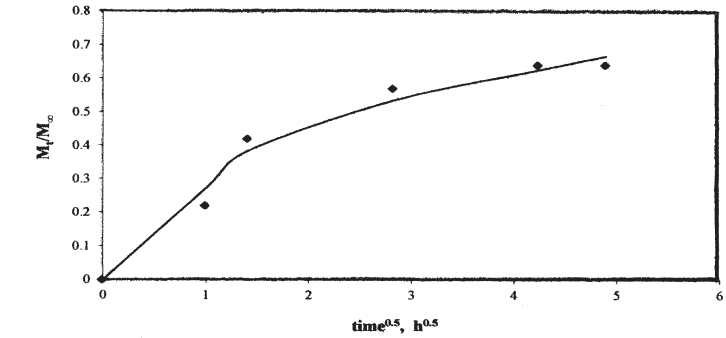

Fig.3 The release profiles of cephalexin from amino-functionalized SBA-15 matrices.
♦ Experimental profile; - Predictions of the Higuchi model

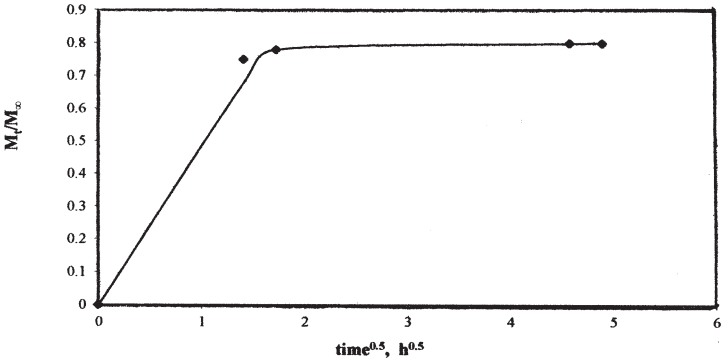

Fig.4 The release profiles of cephalexin from sulfonic-functionalized SBA-15 matrices.
♦ Experimental profile; - Predictions of the Higuchi model

Carrier	k,cm^3/mg·h	R_e, %	e
Amino-functionalized SBA-15	$7.72 \cdot 10^{-5}$	75.75	0.00483
Sulfonic-functionalized SBA-15	$4.80 \cdot 10^{-4}$	80.64	$7.1158 \cdot 10^{-5}$

Table 3
THE VALUES OF THE PARAMETERS OF THE KINETIC INTERACTION/REACTION MODEL AND THE STANDARD ERROR FOR THE RELEASE OF CEPHALEXIN FROM FUNCTIONALIZED SBA-15 MATRICES

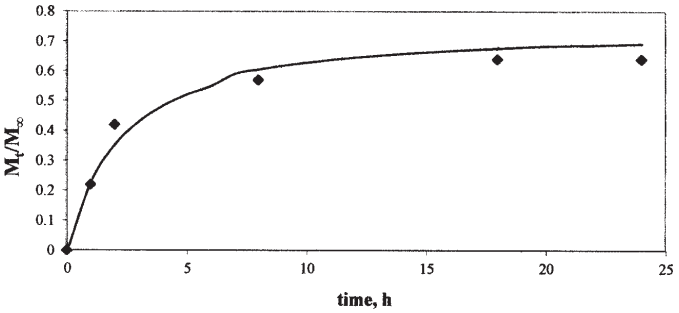

Fig.5 The release profiles of cephalexin from amino-functionalized SBA-15 matrices.
♦ Experimental profile; - Predictions of the kinetic interaction/reaction model.

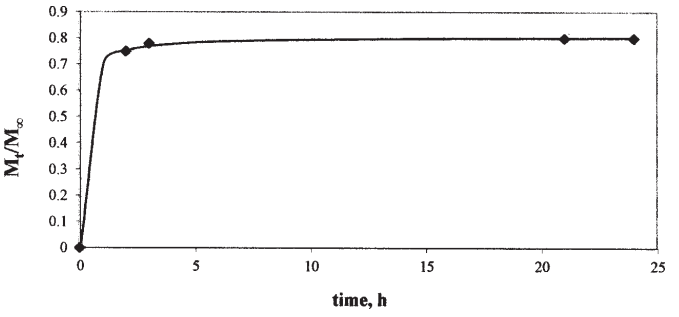

Fig.6 The release profiles of cephalexin from sulfonic-functionalized SBA-15 matrices.
♦ Experimental profile; - Predictions of the kinetic interaction/reaction model.

By comparing the values of the standard error between the Higuchi model and the kinetic interaction/reaction model (table 1-3) it is found that for the release from amino-functionalized SBA-15 matrices, the kinetic Higuchi model gives the best predictions (0.276%). Such a result sustains the conclusion that the amino functionalization is responsible for the reinforcement of the chemical interaction between the silica surface and the cephalexin molecule. In the case of the release from sulfonic-functionalized SBA-15 matrices, the kinetic interaction/reaction model gives a better performance than the Higuki model, showing that the interaction between the cephalexin molecule and the silica surface is not so strong and the influence of the release medium becomes important. In concordance to the high standard errors for the classical unsteady state Fick's diffusion model, one can presume that in the present case this model is not adequate.

Conclusions

Based on the experimental data from the recent literature and hypothesized drug release mechanisms, appropriate mathematical models were used to predict the release kinetics of cephalexin from oral dosage forms prepared with amino-functionalized and sulfonic-functionalized SBA-15. The study showed that the release mechanism of cephalexin depends on the structure of the silica material and on the the surface functionalization.

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Notations

A- total amount of drug in the matrix per unit volume
C- concentration of drug
C_0 - initial concentration of drug
C_e- concentration of drug at liquid interface at equilibrium
D - diffusivity
e - standard error
h - mass transfer coefficient
k- kinetic constant
k_H- release rate constant for the Higuchi model in the dissolution medium
L - mid-depth of the tablet
M_t - amount of drug released after a period of time *t*
M_∞- amount of drug released after infinite time
R- percentage release in bulk liquid
R_e- percentage release in bulk liquid at equilibrium
S- solubility of drug
t- time
ε - porosity
$\|\bullet\|_2$ - Euclidean norm

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