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ORIGINAL ARTICLE

Interactions of terbinafine with β-cyclodextrin polymers: sorption and release studies

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Abstract β-cyclodextrin insoluble polymers (βCDP), a type of hydrogels with a high swelling capacity, can be obtained by crosslinking β-cyclodextrin (βCD) with epichlorohydrin. Terbinafine (TB) is an oral and topical antifungal drug that can be housed into the cavity of β-cyclodextrin, so it seems probable that the drug could interact with the insoluble βCDP. Different organic molecules can be sorbed on the polymer network and also included within the βCD cavities, so these hydrogels have potential applications in the pharmaceutical field as drug carriers. In this work, the sorption of TB on βCDP and the optimal conditions to load the polymer with the drug were studied. Sorption kinetics and Freundlich isotherms of TB on βCDP at 25°C were obtained and the influence of several parameters on the sorption process of TB was investigated. It was found that a high initial concentration of drug, high TB:β-CD molar ratios and low ionic strengths were the most favourable conditions. No significant influence of temperature was observed. Moreover, the sorption kinetic profile obtained for terbinafine was compared to that of naftifine, another antifungal agent of similar structure. Terbinafine presented higher affinity for the polymer, according to the higher stability constant of the drug-βCD inclusion complex. In relation to the release studies from the loaded polymer, 0.1 M HCl was the most favourable medium to allow the release of the drug. The maximum amount of drug released in 24 h was up to 50% of TB loaded. The predominant mechanism of drug release was Fickian diffusion.

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Introduction

Cyclodextrins (CDs) are torus shaped oligosaccharides capable of forming inclusion complexes with a wide variety of molecules, especially aromatic compounds, either in solution or in the solid state. This property makes CDs useful in different fields, extensively described in the literature [1].

In the last few years, the interest has been focused on the synthesis of polymeric cyclodextrins (βCDP). These are usually obtained by reaction of the native CDs with a crosslinking agent, such as epichlorohydrin (EP). Although EP is not safe for humans and the environment, it is widely used as an intermediate for the synthesis of many products. The polymers are purified before use and the presence of free unreacted EP can be discarded [2]. Depending on the polymerization conditions the crosslinking degree is different, and either soluble or insoluble CD polymers can be obtained. Hydrogels are polymeric compounds; they are insoluble in water at physiological temperature and pH and show a high swelling capacity. Because of their ability for retaining a large amount of water, these three-dimensional hydrophilic networks maintain a certain degree of structural integrity and elasticity [3]. Previous studies have revealed that two complementary sorption processes take place with different organic molecules: they can be sorbed on the polymer network and also included within the βCD cavities [4, 5]. The presence of βCD in the polymer increases the sorption values in comparison with those of dextran polymers; this fact shows that the inclusion phenomena play an important role in the sorption process and explains the higher host:guest ratios often obtained with these polymers [4].

The application fields of these materials are in continuous development as new cyclodextrin polymers are being synthesised [4]. These polymers have been used to remove water pollutants [5–7], in chromatography [8] and in the food and pharmaceutical industries [9–11]. In this sense, these hydrogels could have potential applications in the pharmaceutical field as drug carriers.

The drug selected for this study was terbinafine (TB), an antifungal agent of the allylamine group that selectively inhibits fungal squalene epoxidase (Fig. 1). This compound shows activity against yeast, fungi, moulds and dermatophytes and it is indicated for both oral and topical treatment of mycoses [12, 13]. Terbinafine can be housed into the cavity of β-cyclodextrin leading to non covalent inclusion complexes and the values of the corresponding stability constants make them suitable for possible pharmaceutical applications [14].

In this work, the possibility of using a βCDP as drug carrier system has been explored. Two main aspects were investigated, firstly, the sorption of TB on the polymer and, secondly, the release of the drug from the loaded polymer. In this sense, the sorption kinetics and Freundlich isotherm of TB on βCDP at 25°C were obtained and the influence of several parameters, such as the initial drug concentration, TB:β-CD molar ratio, temperature and ionic strength was investigated with the aim of finding the best conditions for loading the polymer. Moreover, the sorption kinetic profile obtained for TB was compared with that of naftifine (NF), another antifungal agent of similar structure, in order to study the influence of the drug structure on the sorption process.

Finally, once the polymer was loaded, the drug release profiles were studied in water and in 0.1 M HCl.

Materials and methods

Materials

Terbinafine and Naftifine hydrochlorides were kindly supplied by Novartis (Basel, Switzerland) and Schering (Milan, Italy), respectively. Insoluble βCDP was purchased from Cyclolab (Budapest, Hungary) in spherical beads. The polymer contains ca. 65% β-CD and has a swelling capacity of 5 cm^3/g. It was used sieved between 100 and 315 μm and the polymer was swollen before the sorption assays. All the other reagents were of analytical grade, from Panreac (Barcelona, Spain).

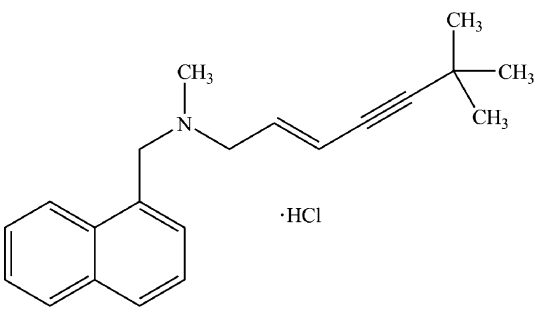

Fig. 1 Chemical structure of terbinafine

Methods

Sorption studies and optimization of drug loading

The sorption isotherm was obtained by stirring 50 mL of 5.0×10^{-5} M TB aqueous solutions with different amounts of polymer during 1 h at 25°C. Once the sorption equilibrium was reached, samples were measured spectrophotometrically at 222 nm. The results were fitted to the empirical Freundlich equation. This relationship assumes that there are multiple types of sorption sites acting in parallel, each one exhibiting a different sorption free energy.

$$q = K_F C_{eq}^{1/n_F}$$

where q is expressed as μmol TB sorbed/g dry polymer; C_{eq} is the equilibrium TB concentration (M); K_F and $1/n_F$ are the capacity constant and the heterogeneity factor, respectively. Both are empirical constants dependent on several environmental factors.

The sorption kinetic tests of TB on βCDP were performed in aqueous solutions at different temperatures (from 25 to 45°C). 200 mL of TB aqueous solution were stirred in the presence of the polymer. Samples were taken at different times during 60 min and measured in the aforementioned conditions. The sorption efficiency was expressed as percentage uptake in relation to the initial amount of drug.

The influence of TB:β-CD molar ratio was studied being $[TB]_o = 5.0 \times 10^{-5}$ M. The assays using different values of TB initial concentration were developed at 1:40 TB:β-CD molar ratio and 25°C.

With respect to the influence of the ionic strength, the tests were performed in 5.0×10^{-5} M TB in water (aprox pH 4, $I = 5.0 \times 10^{-5}$ M) and in 1.0×10^{-4} M HCl ($I = 1.5 \times 10^{-4}$ M) at 25°C.

The kinetic studies of NF were performed employing 5.0×10^{-5} M NF aqueous solutions and the samples were measured spectrophotometrically at 254 nm.

Each experiment was repeated at least three times under identical conditions.

Release studies

The release assays were carried out using a Sotax dissolution testing apparatus. A total of 1 g of loaded dry

polymer was stirred in 900 mL of water or 0.1 M HCl during 24 h at 37°C; 3 mL samples were taken at fixed times and measured spectrophotometrically. After taking each sample, 3 mL of dissolution medium were replaced in order to keep the volume constant.

Results and discussion

Sorption studies and optimization of drug loading

A sorption isotherm represents the relationship between the amount of solute loaded and the solute concentration remaining in solution. The sorption equilibrium is established when the rates of the sorption and desorption processes are equivalent. There are several isotherm equations for analyzing the data of the sorption assays; it has been found that the experimental data fit quite well to the Freundlich isotherm [2]. It is a suitable model for systems with heterogeneous binding sites and, as it was said before, the type of polymer employed in this work exhibits the possibility of the inclusion of solutes in the cyclodextrin cavities and also the adsorption on the polymer network. The experimental data of the amount of TB retained at different TB:βCD molar ratios at 25°C was fitted to the Freundlich model (Fig. 2). The Freundlich parameters have been calculated, being $K_F = 305$ µmol g^{-1} $(mol/L)^n$ and $n_F = 4.2$ ($r^2 = 0.940$), which indicates a favourable sorption process [2, 15].

In addition, the influence of initial drug concentration, temperature, TB:βCD molar ratio and ionic strength of the solution medium on the sorption of TB on βCDP has been studied to achieve the optimal conditions to load the polymer in order to use it for the drug release analysis.

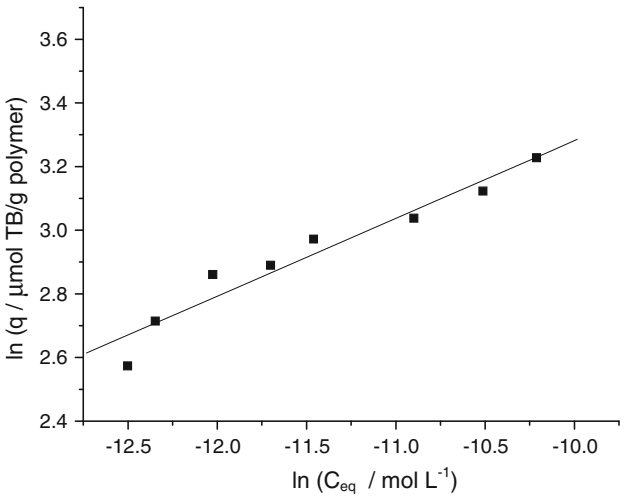

Fig. 2 Freundlich isotherm of TB sorption on βCDP, at 25°C

The comparison between 1:20 and 1:40 TB:βCD molar ratios pointed out that the percentage of drug sorbed increases with the ratio at 25°C (Fig. 3a). The polymer was able to retain up to 86 and 93% of drug, respectively. It can be observed that the loading equilibrium was reached quickly due to the fast diffusion of the drug in the swollen gel [16]. The sorption process was faster with the higher concentration tested (5.0×10^{-4} M), the equilibrium was reached in about 20 min; however, for the lower concentration it occurred in approximately 30 min (Fig. 3b). The sorption efficiency significantly increased with contact time; this fact evidences stable interactions between the drug, the βCD cavities and the polymer network [17]. In addition, the percentage of TB sorbed in both cases was practically the same ($\approx$90%), being slightly higher at the lower concentration, as it was found by Crini and Wang et al. for different compounds [17, 18]. In terms of pharmaceutical applications, it seems interesting to use an initial concentration of drug as high as possible for loading a fixed amount of polymer.

In relation with the influence of temperature, taking into account that the sorption process is exothermic, it could be expected an increase of the polymer sorption efficiency, reaching practically the same plateau value, at low temperatures. The kinetic profiles obtained at all the temperatures tested were similar, so no significant influence of this parameter was observed. This fact has also been observed in the sorption studies of dibenzofuran derivatives on the same polymer [16].

The influence of the ionic strength on the sorption capacity of βCDP in water ($I = 5.0 \times 10^{-5}$ M) and in 1.0×10^{-4} M HCl ($I = 1.5 \times 10^{-4}$ M) has been studied. Figure 4 shows that, at the lower ionic strength tested, a rapid increase of TB sorbed during the first 10 min was observed and equilibrium was reached in 20 min. On the other hand, in 1.0×10^{-4} M HCl, the TB retained increased slowly, reaching the equilibrium in about 40 min. These differences can be related to the interactions between Cl^- ions and charged TB (pK_a 6.7) which could make the diffusion process slower.

It has been reported that the amount of retained sorbate can either increase or decrease with the ionic strength, depending on the acidic or basic character of the solutes. Crini observed that the percentage of some dyes retained increased with NaCl concentration and Wang et al. reported that the sorption of bilirubin decreased with the phosphate buffer concentration, indicating the predominance of the solvation forces over the interactions with the cyclodextrin cavities [17, 18]. In the present case, the amount of TB loaded was similar, about 90% in both media, so the maximum sorption capacity does not depend on the ionic strength.

Finally, as an attempt to relate the inclusion phenomena of the drugs in the βCD cavity with the sorption capacity of

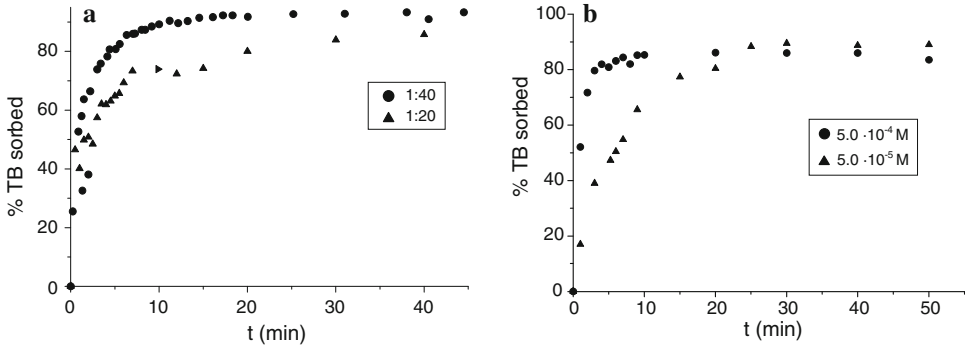

Fig. 3 **a** Comparison of the βCDP sorption profiles at different TB:βCD molar ratios, $[TB]_o = 5.0 \times 10^{-5}$ M, 25°C, **b** Influence of the initial concentration of TB in the βCDP sorption efficiency, at 1:40 TB:βCD molar ratio, 25°C

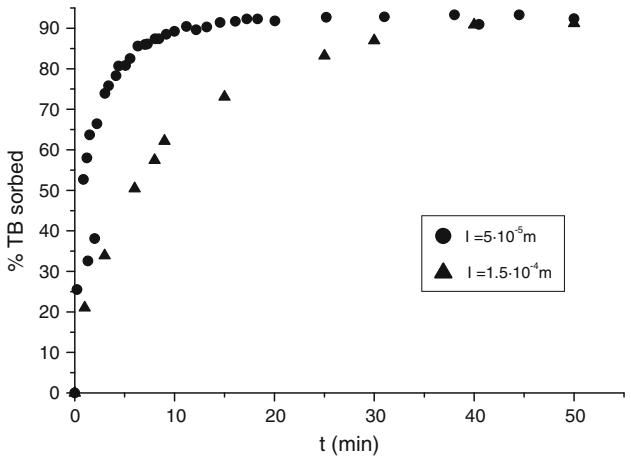

Fig. 4 Influence of the ionic strength on the sorption of TB on βCDP, $[TB]_o = 5.0 \times 10^{-5}$ M, at 1:40 TB:βCD molar ratio, 25°C

the polymer tested, the loading of TB was compared with that of its analogue compound, naftifine (NF) at 25°C [19]. The kinetic profiles are similar (Fig. 5); equilibrium was reached in about 20 min, although the % TB sorbed was higher than that of NF (92% TB and 85% NF). As described before, the sorption process on βCD polymers involves the physical sorption of the drug on the polymer network and the inclusion complex formation. In general, because of the small specific surface area of βCDP, physical sorption plays a small role in the interaction between the polymer and the solutes, so complex formation may well be the main mechanism of sorption [18, 20]. In this sense, the stability constant of the complex TB-βCD is higher (1400 ± 300 M^{-1}) than that reported for NF-βCD (900 ± 30 M^{-1}) at 25°C [14], in accordance with the higher amount of drug retained in the βCDP. Complexation of these drugs with βCD takes place when the naphthalene group enters the cavity by its wider rim and also, and more deeply buried, the *tert*-butyl chain of TB. However, in the case of NF, the benzene ring instead of the *tert*-butyl group of TB competes with the naphthalene group to enter the CD cavity, and a mixture of 1:1 complexes is obtained, in which either the benzene or the naphthalene moiety of NF is included [14]. It can be concluded that the higher affinity of TB for the CD is mainly due to the inclusion of the aliphatic part of the guest, which favours the loading on the polymer.

Release studies

Once the most favourable conditions for loading the polymer were obtained, the possible pharmaceutical applications of the polymer were investigated through the study of the in vitro drug delivery from the loaded hydrogel. The assays were performed in water and in 0.1 M HCl. It was observed that 0.1 M HCl was the most favourable medium to allow the release of the drug from the loaded polymer, probably due to the higher solubility of the drug in this medium. The percentage of TB delivered was calculated with respect to the amount previously loaded in the polymer. The maximum released in 24 h was up to 50% of TB loaded. In 120 min 60% of the TB maximum release was delivered (Fig. 6).

The physicochemical properties of the hydrogel network as well as the drug-loading method employed can determine the mechanism by which the loaded drug is released from the crosslinking matrix. The results obtained in the

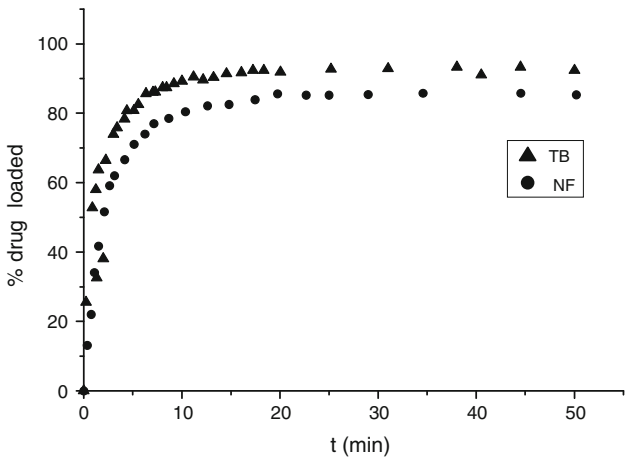

Fig. 5 Loading profiles of NF and TB on βCDP as a function of time in water, $[drug]_o = 5.0 \times 10^{-5}$ M and 1:40 drug:β-CD molar ratio, at 25°C

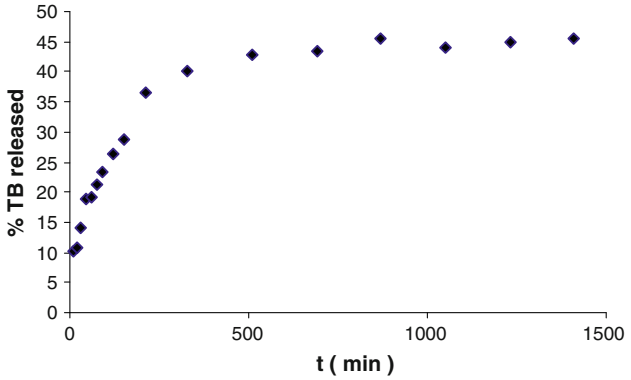

Fig. 6 TB release profile from loaded βCDP in 0.1 M HCl, at 37°C

release experiments were fitted to the empirical equation developed by Peppas et al. [21], $(Mt/M_{\infty}) = k\ t^n$, where Mt/M_{∞} is the drug fractional release, k is a structural/geometric constant for a particular system and n is the release exponent representing the release mechanism. The values of k and n obtained for the system were $0.07 \pm 0.01\ min^{-n}$ and 0.44 ± 0.02, respectively. Taking into account the spherical geometry of the polymeric beads, the value of n obtained is indicative of a drug release mechanism based on Fickian diffusion. This result indicates that the polymer tested can be considered a diffusion-controlled delivery system, suitable for pharmaceutical applications [22].

Conclusions

Taking into account the results described in this work, it can be concluded that the most favourable conditions for the incorporation of TB on the βCDP studied are a high initial concentration of drug, a high TB:β-CD molar ratio and a low ionic strength of the solution medium. Moreover, the comparison of the loading kinetic profile of TB with that of NF, another antifungal agent of similar structure, reveals that TB presents a higher affinity for the polymer, according to the higher stability constant of the TB-βCD inclusion complex, mainly due to the inclusion of the aliphatic part of the drug.

In relation to the release studies, 0.1 M HCl was the most favourable medium to allow the release of the drug from the loaded polymer. The maximum amount of drug released in 24 h was up to 50% of TB loaded. Finally, it is concluded that the polymer tested can be considered a diffusion-controlled delivery system, suitable for pharmaceutical applications.

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