Drug release system: Chlorambucil loaded in mesoporous cellular foam (MCF)

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Introduction

Nanotransporters have received a great deal of research attention because of their promising opportunities in drug delivery [1-5]. Attempting to minimize the secondary adverse events of anticancer drugs and enhance the therapeutic rate, various nanotransporters have been devised, including dendrimers [6, 7], liposomes [8, 9], inorganic nanoparticles, and polymeric nanoparticles [10-13].
Chlorambucil (CLB), is a substance classified as a human carcinogen [14], it is used as a chemotherapy drug administered for treating some types of cancer. It is mainly used to treat chronic lymphocytic leukemia, low-grade non-Hodgkin's lymphoma, Hodgkin's lymphoma and ovarian cancer. Chemically, it is 4-[4-bis(2-chloroethyl) amino phenyl butyric acid. MCFs (mesostructured siliceous cellular foams), that can be derived after the inclusion of a bulking medium in the synthesis procedure of SBA-15 [4], are composed of spherically uniform cells 15-50 nm diameter [15], exhibit high surface areas and porosities, and have adjustable pore size distributions [15, 16]. The open large pore system gives MCF unique advantages as catalyst support and separation media for processes involving large molecules. In addition to their specific physicochemical properties, they possess high biocompatibility and low adverse effects, which with their biodegradability, making them attractive for controlled drug release applications.

Experimental

For the synthesis of the MCF host, a one-pot synthesis method was used [17]. For the synthesis mesitylene was used as a swelling agent, TEOS as the silica source, a triblock copolymer P123 as a surfactant and ammonium fluoride as a mineralizing agent. The procedure was described in our previous work [4].
MCF-CLB nanocomposite was prepared by the adsorption of the drug into the porous of the MCF host in an ethanol solution. The release of the drug was implemented by simulating the physiological conditions, for which the composite was immersed, in tablet form, initially in a HCl solution (0.1M) for two hours and then in a pH 7 buffer solution to reproduce the conditions of the organism. The experiment was performed in a bath at 37 ° C and under continuous stirring. At the specific time interval, an amount of sample was withdrawn and filtered, and the quantity of CLB was determined by UV-Vis spectrophotometry (λ = 258 nm).

Results and Discussion

Figure 1 A) presents the wide-angle patterns of the host MCF, the composite MCF-CLB and the pure drug CLB. For the host MCF, wide XRD peaks were observed in the range of 2θ to 20-25°, which correspond to the mesoporous nature [18]. The drug-loaded MCF XRD pattern (MCF-CLB) exhibits the characteristic peaks of CLB, indicating that the drug is present in the pores of the mesoporous foam, with its crystalline structure. However, after the adsorption of the drug, the MCF maintained the characteristic mesoporous structure. Figure 1 B) shows the diffuse reflectance spectrum of the host, the composite and pure drug. As expected, the host shows no absorption band. The band at 252 nm is attributable to Aromatic π → π* transitions. The band at 305 nm is characteristic of π → π* transitions, from methyl- and nitrogen-substituted aromatic rings in the p-position (methyl p-toluidine) [19], which appears in the analysis of the composite. The two species that generate these electronic transitions are characteristic of CLB.

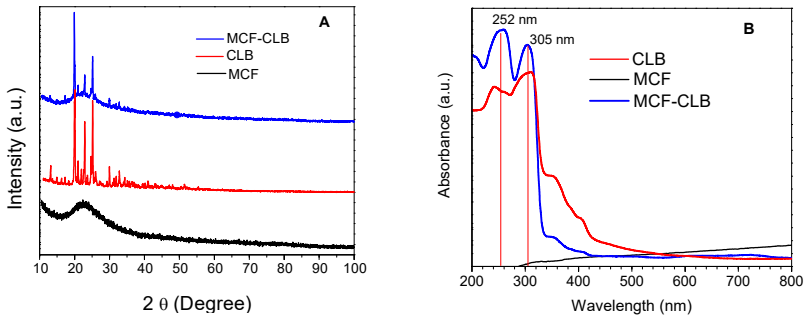

Figure 1: A) Wide angle XRD patterns, B) UV-Vis DRS of MCF, MCF-CLB and pure CLB.

Figure 2 shows the release of CLB contained in MCF. Dissolved commercial LEUKERAN® tablets (sugar-coated), were used as a control, releasing 80% at 2 h and entirely at 8 h (first order kinetics). While CLB release from MCF was first

released rapidly (pH=1, gastric tract) 66% at about 4 h and then continued for a prolonged time to reach 100% at 35 h, at pH 6.7 (intestinal tract), which are the absorption pathways of the drug (see Figure 2).
The models used to fit the mechanism of chlorambucil release from the MCF matrix are the first-order kinetic model, the Schott model, the Weibull model and the Ritger and Peppas model (see Table 1). These mathematical models are widely used to determine the mechanism of drug release from a delivery system. The drug release profile for CLB-MCF can be interpreted as a biphasic. Thus, there is a fast release phase associated with the diffusion of the drug, adsorbed or weakly bound, to the polymeric carrier matrix, followed by a slow release phase associated with the diffusion of the drug into the porous host or into the smaller pores.

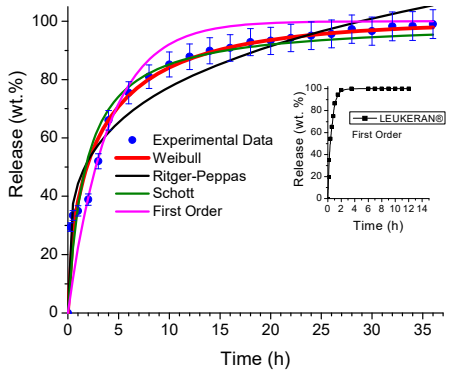

Figure 2: Release of chlorambucil

Table 1. Fitting parameters and fitting statistics of models

	Fitting parameters	R^2	Adj-R^2	SSE	S
Ritger Peppas	k 0.443 n 0.242	0.960	0.956	0.0714	0.0613
First Order	k 0.253	0.913	0.908	0.1569	0.0864
Weibull	a 0.488 b 0.579	0.971	0.967	0.0346	0.0426
Schott	k 0.575	0.935	0.931	0.0773	0.0623

R^2 coefficient of determination, Adj-R^2 adjusted R^2, SSE final sum of squared errors, S standard deviation of the distance between the data and the fitted values.

Conclusions

In this study, we demonstrate an auspicious drug host material for efficient encapsulation and controlled release of CLB, performing the required therapeutic efficacy. Studies indicate that the drug is present in the pores of the mesoporous foam, with its crystalline structure, without affecting the structure or chemical composition of CLB. The models used to fit the mechanism of chlorambucil release from the MCF matrix are the first-order kinetic model, the Schott model, the Weibull model and the Ritger and Peppas model. All statistical parameters indicate that the best model describing the phenomenon under study over the entire period is the Weibull model. The main advantage of this release is that the rate of release is fast at the beginning and then gradually decreases until 24 h practically all of the drug contained in the carrier is released (>95%) achieved advantageous therapeutic effects.

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