

Influence of inclusion complexation with β -cyclodextrin on the photostability of selected imidazoline-derived drugs

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Abstract In this paper, the influence of inclusion complexation with β -cyclodextrin (β -CD) on the photostability of antazoline, xylometazoline, and naphazoline in aqueous media was investigated. The photodegradation reaction of these drugs molecules was explored using UV–vis spectrophotometry-based kinetic analysis and high performance liquid chromatography (HPLC). Quantitative evaluation of the influence of β -CD was judged based on the observed rate constant (k_{obs}), half-life time ($t_{0.5}$) and $t_{0.1}$ of the photodegradation reaction and the peak area of the corresponding analyte after photodegradation using HPLC separation. It has been demonstrated that the photostability of these selected imidazoline-based drugs has been enhanced upon forming inclusion complexes with β -CD in aqueous media. Moreover, high consistency regarding the photostability enhancement was obtained using both techniques. Hypothetical structure for 1:1 inclusion complexes was proposed based on molecular mechanics calculations, which in turn provide an insight for the energetically preferential structure of the inclusion complexes. The results obtained demonstrate that β -CD can be utilized as photostabilizer additive for enhancing the photostability of imidazoline-derived drugs molecules.

Keywords Photostability · Photodegradation · β -Cyclodextrin · Imidazoline-derived drugs · Inclusion complexes

Introduction

Drugs stability is of considerable importance for the pharmaceutical and biomedical societies. In particular, photostability of drugs has recently received a significant amount of attention due to the increase in the UV light that reaches the earth nowadays. The photodecomposition drug molecule upon exposing to light reduces the bioavailability of the drug, which in turn of particular concern in the pattern of producing toxic photodegradation products in the form of free radicals [1–4].

Several studies have been conducted on studying the photostability of wide spectrum of drugs and drugs formulation [1, 5–7]. Meanwhile, several methodologies and technologies have been developed in order to enhance the photostability of drugs; this includes using light protective wrapping and formulating the drug with some additives, such as photoabsorbents [8]. Chemical complexation with appropriate carrier is another approach that is of particular interest in the pharmaceutical industries, such as complexation with cyclodextrins (CDs) and liposomes [9–11].

CDs are cyclic oligosaccharides with truncated-shape cone that can be obtained via enzymatic conversion of starch [12–14]. They are featured by the hydrophilic outer surface and apolar cavity that enable them to form host–guest inclusion complexes with wide range of molecules through the insertion of the hydrophobic portion of the guest molecule inside the apolar cavity, which in turn leads to dramatic changes in the physico-chemical properties of the guest molecule. CDs are widely employed as additives

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in the food, cosmetics, and pharmaceutical industries. Particularly, CDs have been widely utilized as universal additives that can form inclusion complexes with wide range of drugs molecules for the purpose of increasing the drugs' solubility and/or enhancing their stability, and thus augmenting their bioavailability.

Imidazoline-derived drugs have the capability to interact with α -adrenergic receptors through stimulating or antagonizing presynaptic and postsynaptic α -adrenoceptors [15–17]. While the majority of the imidazoline-derived drugs are commonly used for their agonist activity, other drugs are used for their antagonist, antihistaminic, and antihypertensive activities. In particular, naphazoline (NP) (4,5-dihydro-2-(1-naphthalenylmethyl)-1H-imidazole), antazoline (AZ) (4,5-dihydro-*N*-phenyl-*N*-(phenylmethyl)-1H-imidazole-2-methanamine,2-[(*N*-benzyl anilino) methyl]-2-imidazoline, and xylometazoline (XM) (2-(4-tert-butyl-2,6-dimethylbenzyl)-2-imidazoline) were selected as typical imidazoline-derived drugs in the this study. The chemical structures of these drugs are presented in Fig. 1. These drugs are pharmaceutically manufactured and present in the market as nasal and eye drops due to their vasoconstrictive effect. It is noteworthy mentioning that numerous drugs (e.g., NP) have the potential to initiate DNA cleavage upon exposing to light irradiation [18]; and thus, it is not recommended to expose drugs to light after purchase. Exploring the photostability of drug molecules, mainly those which possess nitrogen or hydroxyl (OH) groups, is of particular importance. It has been reported that nitrogen- and OH-centered radicals that are generated from various molecules upon being irradiated have the potential to initiate DNA photocleavage under anaerobic and aerobic conditions, respectively [19–21]. With this in mind, it is essential to explore the potentiality of enhancing the photostability of imidazoline-derived drugs via employing various additives.

In our previous study, we explored the formation of inclusion complexes of these drug molecules with β -CD in aqueous media and solid state [22]. The binding coefficient of the 1:1 inclusion complexes ($K_{1:1}$) was calculated using fluorescence spectroscopy technique at different temperature, which in turn was employed to determine the thermodynamic parameter of the inclusion complexation process. In addition, the formation of the inclusion complexes was confirmed by conducting differential scanning calorimetry (DSC) analysis [22].

In this study, the influence of inclusion complexation with β -CD on the photostability of three selected imidazoline-derived drugs, AZ, NP, and XM, is investigated. Drug- β -CD complexes were prepared in buffer-free aqueous solution at room temperature. The photodegradation process was monitored kinetically using absorption spectra of each drug. Separation of drugs' solutions after irradiation

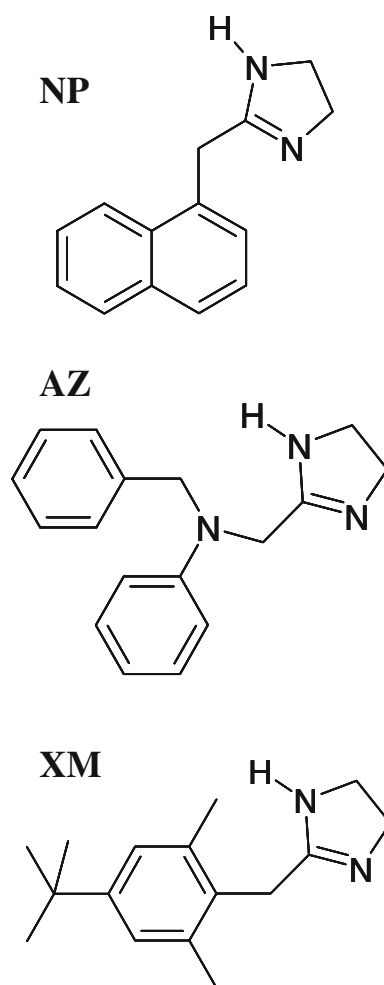


Fig. 1 Chemical structure of AZ, NP, and XM

using high performance liquid chromatography (HPLC) was also performed. The present study provides an insight on the importance of investigating the photostability of photosensitive drug molecules and proposes a remedy for enhancing such imperative property.

Experimental

Chemicals

The antazoline sulfate and naphazoline nitrate were supplied by Al-Hekma Pharmaceuticals (Amman, Jordan), whereas xylometazoline hydrochloride was supplied by Amman Pharmaceutical Industries (Amman, Jordan). β -cyclodextrin, sodium 1-heptanesulfonate, and sodium phosphate were purchased from Sigma. Acetonitrile (ACN) and acetic acid (AA) were provided by Fisher Scientific. All chemicals were used as received. Aqueous solutions were prepared in buffer-free solutions with deionized water (18 M Ω /cm).

Measurements and methods

Spectrophotometry study

The photostability of each drug was monitored spectrophotometrically using a UV–vis double-beam Unicam-Herios- α spectrophotometer. The photodegradation of the drugs was followed by monitoring the decrease in the intensity (absorbance) of the most intense absorption peak as a function of time. Each solution (1 mM β -CD and 6×10^{-6} g/L drug in water) was placed in a water-jacketed photolysis vessel and irradiated with stirring at room temperature (~ 25 °C). The photolysis experiments were performed using a 150-watt mercury arc UV immersion lamp (Heraeus Instruments). An aliquot was withdrawn from the glass cell in time interval of 3 min for NP and XM, and 0.5 min for AZ, and then absorption spectra were collected immediately.

High performance liquid chromatography (HPLC) study

The photostability of each drug was also studied by HPLC. The separation experiments were performed using Beckman HPLC system/gold analysis equipped with phenyl column (250 \times 4.6 mm) as a stationary phase, which was controlled by programmable solvent module 126 and programmable detector module 168. The separation and detection parameters were as follow: wavelength of absorption detection was set at 280 and 220 nm for NP and AZ, and XM, respectively; for NP and AZ, the mobile phase consisted of 5 mM sodium 1-heptanesulfonate in H₂O/ACN/AA (74:25:1 v/v/v) (pH 3.5), whereas for XM, the mobile phase consisted of 5 mM phosphate buffer in H₂O/ACN (80:20 v/v) (pH 3); the flow rate was 2.0 mL/min; an equal sample volumes of 20 μ L was injected. The injected sample was withdrawn from the vessel after an irradiation time of 25, 10, and 40 min for NP, AZ, and XM, respectively.

The molecular mechanics and modeling calculations were performed using Hyperchem software (release 4, Hyperchem Inc., Waterloo, Canada) as described previously [22]. Briefly, MM + force field was applied to minimize the geometrical energies for β -CD and drugs' structures in free and inclusion complexation modes.

Results and discussion

There is a wide range of chemical and photochemical reactions that can be influenced by CDs as a consequence of the inclusion process, which can be attributed to a variety of physico-chemical transformations that occur upon the formation of the inclusion complexes. Among

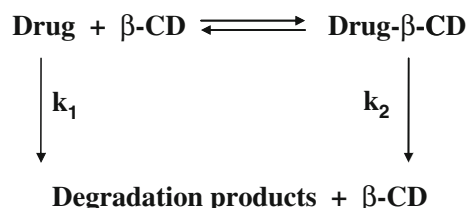
these photochemical reactions, the photodegradation of drugs molecules is of particular importance for the communities of the pharmaceutical industries, and thus enhancing the photostability of these photosensitive drugs molecules is essential.

In general, the photodegradation reaction in the presence and absence of CD proceeds as illustrated in scheme 1. Assuming a pseudo-first order reaction for the photodegradation process, the apparent rate constant can be determined by employing the equation:

$$\ln(c) = \ln(c_0) - k \cdot t \quad (1)$$

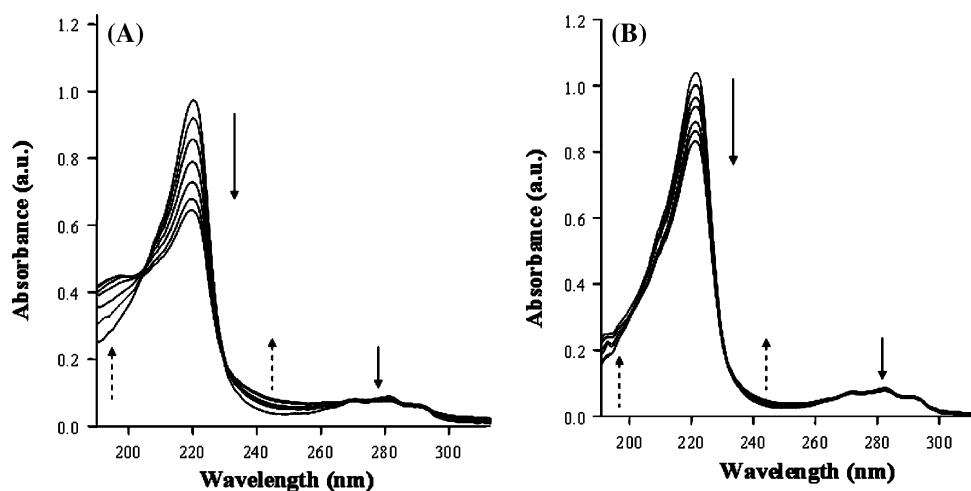
where c corresponds to the concentration after a certain irradiation time of t , c_0 is the initial concentration before irradiation, and k is the apparent rate constant. Accordingly, a comparison between the rate constants of the degradation reaction in the presence (k_2) and the absence (k_1) of CD was performed in order to ascertain the influence of CD on the photostability of the drugs under investigation.

Absorption spectra after various irradiation times were collected in order to estimate the concentration of each drug. However, direct input of the absorbance's values at the most intense peak within the absorption spectra was applied. Frames A and B of Fig. 2 show typical absorption spectra of NP after various irradiation time obtained in the absence and presence of β -CD, respectively. The arrows indicate the direction of decaying or growing of peaks' intensities. As it is apparent from Fig. 2, while the main absorption band at λ_{220} notably decreased as a result of the photodegradation reaction, a new absorption bands appeared at $\sim \lambda_{195}$ and λ_{250} , hence two isobestic points were observed at λ_{205} and λ_{235} . In Addition, a drop in the absorption band's intensity at λ_{283} was observed with two additional isobestic points at λ_{268} and λ_{293} . However, the changes in absorption band's intensity at λ_{220} are more perceptible than at λ_{220} ; thus, the kinetic calculation were conducted based upon the changes in the peak intensity at λ_{220} . Likewise, the same behavior was observed for AZ and XM (data not shown), where changes in the main absorption band were observed at λ_{243} and λ_{198} for AZ and XM, respectively; also, two isobestic points were observed at λ_{234} and λ_{261} for AZ, and at λ_{190} and λ_{210} for XM.



Scheme 1 Photodegradation reaction of drug molecule in the presence and absence of β -CD

Fig. 2 Changes in absorption spectra of 1×10^{-5} M of NP after different times of irradiation in the absence (a) and presence of 1 mM of β -CD (b). The arrows indicate the direction of growing or decaying absorption bands



Importantly, the influence of β -CD on the photodegradation process of NP is apparent in Fig. 2; hence, inclusion complexation with β -CD has significantly retarded the rate of the photodegradation reaction of NP. Similarly, the inclusion complexation with β -CD has enhanced the photostability of XM. Unexpectedly, the results obtained from spectrophotometric monitoring of the photodegradation of AZ revealed that β -CD has no effect on the photostability of AZ. Kinetic calculation was conducted in order to provide quantitative evaluation for the influence of β -CD on the photostability of the drugs. Figure 3 illustrates the linear plot of $\ln(A)$ as a function of irradiation time for the NP and XM. As can be noticed from Fig. 3, the slope of the linear plot for both NP and XM is lower in the presence of β -CD, which is an indication for enhancing the photostability of NP and XM upon forming inclusion complexes with β -CD. The linear plot for the degradation reaction of AZ is presented as an inset in Fig. 3, where analogous degradation process was observed in the presence and absence of β -CD, which indicates a similarity in the photodegradation process of AZ in both cases. AZ is highly photosensitive drug; hence, the photodegradation process of AZ was performed within a total time interval of 3 min. The inefficiency in enhancing the photostability of AZ upon forming an inclusion complex with β -CD could be attributed to the large geometrical structure of AZ, where possessing three different rings that have the potential to be included individually inside the β -CD's cavity would leave large portion of the molecule outside the cavity, and hence being not shielded by the β -CD. Table 1 summarizes the estimated rate constant of the photodegradation reaction for the three drugs in the presence and absence of β -CD. Based on the results provided in Table 1, the half-life time ($t_{0.5}$) for the three drugs in the absence of β -CD were estimated to be 20, 29, and 37 min for AZ, NP, and XM, respectively; whereas $t_{0.5}$ in the presence β -CD was estimated to be 20, 55, and 83 min for AZ, NP, and XM, respectively.

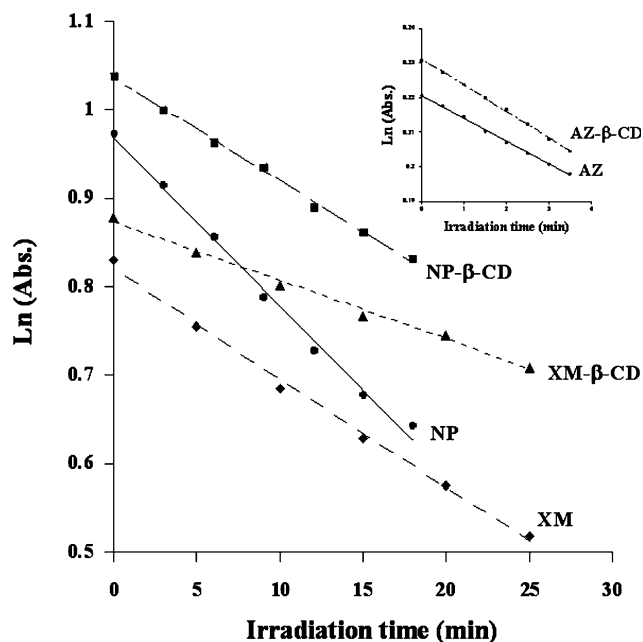


Fig. 3 Pseudo first order kinetic plots of the photodegradation reactions of AZ, NP and XM in the absence and presence of 1 mM of β -CD

Furthermore, the time that is required for 10% degradation of the drug sample ($t_{0.1}$) in the presence and absence of β -CD was estimated to be, respectively, 3.3, 4.4, and 5.7 min; and 3.1, 8.5, and 12.5 min for AZ, NP, and XM, respectively.

It is noteworthy mentioning that light brownish color for the solutions was observed after the irradiation process. Reversed phase HPLC separation process was performed for each drug molecule using a mixture of drug and β -CD before and after a certain time of irradiation. Figure 4 illustrates typical chromatograms for NP before and after 25 min of irradiation in the absence (frames A and B) and presence of β -CD (frames C and D). As can be noticed from Fig. 4, the photodegradation reaction in

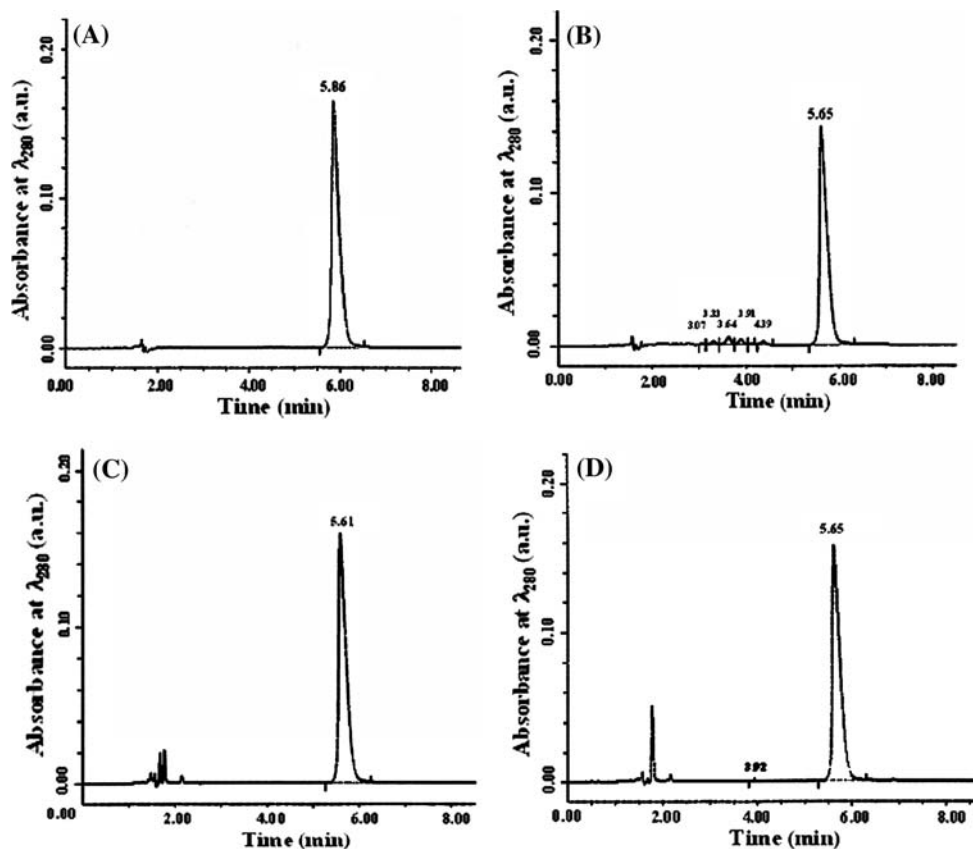
Table 1 Observed rate constants of the photodecomposition of AZ, NP, and XM in the presence and absence of 1 mM β -CD

Drug	k_{obs} without β -CD $\times 10^2(\text{min}^{-1})$	k_{obs} with β -CD $\times 10^2(\text{min}^{-1})$
Naphazoline	2.38	1.24
Antazoline	3.16	3.47
Xylometazoline	1.86	0.84

Other conditions are the same as in Fig. 2

the absence of β -CD generated five products in addition to the original analyte, whereas only one product was detected in the presence of β -CD. In principle, the general pathway for photodegradation reaction proceeds through the formation of free radicals [23, 24]. Accordingly, the shorter retention times observed for the photodegradation products are indicative for relatively higher polarity of these molecules; and thus, we believe that these peaks correspond to free radicals products of NP photodecomposition. Comparable results were observed for AZ and XM (data not shown). Importantly, it is noteworthy mentioning that HPLC results revealed closely related retention times for the three drugs after the irradiation process in the presence and absence of β -CD, which indicates identical photodegradation pathways.

Fig. 4 Chromatograms of NP before (a & c) and after irradiation for 25 min (b & d) in the absence (a & b) and presence of 1 mM of β -CD (c & d)



Quantitative evaluation based on the results obtained using the reversed phase HPLC was conducted. The integrated peak value for each analyte before irradiation was set as a reference, where the extent of degradation was estimated based on the equation:

$$\% \text{ remain} = \frac{A_a}{A_b} \times 100\% \quad (2)$$

where A_a and A_b correspond to peak area after and before irradiation, respectively. The % remain results after irradiation for the three drugs in the presence and absence of β -CD are summarized in Table 2. Interestingly, although it was expected that β -CD would have no effect on the photostability of AZ according to the results obtained spectrophotometrically, the % remain of AZ in the presence of β -CD is approximately twice the value in the absence of β -CD. Moreover, the results obtained for NP and XM using the HPLC based quantitative method are consistent with those obtained using the spectrophotometric methods.

It is noteworthy mentioning that an increase in the solution temperature was observed after irradiation, where an increment of approximately 10 °C was observed. Thus, in order to validate that the degradation process is mainly due to photodecomposition, temperature dependent experiments were conducted. The solutions were kept under heated environment (45 °C) for a time period of 5 h.

Table 2 % remain of AZ, NP, and XM after ~25 min of irradiation in the presence and absence of 1 mM β -CD

Drug	Without β -CD(%)	With β -CD(%)
Naphazoline	81.1	98.3
Antazoline	11.9	20.0
Xylometazoline	40.5	57.7

Other conditions are the same as in Fig. 4

Absorption spectra were collected before and after heating (data not shown), where no changes were observed in the absorption spectra of the drug molecules. Thus, we concluded that the degradation reaction proceeds mainly through photochemical pathway.

Typically, the enhancement of photostability of the drugs molecules in the presence of CDs can be attributed to the inclusion of the guest molecule inside the CD's cavity, either partially or entirely. Accordingly, molecular mechanics and modeling simulations for the inclusion process were performed in order to provide a hypothetical structure for the inclusion complexes of NP, AZ, and XM with β -CD in vacuum. However, comprehensive details regarding these experiments were presented in our previous work [22]. Figure 5 shows a typical 1:1 inclusion complex structure obtained for NP with β -CD, which was optimized based on the values of energy of formation. It was evident that the majority of NP molecule can be included inside the β -CD's cavity, which could explain the enhanced photostability of NP in the presence of β -CD. Although comparable results were obtained for AZ and XM, AZ showed the lowest energy of formation values that is consistent with partially inclusion inside the β -CD's cavity

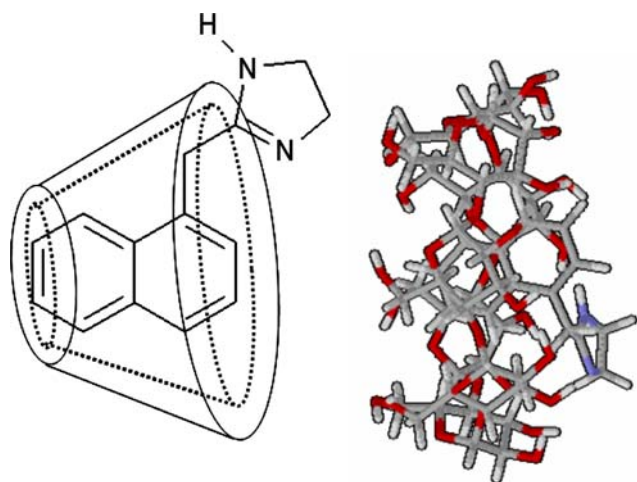


Fig. 5 Hypothetical structure of NP- β -CD inclusion complex obtained based on MM + calculations in vacuum; side view

Concluding remarks

Results obtained in this study have shown that inclusion complexation with β -CD has the potential to enhance the photostability of selected imidazoline-derived drugs; namely, AZ, NP, and XM. Retarding the photodecomposition of the drugs' molecules in the presence of β -CD can be attributed mainly to the protection role of β -CD upon including the drug molecule inside its cavity. However, although spectrophotometric-based kinetic studies have shown no effect for β -CD on the photostability of AZ, HPLC results indicated that β -CD has doubled the photostability of AZ under the same experimental conditions. Whereas results obtained using both techniques were highly consistent for NP and XM photostability studies. This research provides an assortment of insights on the importance of exploring the photostability of drugs molecules, imidazoline-derived drugs particularly.

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