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THE SYNTHESIS AND STUDY OF PROFILES OF THE ORNIDAZOLE IMPURITIES

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Фармакопейні стандартні зразки (ФСЗ) забезпечують порівнянність результатів випробувань препаратів-генериків. ФСЗ домішок орнідазолу не описані в фармакопеях. Тому введення ФСЗ Державної Фармакопеї України (ФСЗ ДФУ) домішок орнідазолу є актуальним завданням, невід'ємною частиною якого є синтез та характеризація домішок орнідазолу.

Мета: *Синтезувати домішки орнідазолу як кандидат-матеріалу для атестації ФСЗ ДФУ та вивчити їх профілі в субстанції та інфузійному розчині орнідазолу.*

Методи: *Традиційні методи органічного синтезу, ^{1}H ЯМР-спектроскопія, абсорбційна ІЧ-спектрофотометрія, капілярний метод визначення температури плавлення, рідинна хроматографія із спектрофотометричним детектором.*

Результати: *Синтезовано орнідазол-діол та орнідазол-епоксид й підтверджено їх структури за допомогою ^{1}H ЯМР- та ІЧ-спектрів. Вивчено їх хроматографічні профілі в субстанції та розроблюваному лікарському засобі орнідазолу для інфузій. Виявлено проблему з визначенням орнідазол-діолу за методикою виробника й запропоновано її корекцію. Чистота синтезованих сполук становила близько 99.5 %. Вміст орнідазол-епоксиду у субстанції перевищував 0.1 %, а орнідазол-діолу – був незначним. Вміст орнідазол-епоксиду у лікарському засобі з часом знижувався до нуля, а орнідазол-діолу – значно збільшувався (до приблизно 3 %).*

Висновки: *Розроблено методики економічного синтезу орнідазол-епоксиду та орнідазол-діолу. Синтезовано домішки та вивчено їх профілі у субстанції та розроблюваному лікарському засобі орнідазолу для інфузій. Встановлено, що орнідазол-епоксид та орнідазол-діол є наявними в субстанції та лікарському засобі на рівні, що потребує їх ідентифікації та кількісного визначення. Запропоновані методики синтезу забезпечують одержання орнідазол-діолу та орнідазол-епоксиду високої якості, що дозволяє використовувати їх як матеріал для атестації як ФСЗ ДФУ*

Ключові слова: *домішки орнідазолу, синтез, орнідазол-діол, орнідазол-епоксид, профіль домішок, субстанція орнідазолу, інфузійний розчин орнідазолу, фармакопейні стандартні зразки, Державна Фармакопея України*

1. Introduction

Ornidazole is chemically [α-(chloromethyl)-2 methyl -5 nitroimidazole -1-ethanol], a synthetic derivative of 5-nitroimidazoles [1]. It is active against protozoa and anaerobic bacteria and is widely used both alone and in combination with other drugs in different dosage forms for oral, vaginal, or intravenous administrations [2]. Ornidazole is reported to decompose into different degradation products [3]. It is necessary to standardize their impurities to provide the quality and safety of ornidazole-containing medicines, which can be done using pharmacopoeial reference standards (PhRSs). However, there are no PhRSs of ornidazole impurities. Therefore, certification of PhRSs of ornidazole impurities is an essential task for standardization of ornidazole-containing medicines at the pharmacopoeial level.

This work is devoted to the synthesis of ornidazole impurities, ornidazole-diol and ornidazole-epoxide, for further certification of the synthesized materials as pharmacopoeial reference standards of the State Pharmacopoeia of Ukraine (SPhU RSs), and the study of their profiles in substance and infusion solution.

2. Formulation of the problem in a general way, the relevance of the theme and its connection with important scientific and practical issues

Medicines containing ornidazole as an active pharmaceutical ingredient (API) are widely used in the treatment of infections of the urogenital system caused by *Trichomonas vaginalis*; all intestinal infections caused by *Entamoeba histolytica*, including amoebic dysentery, all extraintestinal forms of amoebiasis, especially amoebic liver abscess; giardiasis, as well as for prevention of infections caused by anaerobic bacteria, in surgical interventions, especially in the colon, or gynecological operations [4, 5].

The control of related impurities is an essential issue for providing the quality of drugs. The presence of impurities may have a significant impact on the effectiveness and safety of drugs. Therefore, the regulatory bodies pay much attention to the control of impurities.

For a reliable determination of impurities, the reference standards of related impurities that are present in the medicinal product are required. PhRSs provide comparability of the test results of generic drugs [6].

The presence of PhRSs of related impurities appreciably facilitates the pharmaceutical development of new drugs when developing both a robust composition and the proper methods for the quality control. The absence of PhRSs of impurities creates a risk that the generic drugs lacking compelling evidence of adequate control of the content of impurities and containing inconsistent requirements for the quality of medicines will be approved.

Thus, to provide the effectiveness and safety of ornidazole-containing drugs, PhRSs of impurities of ornidazole are required. However, PhRSs of impurities of ornidazole have not been described in pharmacopoeias

[7–9]. Therefore, certification of SPhU RSs of ornidazole impurities is an issue of great importance. The synthesis and characterisation of impurities of ornidazole as candidate materials for certification as SPhU RSs are necessary to perform this task.

3. Analysis of recent studies and publications in which a solution of the problem is described and to which the authors refer

Ornidazole is a toxic drug, and this limits its long-term use [10]. Therefore, the control of related impurities of ornidazole is a vital element for the safety and effectiveness of drugs containing ornidazole.

In accordance with the ICH guidelines, individual impurities of API (identified and unidentified ones), and their sum should be controlled in drugs [11, 12]. For the substance, the potential process-related impurities and degradation products of API must be controlled; while for finished drug products, the control of degradation products may be sufficient. Typically, for impurities with the content more than 0.1 %, it is necessary to achieve structural elucidation.

The impurities of ornidazole that are its degradation products – ornidazole-diol (CAS 62580-80-7) and ornidazole-epoxide (CAS 16773-52-7) are known to be formed in aqueous solutions (Fig. 1) [13].

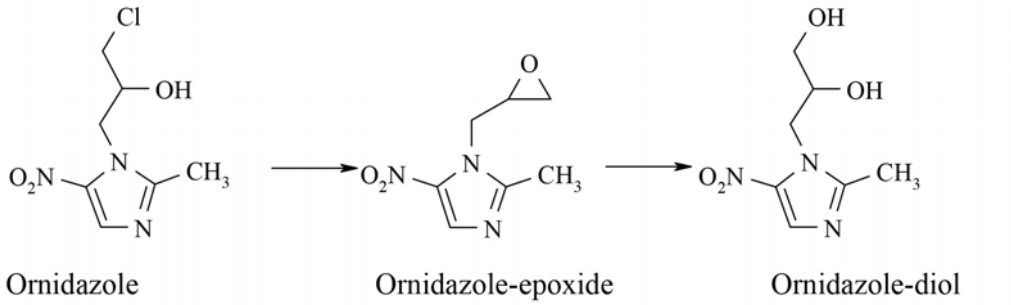


Fig. 1. Products of ornidazole degradation in aqueous solutions

Many ornidazole impurities that are potential degradation products and process-related impurities have been described. They are offered as commercially available authentic substances for research purposes (e.g., TLC Pharmaceutical Standards, LGC Standards, etc.) [14–17].

The ornidazole substance and its dosage forms, tablets and injections, have been described in the Indian Pharmacopoeia monographs, which include the test "Related impurities" but do not specify the use of PhRSs of impurities [18].

In the publication [19], it has been shown that ornidazole is prone to degradation under stress conditions: impurities are formed during the oxidation of ornidazole, under extreme pH values, and as a result of photodegradation [20]. In the work [21], it is shown that injection drugs of ornidazole contain the impurity identified as ornidazole-diol in large quantities. Accumulation of the impurity in an injection drug of ornidazole depends on the drug composition and the sterilization procedure, the patent reveals [22].

4. The field of research considering the general problem, which is described in the article

Despite the fact that drugs with ornidazole are widespread and the actual content of impurities in them is at the level that requires identification and control of individual impurities, there are no PhRSs of ornidazole impurities.

We have previously shown that the infusion solution of ornidazole, a potential new generic drug that is at the stage of pharmaceutical development, contains an impurity preliminary identified by liquid chromatography with a mass-selective detector as ornidazole-diol [23]. The PhRS of this impurity is also required for its final identification, determination of the actual content, development of the appropriate procedure for the control and specification establishment. Since the ornidazole-epoxide impurity is the precursor of ornidazole-diol formed in aqueous solutions in the process of degradation of ornidazole, the synthesis of this impurity and the study of its content in the substance and the infusion solution of ornidazole are also relevant.

5. Formulation of goals (tasks) of article

It is necessary to develop methods for the synthesis of impurities of ornidazole – candidate materials for certification as PhRSs to provide the quality of drug products containing ornidazole. The methods should provide the possibility of synthesizing related impurities in the laboratory, with the purity acceptable to PhRS. The control of these impurities using PhRSs should be a relevant task, i.e. the impurities must be actually present in drugs containing ornidazole in concentrations requiring their identification and individual content limits establishment.

The aim of our work was to synthesize the materials for certification as SPhU RSs of ornidazole impurities and to study their profiles in the substance and the infusion solution of ornidazole. To achieve the goal, it was necessary:

– to develop methods of synthesis and synthesize ornidazole impurities – ornidazole-diol and ornidazole-epoxide;

– to confirm the structure and determine the purity of the impurities synthesized;

– to study the profile of impurities in the substance and infusion solution of ornidazole using the impurities obtained.

6. Presentation of the main research material (methods and objects) with the justification of the results

6.1. The synthesis of the material for certification as SPhU RSs of ornidazole impurities

The synthesis of ornidazole-diol and ornidazole-epoxide was carried out using the ornidazole

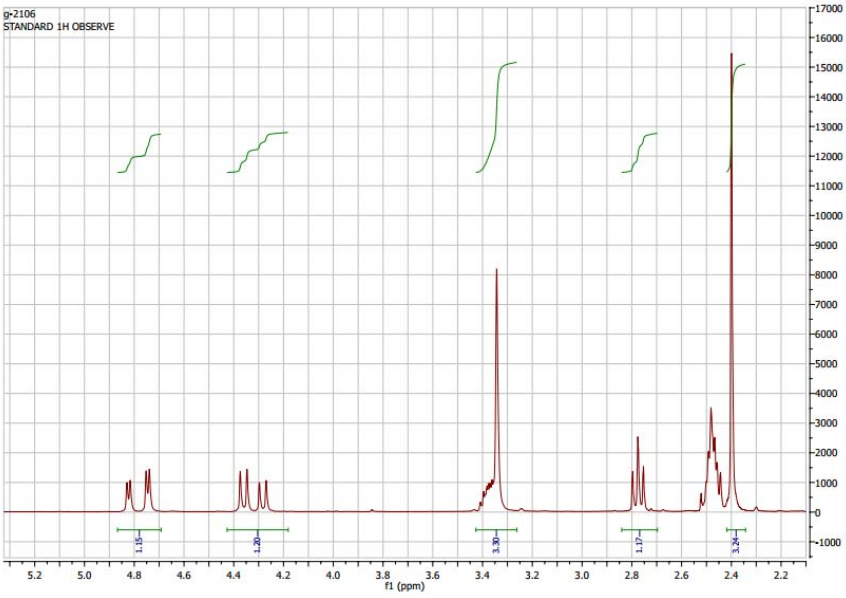
substance as a starting compound. At the first stage of the synthesis, the initial cyclization of ornidazole to the corresponding oxirane (l-(2,3-epoxypropyl)-2-methyl-5-nitroimi-dazole) was performed in an aqueous solution of sodium hydroxide [24, 25]. For this purpose, the solution of ornidazole in 3 M solution of sodium hydroxide was heated at the temperature of 60–70 °C for 10–15 min. The crystals, obtained after cooling the solution to 0 °C, were recrystallized from ethyl acetate with the product yield of 85 %. The melting point of the compound synthesized was observed at the temperature of 113.0 °C, with decomposition, which coincides with the work [24].

Formic acid was used to open the oxirane ring, and then intermediate formiate formed was hydrolyzed to the corresponding diol. The following procedure was used: the substance of ornidazole-epoxide synthesized was heated in 85 % formic acid for 15 h. The reaction mixture was evaporated almost to dryness under reduced pressure, and then water was added and distilled. The procedure was repeated twice. 10 % sodium hydroxide solution and a sufficient amount of methanol were added to the residue; then the mixture was heated at 100 °C for 1 h. The solvent was evaporated under reduced pressure and residue was recrystallized from ethyl acetate. The product yield was 98 %.

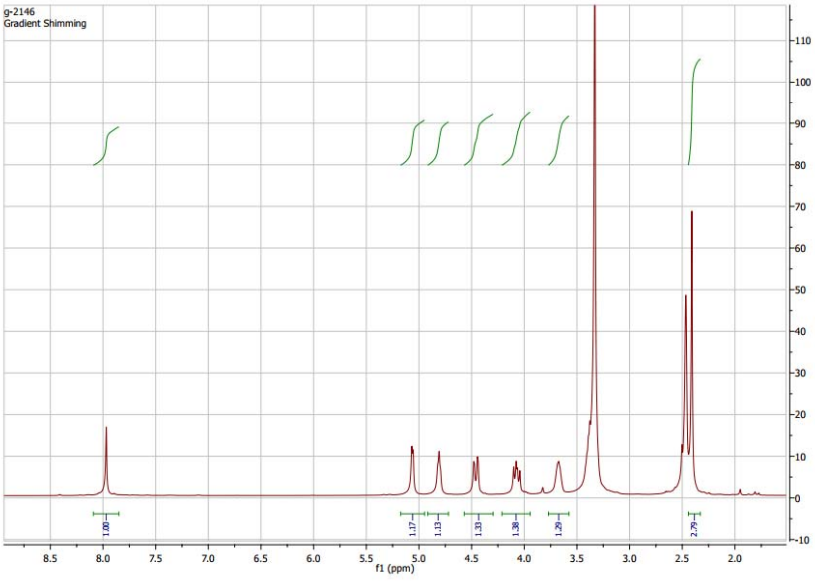
The melting point of the synthesized compound was observed at the temperature of 103 °C, which correlates with the work [26], according to which the melting point of ornidazole-epoxide is 102.0–104.0 °C.

6.2. Confirmation of the structure of the materials synthesized for certification as SPhU RS of ornidazole impurities

^{1}H NMR spectra were recorded using an Agilent DD2 NMR System 600 spectrometer in dimethylsulfoxide (DMSO) to confirm the structure of the substances synthesized (Fig. 2).



a



b

Fig. 2. The ^{1}H NMR spectra: *a* – ornidazole-epoxide; *b* – ornidazole-diol

The data of the ^{1}H NMR spectra (400 MHz, DMSO – *d6*) confirm the presence of all protons in the structure of the compounds studied. For ornidazole-epoxide: δ 7.99 (s, 1H, H-4), 5.09 (d, *J*=3.9 Hz, 1H), 4.83 (br.s, 1H), 4.48 (dd, *J*=14.2, 2.7 Hz, 1H), 4.10 (dd, *J*=14.1, 9.3 Hz, 1H), 3.70 (s, 1H), 2.43 (s, 3H, CH_3). For ornidazole-diol: δ 8.01 (s, 1H, H-4), 4.78 (dd, *J*=15.4, 2.6 Hz, 1H, N-CH_2), 4.32 (dd, *J*=15.4, 5.4 Hz, 1H, NCH_2), 3.39 (m, CH), 2.78, br.t.,1H, CH_2O) 2.47 (m, 1H, CH_2O). 2.40 (s, 3H,CH_3).

The IR-spectra of the compounds synthesized were recorded on IRAffinity-1S ("Shimadzu") according to the general monograph 2.2.24 "Absorption spectrophotometry in the infrared region" of the SPhU [27]. The results obtained indicate that the characteristic groups inherent to the basic functional groups of molecules are observed in the IR spectra of the compounds synthesized (Fig. 3, Table 1).

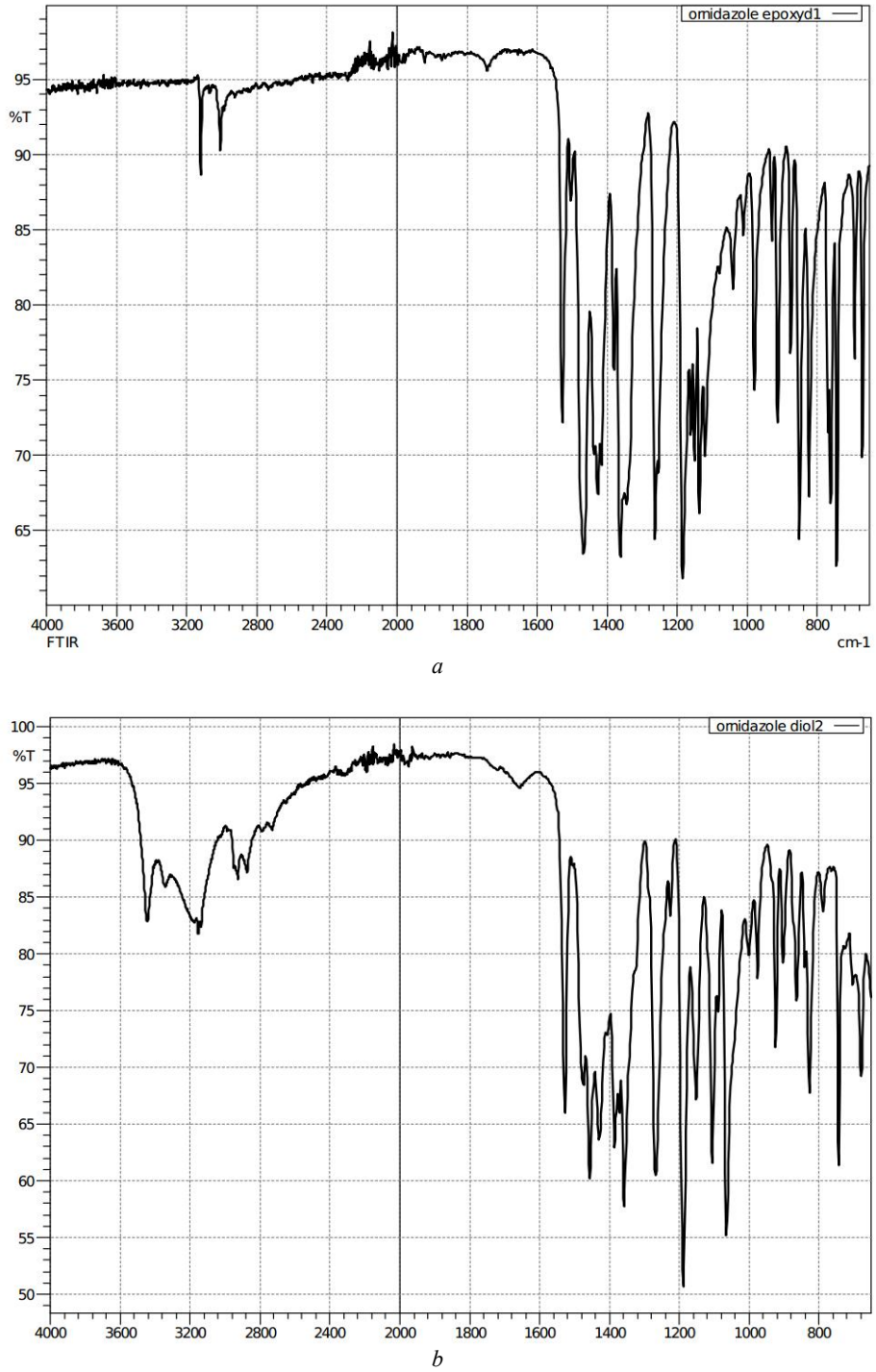
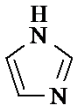


Fig. 3. The IR-spectra of the compounds synthesized: *a* – ornidazole-epoxide; *b* – ornidazole-diol

Table 1

Data of the absorption spectrophotometry in the infrared region

Functional group	Wave numbers, cm^{-1}
	3060–3010 1580–1520 1000–960 875–775
$-NO_2$	1300–1255
$-CH_3$	2975–2950 2885–2860
-O-H	3670–3580
	1700–1800

6.3. The study of the purity of the material for certification as SPhU RS of ornidazole impurities by HPLC and the profile of impurities of the substance and infusion solution of ornidazole

In the study, a Waters 2690 liquid chromatograph with a spectrophotometric detector and a Waters Xterra RP18 column, 250×4.6 mm, 5 μm, were used.

At first, to determine the chromatographic profile the procedure of the manufacturer of the ornidazole substance was used, namely: the mobile phase – water-acetonitrile, 7:3 v/v; the flow rate of the mobile phase – 0.6 ml/min; the temperature of the column thermostat – 25 °C; the detection wavelength – 310 nm; the sample volume – 20 μl; the concentration of the substance to be analyzed – 0.02 % in the mobile phase.

Under these conditions of the analysis, ornidazole-diol had a too small capacity factor, and it gave a double peak in the absence of a buffer component in the mobile phase, preventing correct determination of its content (Fig. 4).

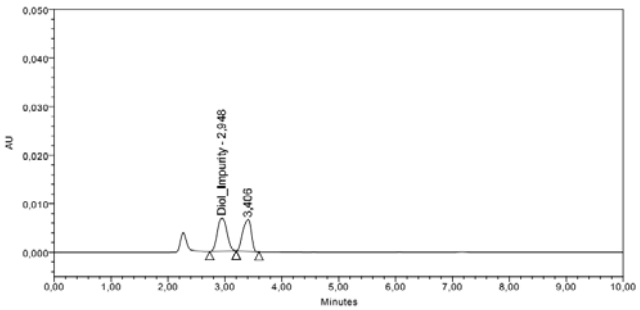
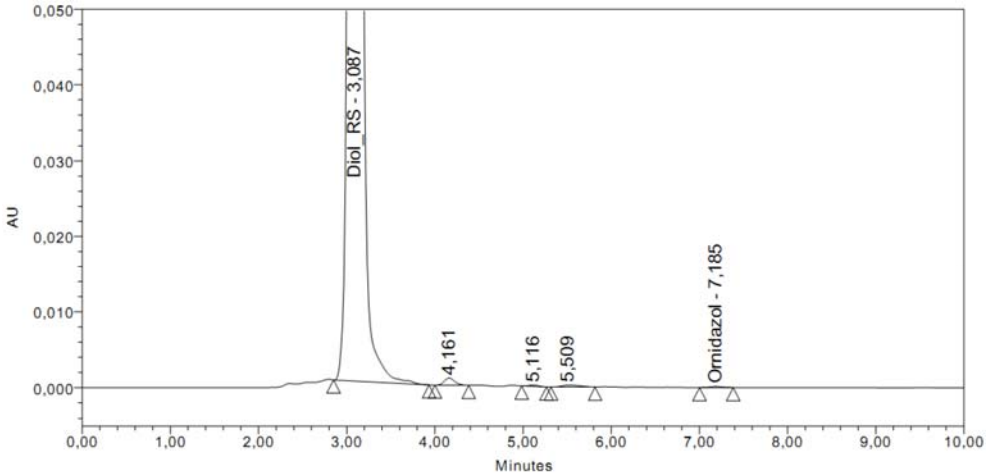


Fig. 4. The chromatogram of the reference solution of ornidazole-diol according to the procedure of the manufacturer of the substance

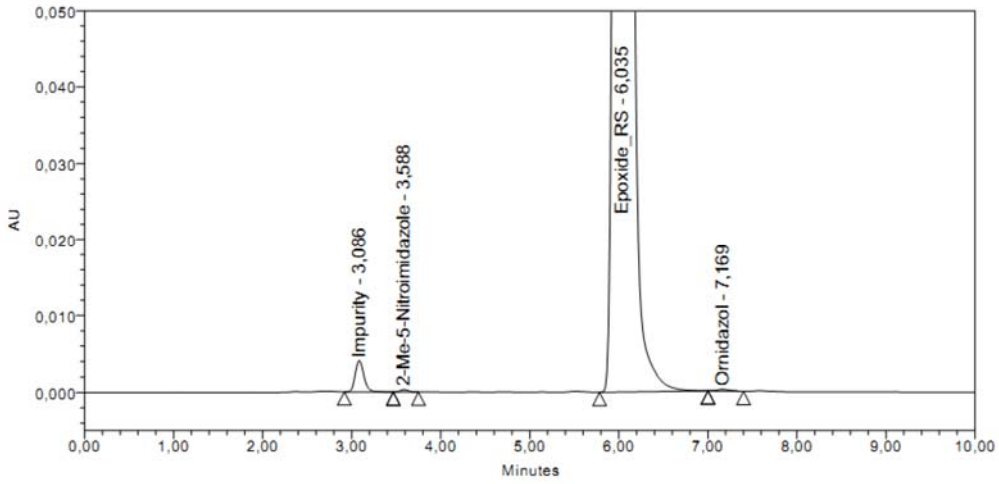
After modification of the procedure, the addition of phosphate buffer to the mobile phase, ornidazole-diol eluted as one symmetric and effective peak.

In conditions of the modified procedure, it has been found that the purity of the compounds synthesized, ornidazole-diol and ornidazole-epoxide, is approximately 99.5 % (Fig. 5, 6).



	Name	RT	RT Ratio	Area	% Area	Resolution	EP Plate	Symmetry
1	Diol_RS	3,087	0,43	3980101	99,65		4918	1,12
2		4,161		7766	0,19	5,55	6168	1,22
3		5,116		1399	0,04	4,63	10337	1,16
4		5,509		3487	0,09	1,29	2877	1,41
5	Omidazol	7,185		1228	0,03	4,91	11052	1,14

Fig. 5. The results of the purity determination for ornidazole-diol

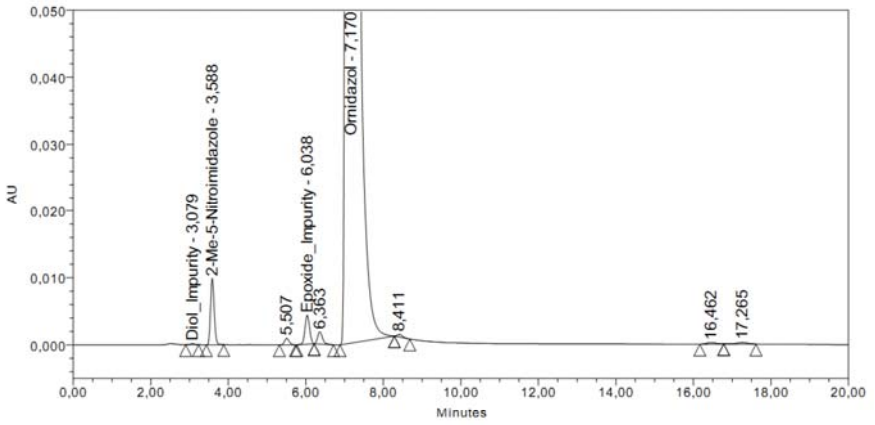


	Name	RT	RT Ratio	Area	% Area	Resolution	EP Plate	Symmetry
1	Impurity	3,086	0,43	27258	0,45		5007	1,18
2	2-Me-5-Nitroimidazole	3,588	0,50	2009	0,03	2,90	6984	1,12
3	Epoxide_RS	6,035	0,84	5968668	99,48	12,33	11381	1,13
4	Ornidazol	7,169		2021	0,03	4,61	11537	1,22

Fig. 6. The results of the purity determination for ornidazole-epoxide

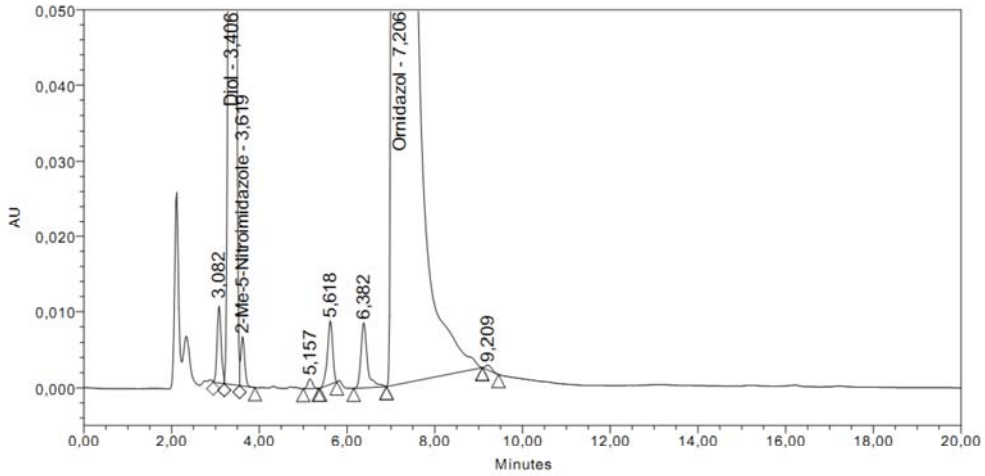
In accordance with the approach of the SPhU, see 5.12N, 5.3.N.2 [27], for PhRSs intended for the quantitative determination of impurities, the certified value of the content may be specified as 100 % in cases when the actual value of the content is not less than 98 %. The materials obtained for certification as SPhU RSs of ornidazole impurities meet these requirements; therefore, they can be used for certification as SPhU RS of ornidazole impurities.

To identify and determine the content of impurities in the substance and infusion solution of ornidazole, SPhU RS of 2-methyl-5-nitroimidazole, the process-related impurity of ornidazole, was also used. The results of determining the impurity profile are shown in Fig. 7, 8.



	Name	RT	RT Ratio	Area	% Area	Resolution	EP Plate	Symmetry
1	Diol_Impurity	3,079	0,43	1210	0,00		3672	0,86
2	2-Me-5-Nitroimidazole	3,588	0,50	65030	0,18	2,71	6858	1,12
3		5,507		8351	0,02	9,69	9683	1,14
4	Epoxide_Impurity	6,038	0,84	36161	0,10	2,38	11711	1,01
5		6,363		16024	0,04	1,44	12145	1,50
6	Omidazol	7,170		35494857	99,61	3,03	8972	1,13
7		8,411		3782	0,01	4,19	13440	1,59
8		16,462		3669	0,01	21,12	19292	0,99
9		17,265		4591	0,01	1,62	17760	1,04

Fig. 7. The results of determination of related impurities in the substance of ornidazole



	Name	RT	RT Ratio	Area	% Area	Resolution	EP Plate	Symmetry
1		3,082		64849	0,11		5296	
2	Diol	3,406	0,47	1825431	3,11	1,45	2395	0,87
3	2-Me-5-Nitroimidazole	3,619	0,50	40799	0,07	0,91	5686	
4		5,157		9594	0,02	7,83	10420	1,08
5		5,618		69529	0,12	2,21	10766	0,83
6		6,382		87616	0,15	3,38	11667	1,47
7	Omidazol	7,206		56669362	96,42	2,37	3920	1,15
8		9,209		6556	0,01	5,41	16992	1,54

Fig. 8. The results of determination of related impurities in the infusion solution of ornidazole

The study of the profile of impurities for the ornidazole substance has shown that the main related impurities with the content at the level of 0.1 % and above are 2-methyl-4-nitroimidazole and ornidazole-epoxide.

The study of the stability of the model solutions of the drug of ornidazole for infusion being under pharmaceutical development has shown that the content of 2-methyl-4-nitroimidazole impurity does not increase in proportion to its level in the substance. For the main degradation product, its identification as ornidazole-diol was confirmed by the retention time. In the model infusion solutions of ornidazole, the content of ornidazole-epoxide impurity reduced to zero with time.

To summarize, it is necessary to establish SPhU RSs of ornidazole-diol and ornidazole-epoxide to provide adequate control of related impurities in drugs of ornidazole. The methods of synthesis developed for these impurities allow the use of the materials synthesized for certification as SPhU RSs.

7. Conclusions from the conducted research and prospects for further development of this field

1. The efficient methods for the synthesis of impurities of ornidazole degradation products, ornidazole-epoxide and ornidazole-diol, were developed.

2. The profiles of the impurities in the substance and the infusion solution of ornidazole to be approved as a new generic drug were studied. It has been found that such impurities as ornidazole-epoxide and ornidazole-diol are present in the substance and the infusion solution of ornidazole at the level which requires their identification and quantitative determination. The problem of providing appropriate quality control for ornidazole-containing drugs can be effectively solved by certification of PhRSs of ornidazole impurities.

3. Ornidazole-diol and ornidazole-epoxide obtained by the proposed methods were shown to be of high purity, which enables to use them for certification as SPhU RSs.

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