www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2019; 8(5): 54-56

www.thepharmajournal.com
Received: 22-03-2019
Accepted: 28-04-2019

Spyrydonova NV
Assistant, Department of Quality Management, National University of Pharmacy, Kharkov, Ukraine

Silin AV
Ph.D., Chemical Engineer LLC NVP Ukrorgsintez, Associate professor, Kiev, Ukraine

Lebedynets VA
Professor, Department of Quality Management, Doctor of Pharmacy, National University of Pharmacy, Kharkiv, Ukraine,

Zavada OA
Assistant Professor, Department of Medical and Bioorganic Chemistry, Kharkiv National Medical University, Ukraine

Kalinenko OS
Ph.D., Assistant, Department of Medical and Bioorganic Chemistry, Kharkiv National Medical University, Ukraine

Correspondence
Spyrydonova NV
Assistant, Department of Quality Management, National University of Pharmacy, Kharkov, Ukraine

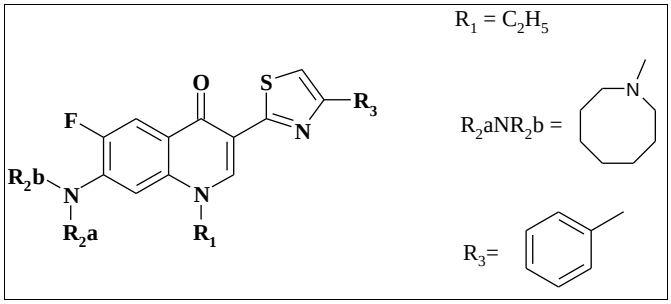
Development of specification for substance 7-azepan-1-il-1-ethil-6-ftor-3- (4-phenyl-1, 3-tiazol-2-il) - Quinoline-4 (1h)-one

Spyrydonova NV, Silin AV, Lebedynets VA, Zavada OA and Kalinenko OS

Abstract
The paper presents the results of the development of specifications for a new first-synthesized chemical compound exhibiting antibacterial activity and positioned as a perspective drug substance. According to the recommendations of the European Pharmacopoeia quality control procedures have been developed for standardization the substance of 7-azepan-1-yl-1-ethyl-6-fluoro-3-(4-phenyl-1,3-thiazol-2-yl))-quinoline-4(1H)-one - a modified derivative of the fluoroquinolone series.

Keywords: Quality control method, specification, active pharmaceutical ingredient, quinolone, antibacterial agent

Introduction
An important stage of the creation of new active pharmaceutical ingredients (API) is a standardization of new synthesized substances, in particular, the development of specifications: the list of tests regulated in accordance with the current legislation, references to analytical methods and acceptance criteria. The specification for APIs indicates the requirements to a substance that must be considered suitable for use.
The purpose of our research was the development of quality control techniques (QCT) for the standardization of the new synthesized substance 7-azepan-1-yl-1-ethyl-6-fluoro-3-(4-phenyl-1,3-thiazol-2-yl)-quinoline-4(1H)-one [1, 2], positioned as a potential antibacterial agent (Scheme 1).



Scheme 1: Structure of 7-azepan-1-yl-1-ethyl-6-fluoro-3-(4-phenyl-1,3-thiazol-2-yl)-quinoline-4(1H)-one

Materials and Methods
The methods of qualitative and quantitative analysis were used at performing the research. The quality control techniques for the substance of 7-azepan-1-yl-1-ethyl-6-fluoro-3-(4-phenyl-1,3-thiazol-2-yl) -quinoline-4 (1H)-one were developed in accordance with the recommendations given in the European Pharmacopoeia (EP) [3].
Indicators of quality control of a leading substance were carried out using the following methods:

- Indicators "Description", "transparency", "solubility", "chromaticity" were determined by a visual method;
- Identification test was carried out by the method of absorption spectrophotometry in the infrared region (EP, 2.2.24.) фnd absorption spectrophotometry in the ultraviolet and visible spectral regions (EP, 2.2.25.);

- Melting point was determined by the capillary method (EP, 2.2.14.);
- Related impurities were determined by liquid chromatography (EP, 2.2.29);
- loss on drying was determined by the gravimetric method (EP, 2.2.32);
- Quantitative determination was performed by potentiometric titration method (EP, 2.2.20).

Results and Discussion

The following indicators in the specification for substance: "Description", "Transparency", "Solubility", "Color of liquid" (visually); "Identification "; "pH value"; "Melting temperature"; "Impurities"; "Loss on drying"; "Quantitative determination" were included on the base of a literature study and characteristics of the synthesized substance.

It was shown that the samples of the substance are yellow powders. Therefore, the section in the QCT for the substance is provided in the following edition "Amorphous yellow powder".

The technique for dissolution test and the actual data of the solubility of the substance are given in our previous work [4].

The identification of 7-azepan-1-yl-1-ethyl-6-fluoro-3-(4-phenyl-1,3-thiazol-2-yl)-quinoline-4(1H)-one was proposed to be carried out using spectrophotometry methods in the IR and UV spectral regions.

The technique for identification a substance by the spectrophotometry method in UV spectral region was described in [5, 6]. The method of spectrophotometry in the IR region for identification was also proposed.

IR transmittance spectrum of 7-aze-pan-1-yl-1-ethyl-6-fluoro-3-(4-phenyl-1,3-thiazol-2-yl)-quinoline-4(1H)-one in potassium bromide disks (1 mg of the substance is ground with 200 mg of thoroughly crushed potassium bromide) in the range from 400 to 4000 cm^{-1} is shown in Fig. 1.

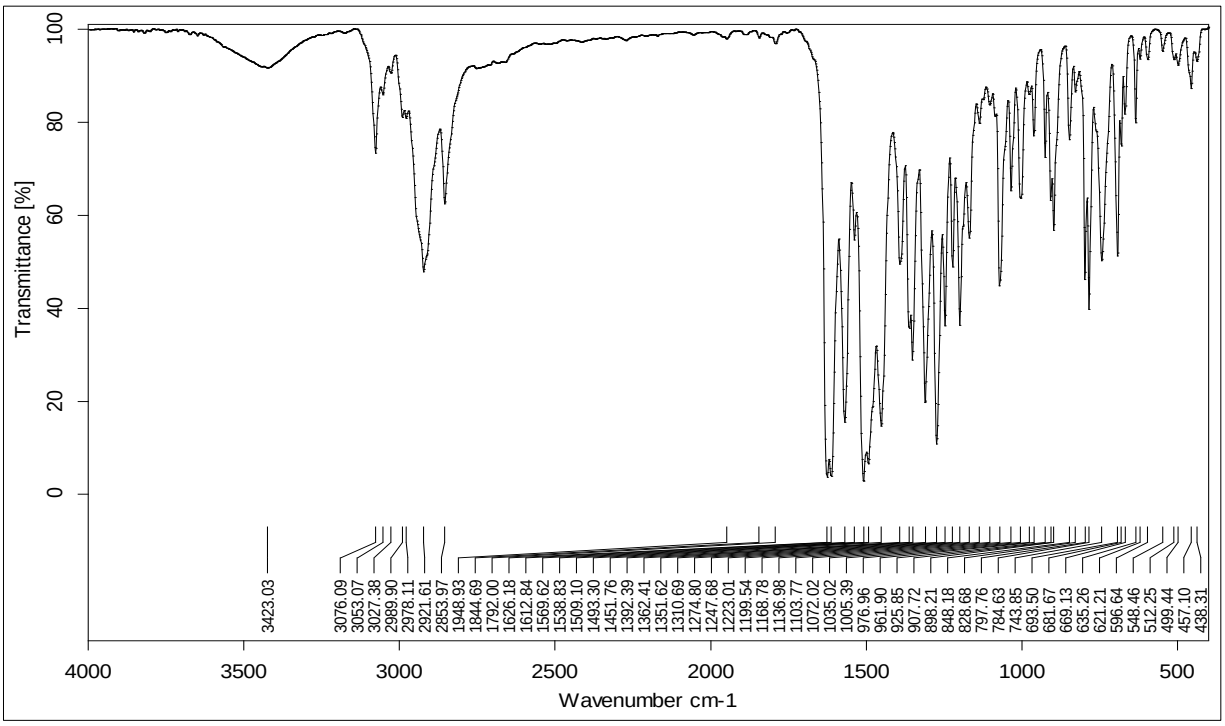


Fig 1: IR spectrum of a sample of a substance in the range of 400-4000 cm^{-1}.

High performance liquid chromatography (HPLC) has been chosen as instrumental analysis method. The choice was based on the use of approach of European Pharmacopoeia for quality of medicines at determining of impurities in the substance 7-azaban-1-yl-1-ethyl-6-fluoro-3-(4-phenyl-1,3-thiazol-2-yl)-quinolin-4(1H).

The indicator "Loss on drying", which was carried out in accordance with the requirements of the general article, was included into the specification. Based on the experimental data, the loss on drying of the substance 7-azepan-1-yl-1-ethyl-6-fluoro-3-(4-phenyl-1,3-thiazol-2-yl)-quinoline-4(1H)-one was 0.3-0.4%.

The quantitative determination technique was developed using the of non-aqueous potentiometric titration method in the course of research. The choice of the direct method of quantitative determination is primarily due to its high sensitivity and accuracy.

In accordance with the requirements of the EP and taking into account the specificity of the use of the substance, it was proposed to include the indicators given in the table below into the specification:

Table 1: The allowable limits of control methods

Indicators	Allowable limits	Control methods
Description	Amorphous yellow powder	According to p. 1 QCT. Visual, EP 5.11
Solubility	"Easily soluble in *dimethyl sulfoxide P*, slightly soluble in *methanol P*, *ethanol P*, very slightly soluble in *water P*"	According to p. 2 QCT, EP 1.4, 5.11
Identification	Maximum should be expressed at wavelengths of 290 ± 2 nm and 326 ± 2 nm in the ultraviolet absorption spectrum of a solution in the range from 250 nm to 350 nm.	According to p. 3.2 QCT, EP 2.2.24

	The infrared spectrum of a substance obtained in disks with *potassium bromide P* should correspond to the IR spectrum given in the QCT	
Impurities	The peak area of any impurity is not more than 0.2%. The sum of the peak areas of all impurities is not more than 1.0%. Peaks whose area is less than 0.1% of the peak area in the chromatogram of the reference solution (0.1%) are not taken into account	According to p. 4 QCT, EP 2.2.29, HPLC method
loss on drying	Not more than 0.5%	According to p. 5 QCT, EP 2.2.32
Sulphated ash	Not more than 0.1%	According to p. 6 QCT, EP 2.4.14
Residual amounts of organic solvents	2-propanol: not more than 5000 ppm	According to p. 7 QCT, EP 2.4.24, 5.4, 2.2.28
Microbiological purity	Total number of aerobic microorganisms (TAMS): 103 COO/g. Total number of yeast and mold fungi (TYMS): 102 COO/g.	According to p. 8 QCT, EP 5.1.4, 2.6.12, 2.6.13
Quantitative determination	Not less than 99.0% and not more than 101.0% calculated on the dry substance.	According to p. 9 QCT, EP 2.2.20

Conclusion

Thus, we have prepared a basis for specifying quality for a perspective substance of antibacterial action. In the future, we will plan to develop the composition based on this substance for a soft dosage form for external use (emulgel, ointment based on the emulsion of the 1st kind "oil-water" or the 2nd kind of "water-oil"). We are going to develop an industrial technology and determine the quality indicators of a perspective new drug and develop a project of an appropriate quality control technique.

References

1. Spyrydonova NV. Sintez N`1-alkil-7-dialkilamino-6-ftorohinolin-4-on-3-karbonitriliv / N. V. Spyrydonova, O. V. Silin, S. M. Kovalenko, I. O. Zhuravel // Zhurn. org. far. Him. 2011; 9(4):65-69.
2. Spyrydonova NV. Sintez funktsionalnyih proizvodnyih na osnove vzaimodeystviya 3-tsiano-ftorhinolonov s nukleofilnyimi reagentami / N. V. Spiridonova, A. V. Silin, S. N. Kovalenko, I. A. Zhuravel // Vestnik KazNMU. 2015; 3:420-423.
3. European pharmacopoeia. – 8.2ed. – Strasbourg. EDQM, 2014, 4154.
4. Spyrydonova NV. Opredelenie rastvorimosti kak pokazatel kachestva substantsii N`1-alkil-7-dialkilamino-3-tiazolil-6-ftorhinolonov / N. V. Spiridonova, V. A. Lebedynets // Perspektivyi razvitiya biologii, meditsinyi i farmatsii: mater. IV Mezhdunar. Nauch. Konf. Molodyih uchenyih i stud., g. Shyimkent, 9–10 dek. 2016 g. – Sh. YuKGFA, 2016, 133-134.
5. Spyrydonova NV. Zastosuvannya metodu absorbtsIynoYi spektrofotometrIYi v InfrachervonIy oblastI dlya pIdtverdzhennya strukturi pohIdnih 3-(tIazolIl- 2)-N1-R1- 6-ftor-7- dIal kIlam In ohInolonIv / N. V. Spiridonova, V. O. Lebedynets, O. O. Zavada // AktualnI problemi suchasnoYi hImIYi: mater. Vseukr. nauk.-Prakt. Konf., m. Mikola Yiv, 20–22 kvIt. 2017 r. – M. NUK, 2017, 61-62.
6. Spyrydonova NV. Identifikatsiya substantsiиi 7-azepan-1-il-1-etil-6-ftor-3-(4-fenil-1,3-tiazol-2-il)-hinolin-4 / N. V. Spyrydonova, O. V. Silin, V. O. Lebedynets, O. O. Zavada // Upravlinnya yakistyu v farmatsiyi: mater. XI nauk.-prakt. konf., m. Harkiv, 19 trav. 2017 r. – H. Vid-vo NFaU, 2017, 162-163.