



The effect of β -cyclodextrin in the photochemical stability of propranolol hydrochloride in aqueous solution

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ABSTRACT. The degradation of propranolol hydrochloride (1-isopropylamino-3-(naphthoxy)-2-propranolol) in an aqueous solution was analyzed when irradiated by light UV, with and without β -cyclodextrin. There was an increase in the compound's photostability in nanocavity when compared with the drug without the cyclodextrins' cavity. First order kinetic model was employed for the degradation of propranolol in aqueous media and in cyclodextrins' cavity. The kinetic parameter was obtained by the drug's absorption and electronic fluorescence. As a rule, encapsulation of propranolol in β -cyclodextrin decreases photodegradation speed by 53%.

Keywords: nanocavity, drug, photochemical.

O efeito da β -ciclodextrina na estabilidade fotoquímica do cloridrato de propranolol em solução aquosa

RESUMO. Neste trabalho, foi estudada a degradação do cloridrato de propranolol (1-isopropilamina-3-(nafitiloxi)-2-propranolol) em solução aquosa por irradiação UV na presença e ausência de β -ciclodextrina. Verificou-se o aumento da fotoestabilidade da substância na presença da nanocavidade, quando comparado com a mesma na ausência da cavidade do ciclodextrinas. Foi utilizado o modelo de cinética de primeira ordem para a degradação de propranolol em meios aquosos e na cavidade ciclodextrinas, a espectroscopia de absorção e de fluorescência eletrônica da droga foi usada para obter o parâmetro cinético. De uma maneira geral, a encapsulação do propranolol em β -ciclodextrina reduz a velocidade de fotodegradação em 53%.

Palavras-chave: nanocavidade, fármaco, fotoquímica.

Introduction

Cyclodextrins (CDs) are complex carbohydrates composed of glucose units (α -D-glucopyranose) linked by type α -1, 4, with a structure similar to a cone branch. Franz Schardinger identified cyclodextrins in 1903 as products produced by the degradation of starch through the action of amylase enzyme cyclodextrin glycosyl transferase (CGTase) produced by the microorganism *Bacillus macerans* which may break a segment of the starch helix and join the end portions of the fragment in one cyclic molecule. The cyclization of six, seven or eight glucose units may be obtained by enzymatic modification and thus give rise to α , β and γ -CD, respectively.

The crystal structure of CDs was established in 1942 when diffraction X-rays were studied. Studies showed that annular molecules had primary hydroxyls at the narrowest part of the branch, while

secondary hydroxyls were found in its widest section. Extremities' hydroxyls provide water soluble cyclodextrins since they form hydrogen bonds with the solvent. On the other hand, the cavity's interior is limited by alignment of hydrogens C(3)-H and C(5)-H and by ether linkage C(1)-O-C(4), giving them a hydrophobic behavior.

CDs may be used not only as suitable excipient for pharmaceutical formulations but also as carrier material in the body of endogenous or exogenous lipid (UEKAMA, 2002). According to the above researcher, some natural lipids become toxic agents when the organism is unable to transport and to redistribute them properly by carrier proteins and their receptor systems. One strategy is the use of biocompatible molecular solubilizers, such as those derived from β -CD, hydropropyl- β -CD.

Cyclodextrins are used in the pharmaceutical industry to increase the solubility of drugs in water. The molecules of the active ingredient are included

in the cavity and may be transported by cyclodextrin to the place of performance. Encapsulation may occur in organic solvents (SHIGA et al., 2003). They protect them from oxygen and UV irradiation (PITARELLO et al., 2005) and release them uniformly over a prolonged time.

Drug inclusion in CDs may change considerably its characteristics, especially in the pharmacotechnical field, by modifying solubility and bioavailability, reducing side effects, increasing stability in the solid state and sometimes in the liquid medium (SZEJTLI, 1998).

Due to the unique properties of cyclodextrins, their use has been suggested to increase the stability of propranolol. The hydrochloride salt of propranolol (1-isopropylamino-3-(naphthoxy)-2-propranolol) is an antihypertensive drug indicated for the treatment and prevention of myocardial infarction, angina and arrhythmia. It may be employed with or without other drugs for the treatment of hypertension. Since the cost of the drug is low, it is widely prescribed by physicians and easily accessible to the population. Encapsulation in CD may increase the stability of the drug and prolong the duration of its shelf life.

Material and methods

A stock solution of pharmaceutical pure propranolol hydrochloride was prepared by weighing the drug and diluting it in a 100 mL flask to yield a concentration of 1.0×10^{-4} mol L⁻¹. Pre-established aliquots were retrieved and added to properly identified flasks, or rather, 1.5 mL aliquots were removed from the stock solution to the 10 mL flasks. Two samples were prepared, one with a predetermined mass of β -cyclodextrin (0.0183 g) and one without β -cyclodextrin, completing the remainder of the volume with distilled water.

Spectroscopic readings were performed on spectrophotometer Shimadzu model 1601-PC between 200 nm and 600 nm and in a spectrofluorimeter Aminco SPF-500C. The samples were analyzed using the absorption maximum.

Irradiations of solutions were performed simultaneously in two quartz cuvettes with a 10 mm optical path. Cuvettes were fixed on a black metal support symmetrical to the 80 W mercury bulb, at a 7 cm distance from the source.

Results and discussion

Figure 1 shows variation in absorption intensity when the drug solutions are irradiated. According to these results, the irradiation of the solutions causes the simultaneous degradation of the two solutions,

characterized by absorbance reduction at the regions close to 220 nm and 280 nm. However, solutions with nanocavity decreased at their less intense absorbance (Figure 1B) when compared to those obtained without nanocavity (Figure 1A). The spectral changes in the solution without nanocavity were similar to those reported for solutions with β -cyclodextrin. The above shows that nanocavity does not affect the reaction's mechanism, but only the speed.

According to Matsuura and Omura (1974), the hydroxylation of the benzene is the preferred product when this class of compounds is irradiated. Studies with propranolol photolysis by Sortino et al. (2002) observed the formation of 6-hydroxy 1,4-naphthoquinone at pH 12, whereas Piram et al. (2012, 2008) reported the formation of mono-, di- and tri-hydroxy derivatives of propranolol.

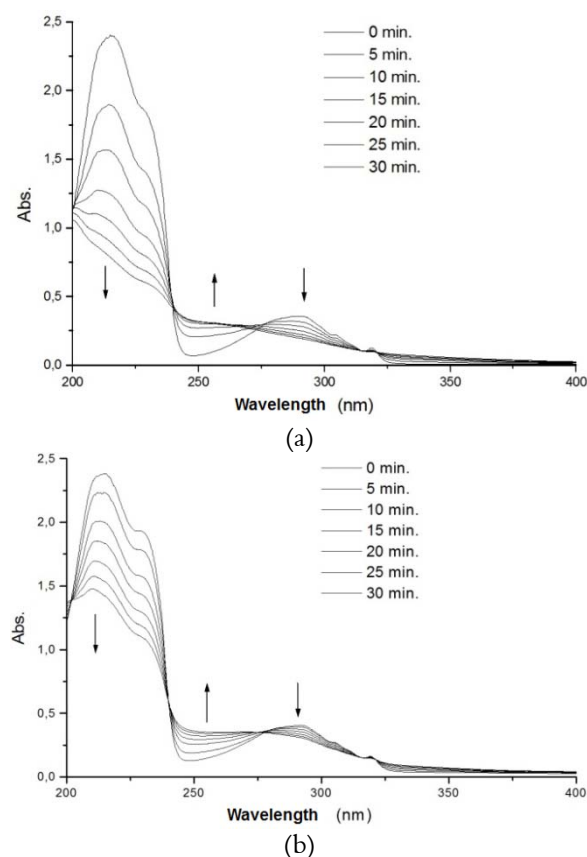


Figure 1. Chart showing spectra of propranolol absorption in a solution without β -CD (a) and with β -CD (b), irradiated every 5 minutes.

Uwai et al. (2005) identified, among other products, 1-naphthol when irradiated with a halogen lamp (visible light) for 5 days. An attack on the aromatic system or isomerization of side chain of propranolol is required to obtain hydroxyl derivatives. Since the system is protected by nanocavity, the hydroxylation or isomerization of the propranolol is

rather difficult due to alterations in the kinetics of photolysis.

The kinetics of propranolol degradation was measured by a pseudo first order mechanism (SU et al., 2009), where the logarithm of the relationship between absorbance and initial absorbance was plotted as a function of time. Figure 2 shows the results obtained according to this model: constant of drug solution degradation without nanocavity (0.0396 min^{-1}) is greater than that with nanocavity (0.0182 min^{-1}).

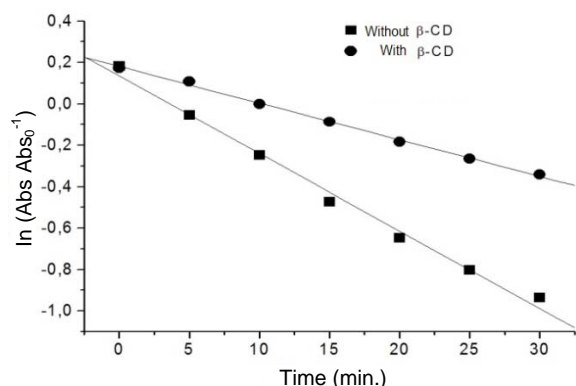


Figure 2. Log graph of the ratio of absorbance obtained at 220 nm versus irradiation time (min.).

Photodegradation studies may also be monitored by fluorescence (CHUNMAO et al., 2005). Figure 3 shows the fluorescence spectra of propranolol. According to the fluorescence spectra in Figures 3a and 3b, irradiation causes drug degradation and the extinction of its fluorescence spectrum. Different results were obtained by absorption spectroscopy where the photoproduct had a residual absorbance (Figure 1a).

Degradation kinetics was also calculated by the pseudo first order mechanism using fluorescence intensity in maximum emission (Figure 4) and degradation constant, shown in Table 1. The constants obtained from the fluorescence spectra are greater than those obtained by absorption spectroscopy. As the photoproduct has an absorbance residual, it provides a constant difference from that obtained by fluorescence, which is fully extinguished. However, regardless of the technique, degradation constant of propranolol to be encapsulated is reduced by approximately 53%.

According to our results, nanocavity in aqueous solution increased the drug's photostability. Studies by Nowakowska et al. (2001) with coumarin derivatives also indicated a 60% increase in stability against radiation of the substance in an aqueous medium. Similar results

were obtained in studies by Mielcarek and Daczowska (1999), where the methyl derivative of β -cyclodextrin doubled the photostability of isradipine. Other studies revealed that β -cyclodextrin not only increased the photostability of the encapsulated substance but also the thermal stability of the host (TAKAHASHI et al., 2011).

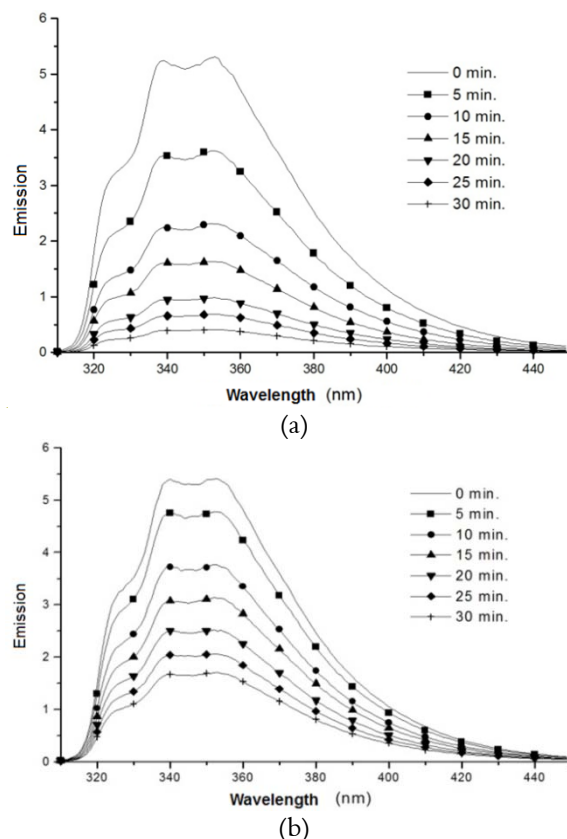


Figure 3. Chart showing the emission spectra of propranolol in solution without β -CD (a) and with β -CD (b), irradiated every 5 minutes.

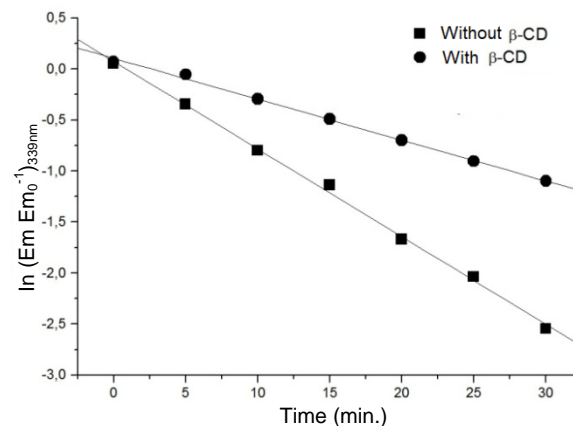


Figure 4. Graph of $\ln(\text{emission}/\text{initial emission})$ at 339 nm versus time of irradiation (min.).

Table 1. Degradation constant obtained by absorbance (K_{Abs}) and emission (K_{Em}) and stabilization percentage.

	K_{Abs} (min ⁻¹)	K_{Em} (min ⁻¹)
Without β -CD	-0.0396 ± 0.0014	-0.0860 ± 0.0017
With β -CD	-0.0182 ± 0.0007	-0.0401 ± 0.0009
% Stabilization	54.0	53.4

Conclusion

The photolysis of propranolol is reduced for the encapsulation of cyclodextrin due to the protection of the aromatic system by nanocavity, which impedes or prevents the hydroxylation of aromatic rings catalyzed by UV radiation. A constant rate of approximately 53% stabilization occurs.

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