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SOLVENTS IN THE INDUSTRIAL SYNTHESIS OF NAPHAZOLINE NITRATE: IMPLEMENTATION OF THE PRINCIPLES OF "GREEN CHEMISTRY" AND ANALYSIS

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The aim: *implementation of the principles of green chemistry by regenerating the synthesis solvent 1,2,4-trichlorobenzene and reusing it during the synthesis of the Naphazoline nitrate substance. Study of the influence of the regenerated solvent on the quality of the final product by controlling analytical quality parameters. Development of a method for the quantitative determination and validation of synthesis solvents in a substance.*
Materials and methods: *samples of the substance were synthesized according to the optimized proprietary technology of Farmak JSC. The obtained batches of fresh and regenerated 1,2,4-trichlorobenzene were analyzed according to the monograph of the European Pharmacopoeia on Naphazoline nitrate 0147.*
Results*: the possibility of using regenerated 1,2,4-trichlorobenzene for the synthesis of the substance Naphazoline nitrate has been proven. It is shown that the regenerated solvent does not have a negative effect on the profile of impurities and the polymorphic form of the substance. Analytical quality parameters met the requirements of the internal specification and the requirements of the European Pharmacopoeia monograph. The developed and validated method of quantitative determination of synthesis solvents makes it possible to determine them at the required level.*
Conclusions*: the introduction of regenerated 1,2,4-trichlorobenzene into the synthesis scheme made it possible to significantly reduce the amount of waste per 1 kg of product, which in turn significantly reduced the negative impact on the environment. Analytical quality parameters for regenerated 1,2,4-trichlorobenzene meet the requirements of the internal specification. Industrial series obtained on the regenerated solvent meet the requirements of the monograph of the European Pharmacopoeia. The polymorphic form of the substance batches manufactured on regenerated 1,2,4-trichlorobenzene corresponds to the polymorphic form of the substance batches manufactured on the fresh solvent. The obtained results on the influence of the regenerated solvent on the profile of impurities in the finished substance show the similarity of the profile of the series manufactured on both solvents. According to the requirements of ICH Q3C Impurities: Guideline for residual solvents, a method for quantitative determination of the residual content of 1,2,4-trichlorobenzene in the final product by gas chromatography was developed and validated. The absence of synthesis solvents at the limit of detection is shown*
Keywords*: naphazoline nitrate, industrial synthesis, 1,2,4-trichlorobenzene, green chemistry, waste, impurity profile, gas chromatography, ethanolamine, 2-propanol, regeneration*

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1. Introduction

The manufacture of chemicals has the potential to generate significant amounts of waste by-products and pollutants, such as contaminated solvents, depleted reagents, and air pollutants [1]. Green chemistry is a production concept aimed at the efficient use of raw materials and resources, avoidance of toxic and dangerous reagents, and reduction of waste and by-products, including through their processing and regeneration with subsequent reuse [2]. With the increasing emphasis on green chemistry recently, pharmaceutical process chemists have concentrated their focus and creative energies toward minimizing the environmental impact of their craft. Solvents have received much attention under the remit of green chemistry. The selection of solvents for the synthesis of pharmaceuticals is critical on a number of levels [1].

Solvents are widely recognized to be of great environmental concern. The reduction of their use is one of the most important aims of green chemistry. In addition to this, the appropriate selection of solvent for a process can greatly improve the sustainability of a chemical production process [3].

The pharmaceutical industry is one of the major consumers of solvents for its active pharmaceutical ingredient (API) purification and refinement processes [4, 5]. The continuous growth in demand for solvents has inadvertently increased waste generation. For example, approximately 25–100 kg of waste is generated per kg of a product by the pharmaceutical industry. The forefront of this generation issue is the inefficiencies associated with industrial processes and the poor solvent selection criteria [6]. Undeniably, there is excessive use

of solvents to achieve desired purities and quantities of products. Therefore, the increasing trends in waste solvent generation have necessitated process intensification methods such as solvent recovery to curb the growing environmental, health, and safety concerns [7].

Offsite and onsite disposals are not energy-intensive, but the waste solvents are prone to leakage into the nearby water supply and land, contaminating the affected resources [8]. Thus, solvent recovery presents a better mitigation option than conventional disposal methods due to lower implementation costs and fewer emissions [9, 10].

Solvent recovery is defined as the process of extracting useful materials from waste or by-product solvents during the manufacturing process. These recovered chemicals can then be reused in the manufacturing process, which greatly reduces the need for new solvents and decreases waste significantly [11].

Recovering waste solvent for reuse presents an excellent alternative to improving the greenness of industrial processes. Implementing solvent recovery practices in the chemical industry is necessary, given the increasing focus on sustainability to promote a circular economy. However, the systematic design of recovery processes is a daunting task due to the complexities associated with waste stream composition, techno-economic analysis, and environmental assessment [7].

The selection of solvent recovery technology does not necessarily need to adhere to conventional methods. The theory of process intensification aims to optimize the existing processes by condensing multiple methods into fewer units or steps without sacrificing the efficiencies or changing the driving forces. Yadav et al. designed an intensified process to extract algae oil and convert the biomass to biodiesel using CO_2 and methanol. This intensification was done by premixing the algae extract stream with methanol solvent before sending the material in for transesterification. Supercritical CO_2 was added [12].

Many companies such as AstraZeneca, Pfizer, GSK, and Sanofi have taken the necessary steps to publish their guides on solvent selection [13–15]. The latest solvent selection guide has been designed with inspiration from other companies, including a database of 272 known, new, and green solvents typically used in processes. Solvents were grouped and differentiated based on chemical functionality and categorized into different solvent classes such as acid, alcohol, alkene, ester, hydrocarbon, amine, and aromatics. In addition, seven SHE categories from AstraZeneca, namely, health, air impact, water impact, life cycle analysis, flammability, static potential, and VOC (volatile organic carbon) potentials, were included. Classifying the solvent system during the design phase or recovery phase provides a better understanding of the physical properties and chemical interactions that may cause a change in density, affinity toward a specific substance, or solution stability. Solvents can thus be analyzed and compared based on their physical and chemical properties, safety, health, and environmental impacts to suit the process needs [16].

Chea et al. (2020) developed a framework for waste solvent recovery using a superstructure-based optimization approach (Chea et al., 2020). They evaluated the techno-economic feasibility of the framework by using two case studies of varying complexities and formulated their recovery framework model as a mixed-integer non-linear programming problem (MINLP) [17].

Ooi et al. (2019) proposed a Computer-Aided Molecular Design (CAMD) framework that simultaneously factors solute extraction and solvent recovery. They aim to design solvents that can be recovered with low economics, environmental impacts, and health hazards. Their framework can systematically predict, estimate, and design solvents in separation processes by analyzing their molecular properties. Their approach follows techniques similar to Chea et al.'s (2020), which screens for existing separation technologies, determines the best recovery pathway combinations, identifies crucial parameters, and determines costs [18].

Synthesis of naphazoline nitrate was implemented at JSC Farmak many years ago. "Green chemistry" is actively implemented now in manufacturing. So nowadays, there are tasks to optimize the conditions for the synthesis of Naphazoline nitrate in order to reduce the impact of reagents on the environment and production personnel. Previously, we optimized the conditions for the synthesis and purification of naphazoline nitrate and naphazoline hydrochloride, taking into account the principles of green chemistry. To ensure an acceptable yield and quality parameters of the substance, the use of such solvents as 2-propanol and 1,2,4-trichlorobenzene (1,2,4-TCB) has been experimentally justified. Although 2-propanol is a toxicity Class 3 solvent (according to ICH Guideline Q3C classification), widely used in the synthesis of pharmaceutical substances, 1,2,4-TCB can be quite toxic.

The EPA has stated that 1,2,4-trichlorobenzene is not classifiable as to human carcinogenicity. However, this was based on studies prior to 1990, and newer information has not been evaluated [19].

Trichlorobenzenes have primarily been used as solvents and chemical intermediates. In the past, mixed isomers of trichlorobenzene had been used for termite control in soil; however, there are currently no registered uses of trichlorobenzenes as a pesticide [20]. 1,2,4-Trichlorobenzene is currently used in solvents in chemical reactions and to dissolve special materials such as oils, waxes, resins, greases, and rubber. It is used as a dye carrier and in the production of dyes [21]. Other uses are associated with textile auxiliaries and as a dielectric liquid (a substance that conducts little or no electricity). In Europe, 1,2,4-trichlorobenzene, has also been used in anti-corrosives paint or rust removing agents and as an additive in polish and maintenance products; however, most of these uses have been discontinued. Other former uses of trichlorobenzene include the use of the substance in degreasing agents, septic tanks and drain cleaners, wood preservatives, and abrasive formulations [22].

Trichlorobenzenes can be released into the environment from their production and used as solvents, dye carriers and chemical intermediates. They are also formed unintentionally during the combustion of organic

materials when chlorine is present and from the degradation of higher chlorinated benzenes, such as tetrachlorobenzene, pentachlorobenzene, and hexachlorobenzene, or the degradation of the pesticide, lindane (γ-hexachlorocyclohexane). Since trichlorobenzenes are minor impurities in mono- and dichlorobenzene, their production and use may also result in the release of trichlorobenzenes into the environment [21].

Estimated releases of 7,110 pounds (~3.2 metric tons) of 1,2,4-trichlorobenzene to the atmosphere from 14 domestic manufacturing and processing facilities in 2012, accounted for about 82 % of the estimated total environmental releases from facilities required to report to the TRI [23].

EPA has designated 1,2,4-trichlorobenzene as a hazardous air pollutant (HAP) under the Clean Air Act (CAA) [24].

Unfortunately, the replacement of 1,2,4-TCB in the synthesis of naphazoline nitrate with other solvents leads to either a decrease in yield or a deterioration in the characteristics of the substance. The only option to reduce the amount of 1,2,4-TCB used in the production process and which may enter the environment is its regeneration.

Therefore, our task was to study the possibility of using regenerated 1,2,4-TCB in the synthesis of naphazoline nitrate, namely the influence of the regenerated solvent on quality parameters of the final substance produced on regenerated 1,2,4-TCB. For this, it is necessary to check the particle size, polymorphism, impurity profile and other analytical parameters, as well as to develop and validate the method of determining residual organic solvents for the received product. It was also important to show the efficiency of using regenerated 1,2,4-TCB by comparing the amount of generated waste per 1 kg of product.

2. Research planning (methodology)

1. First of all, it is necessary to carry out the regeneration of 1,2,4-TCB in industrial conditions. After regeneration, it is necessary to confirm the quality of the obtained regenerated solvent in accordance with the developed internal specification (ISP) and compare it with the quality of fresh 1,2,4-TCB.

2. After proving the conformity of the quality of the regenerated solvent, it is necessary to prove its stability for at least 2 months since it is with this periodicity that the substance is worked up in the workshop. However, the study design provides a 6-month stability control for the possibility of its use over a longer period of time, thereby preventing its further disposal if not used for 2 months.

Stability studies are carried out under two storage conditions: long-term (25±2) °C/(60±5) % RH and accelerated (40±2) °C/(75±5) % RH with the following time interval: 0 point, 1 month, 2 months and 6 months. The following parameters are controlled: appearance, identification, relative density and water. According to the obtained results, a decision will be made about the shelf life of regenerated 1,2,4-TCB and the possibility of its use during this period for the development of commercial batches of the Naphazoline nitrate substance.

3. The next stage was the determination of the possible influence of the use of regenerated 1,2,4-TCB on the quality parameters of naphazoline nitrate in comparison with the use of fresh solvent. The research design included the following stages:

– a comparative study of the crystal structure. With the help of X-ray phase analysis, diffractograms of the substance synthesized using fresh and regenerated 1,2,4-TCB were obtained and compared to understand the preservation of the crystalline structure of the substance.

It's well-known that beyond the obvious function of solvents to allow compounds to react efficiently in solution, they may further influence the particle size of the API and impact manufacturing costs by leading to difficult isolations or requiring milling. Solvents often influence the crystal form of the API, which directly determines dissolution rates, formulation, and bioavailability. The utilization of solvents also brings the disadvantage of solvent incorporation into the API [1];

– comparison of the quality of API batches manufactured on fresh and regenerated 1,2,4-TCB and their compliance with the requirements of the Ph. Eur. monograph for Naphazoline nitrate;

– a comparative study of the profile of impurities. Since in regenerated 1,2,4-TCB, as well as in fresh, according to ISP, impurities are not controlled, it was important to compare the profiles of impurities of batches obtained on fresh and regenerated 1,2,4-TCB to confirm the absence of changes in the profile of impurities. A change in the profile of impurities may occur when the synthesis regulation is changed. This, in turn, can significantly affect the pharmacological action and toxicity of API. Also, due to the lack of a parameter of related substances according to the ISP in regenerated and fresh 1,2,4-TCB, we additionally planned studies comparing the profile of impurities in substances synthesized using fresh and regenerated 1,2,4-TCB. To determine the effect on the profile of impurities, the determination was carried out by the method of liquid chromatography according to the methodology given in Ph. Eur. [25];

– development, control and validation of the control method of solvents in the finished API. In order to prove the absence of 1,2,4-TCB and other synthesis solvents (ethanolamine, 2-propanol and 1,2,4-TCB), it was important to develop and validate a methodology for the quantitative determination of these solvents in the final API;

– comparison of the amount of waste when using fresh and regenerated 1,2,4-TCB for the synthesis of API.

3. Materials and methods

This study was conducted from 2014 to 2022. 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), 1-naphthaleneacetic acid with a purity 99.9 % (Sigma Aldrich), Naphazoline nitrate CRS, naphazoline impurity A CRS, 2-propanol with a purity 99.9 % (Sigma Aldrich), N,N- dimethylformamide with a purity 99.9 % (Sigma Aldrich), *ethanol* (96 per cent) *R* (SE «Ukrspyrt»), 1,2,4-trichlorobenzene with a pu-

rity 99.97 % (Sigma Aldrich), ethanolamine with a purity 99.8 % (Sigma Aldrich), 1-naphthaleneacetic acid (Shenzhen Nexconn Pharmatechs Ltd, 99.0 %), ethylenediamine (Nouryon Functional Chemicals AB, 99.6 %), ethylenediamine dihydrochloride (Merck KGaA, 100.0 %), 1,2,4-trichlorobenzene (Shimagchem Corporation).

To analyze the quality of the substances used: titrator (Mettler Toledo, T 70), infrared Fourier spectrometer (Bruker, Alpha), liquid (Agilent Technologies, 1260) and gas chromatographs (Agilent Technologies, 7890 B), analytical balance (Mettler Toledo, MS104S), pH-meter (Mettler Toledo, Seven Compact S220), chromatographic column Zorbax-C8 (Agilent Technologies, 250 mm, 4.6 mm, 5 mkm), quartz capillary column PTA-5 (Agilent Technologies), density meter (Mettler Toledo, DM 40), refractometer (Mettler Toledo, RX 40), drying oven (Pol-Eko-Aparatura SP. J., SLW53 STD).

An X-ray powder diffraction pattern of the little compound was registered using a Siemens D500 powder diffractometer (Cu Kα radiation, Bragg-Brentano geometry, curved graphite monochromator on the counter arm, $4<2\theta<60°$, $D2\theta=0.02°$).

Reagents and titrated solutions for analysis were prepared according to the requirements of the European Pharmacopoeia (Ph. Eur.).

The analysis was performed according to the monographs of the European Pharmacopoeia on the substance (0147 for Naphazoline nitrate) [25].

3. 1. Regeneration of 1,2,4-TCB

During the synthesis of Naphazoline nitrate at JSC Farmak, the technological process consists of the following consecutive stages of synthesis:

– obtaining of 2-(α-naphthylmethyl)imidazoline chlorohydrate (naphazoline hydrochloride);

– obtaining of naphazoline nitrate, crude;

– obtaining of naphazoline nitrate, substance.

The first stage consists of the condensation reaction of 1-naphthaleneacetic acid with ethylenediamine hydrochloride, which is carried out during the distillation of an azeotropic mixture of 1,2,4-TCB and water, which is formed during the reaction.

Crude naphazoline hydrochloride is crystallized from an aqueous solution of 2-propanol, in which 1,2,4-TCB is well soluble, which ensures the removal of its residual amounts from the obtained product.

Production of technical naphazoline nitrate is carried out using ethanolamine as a base and nitric acid. The remaining unreacted ethanolamine is neutralized with an excess of nitric acid, resulting in the formation of a well-soluble salt in the course of this reaction, which ensures the absence of ethanolamine in the final product.

Regeneration of 1,2,4-TCB is performed as described below. The mother liquor from filtration of the crude naphazoline hydrochloride feed from the condensation stage and the distilled aqueous 1,2,4-TCB are placed in a glass reactor equipped with a stirrer, thermometer and straight condenser. The mixture is heated with stirring at atmospheric pressure to distill the 1,2,4-TCB. The first fraction of an aqueous solution of ethylenediamine with impurities of 1,2,4-TCB (boiling point up to 210 °C) was sent for waste disposal. The fraction with a boiling point range 210 °C to 218 °C (which is exactly regenerated 1,2,4-TCB) is collected and may be used in the condensation stage.

3. 2. Validation of the residual solvent control method

According to the requirements of the ICH Q3C Impurities: Guideline For Residual Solvents, testing should be performed for residual solvents when production or purification processes are known to result in the presence of such solvents. It is only necessary to test for solvents that are used or produced in the manufacture or purification of drug substances, excipients, or drug products. Although manufacturers may choose to test the drug product, a cumulative method may be used to calculate the residual solvent levels in the drug product from the levels in the ingredients used to produce the drug product [26].

The analysis of residual solvents was carried out using gas chromatography.

2-propanol belongs to the 3rd class of organic solvents, and the established limit is not more than 5000 ppm (0.5 %). For 1,2,4-TCB and ethanolamine, the established limit is not more than 360 ppm (0.036 %) and 500 ppm (0.05 %), respectively.

The following characteristics were considered to confirm the capability of the analytical procedure: specificity, linearity, accuracy, precision, range, limit of detection and limit of quantitation.

The standard solution and test solution were analyzed using the GC technique using the following conditions (Table 1).

Table 1

Chromatographic conditions

Parameters	Descriptions
Column	PTA-5
Column size	30 m×0.53 mm×3.00 μm
Carrier gas	Helium for chromatography R
Injector temperature	220
Detector temperature	240
Split ratio	1:5
Flow	3.5 ml/min
Temperature program	120 °C initial temperature, holding for 5 min, rate of 20 °C/min to 200 °C and holing for 3 min
Injection volume	1 μl
Concentration of the test solution	200 mg/ml in dimethylformamide
Concentration of the reference solution	1 mg/ml of 2-propanol, 0.2 mg/ml of ethanolamine, 0.072 mg/ml of 1,2,4-trichlorobenzene

The chromatographic system is considered suitable if:

– the relative standard deviation calculated from the areas of the 2-propanol, ethanolamine and 1,2,4-trichlorobenzene peaks obtained from the reference solution should not exceed 15 %;

– there are no peaks on the chromatogram of dimethylformamide, which coincide with the retention time of the peaks of 2-propanol, ethanolamine and 1,2,4-TCB.

3. 3. Preparation of model solutions for studying linearity

Reference solution for linearity (*RS*).

100 mg/ml of 2-propanol, 20 mg/ml of ethanolamine, 7.2 mg/ml of 1,2,4-trichlorobenzene. Dissolve aliquots of the RS according to Table 2 in dimethylformamide and dilute to the volume according to Table 2 with the same solvent.

4. Research results and their discussion

4. 1. Comparison of the quality of regenerated 1,2,4-TCB with the quality of fresh 1,2,4-TCB

To confirm the possibility of using the regenerated solvent in the synthesis, at the first stage, a comparative study of fresh and regenerated 1,2,4-TCB was carried out for the conformity of the quality parameters of regenerated 1,2,4-TCB according to ISP.

The internal quality control specification of 1,2,4-TCB used in the synthesis of naphazoline nitrate includes such parameters as appearance, identification, relative density and water. Below is a comparative table (Table 3) of data quality parameters for fresh and regenerated 1,2,4-TCB.

4. 2. Study of the stability of regenerated 1,2,4-TCB

For the possibility of further use of regenerated 1,2,4-TCB for the synthesis of API, its stability was investigated according to long-term testing (25±2) °C/(60±5) % RH and accelerated testing (40±2) °C/(75±5) % RH. The results of the study of stability in long-term testing and accelerated testing are given in Table 4.

Table 2

Model solutions for linearity study

Solution	Concentration level, %	Theoretically calculated concentration of solvents, mg/ml			Aliquot RS, ml	Volume, ml
		ethanolamine	1,2,4-TCB	2-propanol		
L1	20	0.04	0.014	0.2	0.2	100.0
L2	40	0.08	0.029	0.4	0.4	100.0
L3	60	0.12	0.043	0.6	0.6	100.0
L4	80	0.16	0.058	0.8	0.8	100.0
L5	100	0.20	0.072	1.0	1.0	100.0
L6	120	0.24	0.086	1.2	1.2	100.0

Table 3

Comparison table for fresh and regenerated 1,2,4-TCB according to the requirements of the ISP

Test	Specification	Test methods	Results for fresh 1,2,4-TCB	Results for regenerated 1,2,4-TCB
Appearance	At a temperature 17 °C clear, colourless liquid	Visual examination	Complies	Complies
Identification	1. Relative density (see test)	Ph. Eur.*, 2.2.5	1.446	1.454
	2. Refractive index: 1.571–1.573	Ph. Eur.*, 2.2.6	1.571	1.572
Relative density	1.443 to 1.457	Ph. Eur.*, 2.2.5	1.446	1.454
Water	Not more than 0.1 %	Ph. Eur.*, 2.5.12	0.04 %	0.02 %

Table 4

Stability of regenerated 1,2,4-TCB

Batch 30519	Long-term testing				Accelerated testing			
Storage conditions	(25±2) °C/(60±5) % RH				(40±2) °C/(75±5) % RH			
	Months							
Parameter	0	1	2	6	0	1	2	6
Appearance	Complies				Complies			
Identification:								
relative density	1.454	1.453	1.453	1.454	1.454	1.452	1.452	1.453
refractive index	1.572	1.571	1.572	1.571	1.572	1.572	1.571	1.571
Relative density	Complies				Complies			
Water	0.02	0.03	0.02	0.03	0.02	0.02	0.03	0.03

4. 3. Study of the effect of regenerated 1,2,4-TCB on the quality of the final API and comparison with the quality of API obtained using fresh solvent

4. 3. 1. Polymorphic form comparison

It is known that changing the solvent at any stage of the synthesis or purification of the substance can lead to obtaining another polymorphic modification of the target product and, in turn, can cause changes in the bioavailability of APIs. In view of this, the polymorphism of substances attracts a lot of attention from scientists, and when making changes to the synthetic process, the similarity of the crystal structure of substances is a necessary condition for the similarity of pharmacokinetics. Considering the above, the first objectives of the study were to determine and compare the polymorphic modifications of substances obtained on fresh and regenerated 1,2,4-TCB. Literature data for comparisons found in the Cambridge Crystallographic Data Center were used for the analysis. Version 5.42, updated in November 2020 [27]. Single-crystal data and the results of powder X-ray diffraction calculations are given in Table 5.

The obtained X-ray diffraction patterns are presented in Fig. 1.

4. 3. 2. Comparison of the quality of API manufactured on two solvents

The next stage was a comparison of the quality parameters of substances manufactured on fresh (batches 61218, 10119, 20319) and regenerated 1,2,4-TCB (batches 30519, 10121, 20721). To evaluate the parameters, they were compared with the requirements of the Ph. Eur. monograph on Naphazoline nitrate. The results of the batch analysis are given in Table 6.

Table 5

Single-crystal data and calculation results of X-ray powder diffraction patterns

Sample	*a*, Å	*b*, Å	*c*, Å	α, β, γ, °	Space group	Mass, %	Average crystallite size, nm
Single-crystal data							
Naphazoline	12.028(1)	14.408(2)	15.894(2)	90, 90, 90	Pbca	CCDC=KORYOF	
Samples tested							
F310_z194	12.0389(11)	14.4484(20)	15.8793(14)	90, 90, 90	Pbca	100(2)	27
F311_z195	12.0335(8)	14.4826(15)	15.8800(10)	90, 90, 90	Pbca	100(6)	26
F312_z196	12.0305(11)	14.4579(20)	15.8662(13)	90, 90, 90	Pbca	100(2)	31

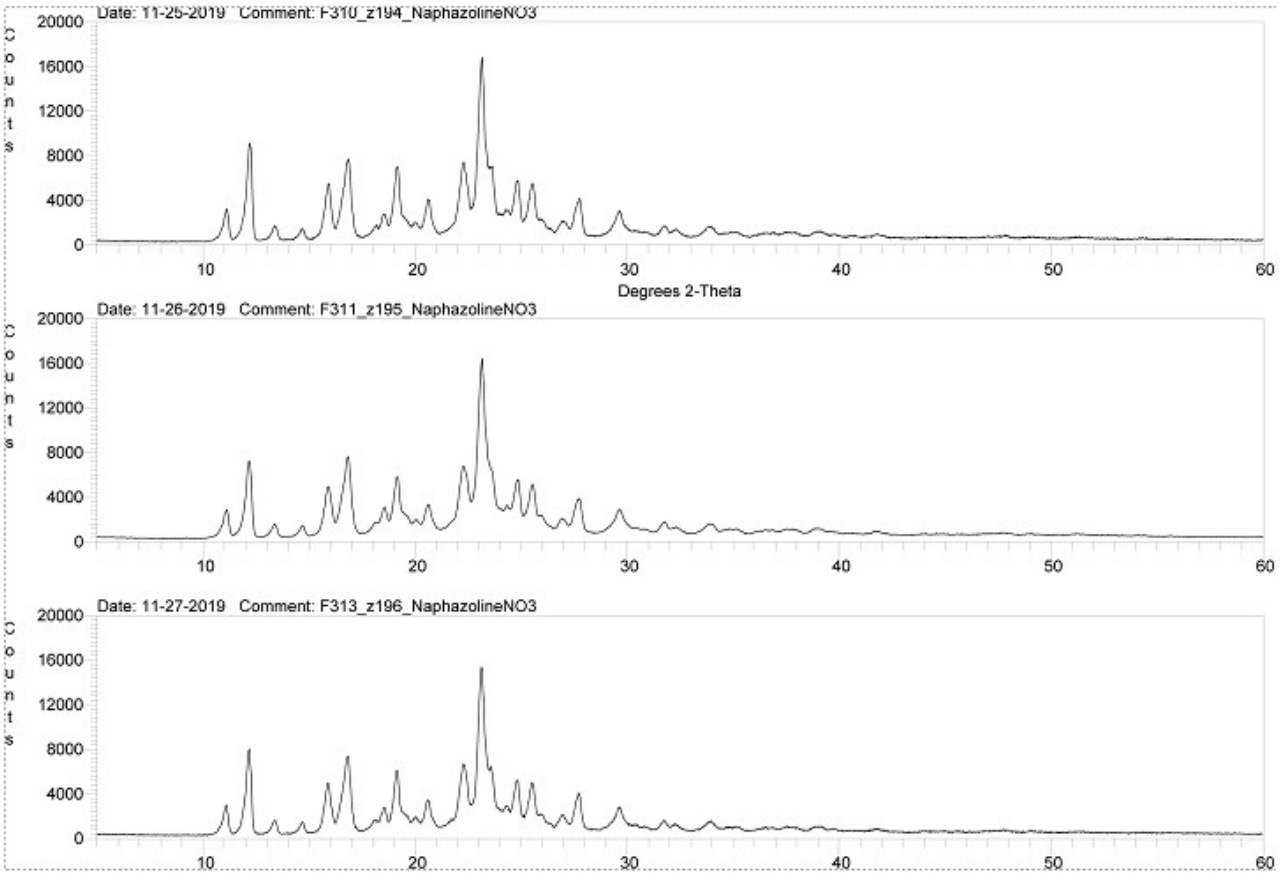


Fig. 1. Diffractograms of the substance: F310_z194 – obtained from fresh 1,2,4-TCB; F311_z195 and F312_z196 from regenerated 1,2,4-TCB

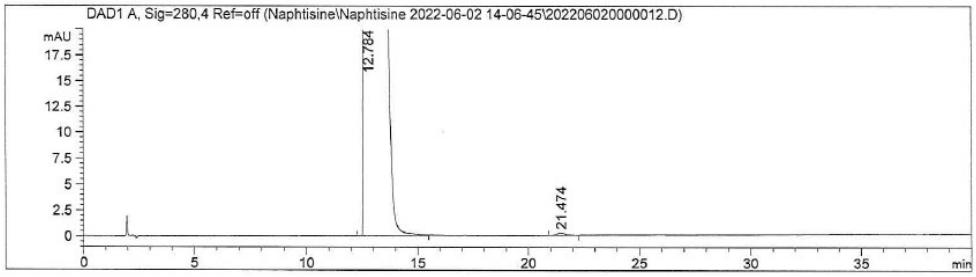
Table 6

The comparison table for batches of Naphazoline nitrate produced on fresh and regenerated 1,2,4-trichlorobenzene

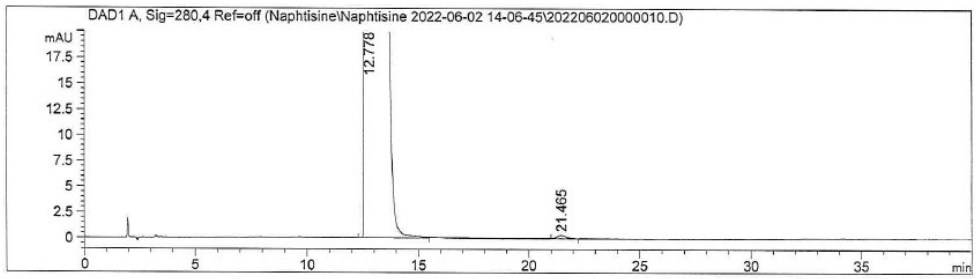
Test	Specifications	Results produced with fresh 1,2,4-trichlorobenzene			Results produced with regenerated 1,2,4-trichlorobenzene		
		b. 61218	b. 10119	b. 20319	b. 30519	b. 10121	b.20721
Appearance	White or almost white, crystalline powder	conforms	conforms	conforms	conforms	conforms	conforms
Solubility	Sparingly soluble in *water R*, soluble in *ethanol* (96 per cent) R	conforms	conforms	conforms	conforms	conforms	conforms
Identification	IR spectrum	conforms	conforms	conforms	conforms	conforms	conforms
Clarity of solution	Solution S is clear	conforms	conforms	conforms	conforms	conforms	conforms
Degree of colouration	Solution S is colourless	conforms	conforms	conforms	conforms	conforms	conforms
pH	5.0 to 6.5	6.2	6.4	6.3	5.8	6.3	6.3
Related substances:							
naphazoline impurity A	NMT 0.5 %	BDL	BDL	BDL	BDL	BDL	BDL
any unspecified impurity	NMT 0.10 %	BDL	BDL	BDL	BDL	BDL	BDL
total of impurities	NMT 1.0 %	BDL	BDL	BDL	BDL	BDL	BDL
1,2,4-TCB	<0.036 %	BDL	BDL	BDL	BDL	BDL	BDL
Ethanolamine	<0.05 %	BDL	BDL	BDL	BDL	BDL	BDL
2-propanol	<0.5 %	BDL	BDL	BDL	BDL	BDL	BDL
Chlorides	NMT 0.033 %	conforms	conforms	conforms	conforms	conforms	conforms
Loss on drying	NMT 0.5 %	0.3 %	0.4 %	0.2 %	0.2 %	0.2 %	0.3 %
Sulfated ash	NMT 0.1 %	less than 0.1 %	less than 0.1 %	less than 0.1 %	less than 0.1 %	less than 0.1 %	less than 0.1 %
Microbial purity	10^3 CFU/g	conforms	conforms	conforms	conforms	conforms	conforms
	10^2 CFU/g	conforms	conforms	conforms	conforms	conforms	conforms
Assay on dried substance	99.0 % to 101.0 %	99.4 %	100.6 %	99.9 %	99.8 %	100.1 %	99.9 %

4. 3. 3. Comparison of the impurities profile

In this experiment, the profiles of substances obtained using fresh and regenerated 1,2,4-TCB were studied; the results are shown in Fig. 2.



a



b

Fig. 2. Chromatograms of the analysis of impurities (Ph. Eur. method) in substances obtained using fresh (*a*) and regenerated (*b*) 1,2,4-TCB

4. 3. 4. Validation of the analytical method

Specificity. System Suitability.

Typical chromatograms obtained with the blank solution (dimethylformamide), reference solution, and test solution are provided in Fig. 3. The results of the suitability of the chromatographic system are shown in Table 7.

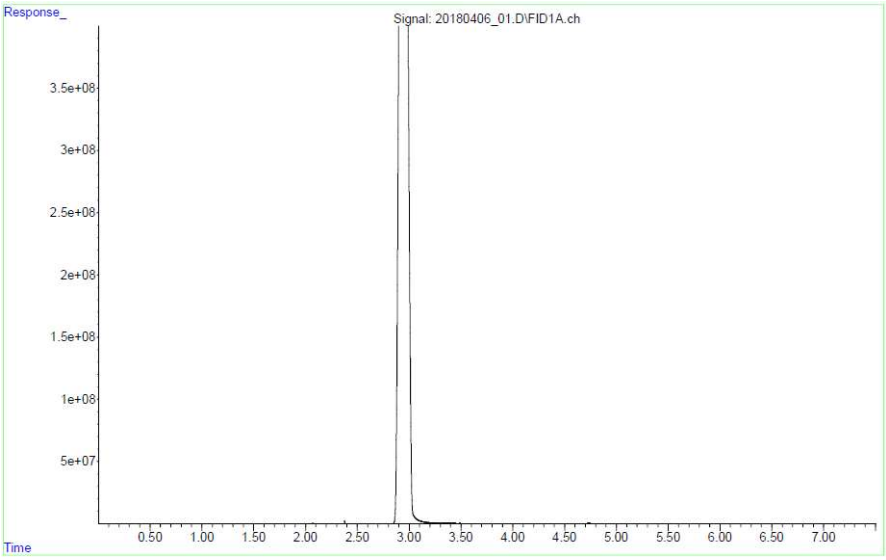
The chromatogram obtained with the blank solution did not show any peaks with the retention time similar to the retention time of the peak of 2-propanol, ethanolamine and 1,2,4-TCB.

The system suitability requirements are met.

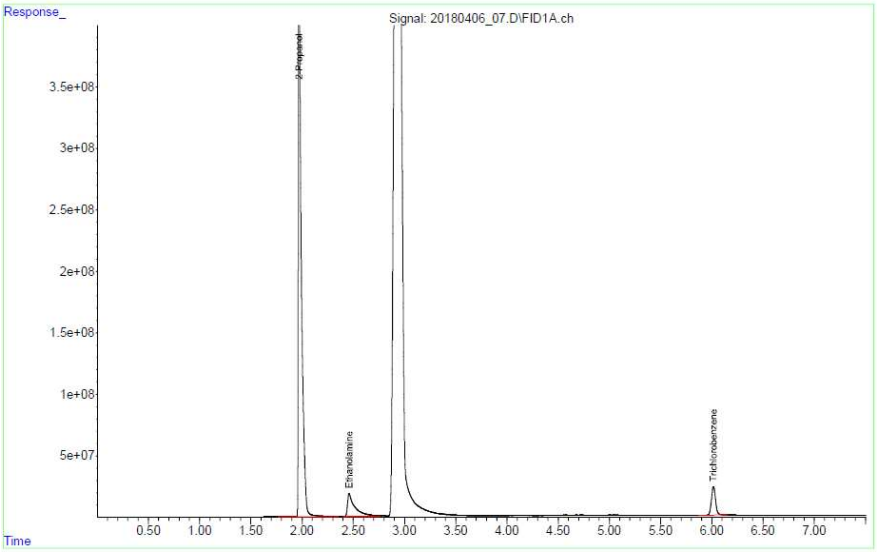
The specificity of the analytical procedure is sufficient.

Linearity and accuracy.

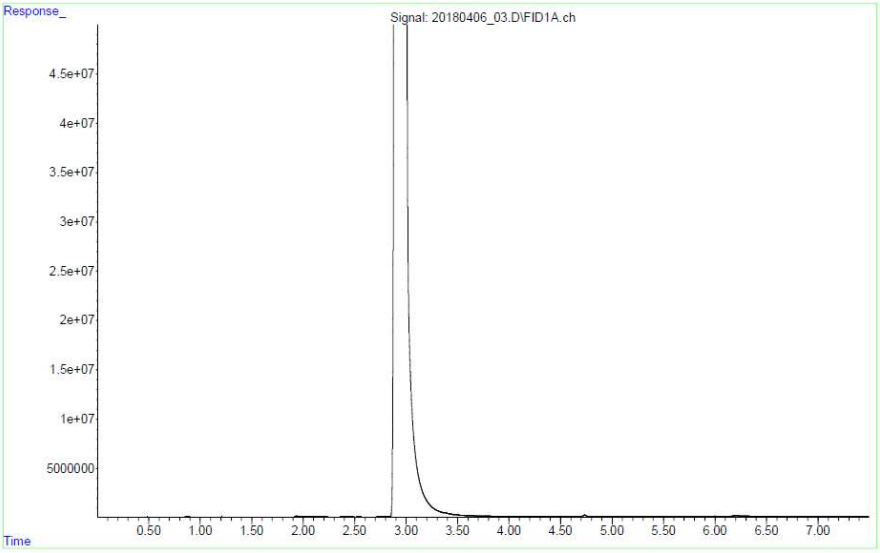
To assess the linearity, the model solutions L1–L6 (Table 2) were analyzed in the chromatographic conditions specified by the method. At least three parallel chromatograms were obtained for each solution, and the average value of the peak areas was calculated to evaluate the results. Linearity regression data, summarized in Table 8, show a good linear dependence between concentration and peak areas over a concentration range of 10–120 % for examined solvents (Fig. 4). The statistical processing for examined solvents is provided in Table 9.



a

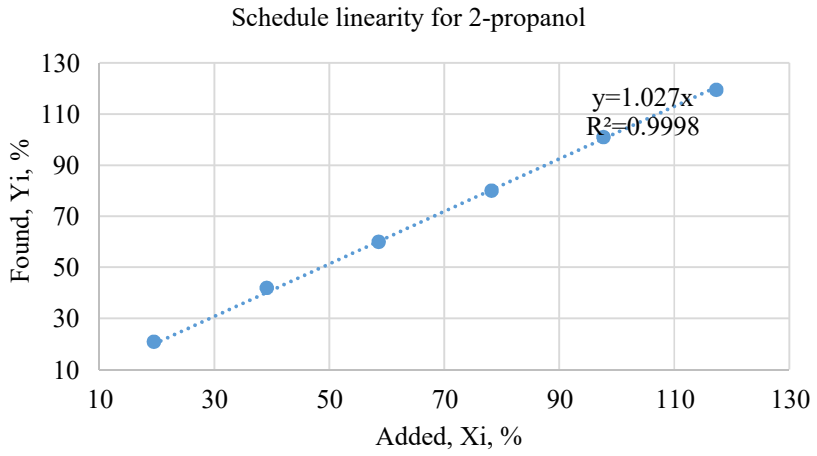


b

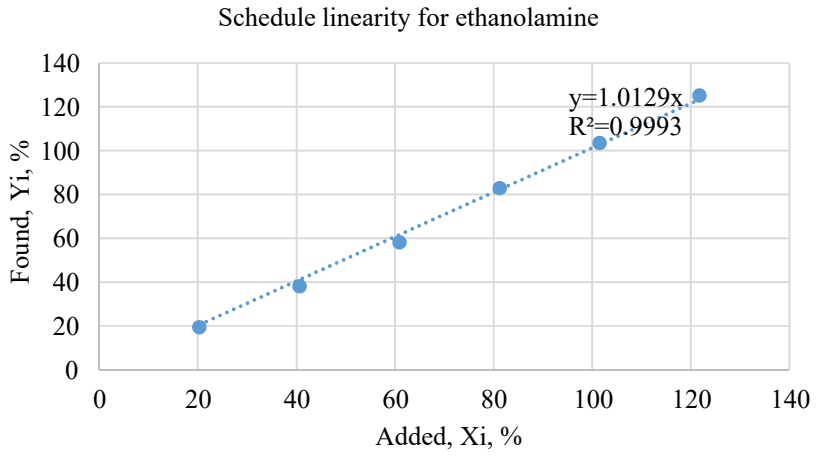


c

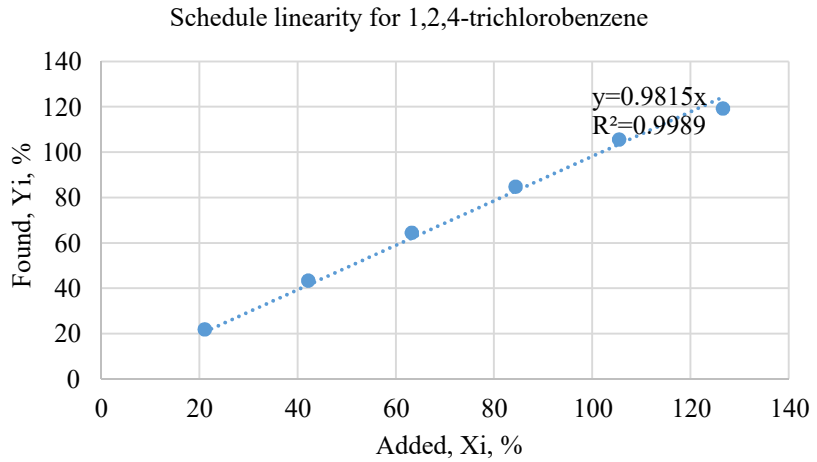
Fig. 3. Typical chromatograms of: *a* – blank solution; *b* – reference solution; *c* – the test solution



a



b



c

Fig. 4. Graph of the dependence of the analytical signal on the concentration of solvents in the model solution: *a* – 2-propanol; *b* – ethanolamine; *c* – 1,2,4-TCB

Table 7

System Suitability Test

Parameter		Criterion	Result
RSD, %	2-Propanol	≤15 %	10.77
	Ethanolamine		8.56
	1,2,4-TCB		10.44
There are no peaks on the chromatogram of dimethylformamide, which coincide with the retention time of the peaks of 2-propanol, tthanolamine and 1,2,4-TCB			Complies

Table 8

The results of determining the parameters of linearity for the determination of the solvents

Solvents	$\|a\|$	B	R	S_b	S_a	S_R	LOD, %	LOQ, %
2-Propanol	1.69	1.01	1.000	0.01	0.76	0.8	0.01	0.04
Ethanolamine	3.65	1.05	0.999	0.019	1.5	1.6	0.002	0.007
1,2,4-TCB	3.83	0.94	0.998	0.030	2.4	2.6	0.003	0.009

Table 9

The result of the analysis of 6 model solutions and their statistical processing for 2-propanol, ethanolamine and 1,2,4-TCB

Parameter	Value		
	2-propanol	ethanolamine	1,2,4-TCB
Z average, %	104.2	98.8	100.5
SD_z, %	2.67	3.95	3.34
RSD_z, %	2.57	3.99	3.33
Relative confidence interval Δz %=t(95 %, 5)*SD_z	5.38	7.95	5.28
Systematic error, $\|Z–100\|$, %	4.2	1.2	0.5
Criterion of significance of systematic error, $\Delta \leq \max \delta$ %	4.2 ≤ 5.0 %	1.2 ≤ 5.0 %	0.5 ≤ 5.0 %

4. 3. 5. The effect of regeneration of 1,2,4-TCB on the "greenness" of the synthesis method

Table 10 shows the results of the amount of waste from the synthesis of API Naphazoline nitrate using fresh and regenerated 1,2,4-TCB.

Table 10

Comparison of the amount of API synthesis waste

Technology on regenerated 1,2,4-TCB (for 1 kg of API)		Technology on fresh 1,2,4-TCB (for 1 kg of API)	
Wastes	Amount, kg	Wastes	Amount, kg
Bottoms and 1,2,4-TCB	2.3	Bottoms and 1,2,4-TCB	8.3
Mother liquor (2-propanol and impurities) and bottoms after 1,2,4-TCB distillation	14.0	Mother liquor (2-propanol and impurities) and bottoms after 1,2,4-TCB distillation	13.0
Mother liquor (water and impurities)	16.1	Mother liquor (water and impurities)	16.1
Activated charcoal paste	0.03	Activated charcoal paste	0.03
Intermediate			
1,2,4-TCB regenerated	5	n/a	
Losses		Losses	
Naphazoline nitrate, API	0.01	Naphazoline nitrate, API	0.01
Total	37.4	Total	37.4

5. Discussion of research results

Various approaches to the synthesis of naphazoline are described in the literature. For instance, according to the patent [28], the basis of naphazoline is synthesized from (1-naphthyl) acetonitrile, which is converted into imino ester by reaction with ethanol.

The «green synthesis» of obtaining naphazoline in the form of hydrochloride in patent is described [29]. The invention uses alpha-naphthylacetic acid, ethylenediamine, and acetone as raw materials to prepare the target product. The preparation method has the advantages of a simple preparation process and mild reaction conditions and avoids environmental pollution.

According to another invention, naphazoline hydrochloride was prepared by the additional reaction of methanol and 1-naphthyl acetonitrile, hetero-cyclization with ethylenediamine, and salification with concentrated hydrochloric acid [30].

Depending on the route of synthesis, namely the use of starting materials of synthesis, different solvents are used.

According to the literature review, the use of 1,2,4-TCB for the synthesis of substances was not carried out, and therefore, there are no results on regeneration and the effect of this solvent on the final quality of the obtained substance.

5. 1. Comparison of the quality of regenerated 1,2,4-TCB with fresh 1,2,4-TCB

According to the obtained data, shown in Table 3, it can be seen that the quality of regenerated 1,2,4-TCB does not differ in terms of analytical parameters from fresh and meets the requirements of the ISP. Therefore, the regeneration of the solvent does not affect its quality, and the reuse of this solvent for API synthesis is acceptable.

5. 2. Stability studies of regenerated 1,2,4-TCB

The results of the stability studies of regenerated 1,2,4-TCB under longterm and accelerated regimes show that the results obtained are within the criteria according to the ISP during the study period of 6 months and can be reused for the synthesis of API.

5. 3. Study of the effect of regenerated 1,2,4-TCB on the quality of the final API and comparison with the quality of API obtained with fresh 1,2,4,TCB

Comparison of polymorphic form.

API sample F310_z194 was manufactured on fresh 1,2,4-TCB, and samples F311_z195 and F312_z196 on regenerated 1,2,4-TCB.

The results of calculating the obtained X-ray diffraction patterns show that all samples are pure, single-phase and belong to the same polymorphic modification described in the literature (X-ray diffraction patterns presented in Fig. 1). Dispersion (average crystallite size in the Table *5*) is almost the same for all samples and approaches nanocrystalline. Therefore, the use of regenerated 1,2,4-TCB does not have a negative effect on the polymorphic form of the final API.

Comparison of the quality of API manufactured on two solvents.

As shown in Table 6, all the studied batches (3 batches of the substance manufactured on fresh and 3 batches on regenerated 1,2,4-TCB) meet the requirements of the Ph. Eur., which indicates the acceptability of using the regenerated solvent for the synthesis of API.

Comparison of the impurities profile.

As shown in Fig. 2, both chromatograms contain, in addition to the peak of the main substance (retention time 12.784 and 12.778 min, respectively), a peak at 21.474 and 21.465 minutes, respectively, which corresponds to αnaphthylacetic acid impurity, which is the starting material in the Naphazoline nitrate synthesis. Peaks of other impurities were not detected in either case. Therefore, the use of a regenerated 1,2,4-TCB in the manufacturing process does not have a negative effect on the profile of impurities in the substance.

Validation of the analytical method.

The method of quantitative determination of 1,2,4-TCB, ethanolamine and 2-propanol is characterized by specific, linearity, accuracy and precision. The uncertainty of sample preparation and the general uncertainty of the method is insignificant.

Approbation of analytical methods on 11 commercial batches of the drug substances confirms the reproducibility of the method and the correctness of the obtained results.

The effect of regeneration of 1,2,4-TCB on the "greenness" of the synthesis method.

As shown in Table 10, due to the solvent regeneration process, the amount of waste per 1 kg of product was reduced; namely, 5 kg of regenerated 1,2,4-TCB was obtained, which was further used for synthesis. Therefore, due to the regeneration and reuse of 1,2,4-TCB for the synthesis of API, the impact on the environment is significantly reduced, which corresponds to the principles of green chemistry.

Practical relevance. The regeneration of 1,2,4-trichlorobenzene significantly reduced the amount of waste, which has a positive impact on the environment. The developed regeneration process was implemented in industrial production at Farmak JSC.

Research limitations. The limitation of this study is the impossibility of using a safer solvent since the process of formation of the imidazole ring requires a high-temperature regime for the reaction. Therefore, a solvent with a high boiling point was chosen, and the number of such solvents is limited.

Prospects for further research. It is planned to investigate the possibility of using only regenerated 1,2,4-TCB in the synthesis of API.

6. Conclusions

This article presents the results of the possibility of using the regenerated solvent 1,2,4-trichlorobenzene (1,2,4-TCB) in the industrial technology of the synthesis of the Naphazoline nitrate API. The introduction of regenerated 1,2,4-TCB into the synthesis process made it possible to significantly reduce the amount of waste per 1 kg of product, which in turn significantly reduced the negative impact on the environment. Considering that the batch size is from 40 to 50 kg and 5 to 10 batches are produced in a year, the use of the regenerated solvent has a positive effect on the environment and on the economic indicator as a result of the cheaper synthesis technology. The quality parameters for regenerated 1,2,4-TCB meet the requirements of the internal specification. Industrial series obtained on the regenerated solvent meet the requirements of the monograph of the European Pharmacopoeia. The polymorphic form of the substance series manufactured on regenerated 1,2,4-TCB corresponds to the polymorphic form of the substance series manufactured on fresh solvent. The obtained results on the influence of the regenerated solvent on the profile of impurities in the final substance show the similarity of the profile of the series manufactured on both solvents. According to the requirements of ICH Q3C Impurities: Guideline for residual solvents, a method for controlling the residual content of 1,2,4-TCB, ethanolamine and 2-propanol in the final product by the gas chromatography method has been developed and validated. The method has a sufficient level of linearity, precision, and correctness. The results on residual solvent control show that their content is below the detection limit, which indicates the completeness of the synthetic stages and the further product washing process.

Conflict of interests

The authors declare that they have no conflict of interest in relation to this study, including financial, personal, authorship, or any other, that could affect the study and its results presented in this article.

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Data availability

Data will be made available on reasonable request.

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