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Desloratadine: research on polymorphism and conditions of polymorphic transitions

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This paper presents research on the polymorphism of Desloratadine substance, which is an active pharmaceutical ingredient used for the treatment of allergic reactions. Desloratadine has three known polymorphic forms (**I**-**III**) simultaneous crystallization of three polymorphs occurs during the substance production. According to the results of our research, Desloratadine polymorphs are prone to polymorphic transitions when external factors change and recrystallization from solvents of various chemical activities. The Desloratadine polymorph **II** is metastable and is not observed in samples after recrystallization. The solvent affects the polymorphic transitions of the substance. According to our research results, the maximum content of polymorph **I** was obtained during recrystallization from chloroform (77 mas.%), and for polymorph **III** – during recrystallization from water (86 mas.%). Pressure and temperature also affect the change in the ratio of polymorphic modifications and the degree of crystallinity in the sample under study.
Keywords: Desloratadine, X-ray diffraction, polymorphism, Rietveld method

Дезлоратадин: дослідження поліморфізму та умов поліморфних перетворень.
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В даній роботі проведено дослідження поліморфізму субстанції Дезлоратадину, що є активним фармацевтичним інгредієнтом та використовується для лікування алергічних реакцій. Дезлоратадин має відомі три поліморфні форми (**I-III**), одночасна кристалізація трьох поліморфів відбувається під час виробництва субстанції. За результатами наших досліджень поліморфи дезлоратадину мають схильність до поліморфних переходів під час зміни зовнішніх чинників та перекристалізацій з розчинників різної хімічної активності. Поліморфна модифікація дезлоратадину **II** є метастабільною та не спостерігається в зразках після проведення перекристалізацій. Розчинник має вплив на поліморфні перетворення субстанції, за результатами наших досліджень максимальний вміст поліморфу **I** отримано під час перекристалізації з хлороформу (77 мас.%), поліморфу **III** – під час перекристалізації з води (86 мас.%). Тиск та температура також вливає на зміну співвідношення поліморфних модифікацій в складі досліджуваного зразка та на ступінь кристалічності.

1. Introduction

Polymorphism and phase transitions have been in focus of recent research due to their great importance for many branches of science and production. They are rather widespread in functional materials and biologically active substances. Polymorphism is the ability of a solid substance to exist in several forms with different crystal structures and properties but with the same chemical composition [1].

There are several main types of polymorphism: conformational, enantiotropic, and monotropic. For example, for each enantiotro-

pic polymorph in a compound, the characteristic thermodynamic parameters (temperature, pressure) at which this polymorph exists are fixed; one enantiotropic form can be converted into another under given thermodynamic conditions characteristic of this polymorph. Therefore, one polymorphic form may be stable under low temperatures, another – under high temperatures, etc. [1-5]. Compounds Acetazolamide and Carbamazepine belong to that type of polymorphism [6, 7].

Polymorphic modifications of a substance have specific physical and chemical properties: melting temperature, solidity, density, electric conductivity, water absorption, solubility, and dissolution speed as well as differences in chemical reactivity [1]

The phenomenon of polymorphism is rather widespread among active pharmaceutical ingredients (API). That is why it is important to study the presence of polymorphism when developing new medicines. Polymorphism is interesting not only from the point of view of crystal structure but also from biological activity which is closely related to the modification of the API. The structure of the solid-state phase is important in determining the effectiveness of a drug and its possible effect on the body. Due to solubility variations of API polymorphs, one may have better therapeutic properties than another. In many cases, an API only receives regulatory approval for one of the polymorphs. Each API requires quite extensive studies of physical, chemical and biological characteristics. Control of the quality and composition of medicines is necessary at every stage of production and storage [8-12]

Our paper presents research on the polymorphism of the Desloratadine substance with the chemical formula $C_{19}H_{19}ClN_2$ (Fig.1) which

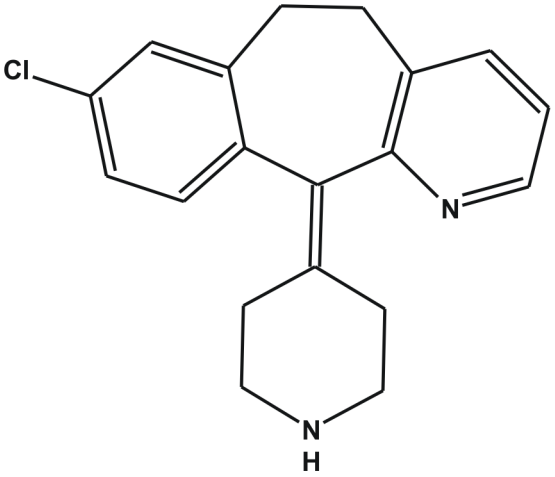

Fig.1. Structure of Desloratadine

has antihistaminic activity and is used for allergic reaction treatment [13]

2. Experimental

2.1 Method of synthesis

Obtaining the substance Desloratadine technical

22 kg (550 mol) of sodium hydroxide and 80 l of methyl alcohol were loaded into a reactor of 500 l volume equipped with a mechanic mixer, a reverse refrigerator, and a thermometer. The reacting mixture was heated up to 75-80°C with vigorous stirring and maintained at this temperature until the alkali is completely dissolved (approximately for 1 hour).

After solid sediment dissolution the solution was cooled down to 45-50°C and 20kg (52 mol) of loratadine were loaded. The mixture was heated up to 80-85°C and kept at a given temperature and vigorous stirring for 3 hours. Then the mixture was forcibly cooled in the reactor to 45-50°C, the refrigerator was immedi-

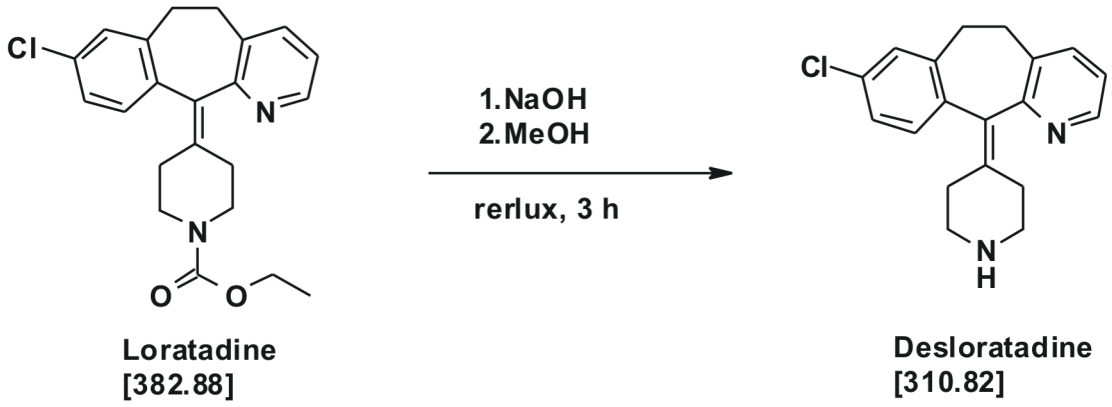

Fig.2. Scheme for obtaining Desloratadine

Table 1. Crystallographic data of Desloratadine polymorphic modifications **I-III** [17].

Form	System/ Sp.gr.	Z	a(Å)	b (Å)	c (Å)	β(°)	V (Å^3)	D_{calc}(g·cm^{-3})
I	Monoclinic/ $P2_1$	4	7.061	12.069	9.559	108.20	773.8	1.335
II		8	14.818	12.223	9.631	113.26	1602.7	1.288
III		4	7.754	12.139	9.608	118.78	792.6	1.302

ately turned on, the pressure in the system was reduced to 30-40 mmHg, and approximately 40 l of methanol distilled from the reacting mixture. After distilling off the solvent, the system was set to atmospheric pressure and 200 l of distilled water was added to the mixture. The reacting mixture was cooled to 10-15°C while stirring and then kept at this temperature for 1 hour.

The reacting mixture was filtered, the product was squeezed out, then washed with 5 portions of 30 l distilled water.

23 kg of raw syrup is obtained and dried at 60°C to a moisture content of no more than 0.5%. 4 kg of dry technical Desloratadine is obtained which is 87% of the theoretical conversion to loratadine.

Obtaining the substance Desloratadine officinal

14kg (550mol) of dry technical Desloratadine, 70 l of ethyl acetate, and 0.35kg of activated coal were loaded into a 250 l reactor equipped with a mechanical stirrer, a reverse refrigerator, and a thermometer. The stirrer was turned on; the mixture was heated up to the temperature of 77-79°C and stirred at this temperature (boiling temperature of the mixture 78°C) for 1.5 hours. After that, coal was filtered off. With intensive stirring, the solution was cooled spontaneously to a temperature of 50-55°C, then forcibly cooled to 4°C and maintained at this temperature for 1 hour. The obtained sediment was filtered, well squeezed, poured onto the filter with two portions of 20 liters of chilled ethyl acetate and dried at 60 °C for 4 hours.

As a result, 10 kg of dry Desloratadine officinal was obtained which is 71% in terms of the technical Desloratadine taken and 62% in terms of the obtained loratadine.

2. 3 Experimental

The powder X-ray diffraction (PXRD) study was carried out with a Siemens D500 powder diffractometer at the room temperature (CuK_α radiation, Bragg-Brentano geometry, curved graphite monochromator on the counter arm, $4<2\theta<60^o$, $\Delta 2\theta=0.02^o$). The initial processing of the obtained PXRD patterns was performed with PowderX program. The FullProf&WinPLOTR program [14-16] was used for the Rietveld refinement. An Al_2O_3 plate (NIST SRM1976) was used as the external standard and to determine the instrumental profile function.

3.Results and discussion

It is known from the literature that there are three polymorphic modifications of Desloratadine [17] (Table 1). The authors identified three polymorphs and recorded the stage of formation of each of them using a single-crystal method on heating a sample *in situ* to 77°C. The sample for the research was obtained as a result of recrystallization from ethyl acetate. Based on the results obtained, the authors proved that desloratadine can be classified as "dynamic molecular crystals", since the single-crystal–single-crystal phase transition occurs not only upon heating, but also upon cooling: **I**(20°C) → **II**(62°C) → **III**(77°C), **III**(77°C) → **II**(47°C) → **I**(20°C)**.** Polymorph **II** is transitional in this system. The structure model data were taken for the calculations of the powder patterns (Table 1).

We have carried out a number of experiments to study the possibility of polymorphic transitions during recrystallization of the desloratadine substance. We used solvents in which the studied substance has maximum solubility and boiling temperatures in the range of polymorph transitions mentioned by the authors [17]. According to the literature data, the melting point of Desloratadine is 157°C [18] and according to the research of the authors [17], the phase transition temperature varies in a fairly small range of 20-80°C. Therefore, the following solvents were chosen for recrystallization: chloroform (t_{boil}=61.2°C), hexane (t_{boil}= 68.7°C), ethyl acetate (t_{boil}=77.1°C), water (t_{boil}=100°C). As the Desloratadine sub-

Table 2. Conditions of the experiments

	Mark	Experiment conditions
1	(0)	Desloratadine substance sample
2	(1)	Recrystallization (0) from chloroform
3	(2)	Recrystallization (0) from hexane
4	(3)	Recrystallization (0) from water
5	(4)	Recrystallization (0) from ethyl acetate
6	(0a)	Pressing (0)
7	(1a)	Pressing (1)
8	(2a)	Pressing (2)
9	(0b)	Recrystallization (0) from melt

Table 3. The results of quantitative refinement of diffraction patterns of the samples after the action of solvent and pressure according to the Rietveld method

Solvent				Pressure			
Sample	Phase	Content (mass.%)	Crystallite size (nm)	Sample	Phase	Content (mass.%)	Crystallite size (nm)
(0)	**I**	39 (1)	36	(0a)	**I**	44 (1)	40
	II	49 (1)	36		**II**	37 (1)	20
	III	12 (1)	33		**III**	19 (1)	31
(1)	**I**	77 (1)	31	(1a)	**I**	60 (1)	26
	III	23 (1)	12		**III**	40 (1)	17
(2)	**I**	36 (1)	35	(2a)	**I**	75 (1)	24
	III	64 (1)	34		**III**	25 (1)	30
(3)	**I**	14 (1)	19				
	III	86 (1)	20				
(4)	**I**	20 (1)	24				
	III	80 (1)	37				

stance is produced in the form of tablets, additional analysis of the samples was carried out after pressing (P = 1.52 GPa), since pressure is one of the factors of a possible phase transition. The samples presented in Table 2 were studied to perceive the possibility of Desloratadine substance phase transitions.

At each stage of the research, the composition of the samples was controlled by powder diffraction and the data obtained were processed according to the Rietveld method (Fig.3, Table 3).

According to the powder X-ray diffraction data, the Desloratadine sample **(0)** contains three phases corresponding to polymorphs **I-III** known from the literature. According to the data obtained after refinement (Table 3), the solvent affects the developing crystal structure of Desloratadine, since in each case **(1) – (4)** after recrystallization only two phases were

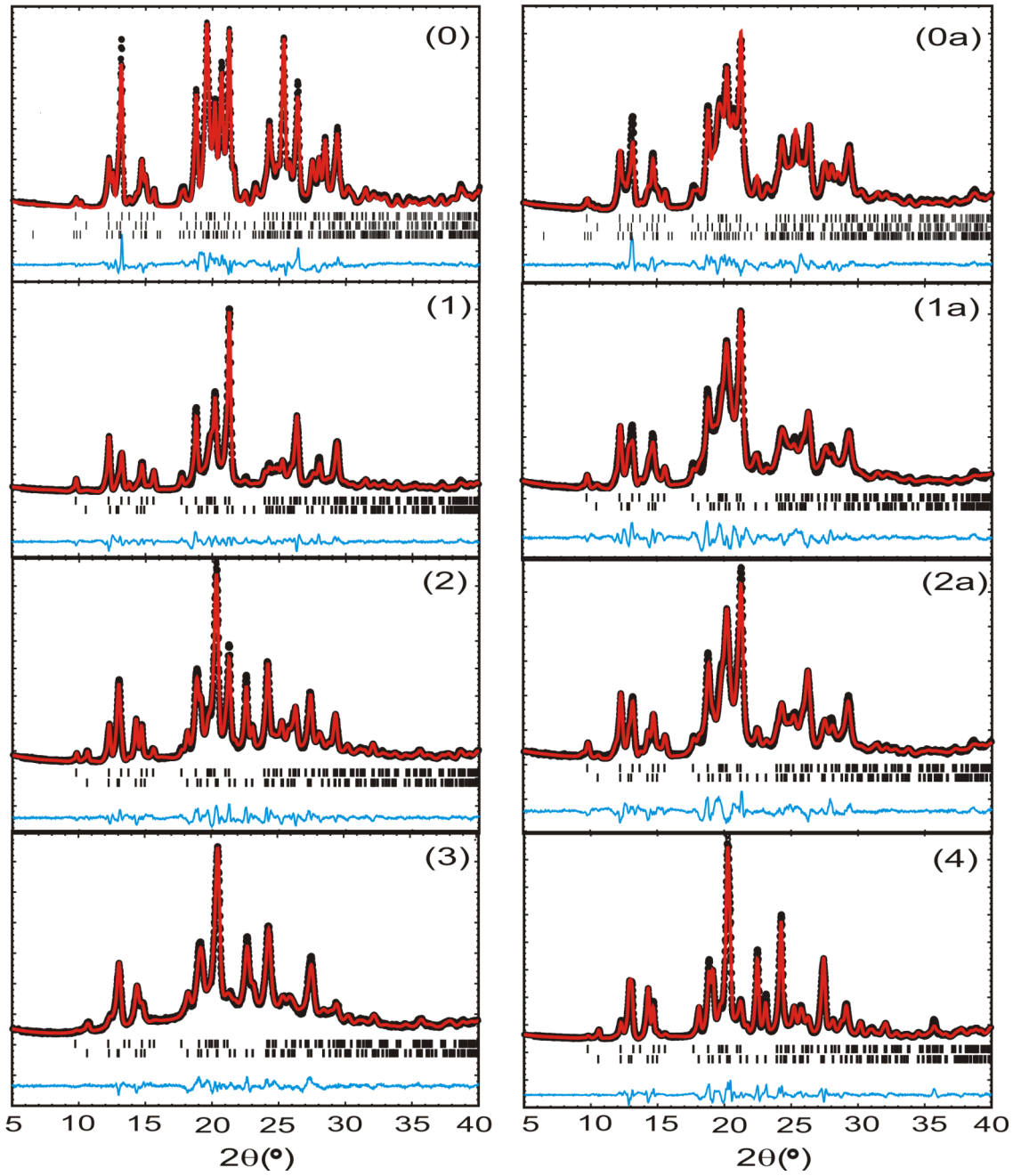

Fig. 3 Results of diffraction pattern refinements using the Rietveld method after experiments **(0)** – **(4)** and **(0a)** – **(2a)**. Black dots show the experimental diffraction pattern; red marks show theoretically calculated data; the difference curve is marked in blue. Vertical lines correspond to the positions of the Bragg peaks.

observed, corresponding to polymorphic forms **I** and **III.** One of the main factors which can influence the formation of the three polymorphic modifications is the method of preparation: the volume of the reaction mixture and the conditions under which constant stirring is carried out, as well as temperature. For each individual case of recrystallization, the formation of one of the polymorphic modifications is most advantageous. In case (**1**), polymorph **I** is present in the predominant amount in the sample under study. For the other experiments **(2)** – **(4**), the formation of the polymorph **III** is predominant; the largest amount of it was obtained in case (**3**), which corresponds to recrystallization from an aqueous solution. It is worth noting that not a single polymorphic modification was obtained in its pure form; polymorph **II** is observed only in sample (**0**) obtained under production conditions. After pressing the sample (0), the

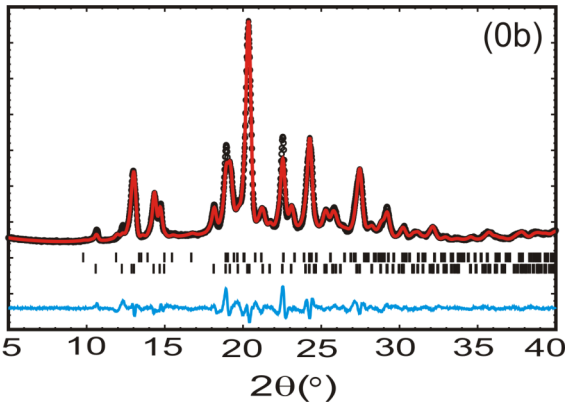

Fig.4 Results of the Rietveld refinement of the powder X-ray diffraction pattern of the sample **(0b)**.

broadening of the lines is quite noticeable, as well as a change in the ratio of line intensities in the powder diffraction pattern (Fig. 3 (0a)). The changes indicate processes of transition of part of the sample into an amorphous state, which is also accompanied by a change in the ratio of crystalline phases and a decrease in the size of crystallites (Table 3, **(0a)**). Based on the results of refinement of the powder pattern, the amount of metastable modification II decreased. Let's compare experiments **(1a)** and **(2a)** for the samples **(1)** and **(2)**. There is a noticeable change in the content of polymorphs; this process can be called a reverse phase transition, since in the first case the amount of polymorph **III** increases, in the second - polymorph **I**. In such cases, line broadening is also observed, which indicates the presence of part of the amorphous phase and a decrease in the size of crystallites in the samples under study.

According to the results of refinement for the melt of sample (**0**), sample (**0b**) contains polymorphs **I** (10 wt.%) and **III** (90 wt.%) (Fig.4). It is worth noting that polymorph **II** is also absent in the sample (**0b**), while a predominant amount of polymorph **III** is observed.

4. Conclusions

According to the results of the research, the following conclusions can be made: polymorph **II** is metastable and is formed only during Desloratadine officinal synthesis in manufacturing, and any further processing of the obtained Desloratadine substance leads to its partial transition into polymorph **I** and/or **III**.

It is worth noting that upon recrystallization of Desloratadine from various solvents, as well as from the melt, polymorph **II** completely disappears in the sample. The balance of polymorphs **I** and **III** in the recrystallized product depends on the type of solvent used for recrystallization. The maximum content of polymorph **I** was obtained during recrystallization from chloroform (77 mass%), polymorphic modification **III** was obtained during recrystallization from water (86 mass%) and from a melt (90 mass%). No foreign impurities were observed.

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