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A.S. Melnyk [a], O.E. Chyhyrynets [a], G. Lazzara [b]

DEGRADATION OF MOXIFLOXACIN HYDROCHLORIDE ENCAPSULATED IN HALLOYSITE NANOTUBES UNDER THE INFLUENCE OF TEMPERATURE AND ULTRAVIOLET AND VISIBLE LIGHT

[a] National Technical University of Ukraine «Igor Sikorsky Kyiv Polytechnic Institute», Kyiv, Ukraine
[b] University of Palermo, Palermo, Italy

The photosensitive pharmaceutical ingredient moxifloxacin hydrochloride degrades during storage under the influence of external factors, such as elevated temperature and ultraviolet and visible light irradiation, resulting in a decrease in the concentration of the active substance. To increase its resistance to these external factors, moxifloxacin hydrochloride was encapsulated in halloysite nanotubes. The aim of this study was to determine the level of degradation of moxifloxacin hydrochloride in its native and encapsulated states under the influence of temperature and ultraviolet and visible light irradiation. Encapsulation was carried out by the vacuum method and confirmed by TEM microscopy. The residual content of the photosensitive pharmaceutical ingredient after degradation was monitored by high-performance liquid chromatography of a model solution with an initial concentration of 2 mg/ml, prepared from samples of native and encapsulated moxifloxacin hydrochloride previously tested under the influence of temperature and light irradiation. Encapsulated moxifloxacin hydrochloride showed increased resistance to degradation caused by visible light irradiation at 200 watt-hours/m^2 (by 10.9%); resistance to degradation was increased by 13.4% and 14% under test conditions during 24 hours of ultraviolet light irradiation and thermostating at a temperature of 60^0C, respectively, compared to non-encapsulated moxifloxacin hydrochloride.

Keywords: nanocomposite, halloysite, moxifloxacin hydrochloride, photostability, thermal stability, encapsulation.

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Introduction

Moxifloxacin (MF) (1-cyclopropyl-6-fluoro-8-methoxy-7-((4aS,7aS)-octahydro-6H-pyrrolo[3,4-b] pyridine-6-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid) is a synthetic broad-spectrum fluoroquinolone antimicrobial agent [1], which exhibits in vitro activity against Gram-positive and Gram-negative microorganisms, as well as atypical organisms and anaerobes [2]. Moxifloxacin hydrochloride is distinguished from other quinolones by having a methoxy function at the 8th position and an S, S-configuration of the diazabicyclononane ring at the 7th position (Fig. 1).

This drug is effective and used for the treatment of community-acquired pneumonia, including that caused by multidrug-resistant Streptococcus pneumoniae, complicated skin infections, bacterial conjunctivitis, and as a second-line agent in tuberculosis [3]. Moxifloxacin hydrochloride is available in various pharmaceutical forms, such as tablets, injections, and eye drops [4]. However, fluoroquinolones have several disadvantages that reduce their effectiveness in treatment. One of the problems is primarily sensitivity to light [5], as evidenced by numerous studies on the photodegradation of MF [6] and other fluoroquinolones [7]. During photodegradation in aqueous solutions, MF undergoes several acid-base equilibria, leading to the formation in solutions of different pH [8] of several ionic forms, which undergo photodegradation. Since moxifloxacin hydrochloride is widely used in clinical

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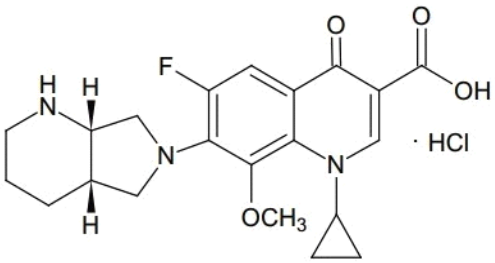


Fig. 1. Structural formula of moxifloxacin hydrochloride

practice, like many other pharmaceuticals, it can be affected by light in the visible and ultraviolet spectrum, which typically significantly reduces its effective concentration. Besides the impact of light, like other active pharmaceutical ingredients (APIs), MF may experience thermal effects when used, which will also contribute to the reduction of the active substance concentration in medicinal products. All the above factors negatively affect the properties of therapeutic substances. Therefore, an effective solution for preserving the properties of APIs is the use of nanocarriers, which are actively researched and used in the pharmaceutical industry today. A wide range of substances are used as nanocarriers, including liposomes, cyclodextrins, dendrimers, and others. However, natural clays that have a nanotube structure have recently gained popularity.

Halloysite is one such clay. Today, halloysite is studied and used as an effective nanocarrier for targeted drug delivery, and a few relevant composites have been developed based on it. Halloysite is a natural phyllosilicate of the kaolin group with an Al:Si ratio of 1:1. Chemically, halloysite nanotubes have the chemical formula $Al_2Si_2O_5(OH)_4 \cdot nH_2O$, where n denotes their state of hydration. Thus, HNTs can be classified as hydrated HNTs $Al_2Si_2O_5(OH)_4 \cdot 2H_2O$, which have a layer spacing of 10 Å, and dehydrated forms $Al_2Si_2O_5(OH)_4$ which have a layer spacing of 7 Å. Structurally, halloysite nanotubes consist of 10–15 alumina-silicate double layers with a distance of approximately 0.72 nm; such arrangement creates an external surface rich in siloxane (Si–O–Si) groups, and an internal one containing arrays of aluminol (Al–OH) groups. The tubes have a length in the range of 0.2–1.5 μm, inner and outer diameters in the range of 10–30 nm and 40–70 nm, respectively [10].

Due to the different chemical composition of the layers forming the nanotubes, they are subject to ionization in an aqueous environment, contributing to the formation of opposite charges on the inner and outer surfaces [11]. The inner surface is positively charged, and the outer surface is negatively charged. Such charge separation occurs in water in a wide pH range from 3 to 8 [12]. Due to this effect, negatively charged compounds can be loaded into the inner lumen of halloysite nanotubes, which at the same time will have additional protection against negative external factors [13]. Modification of the inner and/or outer surface of halloysite nanotubes opens different strategies for introducing new properties and expanding their fields of application. Halloysite is a safe biocompatible material, so it is widely researched in the field of using it as a nanocarrier for biologically active molecules, antioxidants, and pharmaceutical ingredients.

Considering the need to reduce photosensitivity and increase the stability of moxifloxacin hydrochloride at elevated temperatures, the creation of a nanocomposite based on moxifloxacin hydrochloride and halloysite is relevant. The aim of the work was to determine the level of degradation of moxifloxacin hydrochloride in the native state and in the composition of the nanocomposite under the influence of ultraviolet and visible light irradiation and at elevated temperature.

Experimental

Reagents and equipment

Halloysite was used for the research was from Sigma Aldrich (code 685445-100G). Its chemical formula is $H_4Al_2O_9Si_2 \cdot 2H_2O$, molecular weight 294.19 g/mol, density 2.53 g/cm^3, and pore volume 1.26–1.34 ml/g. As a pharmaceutical ingredient, moxifloxacin hydrochloride obtained from EP reference standards was investigated. The identification of moxifloxacin hydrochloride was performed using an Agilent 1290 Infinity II liquid chromatograph, equipped with a 1290 Infinity II Multisampler and an Agilent Max-Light cell with a 60 mm optical path length. Detection was carried out using a DAD detector, with the 1290 Infinity II Flexible Pump serving as the pump.

To study the effects of ultraviolet light, a Fisher Bioblock Scientific VL-215.G 2·15W UV lamp with 365 nm tubes and a power rating of 60 W was used.

For thermal stress tests, a Memmert UNB200 was employed.

Microscopic studies were conducted using a Themis transmission scanning electron microscope (S/TEM) from FEI (Thermo Scientific), capable of operating in STEM and TEM modes. The electron gun features a Schottky field emission cathode. The system offers a resolution limit of 0.7 Å in TEM/STEM modes when using an image and probe corrector. The accelerating voltage range is from 60 to 300 kV. It includes a HAADF detector and triple axis detectors DF1/DF2/BF located on the axis.

The microscope is equipped with a Ceta 16M camera, Gatan US1000/US4000 cameras, a series of Gatan energy filters, and the Super-X: a highly sensitive windowless EDX detector system (patented technology) with an EDS detector solid angle of 0.13 srad.

Additionally, a Hitachi S-4800 field emission scanning electron microscope was used for microscopic studies at 3.0 kV.

Method for loading halloysite nanotubes

The use of the vacuum method as the most widely utilized technique for loading nanotubes with the substance under investigation in this work allows for a significant increase in the amount of drug encapsulated by encapsulation into nanotubes under environmental pressure. According to the European Pharmacopoeia monograph 11.3[1] (EP 11.3), the model solvent preparation involved using 0.50 g of tetrabutylammonium hydrogen sulfate and 1.0 g of potassium dihydrogen phosphate, dissolved in 500 ml of water. To the resulting solution, 2 ml of phosphoric acid and 0.050 g of anhydrous sodium sulfite were added, after which the volume was brought up to 1000 ml with water. In this study, the encapsulation of moxifloxacin hydrochloride into halloysite nanotubes was performed by vacuuming a dense suspension obtained at a mass ratio of halloysite to MF of 2:1 [14]. The emergence of bubbles on the surface of the suspension indicated that air was being removed from the surface of the HNTs. After the pressure was brought back to atmospheric, the air-filled space inside the lumen of individual HNTs was replaced with the API solution. This process was repeated at least two to three times to ensure the halloysite nanotubes were filled with the moxifloxacin hydrochloride solution. After the vacuum cycle was completed, the mixture was centrifuged, decanted, and dried under vacuum.

This encapsulation method leverages the vacuum technique to maximize the drug load within the halloysite nanotubes, providing a promising approach for enhancing drug stability and controlled release. The meticulous preparation of the solvent, as stipulated by the European Pharmacopoeia, ensures the proper conditions for the encapsulation process, thereby facilitating the successful integration of moxifloxacin hydrochloride into halloysite nanotubes. This could lead to improved pharmacological properties and efficacy of the drug, potentially offering a novel formulation strategy for various pharmaceutical applications.

Method for determination of moxifloxacin concentration

To determine the effective concentration of the active pharmaceutical ingredient, a highly sensitive method of liquid chromatography was used, which allows fractionation of moxifloxacin hydrochloride from its degradation products and the solvent.

For the preparation of the comparison solution, 17 mg of moxifloxacin hydrochloride was dissolved in 50 ml of solvent described in 2.2 and then diluted with solvent to a final volume of 100.0 ml. For the solutions under study, a 2.0 ml aliquot of the sample was taken and diluted with solvent to a volume of 100.0 ml.

Chromatography was performed on a liquid chromatograph equipped with a UV-spectrophotometric diode-array detector. The identification of the moxifloxacin hydrochloride peak was conducted using an Inertsil Phenyl chromatographic column. The mobile phase consisted of methanol and a solution containing 0.5 g/l tetrabutylammonium hydrogen sulfate, 1.0 g/l potassium dihydrogen phosphate, and 3.4 g/l phosphoric acid. The flow rate of the mobile phase was 1.5 ml/min. The temperature of the chromatographic column was maintained at 45^{0}C. The detection was performed at an optical density of 293 nm with a sample injection volume of 10 μl.

To purify the solution of the drug under study, dual-layer membrane filters are commonly used. Such a filter consists of two parts: a preliminary coarse filter made of glass fibers and the membrane filter itself. The prefilter is made of borosilicate glass fibers. It is chemically inert and resistant to most solvents. The large surface area of the prefilter ensures its high capacity and the possibility of multiple uses.

In this study, tests were conducted to assess the ability to separate moxifloxacin hydrochloride from halloysite using Agilent membrane filters of various types. Several filters were tested, which allowed determining the filter that best suits the separation of moxifloxacin hydrochloride from halloysite. It was experimentally found that the Agilent PES 0.1 μm membrane filter is most suitable for accomplishing the set tasks. The correctness of the results exceeds 99.86%.

UV, photo, and thermal stability tests of moxifloxacin hydrochloride

Conducting stress tests makes it possible to evaluate the effectiveness of the use of MF as a part of HNTs.

The UV stability test is used to simulate the effect of storage of drugs, as well as to study their reaction to ultraviolet radiation, which can cause unwanted chemical reactions and, accordingly, reduce the effective concentration in the composition of drugs.

[1] https://pheur.edqm.eu.

The research was carried out by UV irradiating the nanocomposite HNTs/MF and API in its native state for 1 h, 2 h, 5 h, 12 h, and 24 h.

Testing of dosage forms for photostability is carried out to determine the stability of medicinal substances that are exposed to light in the visible range without an ultraviolet component. Fluorescent lamps that imitate natural daylight (wave spectrum from 380 to 750 nm) were used for testing. For testing, API samples in their native state and nanocomposite HNTs/MF were first placed in containers transparent to visible light, and then in a chamber where they were directly exposed to visible light. The samples were kept under light until the required accumulation level of 200 watt-hours/m^2 was reached according to Q1B conditions [15].

According to the standardized rules of the ICH (International Council for Harmonization) system, which establishes and regulates regulatory requirements for various tests, including temperature stress, a temperature of 60^{0}C is set as the most critical temperature for drug testing. API samples in the native state and nanocomposite HNTs/MF were placed in a temperature-controlled oven and kept at a temperature of 60^{0}C for 1 hour, 12 hours, and 24 hours.

The thermostability test was carried out by incubating moxifloxacin hydrochloride powdered and its composite with halloysite in a thermal cabinet at a temperature of 60^{0}C. The control of API concentration in the solution was conducted after 1, 12, and 24 hours of testing.

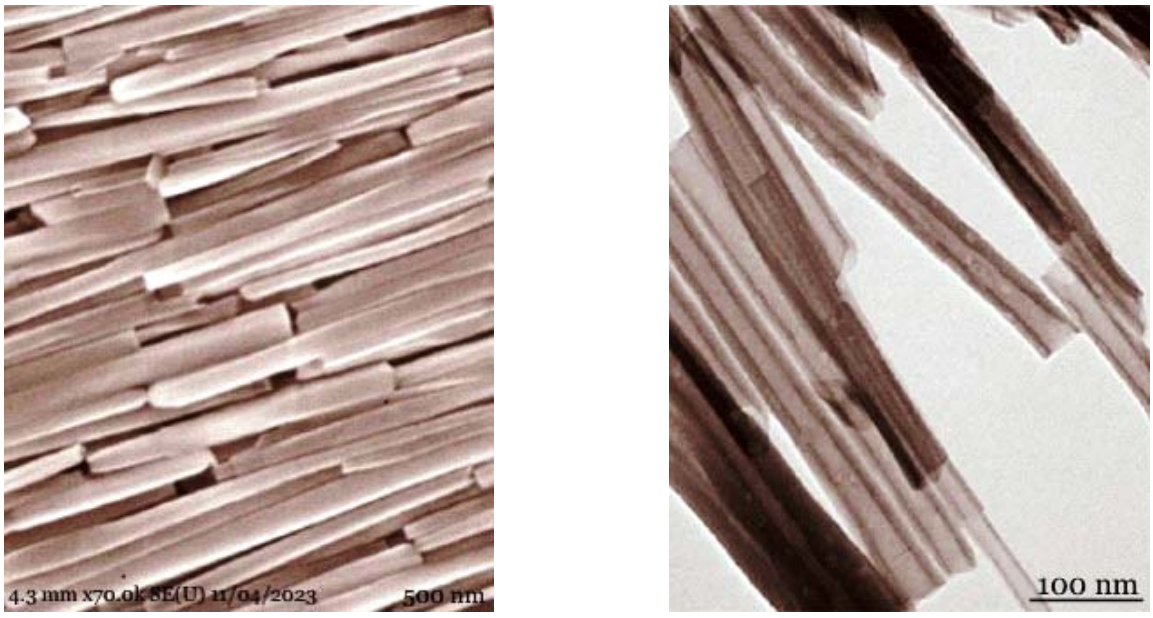
After testing, the samples were dispersed (in an ultrasonic bath for 10–15 min) in the model solution (see above) and the concentration of the active ingredient was determined by the method of high-performance liquid chromatography. Previous studies have shown that the used technique allows completely transferring the encapsulated moxifloxacin hydrochloride into the model solution. For the chromatographic determination of the pharmaceutical ingredient, solutions were prepared according to procedure described above.

Results and discussion

This study examines a sample where the size of the nanotubes ranges from 0.3 to 5 μm in length (Fig. 2).

The formation of the HNTs/MF composite was confirmed by microscopy (Fig. 3), where the presence of API particles inside the nanotubes was observed.

For effective identification of the investigated pharmaceutical ingredient and registration of its concentration changes in solutions, the chromatographic system must meet the requirements of the European Pharmacopoeia 11.3 regarding the characteristics of the identified peak. For this purpose, the method of high-performance liquid chromatography with ultraviolet detection was tested in the work. The obtained chromatogram of moxifloxacin and the characteristics of its averaged peak from three consecutive injections are presented in Fig. 4 and Table, respectively.



a b

Fig. 2 Microscopic images of halloysite: a – SEM; and b – TEM

Characteristics of the 3 consecutive injections moxifloxacin peaks

Parameter	Value
ΔRT (min), %	0.01
RSD, %	0.03
Tail factor	1.0
Average value of theoretical plates EP	10402

Fig. 3 Microscopic image of composite HNTs/MF

According to the requirements of the European Pharmacopoeia 11.3, the relative deviation of the peak retention time (DRT) from three consecutive injections should be no more than 2%, and the relative standard deviation of the peak area (RSD) should be no more than 0.67%. These parameters of the average peak of moxifloxacin are significantly smaller (Table).

Compliance with the criteria of EP 11.3 regarding the suitability of the chromatographic system for the quantitative determination of the pharmaceutical ingredient is indicated by the symmetry factor (Tail factor, Table), which should usually be in the range from 0.8 to 1.5. The theoretical plates EP parameter (Table) is responsible for the effective separation of the component (from the solvent and degradation products) in the chromatographic column and should be as high as possible, but not less than 1000. In our case, it is 10 times more, which indicates a high accuracy of the obtained peak. Thus, the parameters of the selected chromatographic system meet the requirements of EP 11.3, and the selected technique provides reliable results regarding changes in the concentration of the pharmaceutical ingredient. This approach allows determining the concentration of the undegraded ingredient after testing.

We investigated the resistance to degradation of MF in its native state and in the nanocomposite of HNTs/MF under the influence of ultraviolet radiation for 1, 2, 5, 12 and 24 hours. The amount of non-degraded MF was determined in the model solution according to method described above. Results show that moxifloxacin hydrochloride in its native state is quickly destroyed under the influence of ultraviolet radiation. As time increases exposure, the amount of degraded pharmaceutical ingredient increases and in 24 hours of exposure is 15.3%. The most intensive photodegradation occurs in the first 12 hours of exposure, when the amount of native moxifloxacin decreases by more than 11%.

Photodegradation of encapsulated moxifloxacin hydrochloride in HNTs/MF is much slower. The main process of photodegradation of encapsulated moxifloxacin occurs, as in the native state, in the first hours of exposure. After 24 hours of UV exposure 98.1% of MP remained unchanged. The results of the research are presented in Fig. 5.

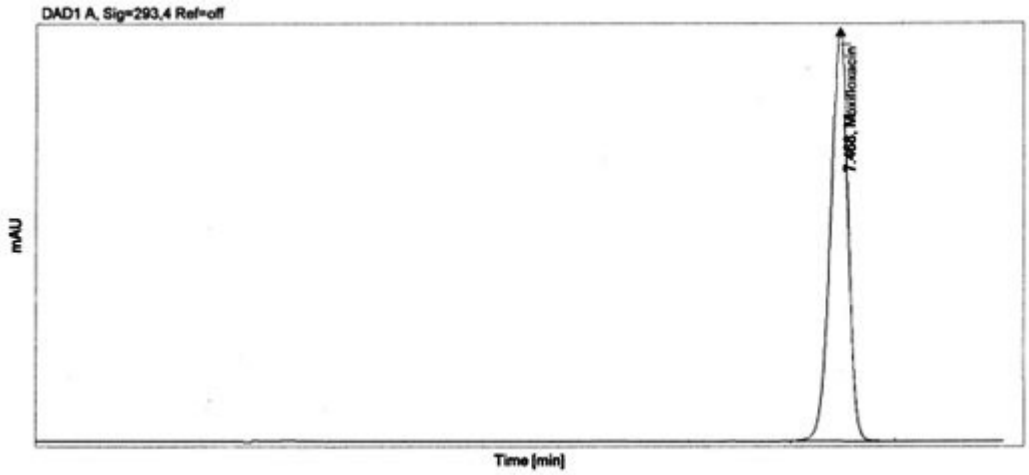


Fig. 4. Chromatogram for the identification of moxifloxacin

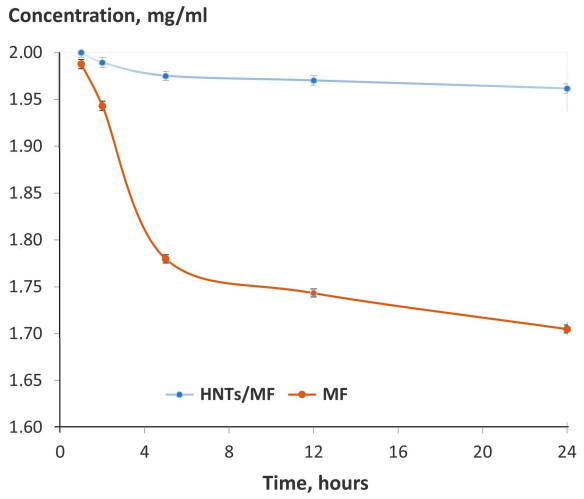


Fig. 5. Photodegradation under the action of ultraviolet irradiation of MP in the native state and in the composition of the nanocomposite. The concentration of non-degraded MP is determined in the model solution

Test for photostability MF in HNTs/MF to exposure in the visible light wavelength range (380 to 750 nm) during the day showed that halloysite acts as an effective protective material against photodegradation. The level of resistance to photodegradation of API is 99.9%. However, 24-hour photostability testing of moxifloxacin hydrochloride in its native state without nanotube encapsulation indicates that this API degrades, with a residual content of 89.0%. The results are presented in Fig 6.

We also investigated the resistance of moxifloxacin hydrochloride to elevated temperature. Moxifloxacin hydrochloride in the native state and in the nanocomposite based on halloysite was heated at a temperature of 60^{0}C for 1, 12 and 24 hours (Fig. 7).

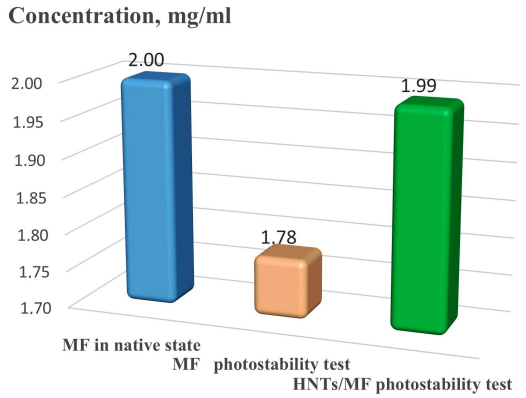


Fig. 6. Photodegradation of MF in the native state and in HNTs/MF after irradiation (200 watt-hours/m^2) in the visible light. The quantity of non-degraded MF is determined in the model solution

The test results indicate that, moxifloxacin hydrochloride in its native state quickly degrades, and the residual MF content is 85.8% after a day of testing. In the composition of the nanocomposite, moxifloxacin hydrochloride does not degrade, as evidenced by the practically unchanged concentration after thermal tests.

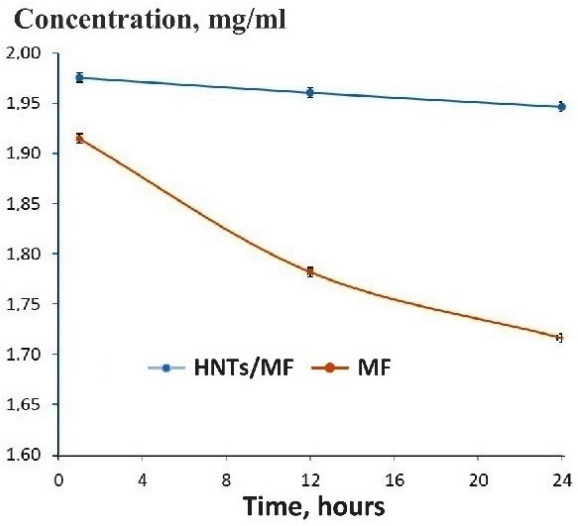


Fig. 7. Degradation of moxifloxacin under the influence of elevated temperature (60^{0}C). The quantity of non-degraded MF is determined in the model solution

Conclusions

Moxifloxacin hydrochloride is a light-sensitive pharmaceutical ingredient, which during storage under the influence of external factors, such as elevated temperature and light irradiation in the ultraviolet and visible ranges, is destroyed with a decrease in the effective concentration in medicinal products.

To increase its stability, it is proposed to create a nanocomposite based on halloysite nanotubes. Moxifloxacin hydrochloride was encapsulated in halloysite by the vacuum method, which was confirmed by TEM microscopy.

Studies have proven that the encapsulation of moxifloxacin hydrochloride in halloysite nanotubes contributes to a significant increase in resistance to external factors.

Only 1.9% of moxifloxacin hydrochloride in the composition of the nanocomposite degrades under conditions of 24-hour exposure to ultraviolet light, while in the native state 15.3% is destroyed. Visible light testing demonstrated that 11% of moxifloxacin hydrochloride in the native state degraded, while only about 1% degraded in the encapsulated state. Under conditions of thermal exposure, 14.2% of moxifloxacin hydrochloride in its native state is destroyed within 24 hours and almost does not degrade in the composition of the nanocomposite.

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ДЕГРАДАЦІЯ ІНКАПСУЛЬОВАНОГО В НАНОТРУБКИ ГАЛУАЗИТУ МОКСИФЛОКСАЦИН ГІДРОХЛОРИДУ ПІД ВПЛИВОМ ТЕМПЕРАТУРИ ТА СВІТЛА В УЛЬТРАФІОЛЕТОВОМУ І ВИДИМОМУ ДІАПАЗОНАХ

А.С. Мельник, О.Е. Чигиринець, Дж. Лаззара

Світлочутливий фармацевтичний інгредієнт моксифлоксацин гідрохлорид під час зберігання під впливом зовнішніх факторів, таких як підвищена температура та світлове опромінення ультрафіолетового та видимого діапазонів, деградує зі зниженням концентрації діючої речовини. Для підвищення його стійкості до зовнішніх факторів здійснено інкапсуляцію моксифлоксацин гідрохлориду у нанотрубки галуазиту. Метою роботи було визначення рівня деградації моксифлоксацин гідрохлориду в нативному та інкапсульованому стані під дією температури та світлового опромінення в ультрафіолетовому і видимому діапазонах. Інкапсуляцію проведено вакуумним методом та підтверджено мікроскопією ТЕМ. Залишковий вміст світлочутливого фармацевтичного інгредієнту внаслідок деградації контролювали методом високоефективної рідинної хроматографії модельного розчину стартової концентрації 2 мг/мл, одержаного на основі попередньо протестованих зразків нативного та інкапсульованого моксифлоксацин гідрохлориду за впливу температури та опромінення. Інкапсульований моксифлоксацин гідрохлорид має підвищену стійкість до деградації світлом у видимому діапазоні 200 Вт·год/м^2 – на 10,9%; в умовах тестування протягом 24 годин шляхом опромінення світлом ультрафіолетового діапазону та термостатування за температури 60^{0}C – на 13,4% та 14%, відповідно, у порівнянні з неінкапсульованим моксифлоксацин гідрохлоридом.

Ключові слова: нанокомпозит, галлуазит, моксифлоксацину гідрохлорид, фотостабільність, термостабільність, інкапсуляція.

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***A.S. Melnyk* [a], *O.E. Chyhyrynets* [a, *], *G. Lazzara* [b]**

[a] **National Technical University of Ukraine «Igor Sikorsky Kyiv Polytechnic Institute», Kyiv, Ukraine**

[b] **University of Palermo, Palermo, Italy**

[*] **e-mail: o.chyhyrynets@gmail.com**

The photosensitive pharmaceutical ingredient moxifloxacin hydrochloride degrades during storage under the influence of external factors, such as elevated temperature and ultraviolet and visible light irradiation, resulting in a decrease in the concentration of the active substance. To increase its resistance to these external factors, moxifloxacin hydrochloride was encapsulated in halloysite nanotubes. The aim of this study was to determine the level of degradation of moxifloxacin hydrochloride in its native and encapsulated states under the influence of temperature and ultraviolet and visible light irradiation. Encapsulation was carried out by the vacuum method and confirmed by TEM microscopy. The residual content of the photosensitive pharmaceutical ingredient after degradation was monitored by high-performance liquid chromatography of a model solution with an initial concentration of 2 mg/ml, prepared from samples of native and encapsulated moxifloxacin hydrochloride previously tested under the influence of temperature and light irradiation. Encapsulated moxifloxacin hydrochloride showed increased resistance to degradation caused by visible light irradiation at 200 watt-hours/m^2 (by 10.9%); resistance to degradation was increased by 13.4% and 14% under test conditions during 24 hours of ultraviolet light irradiation and thermostating at a temperature of 60^{0}C, respectively, compared to non-encapsulated moxifloxacin hydrochloride.

Keywords: nanocomposite; halloysite; moxifloxacin hydrochloride; photostability; thermal stability; encapsulation.

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