

PHOTODEGRADATION OF INCLUSION COMPLEXES OF NAPROXEN AND NIFLUMIC ACID WITH β -CYCLODEXTRIN

M. Bogdan, C.Floare, Diana Bogdan, S. I. Farcas

National Institute for Research and Development of Isotopic and Molecular Technologies, Cluj-Napoca, Romania

Abstract. The paper presents results of the studies on photochemical stability of naproxen (NAP) and niflumic acid (NIF) in their liquid inclusion complexes with β -cyclodextrin (β -CD). The process of photodegradation was studied by UV spectrophotometry. Quantitative evaluation of the photochemical decomposition was performed on the basis of the calculated rate constant, k_0 , for the pure drug, k , the photodegradation rate constant of the drug in the inclusion complex and the stability constant K of the complex.

1. Introduction

Many drugs are known to lose their activity and often form degradation products, when are exposed to factors such as light, temperature and oxygen [1]. This causes problems with storage and also with application, as the products formed may be hazardous. Although attempts to stabilize labile drugs have in some cases been successful [2], there is a need for novel methods to further improve stability.

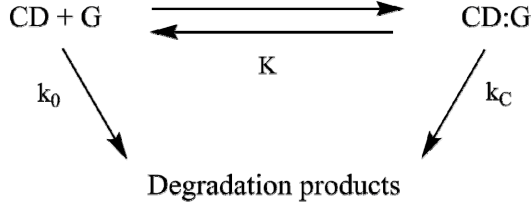
The non-steroidal anti-inflammatory drugs are one of the most commonly used groups of drugs to treat rheumatoid and gouty arthritis. However, they can be associated with gastrointestinal side-effects, drowsiness and different types of adverse cutaneous photosensitive reactions [3]. These problems can be minimised through the use of suitable drug carriers. In this sense, a usual procedure is the inclusion complex formation of the drug with different cyclodextrins [4].

The aim of this paper was to investigate the photodegradation kinetics of two non-steroidal anti-inflammatory drugs (naproxen and niflumic acid) on exposure to UV light in the presence of β -cyclodextrin.

2. Theory

Cyclodextrins can accelerate or decelerate many types of reactions taking place in aqueous solution. The hydrophobic or photolytic decomposition of included compounds can be decelerated by virtue of their being protected from factors in the aqueous media or from UV light, respectively. The reaction is illustrated in Scheme 1, where k_0 is the rate constant for the decomposition of the free guest (G), k_C the photodegradation rate constant of the guest in the form of the inclusion complex, and K the apparent stability constant for complex formation.

Following Loukas [5], the rate of disappearance of the total concentration of the guest is:



Scheme 1.

$$-\frac{d[G_t]}{dt} = k_0[G] + k_C[CD : G] \quad (1)$$

During the decomposition of the guest, G, the overall observed first-order rate constant, k_{obs} , can be expressed as:

$$-\frac{d[G_t]}{dt} = k_{obs}[G] \quad (2)$$

Combining the Eqs. (1) and (2) gives:

$$k_0[G] + k_C[CD : G] = k_{obs}[G] \quad (3)$$

Taking into account that $[G] = [G_t] - [CD : G]$ we have:

$$k_{obs}[G_t] = k_0[G_t] - (k_0 - k_C)[CD : G] \quad (4)$$

At any moment of the reaction, the cyclodextrin inclusion complex in solution is in equilibrium with the free components. The apparent stability constant can be expressed as:

$$K = \frac{[CD : G]}{[CD][G]} \quad (5)$$

Combining all these equations, together with $[CD] = [CD_t] - [CD : G]$ we have:

$$K = \frac{\Delta k_{obs} \Delta k_C}{(\Delta k_{obs} - \Delta k_C)([G_t] \Delta k_{obs} - [CD_t] \Delta k_C)} \quad (6)$$

where: $\Delta k_{obs} = k_0 - k_{obs}$ and $\Delta k_C = k_0 - k_C$.

Eq. (6) represents the final analytical solution which involves no approximation of concentrations and correlates the initial total concentrations $[G_t]$ and $[CD_t]$ with the rate constants, k_0 , k_C and k_{obs} .

The photodegradation rate constant of the pure guest, k_0 , can be calculated, based on Eq. (1), in the absence of CD. The unknown parameters K and k_C can be calculated, using Eq. (6), by a non-linear fitting procedure.

3. Materials and methods

β -cyclodextrin (β -CD) containing an average of 8 water molecules/molecule and naproxen sodium salt (NAP) were purchased from Sigma

Chemie GmbH (Germany). Niflumic acid (NIF) was purchased from Sigma Chemical Company (MO, USA) and double distilled water was used throughout.

Photodegradation studies were carried out using an ultraviolet lamp having 500 W and $\lambda=125 \pm 100$ nm. UV spectra were recorded using a double beam “Carl-Zeiss” Jena spectrophotometer, equipped with an acquisition system and connected to a personal computer.

4. Results and discussion

Two sets of samples were prepared by quantitatively dissolving the substances in double distilled water. In the first set, the concentration of NAP was kept constant at $2.5 \cdot 10^{-5}$ M and the contents of β -CD were varied: 0, 0.1, 0.5, 1.0, 1.5, 2.25, 3 and 4 mM. In the other set, the content of NIF was $2.5 \cdot 10^{-5}$ M and the concentrations of β -CD were varied: 0, 0.1, 0.5, 1, and 2 mM.

Changes in absorbance A , during irradiation are described by the equation:

$$\ln A = \ln A_0 - kt, \quad (7)$$

where k is the photodegradation rate constant, k_0 in the absence of β -CD, or k_{obs} in the presence of β -CD. For pure compounds we obtained the following results.

	NAP	NIF
k_0 (min^{-1})	$6.22 \cdot 10^{-3}$	$1.65 \cdot 10^{-3}$

Photodegradation of NAP in aqueous solution in the presence of β -CD is presented in Fig. 1.

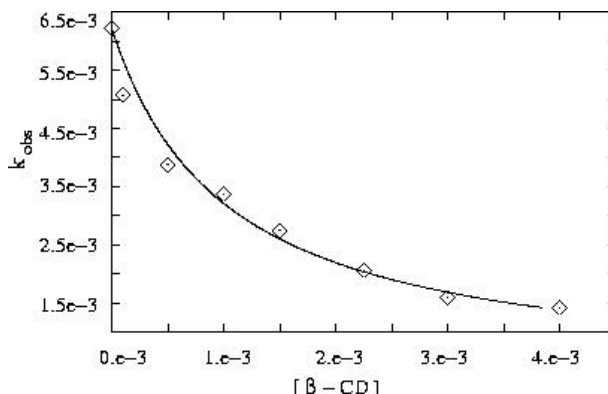


Figure 1 Effect of β -CD concentration on the photodegradation rate constant, k_{obs} , of $2.5 \cdot 10^{-5}$ M NAP. The solid curve represents the best fit to Eq. (6)

It is clear that the presence of β -CD has a pronounced stabilizing effect on NAP. The rate constant for the degradation of $2.5 \cdot 10^{-5}$ M NAP, decreased from $6.22 \cdot 10^{-3} \text{ min}^{-1}$ to $1.43 \cdot 10^{-3} \text{ min}^{-1}$ in the presence of 4mM β -CD.

The stability constant K and the photodegradation rate constant for the pure complex, k_C , were obtained by fitting the k_{obs} data as a function of β -CD concentration with Eq. (6). The obtained results are:

$$K=998.2 \text{ M}^{-1} \text{ and } k_C=0.157 \cdot 10^{-3} \text{ min}^{-1}.$$

For the NIF: β -CD system it is also evident that k_{obs} does not relate linearly to the increasing concentration of added β -CD, but rather asymptotically approaches a minimum value (Fig.2).

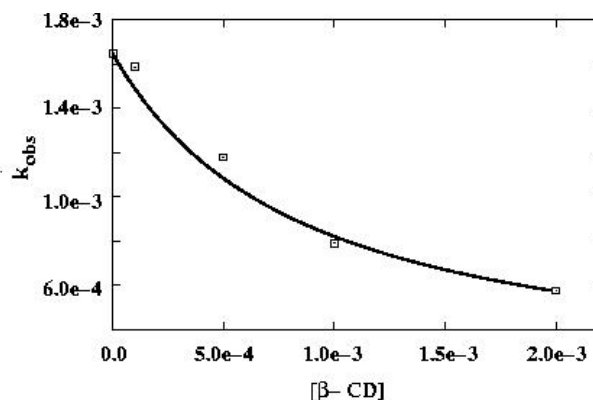


Figure 2 The best order rate constant, k_{obs} , of the degradation NIF as a function of added β -CD.

The kinetic parameters characterising the photodegradation process for NIF: β -CD system, obtained by fitting the experimental data with Eq. (6) are:

$$K=1224.9 \text{ M}^{-1} \text{ and } k_C=0.12 \cdot 10^{-3} \text{ min}^{-1}.$$

5. Conclusions

In conclusion, the present work has shown that the described non-linear curve-fitting procedure can be used for the calculation of K of the drug: β -CD inclusion complexes and the photodegradation rate constants, k_0 and k_C , using kinetic studies. The extent to which β -CD is able to protect drugs from being photodegraded can be defined as the stabilisation ratio $Q=k_0/k_C$. In our case we have obtained $Q_{\text{NAP}:\beta\text{-CD}}=39.6$ and $Q_{\text{NIF}:\beta\text{-CD}}=13.7$. It appears therefore that the inclusion of NIF and NAP in β -CD increases their photostability at least with an order of magnitude and that the NAP: β -CD system is much more well protected against photodegradation than NIF: β -CD.

REFERENCES

- [1] F. Bosca, M. A. Miranda, *J. Photochem. Photobiol.* **B43**, 1, 1988.
- [2] M. Partyka, A. B. Ha, C. H. Evans, *J. Photochem. Photobiol.* **A140**, 67, 2001.
- [3] K. Connors, G. Arnidon, L. Kennon (eds.), "*Chemical Stability of Pharmaceuticals*" John Wiley and sons, New York, 1979.
- [4] K. Thoma, R. Klimek, *Int. J. Pharm.*, **67**, 169, 1991.
- [5] Y. L. Loukas, V. Vraha, G. Gregoriadis, *Int. J. Pharm.*, **144**, 225, 1996.