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# Modification and scaling of industrial synthesis of naphazoline nitrate substance using green chemistry approaches

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**ABSTRACT**: This article presents the results of the modified and optimized synthesis technology of the Naphazoline nitrate substance introduced into the industrial synthesis and included in the registration dossier. The introduction of the 1,2,4-trichlorobenzene solvent into the synthesis scheme at the condensation stage made it possible to increase the yield of the substance by up to 50% compared to the traditional technology. The final product Naphazoline nitrate meets the requirements of the European Pharmacopoeia monograph and has high purity, suitable particle size, high homogeneity, easy industrialization and high productivity. The assay of the substance was increased from 98.7% to 100.0%, and the total of impurities was reduced from 0.5% to 0.1% and below. Carrying out the regeneration of the 1,2,4-trichlorobenzene solvent improves the indicator of economic efficiency due to the possibility of its repeated use. The calculated E-factor for the modified technology is 7 times higher compared to the traditional one, which indicates a reduction in the amount of waste, and therefore a reduction in the negative impact on the environment and production personnel.

**KEYWORDS**: Green chemistry; naphazoline nitrate; industrial synthesis; pharmacopeial requirements; risk analysis.

## 1. INTRODUCTION

Green chemistry is a fascinating research area due to its respect to environment and effectiveness for more purified organic compounds, which will be active pharmaceuticals [1]. Twelve principles of green chemistry should be obeyed, and these principles can manage the researchers to enhance productivity and reduce hazardous effects on human health [2]. Active pharmaceutical ingredients (API) should have adequate purity due to their use in human health. Any contamination coming from adopted protocols can influence the product. These disadvantages increase further purification protocols, which led to using more power, chemicals, and increase product cost. All these disadvantages can be dropped using green chemistry principles.

Around the world, pharmaceutical industries afford to do green protocol due to human health and product costs. These aims led them to find out new and greener synthetic protocols that can be utilized on an industrial scale. These protocols are imperative and can be transferred in research and development, which have been progressed in the university or other industries.

Opinion shows that green chemistry principles can save the cost of about 65.5 billion by 2020. The most direct and straightforward way to employ green chemistry in pharmaceuticals is to employ eco-friendly, nonhazardous, reproducible, and cost-effective solvents and catalysts in the synthesis of drug molecules and researches involving synthetic chemistry [3]. Also, flow chemistry will be a powerful tool for the synthesis of API, as well [4]. That is why the principles of green chemistry were implemented in the pharmaceutical company JSC «Farmak», using the substance naphazoline as an object.

Naphazoline has been used in clinical practice for more than seven decades and belongs to the sympathetic adrenomimetics, α2-adrenoreceptors stimulators, imidazole derivatives product group [5, 6]. The drug administration leads to vasoconstrictor and anticongestive effects [7]. In clinical practice, this leads

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to the use of drugs containing naphazoline in otolaryngology – to treat rhinitis and in ophthalmology – to relieve redness, swelling, itching of the eyes caused by a cold, or by allergies and irritation (e.g., the effects of smog, swimming or contact lens wear). For the production of naphazoline drugs its soluble salts are usually used as hydrochloride and nitrate (Figure 1) [8, 9]. Naphazoline was described for the first time in the form of hydrochloride (Privine hydrochloride) and was marketed under the Naphthyzin brand-name in April 1941 [10]. In October 1942, the drug entered the United States market [11]. In 1945, the first information was published on the naphazoline hydrochloride pharmacological effect [12].


**Figure 1.** Structural formulas

Drugs containing naphazoline are manufactured by manufacturers in the United States, Australia, China, Romania, the Czech Republic, etc. [13, 14]. In the pharmaceutical market of Ukraine, naphazoline is represented by drugs manufactured by JSC «Farmak» (Naftizin) and Xanthis Pharma Limited (Sanorin).

The main manufacturers of naphazoline substances in the world are LOBA Feinchemie GmbH, Austria, Tianjin Tiancheng Pharmaceutical Co. Ltd., China, Teva Czech Industries, Czech Republic, Xantis Pharma Limited, Cyprus.

In Ukraine, the technology of industrial production of the substance Naphazoline, which was named "Naftizin", was developed in 1960 at the Kyiv Chemical-Pharmaceutical Plant. M.V. Lomonosov, and in 1965 began production of the drug "Naftizin". Since 1967, the chemical-pharmaceutical plant. Lomonosov was the only manufacturer of the drug under the brand name "Naftizin".

Currently, only the industrial synthesis of Naphazoline nitrate has been implemented at JSC «Farmak». However, the development and implementation of industrial synthesis and Naphazoline hydrochloride to expand the range of drugs is important.

According to the patent [15], the basis of naphazoline (6) (4,5-dihydro-2-(1-naphthylmethyl)-1*H*-imidazole) is synthesized from (1-naphthyl) acetonitrile (3), which is converted into imino ester (4) by reaction with ethanol. As a result of the subsequent heterocyclization of the latter with ethylenediamine (5) the target product is formed (Figure 2). Intermediate (4) is unstable, easily hydrolyzed to form by-products, so it is very difficult to obtain a high-quality form of imino ester (4) with high yield. To eliminate these shortcomings of the synthesis requires anhydrous conditions or complex purification. And although naphazoline from the ether is obtained with a yield of 90% or more, this is not a commercially viable method. In addition, both the degree of purity and the yield of the finished product are unacceptable given the pharmacopoeial quality substance.

Sulfur-containing catalysts have been used by scientists to increase yields and obtain a cleaner finished product. It is proposed [16] to synthesize imidazole derivatives by cyclization of nitriles in excess of 1,2-diaminopropane saturated with hydrogen sulfide. The yield of the target compounds in this way reaches 72 – 88%, but it requires refluxing for a long time, and the use of hydrogen sulfide in industrial production carries certain risks of impact on production staff the environment. Modification of the method of synthesis of naphazoline from the original naphthyl acetonitrile using thioacetamide as a catalyst [17], also has certain disadvantages for use on an industrial scale, as it requires ice quenching during treatment or extraction with chloroform, one of the most toxic organic solvents.

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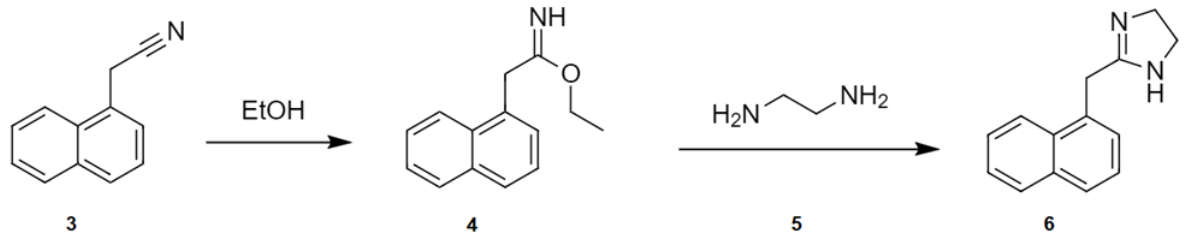


**Figure 2**. Synthesis of Naphazoline base

Consider one of the principles of green chemistry – the use of safer solvents and excipients. This principle promotes the use of safer solvents and auxiliaries. It is about any substances that do not directly contribute to the structure of the reaction product but are still necessary for the chemical reaction or process to occur. Mostly, reactions of organic compounds take place in liquid milieus, where the solvent acts in different ways: it can enable enhanced contact between the reactants, it can stabilize or destabilize generated intermediates, or it can influence transition states. In addition, the applied solvent also governs the selection of adequate downstream and regeneration processes and recycling or discarding techniques. By taking the ecological effect of chemical processes in consideration, innovative concepts for substitution of volatile organic solvents have become a great challenge in green chemistry. A green solvent should meet numerous criteria such as low toxicity, non-flammability, non-mutagenicity, non-volatility and widespread availability among others. Moreover, these green solvents have to be cheap and easy to handle and recycle [18-20].

One of the «green syntheses» of obtaining naphazoline hydrochloride is described in patent CN112209880 A [21]. The invention relates to the technical field of organic synthesis, in particular to a preparation method of naphazoline hydrochloride, which comprises the steps of taking alpha-naphthylacetic acid, ethylenediamine and acetone as raw materials, and preparing 4, 5-dihydro-2- (1-naphthylmethyl) -1H-imidazole hydrochloride through condensation, cyclization, salification and the like. The invention takes alpha-naphthylacetic acid, ethylenediamine and acetone as raw materials to prepare the target product, and the raw materials are easy to obtain and have low price. The invention adopts condensation, cyclization and salification, has mild operation reaction conditions, avoids a large amount of side reactions and obtains higher yield. The preparation process has high consistency, short reaction time and high efficiency and is thorough. The preparation method has the advantages of simple preparation process and mild reaction conditions, and avoids environmental pollution.

Also, in patent CN113912545 A [22] the invention is presented, which relates to preparation and purification of inorganic salt of naphazoline. In particular, the preparation method consists of following steps: (1) condensation reaction of 1-naphthaleneacetonitrile and ethylenediamine in presence of a catalyst to obtain 4,5-dihydro-2-(1-naphthylmethyl)-1H-imidazole; (2) salt-formation reaction of step (1) product with concentrated inorganic acid to obtain crude inorganic salt of naphazoline; and (3) purifying step (2) product by dissolving in ethanol to obtain purified inorganic salt of naphazoline. The inventive method has simple process and convenient operation to obtain inorganic salt of naphazoline with high purity as high as 99.5%, and also suitable for industrial production.

Another invention (CN115636790 A) discloses the preparation of naphazoline hydrochloride, which has the advantages of simple operation, high product yield and purity, low preparation cost and short reaction time. The naphthonazoline hydrochloride was prepared by addition reaction of methanol and 1-naphthylacetonitrile, heterocyclization with ethylenediamine, and salification with concentrated hydrochloric acid [23].

Based on mentioned above, our goal was:

- to develop an industrial technology for the synthesis of Naphazoline nitrate and Naphazoline hydrochloride by modifying the traditional method taking into account the principles of «green chemistry», namely the use of less toxic solvents, ensuring their regeneration and minimization of waste generation and disposal;
- according to the new modified technology to ensure the proper quality of the substances Naphazoline nitrate and Naphazoline hydrochloride according to the monographs of the European Pharmacopoeia (0147 and 0730 respectively);
- Calculate the E-factor for the new modified and old technology of synthesis of the substances Naphazoline nitrate and Naphazoline hydrochloride to confirm the application of the principles of «green chemistry».

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## 2. RESULTS AND DISCUSSION

The main trend in the scientific development of API synthesis is their modification with wide implementation of the «green chemistry» principles to reduce the impact on the environment and personnel and to conserve resources.

At JSC «Farmak», the synthesis of naphazoline nitrate (1) (figure 3) is carried out according to the Operational Regulation from stock 1-naphthaleneacetic acid (7), and one of the intermediates is crude naphazoline hydrochloride (2), which is presented as grey and white crystals with a melting point of 243-248 °C (technology 1).

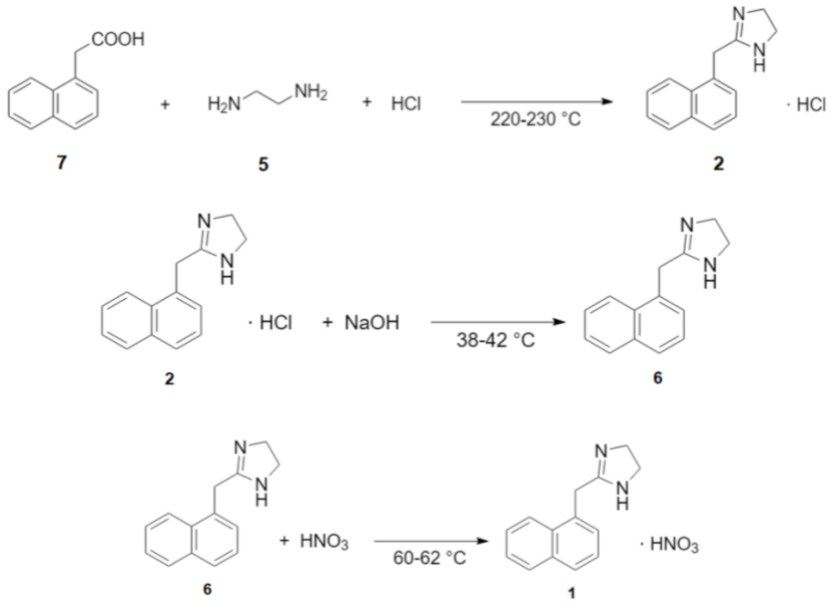


**Figure 3**. Synthesis of Naphazoline nitrate (technology 1)

In the process of fusing of 1-naphthylacetic acid (7) with ethylenediamine (5), tar products are expected to be formed, therefore the purification procedure is very important to obtain a pharmacopeial product. To produce naphazoline hydrochloride, the crude product was purified by transferring into the base, followed by treatment with hydrochloric acid in the mixture of dichloroethane - isopropyl alcohol solvents. Based on the green chemistry principles, it was necessary to determine the ratio of solvents, which allows to obtain the maximum yield of the product after purification. Based on the results of the experimental studies (Table 1), the optimal ratio of dichloroethane and isopropyl alcohol (1:3) was determined, and it was also established that double purification of crude naphazoline hydrochloride is required to produce a pharmacopeial product

**Table 1.** The results of purification of samples of Naphazoline hydrochloride crude

| Experiment | Loaded | | | | | | | Obtained |
|---|---|---|---|---|---|---|---|---|
| | Naphazoline HCl crude, g | Water, ml | Coal, g | Sodium hydroxide 40%, ml | Isopropyl alcohol, ml | Dichloroethane, ml | Hydrochloric acid, ml | Naphazoline HCl crude (wet), g |
| **1** | 200 | 2000 | 5 | 100 | 232.5 | 77.5 | 60 | 120 |
| **2** | 200 | 2000 | 5 | 100 | 228.0 | 76.0 | 61 | 98 |
| **3** | 200 | 2000 | 5 | 108 | 192.0 | 64.0 | 57 | 120 |
| **4** | 200 | 2000 | 5 | 120 | 304.5 | 101.5 | 65 | 116 |
| **5** | 200 | 2000 | 5 | 115 | 258.0 | 86.0 | 63 | 127 |
| **6** | 200 | 2000 | 5 | 100 | 190.5 | 63.5 | 57 | 128 |
| **7** | 200 | 2000 | 5 | 106 | 232.5 | 77.5 | 60 | 120 |
| **8** | 200 | 2000 | 5 | 112 | 249.0 | 83.0 | 60 | 101 |

The data showed that the second purification of Naphazoline hydrochloride crude provides a pharmacopeial Naphazoline hydrochloride with a yield of 36.6% calculated of the initial crude product and 16.05% on 1-naphthylacetic acid. The yield of naphazoline nitrate is 11.66%.

Comparative table 2 shows the main parameters of quality - melting point and assay for crude and final samples of Naphazoline hydrochloride after the second crystallization (Table 2).

**Table 2.** Properties of Naphazoline HCl

| Experiment | Naphazoline HCl crude | | Naphazoline HCl final | |
|---|---|---|---|---|
| | Assay, % | Melting point, °C | Assay, % | Melting point, °C |
| **1** | 85.3 | 243.3 | 98.5 | 254.0 |
| **2** | 83.6 | 245.5 | 99.5 | 254.0 |
| **3** | 84.8 | 246.3 | 98.6 | 254.5 |
| **4** | 88.1 | 248.0 | 100.0 | 254.5 |
| **5** | 83.9 | 245.5 | 99.3 | 254.5 |

The concept of waste minimization involves, where possible, the regeneration of solvents used in synthesis or recrystallization to reduce the impact on the environment. We conducted a study to determine the efficiency of regeneration of mother liquors used for purification of crude Naphazoline hydrochloride (dichloroethane-isopropyl alcohol-water mixture). The regeneration process consisted of distilling a mixture of solvents at atmospheric pressure and a temperature of 76-88 °C. The characteristics of the initial mother liquors and those obtained after regeneration are shown in Table 3.

**Table 3.** The results of regenerated mother liquors

| Experiment | Initial mother liquors | | | Conditions for regeneration | | Regenerated mother liquors | |
|---|---|---|---|---|---|---|---|
| | Volume, ml | Density, g/cm$^3$ | Water, % | Temperature range for distillation, °C | Pressure, millimetre | Volume, ml | Water, % |
| **1** | 640 | 0.916 | 19.15 | 76-88 | 760 | 545 | 16.80 |
| **2** | 620 | 0.897 | 15.70 | 74-83 | 760 | 570 | 14.20 |
| **3** | 660 | 0.911 | 17.70 | 75-86 | 760 | 560 | 15.19 |
| **4** | 590 | 0.898 | 20.00 | 74-83 | 760 | 520 | 17.10 |

The results obtained (table 3) show that under these conditions the yield of the solvent mixture is 87 – 89%. The water content in distillate is 15 – 20%. Such results are acceptable. In order to reuse regenerated mother liquors, they were dried with hot potassium carbonate to a water content of not more than 1%.

In addition, in the process of regeneration of mother liquors it was possible to obtain an additional amount of naphazoline hydrochloride (Table 4), which increased the yield of pharmacopeial naphazoline hydrochloride to 8% calculated of crude.

**Table 4.** The results of Naphazoline hydrochloride obtained from mother liquors

| Experiment | Loaded | | Obtained | | | | |
|---|---|---|---|---|---|---|---|
| | Naphazoline HCl crude | | Naphazoline HCl final | | | | |
| | Weight, g | Appearance | Weight, g | Appearance | Assay, % | Water, % | Yield on Naphazoline HCl crude, % |
| **1** | 110.5 | brown | 52.4 | white | 99.5 | 0.1 | 47.3 |
| **2** | 92.00 | brown | 54.6 | white | 99.4 | 0.1 | 59.4 |
| **3** | 115.0 | brown | 53.6 | white | 99.6 | 0.05 | 46.3 |

Despite the increase in yield during regeneration, the scheme of synthesis of naphazoline hydrochloride does not meet the «green chemistry» principles due to low yield of the finished product and the use of toxic substances such as hydrochloric acid (precursor) and dichloroethane, which is a carcinogen and strong narcotic drug of Class I solvents which should be avoided during the synthesis of substances. That is why this scheme of synthesis was considered unacceptable for commercial manufacture.

However, the technology of synthesis of naphazoline nitrate was introduced into production because crude naphazoline hydrochloride was loaded to receive a crude product that did not require the purification process and allowed to avoid the use of hazardous substances (Table 1).

However, despite the proper quality of the resultant naphazoline nitrate (Table 5), due to the low yield (about 10-15%) this synthesis technology cannot be considered acceptable for commercial synthesis.

**Table 5.** Compliance of naphazoline nitrate samples with Ph.Eur requirements

| **Batch number** | | 1101 | 1201 | 1301 |
|---|---|---|---|---|
| **Test** | Specifications requirements | Results | | |
| Appearance | White or almost white, crystalline powder | almost white, crystalline powder | almost white, crystalline powder | almost white, crystalline powder |
| Solubility | Sparingly soluble in water R, soluble in alcohol 96% R | conforms | conforms | conforms |
| Identification | UV spectrocophy<br>Reaction to nitrates | Conforms<br>Conforms | Conforms<br>Conforms | Conforms<br>Conforms |
| Melting point | 167-170 °C | 168 °C | 169 °C | 168 °C |
| Clarity of solution | Solution 1% is clear | conforms | conforms | conforms |
| Degree of colouration | Solution 1% is colourless | conforms | conforms | conforms |
| pH | 5.5 to 7.0 | 6.5 | 6.8 | 6.7 |
| Related substances naphtylacetic acid | not more than 0.5% | 0.45% | 0.48% | 0.48% |
| Chlorides | Not more than 0.02% | conforms | conforms | conforms |
| Sulfates | Not more than 0.02% | conforms | conforms | conforms |
| Loss on drying | Not more than 0.5% | 0.4% | 0.4% | 0.3% |
| Sulfated ash | Not more than 0.1% | less than 0.1% | less than 0.1% | less than 0.1% |
| Heavy metals | Not more than 0.001% | less than 0.001% | less than 0.001% | less than 0.001% |
| Assay of naphazoline nitrate | 98.5% to 101.0% | 98.5% | 98.6% | 98.9% |

Due to the low yields of finished products and the formation of a large amount of synthesis waste, a modified synthesis technology (technology 2) of Naphazoline hydrochloride 2 and its conversion into Naphazoline nitrate (figure 4) was later proposed and implemented by JSC «Farmak» (Ukraine).

The main modification of the synthesis technology is to use at the stage of condensation as a solvent of 1,2,4-trichlorobenzene, which provides the required temperature and avoids tarring. Purification of crude products was carried out with activated charcoal and recrystallization from water (Naphazoline nitrate).

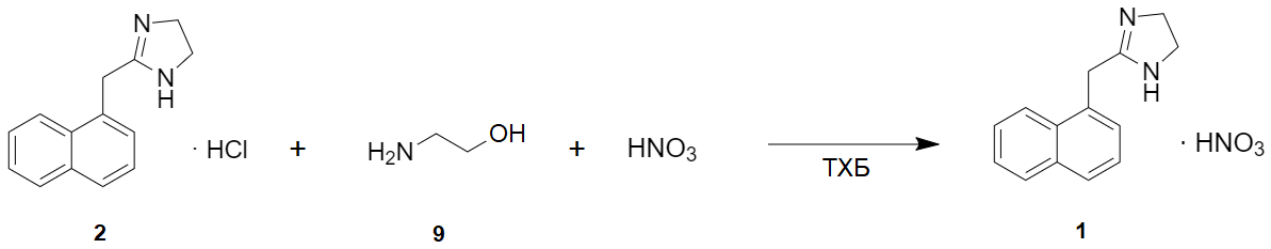


**Figure 4**. Synthesis of Naphazoline nitrate and Naphazoline hydrochloride

The evaluation of the quality of the final products of Naphazoline hydrochloride and Naphazoline nitrate (3 batches each) after purification was carried out in accordance with the requirements of the Ph.Eur [9]. The data in Tables 6 and 7 show that all parameters meet the requirements of the Ph.Eur [9].

**Table 6.** Quality of the obtained batches of naphazoline hydrochloride (technology 2)

| **Batch number** | | 10419 | 20419 | 30419 |
|---|---|---|---|---|
| **Test** | Specifications Ph.Eur [9] | Results | | |
| Appearance | White or almost white, crystalline powder | almost white, crystalline powder | almost white, crystalline powder | almost white, crystalline powder |
| Identification | The infrared absorption spectrum of the substance matches the spectrum of the naphazoline hydrochloride reference standard | conforms | conforms | conforms |
| Clarity of solution | Solution S is clear | conforms | conforms | conforms |
| Degree of colouration | Solution S is colourless | conforms | conforms | conforms |
| Acidity or alcalinity | Not more than 0.6 ml of 0.01 M hydrochloric acid changes the color of the solution to red | conforms | conforms | conforms |
| Related substances<br>*naphazoline impurity A*<br>*any unspecified impurity*<br>*total of impurities* | <br>Not more than 0.1%,<br>Not more than 0.10%,<br>Not more than 0.5% | <br>BDL<br>0.06%<br>0.12% | <br>BDL<br>0.06%<br>0.08% | <br>BDL<br>0.06%<br>0.12% |
| Loss on drying | Not more than 0.5% | 0.07% | 0.08% | 0.2% |
| Sulfated ash | Not more than 0.1% | less than 0.1% | less than 0.1% | less than 0.1% |
| Microbial purity | 103 CFU/g<br>102 CFU/g | Conforms<br>Conforms | Conforms<br>Conforms | Conforms<br>Conforms |
| Assay of naphazoline hydrochloride | 99.0% to 101.0% on dried substance | 100.2% | 100.2% | 100.5% |

**Table 7.** Quality of the obtained batches of naphazoline nitrate (technology 2)

| **Batch number** | | 10419 | 20419 | 30419 |
|---|---|---|---|---|
| **Test** | Specifications Ph.Eur [9] | Results | | |
| Appearance | White or almost white, crystalline powder | almost white, crystalline powder | almost white, crystalline powder | almost white, crystalline powder |
| Solubility | Sparingly soluble in water R, soluble in alcohol 96% R | conforms | conforms | conforms |
| Identification | The infrared absorption spectrum of the substance matches the spectrum of the naphazoline nitrate reference standard | conforms | conforms | conforms |
| Clarity of solution | Solution S is clear | conforms | conforms | conforms |
| Degree of colouration | Solution S is colourless | conforms | conforms | conforms |
| Related substances<br>*naphazoline impurity A*<br>*any unspecified impurity*<br>*total of impurities* | <br>Not more than 0.5%,<br>Not more than 0.10%,<br>Not more than 1.0% | <br>BDL<br>BDL<br>Less than 1.0% | <br>BDL<br>BDL<br>Less than 1.0% | <br>BDL<br>BDL<br>Less than 1.0% |
| Chlorides | Not more than 0.033% (330 ppm) | conforms | conforms | conforms |
| Loss on drying | Not more than 0.5% | 0.3% | 0.4% | 0.2% |
| Sulfated ash | Not more than 0.1% | less than 0.1% | less than 0.1% | less than 0.1% |
| Microbial purity | 103 CFU/g<br>102 CFU/g | Conforms<br>Conforms | Conforms<br>Conforms | Conforms<br>Conforms |
| Assay of naphazoline nitrate | 99.0 % to 101.0 % on dried substance | 99.4% | 100.6% | 99.9% |

The next step was to assess the compliance of the modified technology (technology 2) with the principles of "green chemistry" and its comparison with the previous one (technology 1).

We performed a risk assessment for the solvents used in the modified synthesis technology – 1,2,4-trichlorobenzene, ethylenediamine dihydrochloride and ethanolamine, as well as for the starting material -1-naphthylacetic acid (Figure 4).

With the involvement of experts - representatives of JSC «Farmak» and the National University of Pharmacy, the priority risk number (PRN) were calculated (Table 8) when using these substances.

**Table 8.** Risk priority number PRN (technology 2)

| Substance name | RPN | Acceptance criteria |
|---|---|---|
| 1,2,4-trichlorobenzene | 24 | From 10 to 33 |
| ethylenediamine dihydrochloride | 23 | |
| ethanolamine | 22 | |
| 1-naphthaleneacetic acid | 21 | |

According to the requirements, this parameter should be in the range from 10 to 33. The higher this value, the greater the risk of using this solvent. Example, for 1,2,4-trichlorobenzene the calculation is as follows:

RPN = (Σ low risk X1) + (Σ high risk X2) + (Σ high risk X3) = 3 + 6 + 15 = 24.

According to the calculations, the priority risk number for all substances is within acceptable limits and the proposed solvents are permitted and relatively safe for use in industrial synthesis of the substance.The greatest danger is the use in the synthesis of the solvent 1,2,4-trichlorobenzene, which is a rather toxic compound. However, its use provides a significant increase in the yield of target products (Table 9).

**Table 9.** Waste of two technologies

| Technology 2 (1 kg of API) | | Technology 1 (1 kg of API) | |
|---|---|---|---|
| **Waste** | **Amount, kg** | **Waste** | **Amount, kg** |
| Cubic residue and 1,2,4-trichlorobenzene | 2,3 | Mother liquor from washing and filtration of Naphazoline | 10,38 |
| Mother liquor (isopropyl alcohol and impurities) and cubic residue of distilled 1,2,4-trichlorobenzene | 14,0 | Mother liquor from washing and filtration of Naphazoline crude | 11,49 |
| Mother liquor (water and impurities) | 16,1 | Mother liquor from washing and filtration of Naphazoline base | 55,95 |
| Paste of used activated charcoal | 0,03 | Mother liquor from washing and filtration of Privine | 15,17 |
| **Intermediate** | | Paste of used activated charcoal | 1,46 |
| 1,2,4-trichlorobenzene regenerated | 5 | Water from washing equipment | 167,08 |
| **Loses** | | **Loses** | |
| Naphtizin, powder (substance) | 0,01 | Water, dimethylformamide, ethanol 96%, Naphtizin | 2,2 |
| **Total** | 37,4 | **Total** | 263,7 |

The proposed technology 2 involves the regeneration of this solvent, which reduces the amount of waste and the possibility of its further reuse to reduce the toxic effects.

For the regeneration of 1,2,4-trichlorobenzene, take mother liquors from filtration of the crude Pryvine from the condensation stage and the distilled aqueous 1,2,4-trichlorobenzene are placed in a glass tank equipped with stirrer, thermometer and straight condenser. The mixture is heated with stirring at atmospheric pressure to distill the 1,2,4-trichlorobenzene. The first fraction of an aqueous solution of ethylenediamine with impurities of 1,2,4-trichlorobenzene (boiling point up to 210 °C) sent for waste disposal. The fraction with a boiling point range 210 °C to 218 °C (which is exactly regenerated 1,2,4-trichlorobenzene) is collected and may be used in the condensation stage.

In addition, in the process of synthesis, one of the critical points is the establishment of the absence of solvent residues, which is determined by distillation and control of the distilled volume. Subsequent crystallization of crude naphazoline from aqueous isopropyl alcohol, in which 1,2,4-trichlorobenzene is freely soluble, ensures its complete removal from the resulting product. Additionally, the content of 1,2,4-trichlorobenzene in the final substance is also tested by gas chromatography. This solvent was not detected in any of the test samples.

One of the key and important points of green chemistry is the calculation of E-factor, the so-called Environmental factor. The global impact, over the last 25 years, of the principles of green chemistry and sustainability, and the pivotal role of the E- factor concept in driving resource efficiency and waste minimization, in the chemical and allied industries, is reviewed. Following an introduction to the origins of green chemistry and the E-factor concept, the various metrics for measuring greenness are discussed. It is emphasized that mass-based metrics such as atom economy, E-factors, and process mass intensity (PMI) need to be supplemented by metrics, in particular life cycle assessment, which measure the environmental impact of waste and, in order to assess sustainability, by metrics which measures economic viability. The role of catalysis in waste minimization is discussed and illustrated with examples of green catalytic processes such as aerobic oxidations of alcohols, catalytic C-C bond formation, and olefin metathesis. Solvent losses are a major source of waste in the pharmaceutical and fine chemical industries and solvent reduction and replacement strategies, including the possible use of neoteric solvents, such as ionic liquids and deep eutectic solvents, are reviewed. A higher E-factor means more waste and, consequently, greater negative environmental impact. The ideal E-factor is zero [24].

In short, there are strong economic incentives for the pharmaceutical industry to integrate green chemistry into the entire process research, development, and manufacturing lifecycle. The concepts of atom economy and E-factors have motivated industrial and academic chemists worldwide to explicitly consider waste generation, in addition to the common criteria such as synthetic convergence, chemical yield, and cost of goods, when designing a synthesis of a target molecule [25]. Using this approach to understand the benefits of the new synthesis technology, a detailed table on the amount of waste generated (Table 9), summary Table 10 with E-factor calculated on the basis of these data and data on the practical yield of the finished product in 1 kg of substance were provided, and total impurity content and assay of the substance for two technologies of naphazoline synthesis were shown.

**Table 10.** Comparative table for two technologies of naphazoline synthesis

| | **Waste, kg** | **Practical yield, %** | **Total of impurities in the final API, %** | **Assay, %** | **E-factor** |
|---|---|---|---|---|---|
| Technology 1 | 264 | 10-15 | 0,5% | 98,7 | 263 |
| Technology 2 | 37 | 50-60 | less than 0,1% | 100,0 | 37 |

Thus, a comparative analysis of two schemes of synthesis for naphazoline hydrochloride and naphazoline nitrate and risk assessment showed that the modified procedure of these substances meets the green chemistry principles, increases the practical yield of the final product and its purity, reduces waste, and provides reusability of solvents. In terms of the amount of waste per kilogram of product (E-factor), the modified technology of the production of naphazoline nitrate and naphazoline hydrochloride nitrate is 7 times more efficient than the old method.

## 3. CONCLUSION

Compared with technology 1, its modification (technology 2) has the following advantages and beneficial effects:

1. Modified technology for the synthesis of naphazoline has been introduced into industrial production. The technology does not involve the use of toxic solvents such as dichloroethane and hydrochloric acid, does not require a fusion reaction, which results in the formation of many resins, which further accumulate in the waste and subsequently lead to environmental pollution. The operation is simple, safe and environmentally friendly.

2. After simple salt formation and recrystallization, the obtained naphazoline has high purity, appropriate particle size, bulk particles, good fluidity, description that meets the requirements of pharmacopoeial monograph, high homogeneity, easy industrialization and high productivity.

3. The E-factor calculated for both of technologies of the production of the naphazoline substance is 7 times more efficient for modified technology.

## 4. MATERIALS AND METHODS

Used equipment: industrials tanks with stirrers (K630 L, manufacturer «ZIBOTAIJI», China and HRX-600 «HAOXIN», China), scales for weighing raw materials (CAW1S4-300II-L), centrifuge (LDG-1350),

manufacturer «Jiangsu Saideli», China), pressure filter (FiB-wiH-27-mem, manufacturer «MAAP», Czech Republic), collections (HXR-800 horizontal, manufacturer «HAOXIN», China and K 400L upright, manufacturer «Kavalierglass»), loading funnels.

To analyze the quality of the substances used: titrator (Mettler Toledo, T 70), liquid (Agilent Technologies, 1260) and gas chromatographs (Agilent Technologies, 7890 B), pH-meter (Mettler Toledo, Seven Compact S220), chromatographic column Zorbax-C8 (250 mm × 4.6 mm, 5 mkm), chromatographic column DB-5 (30 m × 0,53 mm, 3.0 mkm).

Used reagents: sodium 1-octanesulfonate monohydrate with a purity 99,9% (Sigma Aldrich), glacial acetic acid with a purity 99,9% (Sigma Aldrich), acetonitrile with a purity 99,9%, (Honeywell), perchloric acid 0,1 M (Merck), sodium hydroxide 1 M (Supelco), hydrochloric acid 1 M (Supelco), 1-naphthaleneacetic acid with a purity 99,9% (Sigma Aldrich), Naphazoline nitrate EP CRS, naphazoline impurity A EP CRS.

Reagents and titrated solutions for analysis were prepared according to the requirements of the European Pharmacopoeia [9].

The analysis was performed according to the monographs of the European Pharmacopoeia on the substance (0147 for Naphazoline nitrate and 0730 for Naphazoline hydrochloride) [9].

### 4.1. Analytical methods

*4.1.1 Assay*

The literature describes titrimetric and spectrophotometric methods for the assay of naphazoline salts. In this study, the following procedures were used for the assay of the active substance:
*Naphazoline hydrochloride (Technology 2).*

Dissolve 0.200 g of the substance in the mixture of 5.0 mL of 0.01 M hydrochloric acid and 50 mL of ethanol 96% R. Titrate potentiometrically using 0.1 M sodium hydroxide. Calculate the volume of the titrant between two points on the titration curve.

1 mL of 0.1 M sodium hydroxide is equivalent to 0.02467 g of naphazoline hydrochloride.

*Naphazoline nitrate (Technology 2).*

Dissolve 0.200 g of the substance in 30 mL of anhydrous acetic acid R and titrate with 0.1 M perchloric acid potentiometrically.

1 mL of 0.1 M perchloric acid is equivalent to 0.02733 g of naphazoline nitrate.

*Naphazoline hydrochloride (Technology 1).*

Shake 0.200 g of the substance in a separatory funnel with 5 mL of water and 5 mL of 1 M sodium hydroxide. Add 10 mL of chloroform and shake again for 5 min until the resulting base is completely dissolved. Allow to stand for 40 min. Carefully pour the lower chloroform layer into a 100 mL conical flask. Extract with chloroform from aqueous solution twice with 5 mL portions of chloroform, pouring the bottom layer into the same conical flask. Add 20 mL of glacial acetic acid and 5 mL of acetic anhydride to the resulting chloroform layer and titrate with 0.1 M perchloric acid to a green color (crystal violet indicator). In parallel, conduct a blank test.

1 mL of 0.1 M sodium hydroxide is equivalent to 0.02467 g of naphazoline hydrochloride.

*Naphazoline nitrate (Technology 1).*

Dissolve 0.250 g of the substance in 30 mL of anhydrous acetic acid R, add 10 mL of acetic anhydride, 5 mL of chloroform and titrate with 0.1 M perchloric acid potentiometrically. In parallel, conduct a blank test.

1 mL of 0.1 M perchloric acid is equivalent to 0.02733 g of naphazoline nitrate.

### 4.2 Technological processes

4.2.1 Description of manufacturing process for naphazoline nitrate (Technology 1)

*Step "Condensing"*

Load 1-naphthaleneacetic acid and ethylenediamine manually through the hatch into a clean, dry and nitrogen blow-through air tight tank. Then load hydrochloric acid into the tank with the stirrer and condenser by gravity from the measuring vessel. Supply hydrochloric acid at a rate that would not increase the temperature of the reaction blend above 45-50 °C. After loading of hydrochloric acid, stir the reaction

blend for 1 hour at 45-50 °C. After exposure, heat the tank for 8-10 hours to 250-260 °C, and the temperature of the reaction blend to 230-235 °C. At this temperature and stirring, allow to stand the reaction blend for 6 hours, after which the reaction blend is cooled spontaneously to150-155 °C.

*Step "Dissolution"*

Load dimethylformamide into the tank and the temperature of the reaction blend is reduced to 80-85 °C, then load absolute ethyl alcohol and heat the reaction blend in the tank to 130-135 °C, mix at this temperature until the filter cake is completely dissolved with reflux condenser connected. After the filter cake is completely dissolved, cool the blend in the tank spontaneously to 80-100 °C.

*Step "Recovery of naphazoline"*

Discharge naphazoline into a dry, clean and nitrogen blow-through air tight tank, in which the blend is self-cooled to 45-50 °C, after which the blend is cooled to 5-10 °C and stir at a given temperature for 6 hours. After crystallization, discharge the reaction blend from the tank into a centrifuge and filter. Wash the paste with a mixture of dimethylformamide - absolute ethyl alcohol, which is thereupon discharged into a weighed dry and clean container.

*Step "Processing of naphazoline with charcoal"*

Load naphazoline from the previous step, tap water and activated charcoal manually into a clean, dry and air tight tank. Heat the reaction blend in the tank with stirring to 80-90 °C. Hold and mix at a given temperature for 30 min. After holding, discharge the reaction blend from the tank with compressed air on the suction filter and filter.

*Step "Production of naphazoline base"*

Add 40% sodium hydroxide to the resultant filtrate. Cool the blend in the tank to 20-25 °C and stir for 1 hour at this temperature. After holding, discharge the reaction blend from the tank with compressed air on the suction filter and filter. Rinse the basis on the suction filter with water to neutral reaction. Load the product from the suction filter into a pre-weighed, dry container and weigh.

*Step "Processing of naphazoline base with charcoal"*

Load the tank with purified water and heat to 40-45 °C, then load the naphazoline base and allow to stand while stirring at a given temperature for 15-20 minutes. After exposure, load nitric acid to constant pH of 1-2, activated charcoal and heat the blend to 80-90 °C and allow to stand for 30 minutes. After holding, discharge the reaction blend from the tank with compressed air on the suction filter and filter, taking the filtrate into a clean, dry and airtight tank.

*Production of crude naphazoline nitrate*

Cool the resulting reaction blend while stirring to 18-20 °C and allow to stand for 2 hours. Discharge the reaction blend from the tank to the suction filter and filter, receiving the mother liquor in the accumulation tank. Rinse the product on the suction filter with pre-cooled purified water. Discharge the obtained crude naphazoline paste into a pre-weighed, dry, clean container and weigh on scales. Process the product with activated charcoal as in the previous steps.

*Production of naphazoline nitrate*

Cool the resulting blend after treatment with charcoal with stirring in the tank to 18-20 °C and allow to stand for 1 hour. Discharge the reaction blend from the tank to the suction filter and filter, taking the mother liquor in the accumulation tank. Rinse the product paste on the suction filter with pre-cooled purified water. Discharge the product from the suction filter into a pre-weighed, dry, clean container and weigh on the balances. Dry the obtained substance of naphazoline nitrate, sieve, and transfer to the packaging step.

4.2.2 Description of manufacturing process for naphazoline hydrochloride (Technology 2)

*Production of crude naphazoline hydrochloride*

1,2,4-Trichlorobenzene, ethylenediamine and ethylenediamine dihydrochloride are loaded into the tank, the mixture is blended. The reaction blend is heated to a specified temperature and held. The suspension of 1-naphthaleneacetic acidin trichlorobenzene is added to the reaction blend. Condensation is performed distilling azeotrope from the reaction blend with trichlorobenzene. After completion of the reaction, the reaction blend is cooled, isopropyl alcohol is added, the blend is held while boiling, cooled and filtered. The

filter cake is blended with purified water, heated, and the hot solution is filtered. After cooling, crystalls of pryvine are centrifuged and washed with isopropyl alcohol.

*Production of naphazoline hydrochloride*

The substance produced in the previous stage, purified water and activated charcoal are loaded into the tank. The mixture is heated to a specified temperature and held. Then, the reaction blend is filtered to separate from charcoal, cooled and held. The formed filter cake is filtered and washed with water. Load the obtained substance and purified water into the tank. Heat the blend to a given temperature and allow to stand. Cool the reaction blend and allow to stand. Filter the filter cake which formed, and wash with water. Dry, sieve the obtained substance and transfer to the packaging step.

4.2.3 Description of manufacturing process for naphazoline nitrate (Technology 2)

*Step "Condensing"*

1,2,4-Trichlorobenzene, ethylenediamine and ethylenediamine dihydrochloride are loaded into the tank, the mixture is blended. The reaction blend is heated to a specified temperature and held. The suspension of 1-naphthaleneacetic acid in trichlorobenzene is added to the reaction blend. Condensation is performed distilling azeotrope from the reaction blend with trichlorobenzene. After completion of the reaction, the reaction blend is cooled, isopropyl alcohol is added, the blend is held while boiling, cooled and filtered. The filter cake is blended with purified water, heated, and the hot solution is filtered. After cooling, crystalls of pryvine are centrifuged and washed with isopropyl alcohol.

*Production of crude naphazoline nitrate*

Pryvine obtained in the previous stage and isopropyl alcohol are loaded into the tank, ethanolamine is added and mixed while heating. The resulting solution is filtered. Nitric acid is added to the filtrate. The resulting solution is held while mixing until filter cake is settled, and is cooled. After cooling, the crystals of crude naphthyzin are filtered and washed with isopropyl alcohol. The resulting crystals are dried. Crude naphazoline is produced.

*Production of naphazoline*

The substance produced in the previous stage, purified water and activated charcoal are loaded into the tank. The mixture is heated to a specified temperature and held. Then, the reaction blend is filtered to separate from charcoal, cooled and held. The formed filter cake is filtered and washed with water.

The resulting substance is dried, sieved and transferred for the packaging stage.

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