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Research Article

Improving the Stability and the Pharmaceutical Properties of Norfloxacin Form C Through Binary Complexes with β-Cyclodextrin

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Abstract. Norfloxacin, an antibiotic that exists in different solid forms, has very unfavorable properties in terms of solubility and stability. Binary complexes of norfloxacin, in the solid form C, and β-cyclodextrin were procured by the kneading method and physical mixture. Their effect on the solubility, the dissolution rate, and the chemical and physical stability of norfloxacin was evaluated. To perform stability studies, the solid samples were stored under accelerated storage conditions, for a period of 6 months. Physical stability was monitored through powder X-ray diffraction, high-resolution ^{13}**C** solid-state nuclear magnetic resonance, and scanning electron microscopy. The results showed evidence that the kneaded complex increased and modulated the dissolution rate of norfloxacin C. Furthermore, it was demonstrated that the photochemical stability was increased in the complex, without affecting its physical stability. The results point to the conclusion that the new kneading complex of norfloxacin constitutes an alternative tool to formulate a potential oral drug delivery system with improve oral bioavailability.

KEY WORDS: norfloxacin C; β-cyclodextrin; dissolution; chemical stability; physical stability.

INTRODUCTION

Norfloxacin (NOR) is a representative antibiotic of the fluoroquinolone family with a broad antibacterial spectrum. This drug is used in the treatment of infections of genital and urinary tracts, prostate, and gonorrhea, displaying desirable therapeutic effects (1,2). However, the poor NOR solubility reduces its oral bioavailability to values between 30 and 40% (3). NOR is a zwitterionic fluoroquinolone almost insoluble in pure water (3,4). It contains two ionizable groups; therefore, depending on the pH, in solution, it can exist in four protonation forms: an acidic cation (H_2NOR+), a neutral unionized species ($HNOR^0$), an intermediate zwitterion (HNOR±), and a basic anion (NOR−). In particular, at the isoelectric point of the molecule (pH of approximately 7), the zwitterionic form prevails, which displays the lowest solubility (5). Two dissociation constants $pKa1 = 6.54 \pm 0.04$ (3-carboxyl proton) and $pKa2 = 8.50 \pm 0.03$ (ionized proton at the piperazinyl nitrogen) have been determined (6,7).

Polymorphism is defined as the capacity of a single compound to exist in various crystalline solid forms. The polymorphs of a particular active pharmaceutical ingredient (API) can exhibit different chemical and physical properties, producing a great impact on its pharmaceutical profile. In the case of NOR, it exists as three different polymorphs (denominated A, B, and C), an amorphous form, a methanol solvate, various hydrate forms, salts, and cocrystals (8–10). Relative thermodynamic stability studies showed an enantiotropic relationship between forms A and C forms, as well as a monotropic relationship between forms B and C (10). In addition, polymorphism has influence on the antimicrobial activity of NOR. Our preliminary studies, by the turbidimetric method, showed differences in the antimicrobial potency of the three polymorphic forms of NOR.

Some studies reported the complexation of NOR with cyclodextrin as an alternative to increases its solubility (11–13). In most of the cases, these new approaches used the commercially available solid form of NOR, without evaluating other alternative crystalline forms.

Current scientific pharmaceutical research is focused on selecting the optimum crystalline form for a particular API**.** This is essential for the pharmaceutical industry, since the release of the API requires adequate profiles of solubility, stability, and bioavailability. In previous studies, we have

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investigated about the impact of β-cyclodextrin (β-CD) on the properties of this API. In particular, solid forms A, C, and a hydrate of NOR form B were studied describing the synthesis and characterization, by numerous spectroscopic techniques, of these innovative complexes (14,15). However, a complete evaluation of the stability of NOR polymorphs in solid state, as well as the impact of the complexation on their physical stability, is not currently available. The stability of APIs in solid state impacts on the safety and efficacy of the pharmaceutical formulations because, at specific conditions, only one form is stable, while the rest are metastable or unstable. In this context, studying the chemical and physical stability of a certain API is essential for the formulation development in pharmaceutical industry. In particular, the chemical degradation of NOR upon exposure to light is well known, yielding three photodecomposition derivatives (16,17). Given the therapeutic importance of NOR, different methods have been reported for its determination in several matrices (18), but stability-indicating methods have special requirements making them not suitable for every laboratory.

In this work, based on the thermodynamic relationship, NOR C was selected as a model polymorph to evaluate the effect of its complexation with β-CD on properties including solubility, dissolution rate, hygroscopicity, and chemical and physical stability. In addition, a simple and specific chromatographic method to evaluate the photostability of the API was developed, validated, and applied to the samples under study.

MATERIALS AND METHODS

Chemicals and Reagents

Norfloxacin was supplied by Parafarm (Argentina) and β-cyclodextrin (MW = 1135) was kindly provided by Ferromet [agent in Argentina of Roquette (France)]. Chemicals of analytical grade and the solvents of HPLC grade were used. A Millipore Milli Q Water Purification System (Millipore, Bedford, MA, USA) generated the water used in these studies.

Obtaining the Form C of Norfloxacin

The solid form C of NOR was prepared as described in our previous report (15). The commercially available NOR (form A) was suspended in acetone, heated to reflux, and then allowed to slowly cool until it reached room temperature.

Solubility Studies

The effect of β-CD on the solubility of NOR C at 25.0 ± 0.1 °C in water and buffered solutions of pH 6.0 and 8.0 was studied. The measurements were performed according to the method of Higuchi and Connors (19). An excess of NOR C was suspended in solutions containing increasing concentrations of β-CD (from 2.4 to 15.5 mM). NOR C free was used to determine intrinsic solubility (S_0). The suspensions were sonicated for 15 min (ULTRASONIC LC 30 H Elma) and then located in a constant temperature water bath (Haake DC10 thermostat) for 72 h. The suspensions were sonicated at several time intervals. After the equilibrium was reached, the remaining solid was separated by filtration using a 0.45-μm membrane filter (Millipore, USA). The clear solutions were suitably diluted and analyzed by UV–vis spectrophotometry (Agilent Cary 60 spectrophotometer) at $\lambda = 274$ nm.

Binary Systems Preparation

The solid-state systems of NOR C with β-CD were prepared in equimolar ratio as described in our previous report (15). The kneading (KN) system was obtained by thoroughly kneading the solids in a mortar for about 45 min, with the addition of drops of an acetone-water (50:50, *v*/*v*) mixture. Then, the resulting paste was dried under vacuum at 40 ± 1 °C for 48 h and protected from light. The physical binary mixture (PM) was prepared by uniformly dry blending the components in a mortar and pestle.

Dissolution Study

The dissolution profiles of NOR C and the systems obtained by KN and PM were evaluated in a dissolution apparatus (Hanson SR II 6 Flask Dissolution Test Station, Hanson Research Corporation, Chatsworth, CA, USA) using the paddle method according to USP apparatus 2 at a temperature of 37.0 ± 0.5 °C and a rotation speed of 50 rpm. Suitable quantities of each powder containing an amount equivalent to 200 mg of pure API were compressed using a hydraulic press at an appropriate force to obtain discs, which will not be disintegrated under test conditions. The discs were immersed in 500 mL of each of the following dissolution media: simulated gastric fluid (SGF, pH 1.2), acetate buffer solution (pH 4.5), and simulated intestinal fluid (SIF, pH 6.8). They were prepared according to the Pharmacopoeia method (20). Aliquots of each of the dissolution samples were collected at appropriate time periods and immediately replaced with equal volumes of fresh medium maintained at the same temperature. Each sample was filtered, adequately diluted with dissolution media, and analyzed for API content by spectrophotometry at 277 nm. The cumulative percentages of the API released from the discs were calculated. All the experiments were performed in triplicate. The results were displayed as mean percentage of the API released (±SD) at the specific sampling time.

The cumulative percentages of the API released from the powder and the similarity factor *f*2 (21) were calculated as follows:

$$f2 = 50\log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0,5} 100\right\} \quad (1)$$

where n is the number of sampling points and R_t and T_t are the percentages of the dissolved reference and of the test product, respectively, at each time point t. This model is used for estimating the closeness between *in vitro* dissolution profiles (22). For curves to be considered similar, *f*2 values should be close to 100. Generally, *f*2 values greater than 50 imply an average difference of no more than 10% at the sample time points. This ensures the equivalence of the two curves and thus of the performance of the test and reference products.

Stability Study

The effect of complexation on the degradation processes of NOR C, under accelerated storage conditions, was studied in accordance with the International Conference on Harmonization guidelines (23). In particular, the solid samples of NOR C, KN, and PM were stored in closed glass vials at 40 °C and 75% relative humidity (RH), and subjected to daylight in a stability chamber for 6 months. The samples were monitored at predetermined intervals to evaluate the chemical stability and possible physical changes.

The content of NOR C in each sample was measured every 30 days to monitor the chemical stability of the solids. The solid samples were appropriately dissolved and analyzed using a stability-indicating HPLC method. This method was developed and validated before use, according to standard procedures (24).

The HPLC system was an Agilent 1100 series instrument (Agilent, Waldbronn, Germany). The HPLC experiments were performed under isocratic conditions. The results were informed as means of three determinations of samples prepared in duplicate. *Chromatographic conditions*: The column used was a Phenomenex Gemini C18, (250 mm × 4.6 mm i.d., 5-μm particle size), with a precolumn (guard cartridge, Security Guard C18 4 mm × 3.0 mm i.d.) supplied by Phenomenex (Torrance, CA, USA); the mobile phase was filtered through a 0.45-μm Millipore membrane filter and degassed prior to use.

Initially, in the development of the HPLC method, the composition of the mobile phase and the flow rate were selected to optimize the retention time and the tailing factor. Different mobile phases containing methanol, acetonitrile, water, and phosphate buffer (KH_2PO_4) with pH values adjusted between 2.9 and 3.0 were tested. The best mobile phase was the mixture water (adjusted to pH 2.9)-acetonitrile (85:15, *v*/*v*). The optimum flow rate was 1.5 mL min^{-1}, and the run time was 5 min approximately. The temperature of the column was 40 °C and the volume of injection was 50 μL. To select the analytical wavelengths, the one corresponding to the maximum absorbance peak of NOR and its degradation products (2,25) in the mobile phase were considered.

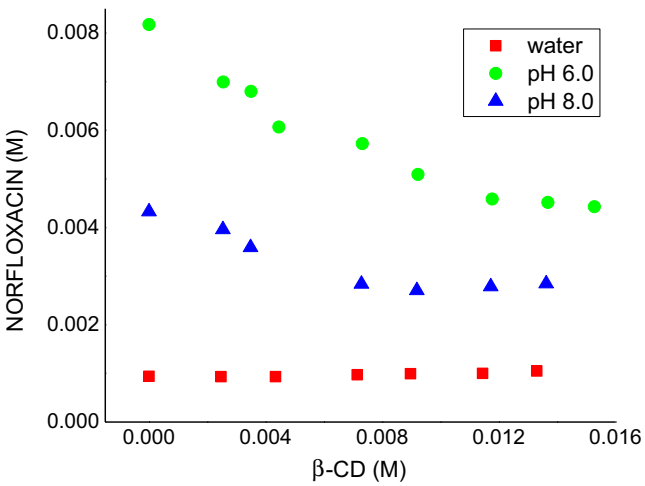

Fig. 1. Effect of β-CD on the solubility of NOR C in aqueous (pH 7.2) and buffer solutions of pH 6.0 and 8.0

Table 1. Summary of solubility studies at 25.0 ± 0.1 °C

Solution	S_0 (mg/mL)[a]	S_{max} (mg/mL)[b]
Aqueous	0.29	0.34
pH 6.0	2.61	2.23
pH 8.0	1.38	1.26

[a] Solubility of NOR C in the absence of β-CD
[b] Maximum solubility in the presence of β-CD

Therefore, the detector was set at wavelengths of 260, 267, 274, and 280 nm. It is important to highlight that differences between the retention times of the different solids of NOR were not determined.

On the other hand, the physical stability of NOR C, KN, and PM was evaluated by ssNMR and PXRD, at the initial time ($t = 0$), 1 month ($t = 1$), 3 months ($t = 3$), and 6 months ($t = 6$). Morphological stability was investigated by SEM at $t = 0$ and $t = 6$.

Content Determination

For the determination of NOR C content in the solid samples, an amount of powder containing 10 mg of NOR C was dissolved in an ethanol-water (50:50, *v*/*v*) mixture. After appropriate dilution with mobile phase, the samples were analyzed by HPLC-UV following the procedure described below. Each assay was performed in triplicate, and the average and standard deviations were calculated every 30 days to monitor the chemical stability of the solids.

Solid-State Nuclear Magnetic Resonance

The high-resolution solid-state ^{13}C spectra of the samples were recorded using the ramp cross-polarization/magic-angle spinning (CP-MAS) sequence with proton decoupling during acquisition (26). All solid-state nuclear magnetic resonance (ssNMR) experiments were performed at room temperature in a Bruker Avance II spectrometer equipped with a 4-mm MAS probe operating at 300.13 MHz for protons. The operating frequency for carbons was 75.46 MHz. Glycine was used as external reference for the ^{13}C spectra and to set up the Hartmann–Hahn matching condition in the cross-polarization experiments. All the spectra were recorded with 1600 scans, a contact time of 2 ms during CP, and a recycling delay of 5 s. The spinning rate for all the samples was 10 kHz.

FT-IR Spectroscopy

The FT-IR spectra were recorded on a Nicolet 5 SXC FT-IR Spectrophotometer (Madison, WI, USA). The potassium bromide discs were prepared by compressing the powder.

Powder X-Ray Diffraction

Powder X-ray diffraction (PXRD) patterns were obtained at room temperature using a Philips PW1800 diffractometer operating at 40 kV and 30 mA with Cu-Kα radiation.

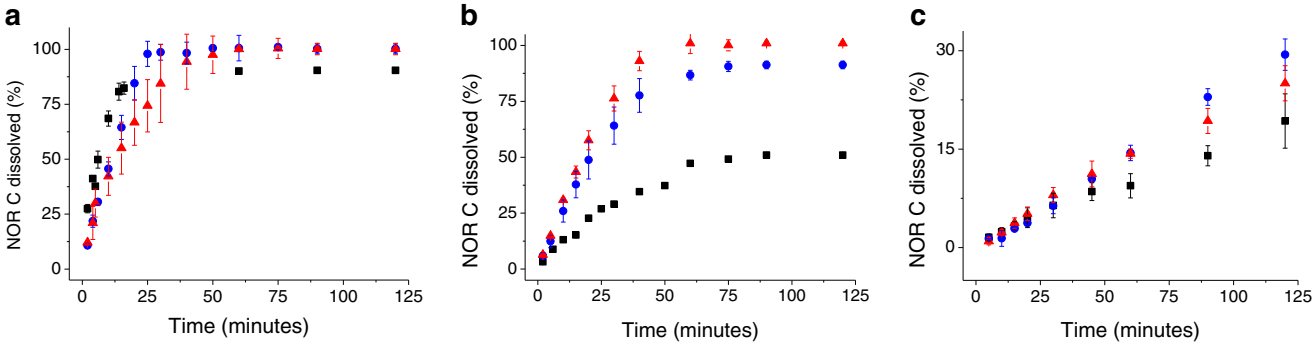

Fig. 2. Dissolution profiles of (black box) NORC, (red triangle) KN, and (gray circle) PM in **a** SGF, **b** acetate buffer solution, and **c** SIF

The powder patterns were collected by scanning 2θ from 2° to 40° with a step size of 0.02° at a scanning rate of 2 s/step.

Scanning Electron Microscopy

The microscopic shape and morphology of the samples were analyzed using a Carl Zeiss Sigma scanning electron microscope. The samples were fixed on a brass stub using double-sided aluminum tape and then gold coated under vacuum by employing a sputter coater Quorum 150 to improve their conductivity.

Hygroscopicity Study

Solid samples of NOR C, KN, and PM were accurately weighed before storage under accelerated conditions. The samples were retired at predetermined periods (every 30 days) to control their weight changes. The experiments were carried out in triplicate.

RESULTS AND DISCUSSION

Phase Solubility Analysis

Table I summarizes the results obtained in the solubility study of NOR C in the absence and in the presence of β-CD in aqueous solution (pH closed to 7.2), and buffered aqueous solutions of pH 6.0 and 8.0. The results indicate that the solubility of NOR in the absence of β-CD in buffer solutions of pH 6.0, was higher than in the buffer solution of pH 8.0, and also higher than in aqueous solution of pH 7.2. These facts are evidence that the solubility of this zwitterionic API was affected by the equilibrium between the neutral unionized form and the poorly soluble zwitterionic form at pH values in the same range of intestinal media (between 6.0 and 8.0). Therefore, small fluctuations in pH may result in significant changes in the solubility of NOR C.

Figure 1 shows the solubility profiles for NOR C molecule at 25.0 ± 0.1 °C, which changed as a function of β-CD concentration.

These studies revealed that all diagrams corresponded to type B, which can be assigned to the formation of insoluble complexes. In particular, the solubility of NOR C in aqueous solution remained practically unchanged with increasing concentrations of β-CD, whereas in buffered solutions of pH 6.0 and 8.0, the solubility decreased showing a typical B_S-type phase solubility curve. These results demonstrated that β-CD does not produce a solubilizing effect on the molecule of NOR C. Our previous studies, in contrast, showed that the complexation with β-CD in aqueous and buffer solutions of pH 6.0 and 8.0 are a useful strategy to improve the solubility of NOR form A (14). In particular, these studies gave evidence that different interactions exist between each NOR polymorph and β-CD, which generates complexes with contrasted behavior.

Dissolution Studies

NOR is better absorbed from the stomach, and, in a smaller degree, from the lower part of the gastrointestinal tract. Then, it is reasonable to analyze these supramolecular complexes as candidates that act as gastroretentive drug delivery systems. Therefore, dissolution experiments were performed to analyze the effect of β-CD on the dissolution rate of NOR C in three different media modeling gastrointestinal tract environments: SGF (pH 1.2), stomach fluid during meals (acetate buffer solution, pH 4.5), and SIF (pH 6.8). The dissolution profiles obtained are presented in Fig. 2.

The profiles showed that β-CD increased the dissolution of NOR C. However, a comparison between them revealed clear differences in the rate and percentage of dissolution under different pH conditions. This can be due to the differences in the solubility of NOR and to the principal role of the pH of the dissolution medium.

The profiles in SGF showed a slower initial dissolution rate for the KN and PM systems than NOR C, which could prolong the gastric residence time of the API. This gradual dissolution behavior can be associated with the capability of β-CD to modulate the release of NOR C from the solid. Moreover, both systems showed complete dissolution within 60 min, while NOR C exhibited the lowest extent of dissolution (90%) after 90 min. The profiles in acetate buffer solution evidenced clear differences in the rate and percentage of dissolution of NOR C, KN, and PM. It is interesting to note that KN and PM showed a higher dissolution rate than the free NOR C. It was determined that KN caused the

Table 2. *f2* values

Dissolution media	KN system	PM system
SGF	35	40
Acetate buffer solution	28	30
SIF	73	65

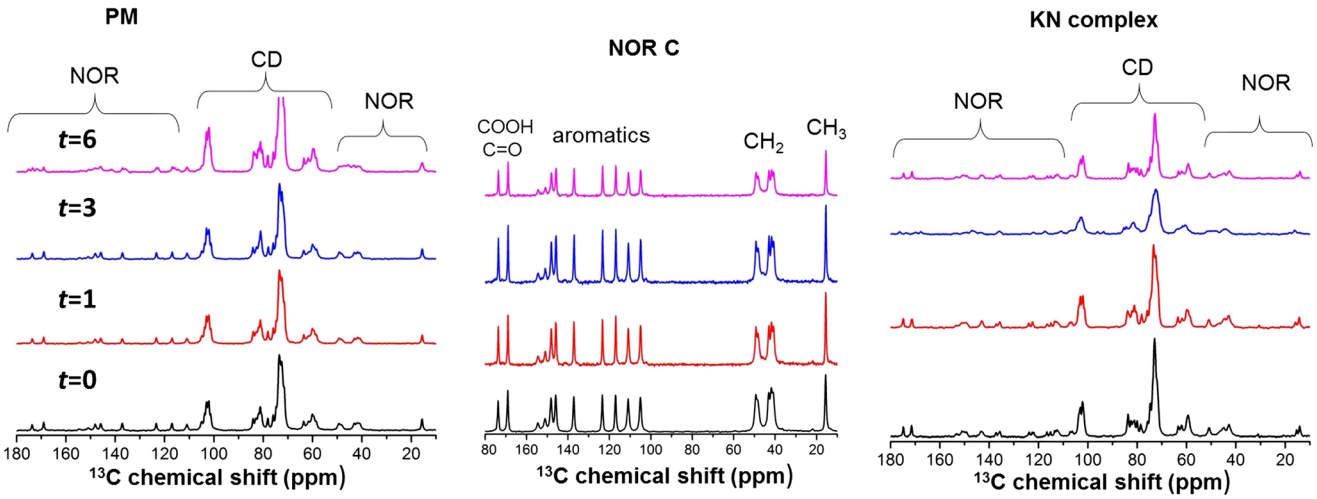

Fig. 3. ^{13}C CP-MAS spectra of NOR C, β-CD, KN, and PM systems at the selected times for the stability study: initial time ($t = 0$), 1 month ($t = 1$), 3 months ($t = 3$), 6 months ($t = 6$)

complete dissolution of the solid within 60 min and PM dissolved 90% of the API within 90 min, while NOR C showed the lowest extent of dissolution (50%) after 75 min. This enhancement of the amount of API dissolved can be attributed to the interaction of the components in the KN system. In contrast, the dissolution studies performed in SIF exhibited the lowest rate and percentage of dissolution of the API. The KN and PM systems slightly improved the dissolution of NOR C. This behavior is related to the poor solubility of NOR C at the pH value of the dissolution medium.

In addition, the profiles of KN and PM were compared with those of free NOR C in the three dissolution media by applying the similarity factor ($f2$). The $f2$ values obtained (Table II) indicate that only the profiles obtained in SIF were similar to that of NOR C.

As expected, the studies demonstrated the excellent capability of NOR C:β-CD to improve the dissolution of NOR C in the portion of the gastrointestinal tract where it is best absorbed. Therefore, these findings evidenced that the supramolecular complex can be used as a promising strategy to enhance the bioavailability of NOR C.

Chemical Stability

An efficient, precise, and simple reversed-phase high-performance liquid chromatographic (HPLC) procedure was developed and validated. This method was used successfully to the measurement of NOR C, without interference from its degradation products in solid samples subjected to photostability studies.

To obtain information on the photodegradation process, each solid sample was exposed to daylight at 40 °C and 75% RH. The drug content in the samples was measured during storage using the mentioned stability-indicating HPLC method.

For the validation of the method, the specificity was demonstrated by analyzing samples previously subjected to stress conditions (exposure to light and heating of an acidic solution of NOR). For the preparation of degraded NOR in acidic solution, a mixture of 0.4 g of pure NOR powder with 75 mL of 2 N HCl solution was refluxed with heating and protection of light for 16 h. The degradation products showed maximum absorption at a wavelength different from that of NOR. Therefore, the method was specific, since NOR could

Table 3. Validation report of the HPLC method for determination of NOR

Parameter	Results			
Linearity	Regression equation[a]		$Y = 252.8\ X - 21.9$	
	Correlation coefficient (r^2)		0.994	
	Linear range (μg/mL)		3.30–8.36	
Accuracy repeatability	Nominal concentration (μg/mL)	Measured concentration (μg/mL)	Recovery (%)	% RSD
	4.40	4.39 ± 0.04	99.9 ± 0.9	0.89
	5.72	5.67 ± 0.02	99.1 ± 0.2	0.31
	7.26	7.25 ± 0.03	99.4 ± 0.1	0.41
Detection limit	0.37 μg/mL			
Quantification limit	1.23 μg/mL			

[a] X is the concentration of NOR in μg/mL; Y is the peak area at 280 nm

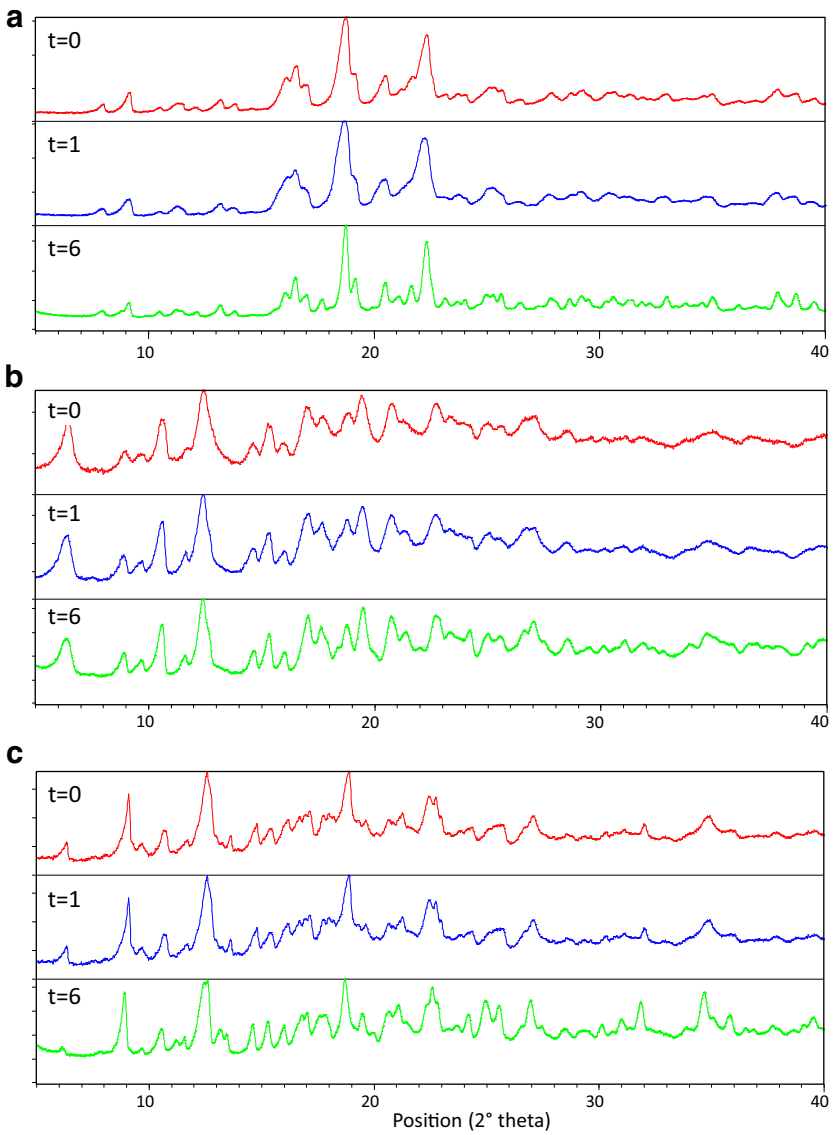

Fig. 4. Powder X-ray diffraction patterns of **a** NOR C, **b** KN, and **c** PM at the selected times for the stability study

be determined without any interference from the degradation products (see Supplementary Material, Fig. S1). The validation parameters of the method are shown in Table III. The correlation between the peak area ratio and NOR concentration was linear. Repeatability and accuracy were evaluated by the recovery studies. Results for percent relative standard deviation (%RSD) values lower than 2% are considered to be satisfactory, showing the acceptable precision of the method. The accuracy of the method ranged from 98.6 to 99.4% (average 99.4%).

The photodegradation of free NOR C and the samples containing β-CD (KN and PM) under identical experimental conditions was compared. The results (Table IV) showed that the amount of NOR in the pure sample and in the PM decreased with time with respect to the initial value, indicating that these solids samples suffered the chemical degradation process. In contrast, the amount of drug remained constant in the KN system, indicating that the supramolecular system had a stabilizing effect that decreased the photochemical reactivity of NOR C.

Table 4. Recovery percentages for NOR C obtained by HPLC in solid samples studied for 6 months

Sample	0 day	30 days	60 days	90 days	120 days	150 days	180 days
NOR C	101 ± 2%	99 ± 1%	98 ± 1%	97 ± 1%	97 ± 2%	96 ± 1%	95 ± 1%
KN	101 ± 2%	99 ± 1%	99 ± 2%	99 ± 1%	99.9 ± 0,6%	100 ± 1%	100 ± 1%
PM	100 ± 1%	96.6 ± 0.4%	95.5 ± 0.8%	95 ± 1%	93.5 ± 0.2%	93.2 ± 0.9%	91.4 ± 0.8%

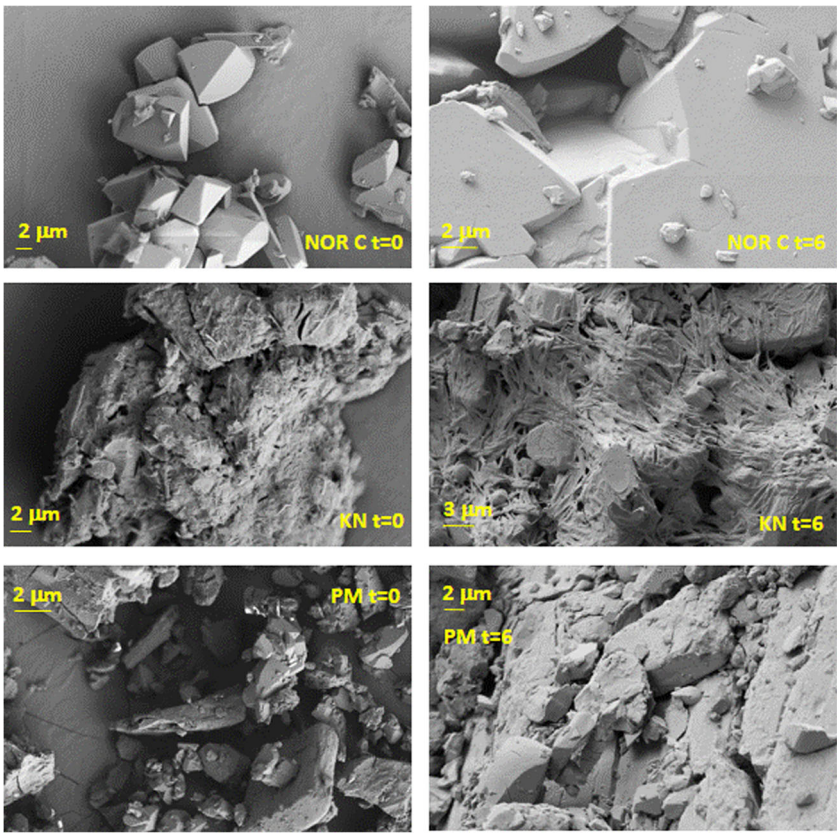

Fig. 5. SEM microphotographs of NOR C, KN, and PM for $t = 0$ and $t = 6$

Physical Stability

The crystal reorganization during drug storage is indicative of physical instability, which could be caused by factors such as temperature and humidity. Polymorphic transformations can be studied by applying several techniques (27,28) used for the identification and characterization of solid-state samples. In the present study, samples of NOR C, KN, and PM were analyzed by ssNMR and PXRD at the initial time, after 1, 3, and 6 months ($t = 0$, $t = 1$, $t = 3$, and $t = 6$), to evaluate possible changes or transformations under accelerated storage conditions (29–31). At the initial time the samples were monitored by FT-IR spectroscopy (see Supplementary Material, Fig. S2), ssNMR, and PXRD, observing the same results than in our previous characterization studies (15), which confirm that the experimental conditions used for the preparation of the NOR C:β-CD complex can be easily reproduced to obtain the same solid samples described in our previous work.

Figure 3 displays the ^{13}C CP-MAS for NOR C, KN, and PM, at $t = 0$, $t = 1$, $t = 3$, and $t = 6$. Taking into account the previous information obtained for these compounds, it is worth to remark that the KN sample constitutes a different solid phase compared with the PM, with remaining amounts of pure drug evidenced by the unchanged NOR C signals in the KN at $t = 0$ (see for example signals in the 10–60 and 100–180 ppm regions) (15). In particular, the NOR C spectra at different studied times are almost identical in chemical shifts and intensities. This fact indicates that NOR C maintained the same structure under storage conditions, revealing the physical stability of the pure drug and absence of polymorphic transformations. For the KN sample at different storage times, some changes are possible to be observed, which are mainly related with the intensity of pure NOR C signals. The region between 60 and 100 ppm, which can be associated to the complex, displays some changes in intensity and shape, with no changes in the chemical shifts. Once again, there is no appearance of new signals or disappearance of the original KN signals, only changes in intensity or shape were observed. The PM sample displays almost the same spectrum for $t = 0$, $t = 1$, and $t = 3$, and for $t = 6$ there are slight changes, as for example changes in the intensities for the signals around 40 ppm and a doublet that appears for the signals at higher ppm. The signals in the central region from 60 to 100 ppm that belongs to CD also display some changes at $t = 6$, mainly in the intensity and shape but there were not major shifts. In spite of the minor changes observed for the different storage times for the KN and PM systems, the absence of disappearance and appearance of signals in the carbon spectra indicate that both compounds were stable under storage conditions, and that they preserved the physical characteristics of NOR C.

Figure 4 displays the PXRD spectra for NOR C, KN, and PM, at $t = 0$, $t = 1$,and $t = 6$. The PXRD diffractogram for NOR C showed reflections at $2\theta = 9.2°$, 16.6°, 18.8°, 20.5°, and 22.4°, which are in agreement with our previous report (15). These characteristic peaks were observed along the 6 months of storage, revealing that NOR C maintained their physical

characteristics. Additionally, the PXRD pattern for KN showed diffraction peaks located at $2\theta = 6.5°$, 10.7°, 12.5°, 16.9°, 19.4°, 20.7°, and 22.7°. After 6 months of storage, unmodified PXRD pattern for this solid indicates no phase transformations. In the same way, PM pattern exhibited the characteristic peaks of NOR C and β-CD at $2\theta = 9.2°$, 12.6°, 18.9°, 22.4°, and 27°. This sample showed unmodified PXRD patterns throughout the 6 months of storage, indicating absence of phase transformations.

Our PXRD results together with ssNMR demonstrated that no relevant changes occurred under storage, revealing that each sample maintain their physical characteristics. Consequently, we conclude that NOR C, KN, and PM are physically stable in accelerated storage conditions.

Additionally, the morphological characteristics and stability of the solids were studied by SEM. Figure 5 shows the structure of NOR C, KN, and PM at the storage times $t = 0$ and $t = 6$. The typical crystals of NOR C were seen as hexagonal-like shape structures, whereas β-CD showed a parallelogram shape (not shown). The initial morphology of the pure components disappeared in the microphotographs of KN, so it was not possible to discriminate the single materials. The particles had an irregular size and shape with needle-like clusters adhered to the surface of large particles. These morphological changes suggest an interaction in solid state and reinforce the formation of a novel solid phase. In the PM, the characteristic NOR C crystals mixed with β-CD particles were clearly detectable, thus confirming the absence of interactions.

After 6 months of storage, the samples maintained their typical morphologies, although NOR C exposed to humidity and temperature, exhibited predominantly agglomerated structures of its original particles.

Hygroscopicity

Our results showed that the solid samples of NOR C, KN, and PM did not increase their weight significantly as a function of time, under storage at 40 °C and 75% RH (see Supplementary Material, Fig. S3). This revealed that the samples were not hygroscopic. In particular, it was observed that the supramolecular complex obtained by the KN method did not cause water vapor adsorption under accelerated storage conditions. It is especially important in regions with tropical climate where the RH is relatively higher than 80% most of the year.

CONCLUSIONS

The results obtained in this study of supramolecular complexes of NOR C demonstrated that the interaction with the ligand β-CD produces an improvement of the properties of the API, maintaining, at the same time, the physical stability. Remarkably, the supramolecular complex NOR C: β-CD (prepared using the kneading method) showed an increment in the dissolution rate of NOR C, with the capacity of modulating the dissolution rate in gastric fluids. By introducing a new method to evaluate photochemical activity, it was evidenced that NOR C: β-CD increases the photochemical stability of NOR C, without affecting its physical stability. Thus, we concluded that the solid NOR C: β-CD complex can be used as a promising carrier to improve the bioavailability of this particular polymorph, through a greater absorption obtained by the increasing of its residence time and gastric dissolution. Furthermore, NOR C: β-CD constitutes an alternative tool to formulate a potential oral drug delivery system.

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