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Original Article

The Use of Isothermal Solution Calorimetry as a Promising Technique to Monitor Drug Release Kinetics

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Abstract

The objective of the present article is to emphasize that isothermal solution calorimetry (ISC) can be used to determine kinetics of reactions of interest in biotechnology. The major advantage of this technique is that it enables to characterize drug release profiles in real time noninvasively. Here ISC was used to monitor pyrimethamine release incorporated in hydrogels of oxidized alginate, ADA, and oxidized alginate blended with chitosan, ADA-Chit. The mechanism of pyrimethamine release was analysed using the semi-empirical equation so-called power law. From plots of cumulative heats concerning drug release, Qrel(t), versus time, values of apparent rate release, k, and diffusion exponent, n, were determined. The values of n were found to be 1.22 for ADA and 1.09 for ADA-Chit, indicating that the drug release is controlled by polymer relaxation.

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Keywords

Solution calorimetry; pyrimethamine, release kinetics

Introduction

Significant research efforts have been focused on the development of controlled release of therapeutic agents. Nowadays, the development of techniques to characterize drug release profiles remains one of the biggest challenges. The article of Wang and coworkers [1] provides a comprehensive overview of the spectrophotometric, chromatographic, mass spectrometric and potentiometric methods, highlighting its advantages and limitations as applied to dissolution testing.

In general, the direct UV/VIS spectrophotometric determination of absorbance has been the traditional analytical method for quantifying drug release in dissolution tests. Nevertheless, among other disadvantages, the linearity of the Lambert-Beer's law is limited by chemical and instrumental factors. This article attempts demonstrate that ISC can offer advantages compared to conventional methods, since it is a noninvasive technique that allows the measurements of continuous energies of drug release in real time.

The use of biodegradable polymers for controlled drug release systems has increased dramatically. There is a growing interest in the production and use of new materials from renewable sources and thus natural polymers are replacing synthetic polymers in pharmaceuticals and biomedical devices [2-10]. A previous study has been focused on the development of hydrogels of oxidized alginate (ADA) and oxidized alginate blended with chitosan (ADA-Chit) [11]. It is shown that the aldehyde groups on the surface of 2,3-dialdehyde alginate may be used for attachment of the amino-containing chitosan, thus creating hydrogel with interconnecting pores for diffusion of an antifolate drug, the pyrimethamine. Pyrimethamine is an antifolate drug that specifically inhibits the enzymes of the folate biosynthetic pathway in infectious microorganisms [12].

It is known that the goal of identifying antifolates with high species selectivity and potency remains unachieved despite the efforts of a number of research groups. Since knowledge of characteristics of the processes that govern the release rate of a drug is essential to tailor release to a specific pharmacological profile [13, 14], in this study we elected ADA and ADA-Chit as polymeric matrix systems to investigate pyrimethamine (PYR) release monitored by ISC.

Experimental section

Materials and methods

Sodium alginate, sodium tetraborate decahydrate, pyrimethamine (PYR) and Phosphate buffered saline (PBS. pH 7.4) were purchased from Sigma (USA). Chitosan with deacetylation degree of 85% and Mv (viscosity-average molecular weight) of 3.22 x 10^5 g/mol was a generous gift of Primex Ingredients A.S. (Norway). Sodium periodate and ethylene glycol were obtained from Aldrich and used as received. Dimethyl sulfoxide (DMSO) was purchased from Merck. All other reagents were

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of analytical or equivalent grade. Double-distilled water was employed throughout.

The methods of alginate modification by oxidation with sodium periodate and subsequent Schiff's base formation in order to obtain ADA and ADA-Chit are previously reported [11].

PYR incorporation in ADA and ADA-Chit

For incorporation of the drug, 1000 mg of ADA and ADA-Chit were added in 50 dm^3 of pyrimethamine solutions prepared in dimethyl sulfoxide in the concentration 1,0 x 10^{-4} mol dm^{-3} and then left overnight in a refrigerator. After, the materials were withdrawn and carefully dried with filter paper and then stored at 277 K. The dye equilibrium concentration, C_{eq}, was determined in the supernatant by using a spectrophotometer (Femto, 700 Plus). For this purpose, previous analytical curve was obtained in the wavelength of 280 nm. From C_{eq} values, the drug amount that interacts, n_{int}, was determined. The values of n_{int} were found to be 3.98 ± 0.15 µmol for ADA and 3.79 ± 0.11 µmol for ADA-Chit. The experiment was repeated in duplicate.

ISC determinations

Calorimetric measurements of pyrimethamine release from ADA and ADA-Chit were performed at 310 K in a SETARAM C80 mixing calorimeter. Calorimeter's performances and details of operation have been previously described [15,16]. Samples of approximately 100 mg of ADA and ADA-Chit with incorporated PYR were put into the lower part of the mixing cell closed by a circular membrane of Teflon. Into the upper part of mixing cell, a volume of 3.0 dm^3 of phosphate buffer (PBS. pH 7.4) was added. After thermal equilibrium was attained, a movable rod enables the phosphate buffer to be pushed into the container with a specific hydrogel (ADA or ADA-Chit) with the adsorbed drug. Each individual experiment yields a thermal effect due to release process, Q_{rel}. The thermal effects corresponding to addition of phosphate buffer in ADA and ADA-Chit impregnated with DMSO were found to be negligible. In order to determine the release efficiency, after each Q_{rel} recording, the drug equilibrium concentration, C_{eq}, was determined in the supernatant. Each experiment was repeated in duplicate.

Results and discussion

Calorimetry plays an important role in biotechnology [17]. Here it is propose to use isothermal solution calorimetry as a potential noninvasive technique to monitor release kinetics of drug delivery in real time. Solution calorimetry has been used to monitor swelling and dissolution of polymers [13], but, from our knowledge, there is no literature report focusing on release kinetic studies using ISC.

In this study we use DMSO in order to impregnate PYR because of the poor solubility of the drug. DMSO is a good solvent for many pharmaceutical products and is capable of penetrating cellular membranes without significant or permanent damage [18]. From n_{int} values it was found that pyrimethamine was incorporated in ADA and ADA-Chit with an efficiency of 79.60 and 75.80%, respectively.

From the ISC responses (power versus time) concerning to thermal effects due to total amount of released drug, Q_{rel}, it was observed that for ADA the drug was released within 1 hour and 34 minutes approximately, while release was faster for PYR impregnated in ADA-Chit. Despite the similar n_{int} values for both hydrogels, the release efficiency was of 68% for ADA and of 82% for ADA-Chit, determined as described ISC determinations. Each average calorimetric response was corrected using the following equation [19]:

$$Q_C = Q_{NC} + \tau\,(d\,Q/\,d\,T)$$

where Q_C is the corrected curve, Q_{NC} is the uncorrected curve, τ is a constant whose value is 100 seconds (according the SETARAM Scientific & Industrial Equipment Guide), and $(dQ/\,dT)$ is the derivative of the uncorrected curve. After correction, the detectable calorimeter signals (power versus time) were integrated joining two points selected to each 2 min of release time, thus obtaining the fraction of released drug to that time, $Q_{rel(t)}$, as can be observed in figure 1. The sums of cumulative heats were performed using the software SETSOFT version 1.54 f (SETARAM).

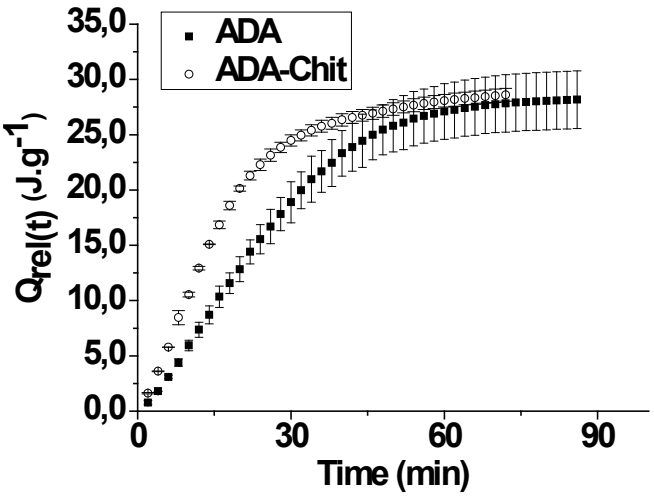

Figure 1. *Fraction of PYR released in time t, $Q_{rel(t)}$, versus time, from the sums of cumulative heats of calorimeter signals.*

To find out the mechanism of drug release, ISC results were fitted in a very frequently used model to describe drug release, the so-called Peppas equation, or power law [20]:

$$\ln \alpha = \ln k + n \ln t$$

where $\alpha = Q_{rel(t)} / Qr_{el}$, k is the apparent release rate, and n is the diffusion exponent that depends on the transport mechanism and the shape of the tested matrix. Plots of ln α versus ln t can be observed in figure 2, which shows that a straight line through the entire range of the release process was not observed. However, values of n and k can be obtained for the range within which the data are linear [20]. The values of n concerning release from ADA and ADA-Chit were found to be 1.22 and 1.09, respectively. The apparent release rate (k) for release from ADA was 0,012, meanwhile a value of 0,028 min-1 was found for PYR release from ADA-Chit. Values of n greater than 1.0 can be regarded as an indicator that drug release is controlled by polymer relaxation [21]. It is possible that the higher k value for ADA-CHIT reflects that release process in which the drug is held by physical entrapment within the hydrogel is faster than that in which the drug is chemically attached. We hypothesized this find based on previous enthalpy change values for interaction of PYR with ADA (-11.73 ± 0.517 kJ mol^{-1}) and ADA-Chit (-4.86 ± 0.156 kJ mol^{-1}) [11] from which was concluded that "the higher enthalpy change

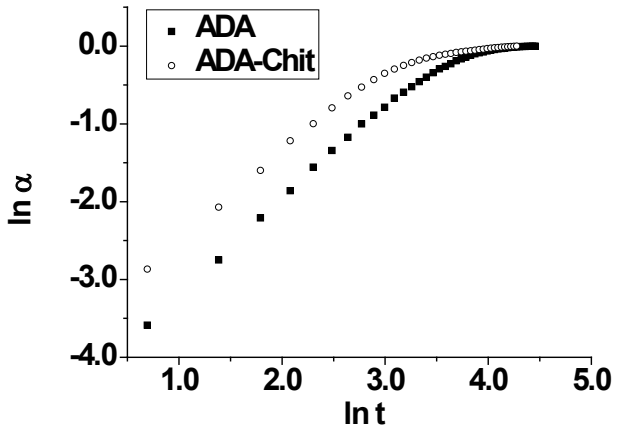

Figure 2. *Plots of ln* α *(*α = $Q_{rel(t)}$ / Q_{rel}*) versus ln t for PYR release from ADA and ADA-Chit at 310 K. .*

value for the interaction of PYR with ADA is probably due to the chemical attachment of the drug whose amino functions can enter into Schiff's reaction with the aldehyde groups in ADA".

Conclusions

This new work shows that isothermal solution calorimetry can be a simple, fast, direct and noninvasive technique to characterize drug release profiles. The outstanding feature is the capability to acquire information on kinetic behaviors of the continuous drug release in real time. It was argued that drug release profiles can be directly correlated to the interaction enthalpies of drugs with a polymeric matrix. Despite the advantages of the ISC technique, we argue that further studies are needed before that isothermal titration calorimetry can be used as an integral alternative technique of future research and development in pharmaceutical technology.

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