

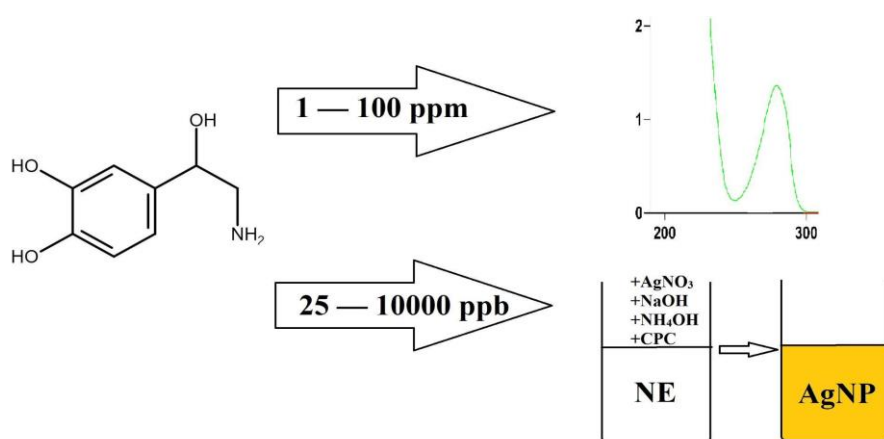
# Spectrophotometric Determination of Norepinephrine in Industrial Equipment Cleaning Rinse Water by Its Own Absorbance and The Tollens' Reagent

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## GRAPHICAL ABSTRACT



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## ABSTRACT

A literature review of the available spectrophotometric methods of determination of catecholamines is presented. Based on this review, two simple spectrophotometric methods for the determination of norepinephrine bitartrate in pharmaceutical formulations and industrial equipment cleaning rinse waters were chosen and validated. The first method for the determination of norepinephrine at ppm levels utilizes the absorbance band of the solution of norepinephrine bitartrate at 279 nm. The second method for the determination of norepinephrine at ppb levels is based on the reaction of norepinephrine with the Tollens' reagent in the presence of the cationic surfactant cetylpyridinium chloride and the colorimetric determination of the formed colloidal silver nanoparticles. The calibration graphs are linear in the range from 1 to 150 mg/l of norepinephrine for the first method and 25 µg/l to 10 mg/l for the second method. The molar attenuation coefficients are 388 and 7560 m<sup>2</sup>/mol, respectively, the limits of detection are 1.1 mg/l and 3.1 µg/l, and the limits of quantification are 3.3 mg/l and 9.4 µg/l, respectively. Both methods are selective concerning the common excipients, show good accuracy (the relative uncertainties do not exceed 4 and 7%, respectively) and precision (the relative standard deviations do not exceed 4 and 7%, respectively), and do not require lengthy sample preparation and sophisticated laboratory equipment.

## 1. INTRODUCTION

Norepinephrine (CAS registry number: 51-41-2, IUPAC name: 1-(3,4-dihydroxyphenyl)-2-aminoethanol, other name: noradrenaline) is a sympathomimetic drug used mainly to treat very low blood pressure levels [1] and the septic or neurogenic shock states [2, 3]. It also finds its usage in sleep pharmacology [4]. When several different pharmaceutical formulations are produced on the single production line, cleaning of pharmaceutical equipment and determination of the product residues on the manufacturing equipment surface become the important production steps [5]. The permitted residual quantities of both the active pharmaceutical ingredients, their degradation products and cleaning agents on the industrial equipment surface after cleaning are usually determined by the values of permitted daily exposure of the contaminants. It depends on several factors and may differ from ppm to ppb levels even at the different production lines of the same manufacturer [6]. For liquid pharmaceutical formulations, the rinse waters from the cleaning equipment are usually collected, and the residual quantities of pharmaceuticals in these rinse waters are determined.

Norepinephrine belongs to the family of catecholamines and, together with epinephrine and dopamine, forms a triad of the physiologically significant catecholamines. There are several analytical methods of determination of catecholamines, including chromatographic, electrochemical, electrophoresis, spectroscopic methods, and immunoassays [7–11]. However, when it comes to determining norepinephrine on the surface of industrial equipment, the method must be rapid and simple to avoid production delays. Therefore, UV-visible spectrophotometry is often the preferred choice [7, 12, 13]. The primary objective of this study is to identify a suitable spectrophotometric method for determining norepinephrine at ppm and ppb levels in industrial equipment cleaning rinse water. This aim is crucial in ensuring the safety and quality of pharmaceutical production. The existing spectrophotometric methods of determination of different catecholamines available in the literature [14–104] were reviewed. These methods are presented in Table 1.

TABLE I. A review of spectrophotometric methods of determination of catecholamines.

Object of analysis <sup>a</sup>	Analyte	Medium	Used reagents	Range, ppm	Reference
BS, PF	AB, NB	Hydroethanolic, pH = 3	Sodium metabilphite, sodium bismuthate, acetaldehyde	1.6 – 270 (AB), 1.6 – 200 (NB)	[14]
BS, PF	PC, DH, LD	0.01 M NaOH	Izoniazid, N-bromosuccinimide	0.8 – 6 (PC), 2.8 – 14 (DH), 2.4 – 12 (LD)	[15]
BS, PF	PC, DH, MD	5% Na <sub>2</sub> CO <sub>3</sub>	Hydroxylamine hydrochloride, sodium nitroprusside	1.5 – 10 (PC), 2.4 – 17 (DH), 5 – 16 (MD)	[15]
BS, PF	AH, NH, INH, MD	0.01 M AcOH	Ammonium metavanadate	9 – 90 (AH), 7 – 65 (NH), 7 – 75 (INH), 1 – 95 (MD)	[16]
BS, PF	AH, NH, INH	Phosphate buffer, pH = 7.4	Bromamine-T, N-bromosuccinimide, N-bromophthalimide, dibromohydantoin	4 – 140 (AH), 4 – 130 (NH), 6 – 190 (INH)	[17]
BS, PF	PC, DH, LD, MD, AH	1 M HCl	<i>p</i> -nitroaniline, sodium nitrite, sulphamic acid, molybdic acid	0.05 – 3.2 (PC), 0.05 – 3.4 (DH), 0.1 – 4 (LD), 0.25 – 9 (MD), 0.25 – 7 (AH)	[18]
BS, PF	C, AH, NH, DH, LD	Acetate buffer, pH = 5.5	Sodium nitrite, sodium molybdate, sodium tungstate	1.4 – 140 (C), 0.9 – 90 (AH), 1.1 – 110 (NH),	[19]

BS, PF	IS, LD, DH, DBH	Hydroethanolic	Sodium metaperiodate, sodium metabisulphite	1.1 – 110 (DH), 1 – 100 (LD) 10 – 50 (IS), 5 – 30 (LD), 5 – 45 (DH), 5 – 55 (DBH) 0.45 – 9.15 (AH), 0.425 – 8.45 (NH), 0.62 – 12.8 (INH), 0.65 – 12 (MD) 0.04 – 2.4 (PC), 0.02 – 2.8 (DH), 0.1 – 2.8 (LD), 0.5 – 7 (MD), 0.5 – 7 (AH)	[20]
BS, PF	AH, NH, INH, MD	Phosphate buffer, pH = 9.0	<i>o</i> -phenylenediamine dihydrochloride	5 – 200 (AH), 10 – 300 (IP)	[21]
BS, PF	PC, DH, LD, MD, AH	H <sub>2</sub> SO <sub>4</sub> , 1:1	Sulphanilamide, sodium nitrite, sulphamic acid, sodium molybdate	0.04 – 0.6 (PC), 0.06 – 0.75 (MD), 0.06 – 0.65 (LD), 0.05 – 0.7 (DH) 0.02 – 1 (PC), 0.04 – 1.3 (MD), 0.05 – 1 (LD), 0.06 – 1.1 (DH) 1 – 27 (AB), 0.5 – 17 (MD), 0.6 – 15 (DH), 1.5 – 19.2 (LD) 0.2 – 18 (DH), 0.1 – 20 (MD), 0.1 – 20 (LD), 0.1 – 13 (C) 0.2 – 3.1 (AH), 0.1 – 2.2 (DH), 0.1 – 2.5 (MD), 0.15 – 3.2 (LD) 0.03 – 0.84 (LD), 0.1 – 1 (MD)	[22]
BS, PF	AH, IP	Carbonate buffer, pH = 8.3	Sodium hydrosulphite, ferrous sulphate, sodium citrate	1 – 17 (AH), 1 – 12 (DH)	[23]
BS, PF	PC, DH, LD, MD, AH	1 M HCl	Ferric ammonium sulphate, 1,10-phenantroline	0.1 – 2.8 (MD), 0.1 – 2 (DH), 0.2 – 6 (AH) 48 – 417 (DH), 68 – 405 (DBH), 59 – 446 (VMA)	[24]
BS, PF	PC, DH, LD, MD, AH	1 M HCl	Ferric ammonium sulphate, 2,2'-bipyridyl		[24]
BS, PF	AB, DH, LD, MD	Hydromethanolic alkaline	Sulphanilic acid, <i>o</i> - phosphoric acid, sodium nitrite		[25]
BS, PF, WS	PC, DH, LD, MD	Acetate buffer, pH = 4	Potassium periodate, 4- aminobenzoic acid		[26]
BS, PF	AH, DH, LD, MD	3 M H <sub>2</sub> SO <sub>4</sub>	Methylene blue, potassium periodate, potassium iodide		[27]
BS, PF	MD, LD	Acetate buffer, pH = 5	Sodium metavanadate, eriochrome cyanine R		[28]
BS, PF	AH, DH	H <sub>2</sub> SO <sub>4</sub> , 1:1	2-aminothiazoline, sodium nitrite, urea		[29]
BS, PF	DH, MD, AH	1 M HCl	Ferric chloride, 1,10- phenantroline		[30]
BS, PF, US	DH, DBH, VMA	Ammonia buffer, pH = 10 – 11	4-aminoantipyrine, copper sulphate		[31]

BS, PF	DH, AH	Acetate buffer, pH = 4.8	Sodium hydroxide	3 – 30 (DH), 4.4 – 40 (AH) 0.02 – 1.7 (DH),	[32]
BS, PF	DH, AH, DBH	Ammonia buffer, pH = 9.8	Haemoglobin, acid chrome blue K, hydrogen peroxide	0.1 – 3 (AH), 0.02 – 2.4 (DBH)	[33]
BS, SS	DH, AH, LD	Aqueous alkaline	Silver nitrate, polyvinylpyrrolidone, sodium hydroxide	0.5 – 3 (DH), 0.03 – 2 (LD), 0.3 – 8.8 (AH)	[34]
BS, PF	MD, DH, AH	Aqueous	<i>p</i> -toluidine, sodium periodate	1 – 50 (MD), 2 – 50 (DH), 5 – 70 (AH)	[35, 36]
BS, PF	AH	Dioxin	5-amino-3-H, 1,3,4-thiodiazole-2-thione, benzaldehyde, <i>p</i> -formaldehyde, dioxin	2 – 20	[37]
BS, PF	MD, DH, AH	1 M HCl	N-bromosuccinimide, calcon	0.5 – 16 (AH), 2 – 40 (MD), 1 – 36 (DH)	[38]
BS, PF	MD, DH, AH	Aqueous	3-aminopyridine, sodium periodate	1 – 40 (AH), 1 – 40 (MD), 1 – 20 (DH)	[39]
BS, PF	DH	Aqueous	Tyramine, potassium metaperiodate	0.5 – 20	[40]
BS, PF	AH, NH, DH, VMA, HVA	Acetate buffer solution, pH = 5	Silver nitrate, sodium citrate, poly-vinylpyrrolidone, hydrogen peroxide, sodium borohydride	2 – 11 (AH), 18 – 36 (NH), 21 – 28 (DH), 0.6 – 16 (VMA), 0.1 – 455 (HVA)	[41]
BS, PF	DH, LD, MD	Borate buffer, pH = 9	Bromanil	1 – 25 (DH), 0.8 – 30 (LD), 1 – 30 (MD)	[42]
BS, PF	Adrenaline nitrate	Phosphate buffer, pH = 7	Sodium molybdate, phosphoric acid, hydrogen peroxide, ammonium chloride	0.33 – 5.5	[43]
BS, PF	AH, L-teranol bitartrate, IP, MD	Ethanol alkaline	2,3,5-triphenyltetrazolium chloride	0.5 – 3	[44]
BS, PF	DH, LD, MD	Phosphate buffer, pH = 7.5	Bromanil, cetyltrimethylammonium bromide	0.2 – 3.5 (LD), 0.1 – 4 (MD), 0.2 – 2.5 (DH) 0.2 – 40 (LD, MD),	[45]
BS, PF	DH, LD, MD, CD	0.2 M NaOH	Pyromellitic dianhydride	0.2 – 50 (DH), 0.2 – 100 (CD)	[46]
BS, PF	DH, MD	Phosphate buffer, pH = 7	Sweet potato root extract	30 – 920 (DH), 40 – 1260 (MD)	[47]
BS, PF	NB	Hydroethanolic, pH = 5	Sodium iodate, sodium perchlorate	3.4 – 37.2	[48]
BS, PF, fruit extracts, US, SS	DH	Aqueous, pH = 4	Ferric chloride, potassium ferricyanide	0.05 – 6	[49]

BS, PF	DH	Aqueous	None	3.8 – 45.5	[50]
BS, PF	DH	1 M NaOH	Potassium permanganate	0.2 – 4.6	[50]
BS, PF	DH	0.8 M NaOH	N-bromosuccinimide, isoniazid	1.2 – 50	[51]
BS, PF	DH	5% Na <sub>2</sub> CO <sub>3</sub>	Hydroxylamine hydrochloride, sodium nitroprusside	1.2 – 50	[51]
BS, PF, US, SS	DH	4 M H <sub>2</sub> SO <sub>4</sub>	Thionine, potassium bromate	0.2 – 103.3	[52]
BS, PF	DH, AH, NB, LD	Aqueous, pH = 7.2	Horseradish peroxidase, <i>p</i> - chlorophenol, 4- aminoantipyrine, hydrogen peroxide	1 – 20 (NB), 0.2 – 5 (AH), 0.4 – 4 (DH), 0.075 – 1.2 (LD)	[53]
BS, PF	DH, MD	0.05 M NaOH	2-furoic acid hydrazide, sodium nitroprusside	1 – 100	[54]
BS, PF, US, SS	LD, CD	3.5 M NH <sub>4</sub> OH, pH = 10.5	4-aminoantipyrine, copper sulphate	19.7 – 69 (LD), 18.1 – 54.3 (CD)	[55]
BS, PF, US, SS	LD	Acetate, borate, and phosphate buffer, pH =5	Iodine, potassium iodide	39.4 – 78.9	[55]
BS, PF, US	DH	Borate buffer, pH = 9.4	Sodium 1,2-naphthoquinone- 4-sulfonate, tetradecyl benzyl dimethyl ammonium chloride	0.16 – 40	[56]
BS, PF	DH	0.5 M NaOH	2,4-dinitrophenyl-hydrazine, potassium periodate	5 – 50	[57]
BS, PF	DH	1 M NaOH	5-aminosalicylic acid, sodium persulphate	2.7 – 31.25	[58]
BS, PF	DH	4 M HCl	Potassium bromate, potassium bromide, potassium iodide	8 – 40	[59]
BS, PF, SS	DH	Phosphate buffer, pH = 7	Chloroauric acid, sodium citrate, oligonucleotide strand	0.02 – 0.6	[60]
BS, PF, US, SS	DH	Phosphate buffer, pH = 7	Chloroauric acid, sodium citrate	0.015 – 0.6	[61]
BS, PF	DH	Phosphate buffer, pH = 7	Silver nitrate, sodium citrate, sodium borohydride, 4'- aminobenzo-18-crown-6, 4- mercapto phenylboronic acid	0.3 – 1.5	[62]
BS, SS	DH	0.001 M NaOH	Silver nitrate, poly- vinylpyrrolidone, sodium hydroxide	0.5 – 3	[63]
BS, SS	DH	Tris buffer, pH = 7	Chloroauric acid, sodium citrate, melamine	0.005 – 500	[64]
BS, PF, US, SS	DH	Aqueous, pH = 4	Chloroauric acid, chitosan, phenylamine-4-sulfonic acid, ferric chloride	0.12 – 2.57	[65]
BS, CF	DH	Phosphate buffer, pH = 7.4	Dithiobis-(succinimidyl- propionate), chloroauric acid, sodium citrate, ferric chloride	0.007 – 0.09	[66]
BS, CF	DH	Aqueous	Chloroauric acid, sodium borohydride, cyclodextrin	0.001 – 0.24	[67]
BS, PF	AH	Aqueous	Ferric chloride, potassium hexacyanoferrate (III)	0.1 – 2	[68]

BS, PF	AH	Acetate buffer, pH = 5	Ferric chloride	25.7 – 257	[69]
BS, PF	AH	Aqueous	Iodic acid	1.14 – 143	[70]
BS, PF	AB, IS	Aqueous	Silver nitrate, sodium hydroxide	5 – 80	[71]
BS, PF	AH	3 M HCl	Sodium vanadate	0.5 – 140	[72]
BS, PF, SS	AH, NH	Acetate buffer, pH = 4	Iodine, sodium thiosulphate	1 – 20	[73]
BS, PF	AH	Aqueous	Ferric chloride, nitroso-R-salt	0.1 – 8	[74]
BS, PF	AH	Acetate buffer, pH = 4.8	Lead dioxide, polyester resin	22 – 176	[75]
BS, PF	AH	Aqueous	Manganese dioxide, poly-tetrafluoroethylene	1 – 17	[76]
BS, PF	AH	Aqueous, pH = 3.7	Cyclohexylene-1,2-dinitrilotetraacetic acid, ammonium molybdate, sodium nitrite	1.47 – 21.98	[77]
BS, PF	AH, NH	0.1 M NaOH	Sodium hydroxide	2 – 30	[78]
BS, PF, SS	AH, MD	Aqueous, pH = 5.4	Ferric chloride, 1,10-phenanthroline	0.01 – 0.8 (MD), 0.03 – 8 (AH)	[79]
BS, PF	AH	0.05 M NaCl + 0.01 M NaOH	Ion-exchange gel	1 – 12	[80]
BS, PF	AH	Aqueous, pH = 6	Praseodymium oxide	1 – 50	[81]
BS, PF	AH	1 M NaOH	Silver nitrate, sodium hydroxide, cetyltrimethylammonium bromide	1 – 12	[82]
BS, PF	AB	Acetate buffer, pH = 4.5	Copper sulphate, potassium hexacyanoferrate (III)	0.6 – 11	[83]
BS, PF	AH	Aqueous	Tyramine, potassium metaperiodate	0.6 – 25	[84]
BS, PF	AH	Phosphate buffer, pH = 7	Potassium iodide, iodine, anion-exchange resin	1.4 – 66	[85]
BS, PF	AH	Borate buffer, pH = 9	Chloranil	0.4 – 28	[86]
BS, PF	AB, NB	Hydroethanolic	Sodium periodate, sodium metabisulphite	10 – 80 (AB), 10 – 100 (NB)	[87]
BS, PF	AH	Carbonate – ammonia buffer	Ferrous sulphate, sodium bisulphite, sodium citrate, mannitol	5 – 500	[88]
BS, PF, US, SS	AH	4 M H <sub>2</sub> SO <sub>4</sub>	Thionine, potassium bromate	0.4 – 12.8	[89]
BS, PF, US	AH	Acetate buffer, pH = 4.5	Silver nitrate, sodium citrate, poly(N-vinyl-2-pyrrolidone), hydrogen peroxide, sodium borohydride	2 – 11	[90]
BS, PF	AH, NH	Acetate buffer, pH = 4.5	Ferric nitrate, 1,10-phenanthroline	1.5 – 10 (AH), 1 – 15 (NH)	[91]
BS, US, SS	AH	Acetate buffer, pH = 6	Silver nitrate, sodium borohydride, starch	0.1 – 10	[92]
BS, PF	DH, AH, NH, LD	Acetate buffer, pH = 5.5	Rose Bengal, ethylenediaminetetraacetic acid, nitrogen	1.3 – 15.4 (AH), 2.0 – 14.3 (NH), 0.8 – 10.7 (DH), 2 – 20 (LD)	[93]
BS, PF, US	AH	Aqueous	Copper chloride	4.4 – 110	[94]



BS, SS	AH	Aqueous	4-amino-3-hydrazino-5-mercapto-1,2,4-triazol, sodium tetra-chloroaurate, sodium citrate,	0.001 – 22	[95]
BS, PF	NH	Aqueous	Alizarin red sulphonate	0.5 – 10	[96]
BS, PF	NH, MD	Acetate buffer, pH = 4.7	Benzaldehyde, <i>p</i> -tolualdehyde, <i>p</i> -anisaldehyde	1.6 – 13.5 (NH), 2.4 – 19.2 (MD)	[97]
BS, PF	NH, MD	Methanolic acetate buffer, pH = 5	<i>p</i> -dimethylamino-cinnamaldehyde, <i>p</i> -dimethylamino-benzaldehyde	3 – 50 (NH), 4 – 60 (MD)	[98]
BS, US	AH, NH, DH, MH, NMH	Aqueous, pH = 5	Cation exchange resin, boric acid, iodine, potassium iodide, sodium metabisulphite	0.5 – 3	[99]
BS, WWS	NH	Aqueous	Gold (III) chloride, sodium citrate	1 – 102	[100]
BS, US	NH	Phosphate buffer, pH = 6.5	Gold (III) chloride, sodium citrate, 4-(liponyloxy)-benzaldehyde, 4-mercatophenylboronic acid	0.014 – 0.2	[101]
BS, US	NMH	Phosphate buffer, pH = 7	Gold (III) chloride, sodium citrate, 4-(liponyloxy)-benzaldehyde, N-acetylcysteine	0.022– 2.2	[102]
BS, SS	NH	Aqueous	Silver nitrate, sodium hydroxide, ammonia, cetyltrimethylammonium bromide	0.014 – 0.21	[103]
BS, PF	AH	0.1 M NaOH, acetone	Methylthiazolyl-diphenyltetrazolium bromide	0.1 – 3	[104]

<sup>a</sup>Abbreviations: BS – bulk substances, PF – pharmaceutical formulations, SS – serum samples, US – urine samples, WS – water samples, WWS – wastewater samples, CF – cerebrospinal fluid, AH – adrenaline hydrochloride, AB – adrenaline bitartrate, NH – noradrenaline hydrochloride, NB – noradrenaline bitartrate, DH – dopamine hydrochloride, LD – L-dopa, MD – methyl dopa, CD – carbidopa, PC – pyrocatechol, DBH – dobutamine hydrochloride, IS – isoprenaline sulphate, IP – isoproterenol, VMA – vanilylmandelic acid, HVA – homovanillic acid, MH – metanephrine hydrochloride, NMH – normetanephrine hydrochloride

These methods are based on either the redox properties of the catechol moiety [14–17, 19, 20, 23, 24, 26–28, 30, 38, 43, 48–52, 55, 59, 68–70, 72–76, 79, 85, 87, 88, 91, 93, 96, 99], the coupling of different reagents with amine group [15, 18, 21, 22, 25, 29, 31, 35–37, 39, 40, 42, 44–46, 51, 53–58, 77, 84, 86, 89, 97, 98, 104], the enzymatic or alkaline degradation of the compounds [32, 33, 47, 78, 80], or the surface plasmon resonance of the formed metal nanoparticles [34, 41, 60–67, 71, 81–83, 90–92, 94, 95, 100–103]. The methods were checked for their rapidness, the usage of the reagents common for pharmaceutical laboratories, and the detection range. Surprisingly, although the aqueous solution of norepinephrine has its own absorption band with the absorption maximum at 279 nm [105], the method of its determination at the ppm level using the absorbance at this wavelength was still not quantified. For the determination of norepinephrine at ppb level the reaction with the Tollens' reagent [103] was found the most suitable due to the rapidness and because it requires only the very common reagents present in each pharmaceutical laboratory. The ammonia complex of silver hydroxide is reduced by norepinephrine to the colloidal silver, which has a surface plasmon resonance band at 450 nm. However, in the paper [103] the analytical performance of the method was not properly studied, the optimization of the experimental conditions was not performed, and the determined range of the method is doubtful. Consequently, in the present study the analytical performance of the spectrophotometric methods of determination of norepinephrine at ppm level by its own absorbance, and at ppb level with the Tollens' reagent is determined, and the suitability of these methods for the determination of norepinephrine in the rinse waters from the industrial equipment cleaning is discussed.

## 2. EXPERIMENTAL METHODS

### 2.1. Reagents and Equipment

Silver nitrate (analytical grade), ammonia solution 25% (analytical grade), sodium hydroxide (analytical grade), cetylpyridinium chloride (reagent grade), poly(vinyl alcohol) (reagent grade), gum arabic powder (reagent grade), corn starch (reagent grade), Tween 80 (reagent grade), sodium chloride (reagent grade), sodium bisulphite (reagent grade), sodium tartrate (reagent grade), tartaric acid (reagent grade), glacial acetic acid (reagent grade), perchloric acid (reagent grade), and crystal violet (reagent grade) were purchased from LLC Lenreaktiv. The intravenous injections containing norepinephrine hydrochloride were purchased from LLC Life Science OHFK (Russia). The flat plates made of stainless steel 12X12H10T were used to model the cleaning of industrial equipment. The analytical balance Sartorius Cubis MSA 225P-ICE-DI was used for weighting. The various micropipettes manufactured by Thermo Fisher Scientific were used for taking aliquots. The spectrophotometer Mettler Toledo UV7 was used for colorimetric measurements. The water bath Stegler WB-4 was used for sample incubations. The microburette Duran AS 5 ml was used for titration. The chemical glassware of the 2nd grade was used. Water for preparation of solutions was twice distilled and then deionised with the Sartorius Arium Pro VF Ultrapure Water system.

### 2.2. Preparation of the Solutions

The 0.005 M silver nitrate, the 0.01 M sodium hydroxide, the 0.5% ammonia, the 0.02% cetylpyridinium chloride, the 0.02% poly(vinyl alcohol), the 0.01% corn starch, the 0.02% gum arabic, the 0.01% Tween 80, the 0.1 M perchloric acid, the 0.5% crystal violet solutions were prepared in the deionised water.

### 2.3. Preparation of the Color Reagent

In a beaker, 50.0 ml of the 0.005 M solution of silver nitrate was placed, and 2.5 ml of the 0.01 M solution of sodium hydroxide was gradually added. The brownish suspension of the silver oxide was formed. Then, 2.5 ml of the 0.5% ammonia solution was gradually added. The ammonia complex of silver hydroxide was formed, and the solution became colorless. Then, 2.5 ml of 0.2% solution of cetylpyridinium chloride was added. The solution was mixed well. Each portion of the solution was prepared immediately before use.

### 2.4. Preparation of the 300 mg/l Stock Solution and the Working Solutions of Norepinephrine Bitartrate

A total of 0.300 g of norepinephrine bitartrate was weighed and dissolved in glacial acetic acid; the solution was transferred to the 100 ml volumetric flask, and the volume of the solution was adjusted by glacial acetic acid. The exact concentration of the solution was determined by titration. For this, the aliquot of 5.0 ml of the prepared solution was transferred to the titration flask, and the solution was mixed and titrated with the solution of 0.1 M perchloric acid using 0.05 ml of the solution of crystal violet as an indicator. Then, the appropriate aliquot of the prepared solution with the determined concentration was taken and transferred to the 500 ml volumetric flask, and the volume of the solution was adjusted with water. The stock solution was stored in a refrigerator. The working solutions of norepinephrine bitartrate with different concentrations ranging from 10 µg/l to 150 mg/l were prepared by appropriately diluting the stock solution with deionized water. The working solutions were prepared daily.

### 2.5. Preparation of Solutions from Injections

The solutions for intravenous injections available on the Russian local market contain a 2 g/l solution of norepinephrine bitartrate. The contents of ten ampoules from the single package were collected into a beaker. The different aliquots were taken, transferred to the 1 l volumetric flask, dissolved in water, and the volume of the solution was adjusted by deionized water. The concentrations of norepinephrine bitartrate in the resulting solution range from 10 µg/l to 150 mg/l.

### 2.6. Preparation of Model Rinse Water Samples

The aliquot of 1.0 ml of the prepared working solutions or solutions from injections was taken, placed onto the flat plate made of stainless steel 12X12H10T, and allowed to dry in the fume hood.



The plate was rinsed several times with water, the combined rinses were transferred to the 100 ml volumetric flask, and the volume of the solution was adjusted with water. The expected concentrations of norepinephrine bitartrate in the model rinse water samples range from 10 µg/l to 150 mg/l.

### 3. RESULTS

#### 3.1. Determination of ppm Levels of Norepinephrine by Its Own Absorbance

*3.1.1. General procedure.* The absorbance of the working solution of norepinephrine or model rinse water at the wavelength of 279 nm in the quartz cuvette with the optical path length 1 cm was measured against the distilled water.

*3.1.2. Selection of the wavelength.* The UV-spectrum of the working solution with the concentration of 100 mg/l was recorded in the wavelength interval from 190 to 1100 nm with the wavelength step of 0.2 nm in the quartz cuvette with the optical path length of 1 cm against the distilled water. The maximum absorbance was observed at the wavelength of 279 nm, which coincides with the earlier studies [105]. This wavelength was chosen for all further measurements.

*3.1.3. Construction of the calibration curve.* The working solutions of norepinephrine bitartrate with different concentrations ranging from 1 to 150 mg/l were prepared, and their absorbances of prepared solutions with the different concentration of norepinephrine at the wavelength of 279 nm in the quartz cuvette with the optical path length 1 cm were measured against the distilled water. The results are shown in Figure 1.

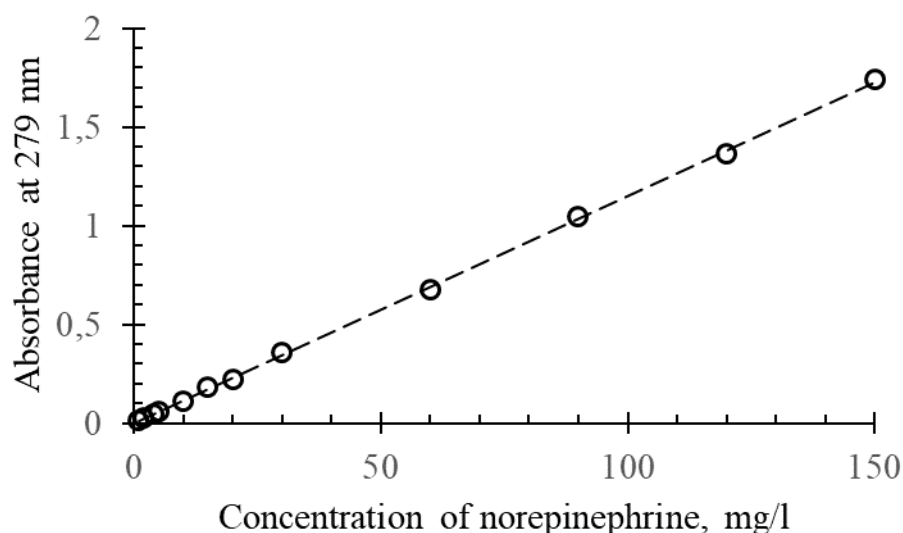


Figure 1. The dependence of the absorbance of the aqueous solution of norepinephrine on its concentration.

*3.1.4. Linearity.* According to Figure 1, the dependence of the absorbance of norepinephrine bitartrate at 279 nm on its concentration is linear in the range from 1 to 150 mg/l. The regression analysis was performed using the least-squares technique [106]. Additionally, the Ringbom's optimum range [107–109], the molar attenuation coefficient, and the Sandell's sensitivity coefficient [110] were calculated. The parameters of the regression equation are listed in Table 2.

TABLE II. The parameters of the linear regression of the dependence of the absorbance of the norepinephrine on its concentration, and the analytical parameters of the method.

Parameter	Value
Slope and its confidence interval ( $f = 10$ , $p = 95\%$ ), l/mg	$0.01152 \pm 0.00006$
Intercept and its confidence interval ( $f = 10$ , $p = 95\%$ )	$-0.00007 \pm 0.00006$

R <sup>2</sup> value	0.9997
Linearity range, mg/l	1 – 150
Ringbom's optimum range, mg/l	5 – 90
Molar attenuation coefficient and its confidence interval (f = 10, p = 95%), m <sup>2</sup> /mol	388 ± 3
Sandell's sensitivity coefficient and its confidence interval (f = 10, p = 95%), µg/cm <sup>2</sup>	0.868 ± 0.006
Limit of detection, mg/l	1.1
Limit of quantification, mg/l	3.3

3.1.5. *Limit of detection and limit of quantification.* The limit of detection and the limit of quantification of the method were calculated according to [111–113]. The values are presented in Table 2.

3.1.6. *Selectivity with respect to common excipients.* According to the Russian State Registry of Pharmaceutical Products, intravenous injections contain sodium chloride, sodium bisulphite, sodium tartrate and tartaric acid as the common excipients. The possible interference of these excipients, as well as of acetic acid (because it was used in the stock solution preparation), was studied. For that, the 50 mg/l solutions of sodium chloride, sodium tartrate, sodium bisulphite and tartaric acid, and the 1% solution of acetic acid were prepared, and their absorbances at 279 nm were recorded. No noticeable absorbance was detected. In addition, according to the literature data, the UV spectra of both the sodium chloride [114], tartaric acid and its salts [115], and acetic acid [116] have no absorption bands at this wavelength. The UV spectrum of sodium bisulphite [117] has an absorption band at 260 nm, but at the concentration levels present in the norepinephrine injections it has no significant absorbance at 279 nm.

3.1.7. *Accuracy.* Four series of experiments were conducted. In the first two series, ten working solutions with concentrations of norepinephrine equal to 5 mg/l and 100 mg/l, and in the other two series, ten solutions from injections with the concentration of norepinephrine equal to 20 mg/l and 50 mg/l were prepared. The absorbance of the solutions was recorded. The concentrations of the solutions were calculated according to the regression equation, and the relative uncertainties were determined. The results are collected in Table 3.

TABLE III. The accuracy test of the method of determination of norepinephrine by its own absorbance.

	Sample number	Absorbance at 279 nm	Concentration of norepinephrine bitartrate, mg/l	Relative uncertainty, %
Working solution, 5 mg/l	1	0.0577	5.02	0.31
	2	0.0581	5.05	1.00
	3	0.0576	5.01	0.11
	4	0.0574	4.99	0.18
	5	0.0567	4.92	1.53
	6	0.0578	5.02	0.41
	7	0.0582	5.06	1.23
	8	0.0587	5.10	2.01
	9	0.0588	5.11	2.11
	10	0.0582	5.05	1.08
	Mean value	0.0579	5.03	0.99
Working solution, 100 mg/l	1	1.1490	99.75	0.25
	2	1.1483	99.68	0.32
	3	1.1543	100.20	0.20
	4	1.1470	99.57	0.43
	5	1.1531	100.09	0.10
	6	1.1475	99.61	0.39

	7	1.1492	99.76	0.23
	8	1.1480	99.66	0.34
	9	1.1555	100.31	0.31
	10	1.1489	99.74	0.26
	Mean value	1.1501	99.84	0.28
Solution from injections, 20 mg/l	1	0.2319	20.13	0.67
	2	0.2310	20.06	0.29
	3	0.2282	19.82	0.92
	4	0.2296	19.94	0.31
	5	0.2295	19.93	0.33
	6	0.2325	20.19	0.95
	7	0.2330	20.23	1.14
	8	0.2290	19.88	0.59
	9	0.2297	19.95	0.27
	10	0.2312	20.07	0.36
	Mean value	0.2306	20.02	0.58
Solution from injections, 50 mg/l	1	0.5800	50.35	0.71
	2	0.5808	50.42	0.74
	3	0.5775	50.14	0.28
	4	0.5827	50.59	1.17
	5	0.5835	50.66	1.31
	6	0.5787	50.24	0.48
	7	0.5823	50.55	1.10
	8	0.5802	50.37	0.74
	9	0.5767	50.07	0.14
	10	0.5701	49.49	1.03
	Mean value	0.5792	50.29	0.78

3.1.8. *Intra-day precision.* Four series of experiments were conducted similarly to those described in the Section 3.1.7, and the relative standard deviations were determined. The results are collected in Table 4.

TABLE IV. The intra-day precision test of the method of determination of norepinephrine by its own absorbance.

Sample number	Working solution				Solution from injections			
	5 mg/l		100 mg/l		20 mg/l		50 mg/l	
	Abs. at 279 nm	Conc. of NB, mg/l	Abs. at 279 nm	Conc. of NB, mg/l	Abs. at 279 nm	Conc. of NB, mg/l	Abs. at 279 nm	Conc. of NB, mg/l
1	0.0562	4.88	1.1527	100.07	0.2308	20.04	0.5744	49.87
2	0.0587	5.10	1.1477	99.63	0.2289	19.88	0.5840	50.70
3	0.0568	4.94	1.1561	100.37	0.2328	20.21	0.5749	49.91
4	0.0562	4.88	1.1496	99.79	0.2300	19.97	0.5803	50.38
5	0.0573	4.98	1.1568	100.43	0.2299	19.96	0.5845	50.75
6	0.0569	4.95	1.1503	99.86	0.2292	19.90	0.5846	50.75
7	0.0566	4.92	1.1497	99.80	0.2285	19.84	0.5708	49.55
8	0.0571	4.96	1.1541	100.19	0.2296	19.94	0.5810	50.44
9	0.0573	4.98	1.1473	99.60	0.2319	20.14	0.5700	49.49
10	0.0578	5.03	1.1502	99.85	0.2300	19.97	0.5745	49.87
Mean value	0.0571	4.96	1.1515	99.96	0.2302	19.99	0.5779	50.17
SD	0.0007	0.07	0.0032	0.28	0.0013	0.12	0.0054	0.47

RSD, %	1.27	1.39	0.27	0.28	0.55	0.58	0.93	0.94
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3.1.9. *Inter-day precision.* Four series of experiments were conducted similarly to those described in the Section 3.1.7. The solutions were prepared each day during five consecutive days. The relative standard deviations were determined. The results are collected in Table 5.

TABLE V. The inter-day precision test of the method of determination of norepinephrine by its own absorbance.

Sample number	Working solution				Solution from injections			
	5 mg/l		100 mg/l		20 mg/l		50 mg/l	
	Abs. at 279 nm	Conc. of NB, mg/l	Abs. at 279 nm	Conc. of NB, mg/l	Abs. at 279 nm	Conc. of NB, mg/l	Abs. at 279 nm	Conc. of NB, mg/l
1	0.0590	5.12	1.1457	99.46	0.2323	20.17	0.5814	50.48
2	0.0555	4.83	1.1596	100.67	0.2257	19.59	0.5700	49.49
3	0.0567	4.93	1.1439	99.31	0.2301	19.98	0.5810	50.44
4	0.0576	5.01	1.1441	99.32	0.2260	19.62	0.5695	49.44
5	0.0562	4.88	1.1510	99.92	0.2344	20.35	0.5741	49.84
Mean value	0.0570	4.95	1.1489	99.73	0.2297	19.94	0.5752	49.94
SD	0.0012	0.11	0.0059	0.52	0.0034	0.30	0.0052	0.45
RSD, %	2.10	2.22	0.52	0.53	1.50	1.53	0.90	0.91

3.1.10. *Accuracy for the determination of model rinse water samples.* Four series of experiments were conducted. In the first two series, five model rinse water samples prepared from the working solutions with the concentrations of norepinephrine equal to 5 mg/l and 100 mg/l, and in the other two series, five model rinse water samples prepared from the solutions from injections with the concentration of norepinephrine equal to 20 mg/l and 50 mg/l were prepared. The absorbance of the solutions was recorded. The concentrations of the solutions were calculated according to the regression equation, and the relative uncertainties were determined. The results are collected in Table 6.

TABLE VI. The accuracy test of the method of determination of model rinse water samples of norepinephrine by its own absorbance.

	Sample number	Absorbance at 279 nm	Concentration of norepinephrine bitartrate, mg/l	Relative uncertainty, %
Rinse water from the working solution, 5 mg/l	1	0.0553	4.81	3.81
	2	0.0562	4.88	2.33
	3	0.0547	4.75	4.94
	4	0.0562	4.88	2.30
	5	0.0562	4.89	2.25
	Mean value		0.0557	4.84
Rinse water from the working solution, 100 mg/l	1	1.1449	99.39	0.61
	2	1.1485	99.70	0.30
	3	1.1375	98.75	1.25
	4	1.1390	98.88	1.12
	5	1.1523	100.03	0.03
	Mean value		1.1445	99.35

Rinse water from the solution from injections, 20 mg/l	1	0.2238	19.43	2.84
	2	0.2244	19.49	2.56
	3	0.2261	19.63	1.83
	4	0.2274	19.74	1.29
	5	0.2239	19.44	2.78
	Mean value	0.2251	19.55	2.26
Rinse water from the solution from injections, 50 mg/l	1	0.5704	49.52	0.96
	2	0.5664	49.17	1.66
	3	0.5656	49.10	1.79
	4	0.5666	49.19	1.61
	5	0.5750	49.92	0.15
	Mean value	0.5688	49.38	1.24

3.1.11. *Precision for the determination of model rinse water samples.* Four series of experiments were conducted similarly to those described in the Section 3.1.10. The relative standard deviations were determined. The results are collected in Table 7.

TABLE VII. The precision test of the method of determination of model rinse water samples of norepinephrine by its own absorbance.

Sample number	Rinse water from the working solution							
	5 mg/l		100 mg/l		20 mg/l		50 mg/l	
	Abs. at 279 nm	Conc. of NB, mg/l	Abs. at 279 nm	Conc. of NB, mg/l	Abs. at 279 nm	Conc. of NB, mg/l	Abs. at 279 nm	Conc. of NB, mg/l
1	0.0529	4.60	1.1576	100.49	0.2245	19.50	0.5809	50.43
2	0.0565	4.91	1.1557	100.33	0.2323	20.17	0.5806	50.40
3	0.0526	4.58	1.1402	98.98	0.2321	20.16	0.5659	49.13
4	0.0547	4.76	1.1390	98.88	0.2234	19.40	0.5660	49.14
5	0.0562	4.88	1.1432	99.25	0.2317	20.12	0.5741	49.84
Mean value	0.0546	4.75	1.1471	99.58	0.2288	19.87	0.5735	49.79
SD	0.0018	0.16	0.0088	0.77	0.0045	0.39	0.0074	0.65
RSD, %	3.32	3.44	0.77	0.78	1.95	1.98	1.29	1.30

3.1.12. *Comparison of the results of titrimetric and spectrophotometric determinations.* A total of 1.000 g of norepinephrine bitartrate was weighed and dissolved in glacial acetic acid; the solution was transferred to the 100 ml volumetric flask, and the volume of the solution was adjusted by glacial acetic acid. The exact concentration of the solution was determined by titration. Ten aliquots of 5.0 ml of the prepared solution were transferred to the titration flask; the solutions were mixed and titrated with 0.1 M perchloric acid solution using 0.05 ml of the solution of crystal violet as an indicator. Then, the aliquot of 5.0 ml of the prepared solution with the determined concentration was taken and transferred to the 2000 ml volumetric flask. The volume of the solution was adjusted by water. The absorbance of ten portions of the solution was recorded, and the concentrations were calculated according to the regression equation. The content of norepinephrine in the weighting was calculated using both methods, and the F-test of equality of variances and the t-test of equality of means was performed. The results are shown in Table 8.

TABLE VIII. The comparison of titrimetric method of determination of norepinephrine and spectrophotometric method of determination of norepinephrine by its own absorbance.

Sample number	Titrimetric method			Spectrophotometric method		
	Volume of the titrant, ml	Amount of NB in the aliquot, mg	Amount of NB in the	Absorbance at 279 nm	Concentration of NB in the aliquot, mg/l	Amount of NB in the

	weighting, mg			weighting, mg		
1	1.58	50.45	1008.99	0.2966	25.75	1030.14
2	1.62	51.73	1034.53	0.2868	24.90	996.07
3	1.60	51.09	1021.76	0.2837	24.64	985.40
4	1.56	49.81	996.22	0.2846	24.71	988.41
5	1.58	50.45	1008.99	0.2834	24.61	984.36
6	1.56	49.81	996.22	0.2949	25.61	1024.30
7	1.58	50.45	1008.99	0.2797	24.28	971.27
8	1.54	49.17	983.44	0.2839	24.65	985.91
9	1.56	49.81	996.22	0.2868	24.90	996.07
10	1.58	50.45	1008.99	0.2882	25.02	1000.85
Mean value	1.58	50.32	1006.43	0.2869	24.91	996.28
Sample variance	0.00052	0.526	210.25	0.00003	0.209	334.21
F-value ( $f_1 = 9, f_2 = 9, p = 95\%$ )			1.59	Critical F-value ( $f_1 = 9, f_2 = 9, p = 95\%$ )		3.18
t-value ( $f = 18, p = 95\%$ )			1.305	Critical t-value ( $f = 18, p = 95\%$ )		1.734

### 3.2. Determination of ppb Levels of Norepinephrine with the Tollens' Reagent

**3.2.1. Selection of the wavelength.** A total of 2.0 ml of the color reagent was mixed with 4.0 ml of the working norepinephrine bitartrate with a concentration of 1 mg/l in a test tube. The blank solution was prepared by mixing 2.0 ml of the color reagent with 4.0 ml of water in another test tube. The contents of the test tubes were mixed, placed in the water bath and incubated at 25 °C for 10 minutes. Then, the UV-spectrum of the formed silver nanoparticles was recorded over the range from 190 to 1100 nm with the step of 0.2 nm in the glass cuvette with the optical path length 1 cm against the blank solution. The maximum absorbance was observed at the wavelength of 450 nm, which coincides with the earlier studies [103]. This wavelength was chosen for all further measurements.

**3.2.2. Selection of the volume of ammonia.** Because the pharmaceutical preparations of norepinephrine contain sodium chloride as the common excipient, it may bind silver ions into an insoluble salt. Consequently, an increased amount of ammonia is required to dissolve a formed silver chloride. In a series of beakers, a total of 50.0 ml of the 0.005 M solution of silver nitrate was placed, a total of 2.5 ml of the 0.01 M solution of sodium hydroxide, and a total of 2.5 ml of the 0.05 M solution of sodium chloride were gradually added to it. Then, the different aliquots of the 0.5% ammonia solution ranging from 0.5 to 5.0 ml were gradually added to the different beakers. The complete dissolution of the silver chloride and silver hydroxide suspensions and the formation of corresponding ammonia complexes was observed upon adding 2.5 ml and more of 0.5% ammonia solution. This volume was chosen for further experiments.

**3.2.3. Selection of the stabilizer.** In the work [103], cetyltrimethylammonium bromide was used to stabilize the formed colloidal silver suspension. However, cetyltrimethylammonium bromide is not a common reagent for pharmaceutical laboratories. It is known that another cationic surfactant, cetylpyridinium chloride, is often used in the analytical methods based on Tollens' reagent [118]. In addition, some other stabilizers common to pharmaceutical laboratories, including poly(vinyl alcohol), starch, and gum Arabic, were tested. In a series of test tubes, a total of 10.0 ml of the 0.005 M solution of silver nitrate was placed, and a total of 0.5 ml of the 0.01 M solution of sodium hydroxide was gradually added to it, followed by a total of 0.5 ml of the 0.5% solution of ammonia. Then to the different test tubes, a total of 0.5 ml of either the 0.02% solution of cetylpyridinium chloride, the 0.02% solution of poly(vinyl alcohol), the 0.01% solution of corn starch, the 0.02% solution of gum arabic, or 0.01% Tween 80 were added. In another series of test tubes, the aliquots of 2.0 ml of the prepared solutions with different stabilizers were mixed with a total of 4.0 ml of the working norepinephrine bitartrate with a concentration of 1 mg/l. The blank solutions were prepared by mixing 2.0 ml of the prepared solutions with different stabilizers and 4.0 ml of water in another



series of test tubes. The contents of the test tubes were mixed, placed in the water bath and incubated at 25 °C for 10 minutes. Then, the absorbances of the formed silver nanoparticles at the wavelength of 450 nm in the glass cuvette with an optical path length of 1 cm were measured against the corresponding blank solutions. The results are presented in Figure 2.

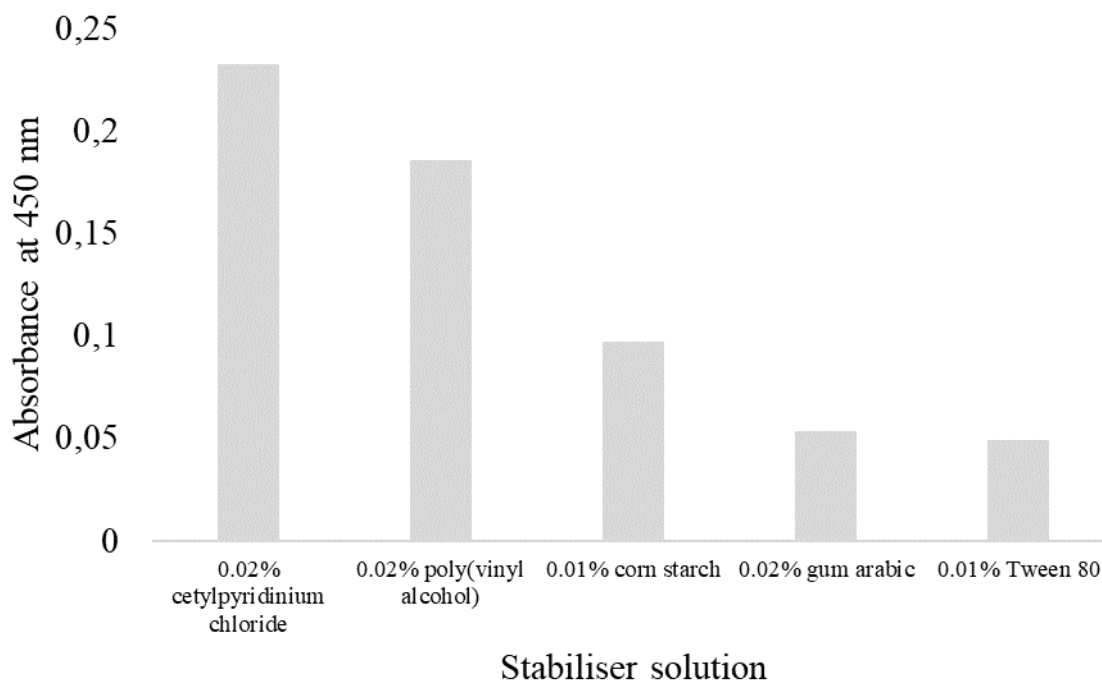


Figure 2. The influence of different stabilizers on the absorption of the colloidal silver suspension.

As Figure 2 shows, the 0.02% solution of cetylpyridinium chloride gives the best results, so it was chosen as the suspension stabilizer for any further experiments.

**3.2.4. Selection of volume of the color reagent.** In a series of test tubes, different aliquots of the color reagent ranging from 0.2 to 4.0 ml were mixed with a total of 4.0 ml of working norepinephrine bitartrate with a concentration of 1 mg/l. The corresponding blank solutions were prepared in another series of test tubes by mixing the corresponding aliquots of the color reagent with a total of 4.0 ml of water. The contents of the test tubes were mixed, placed in the water bath and incubated at 25 °C for 10 minutes. Then, the absorbances of the formed silver nanoparticles at the wavelength of 450 nm in the glass cuvette with the optical path length of 1 cm were measured against the corresponding blank solutions. The results are presented in Figure 3.

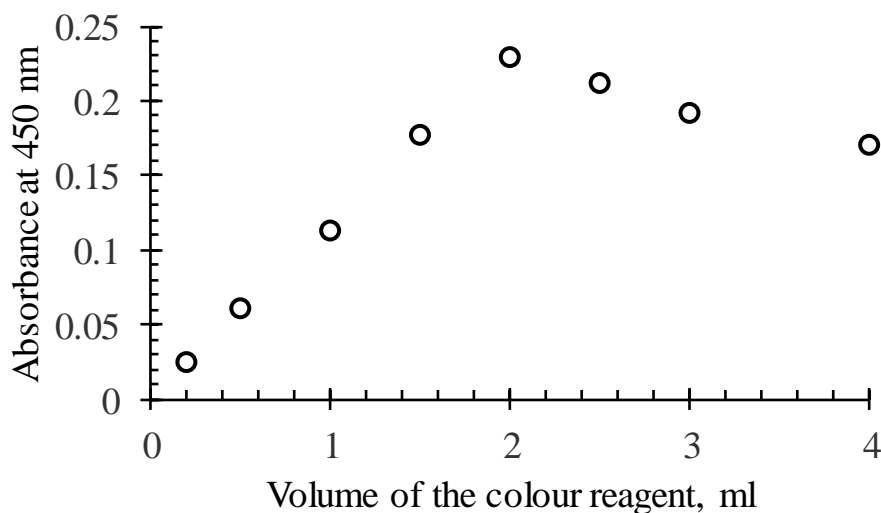


Figure 3. The influence of the color reagent volume on the absorption of the colloidal silver suspension.

As can be seen from Figure 3, the maximum absorbance was reached with the aliquot of 2.0 ml of the color reagent, and this volume was chosen for any further experiments.

**3.2.5. Selection of incubation time.** In a series of test tubes, aliquots of 2.0 ml of the color reagent were mixed with 4.0 ml of working norepinephrine bitartrate with a concentration of 1 mg/l. The corresponding blank solutions were prepared in another series of test tubes by mixing aliquots of 2.0 ml of the color reagent with a total of 4.0 ml of water. The contents of the test tubes were mixed, placed in the water bath and incubated at 25 °C for different periods ranging from 0.5 to 20 minutes. Then, the absorbances of the formed silver nanoparticles at the wavelength of 450 nm in the glass cuvette with the optical path length of 1 cm were measured against the corresponding blank solutions. The results are presented in Figure 4.

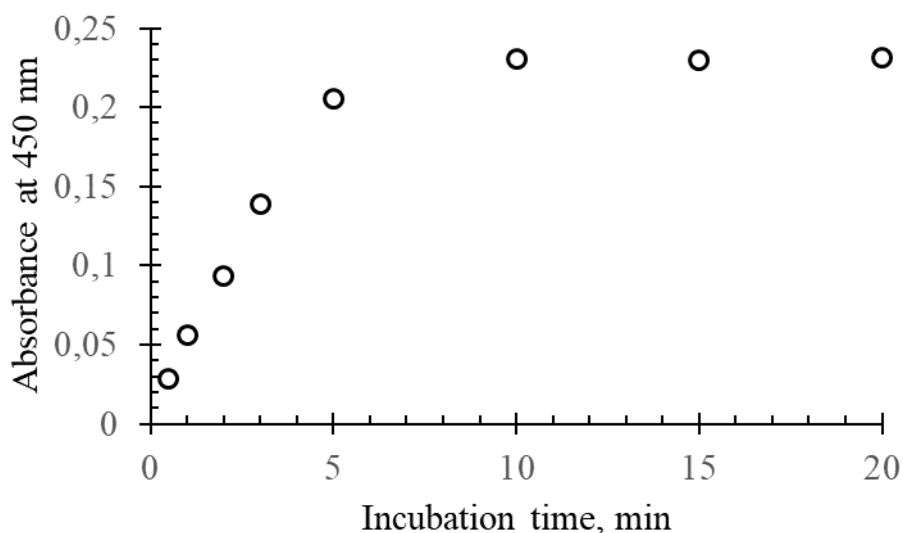


Figure 4. The influence of incubation time on the absorption of the colloidal silver suspension.

As can be seen from Figure 4, the absorbance initially increases with time but stabilizes after 10 minutes of incubation, which is the time period chosen for any further experiments.

**3.2.6. General procedure.** A total of 2.0 ml of the color reagent was mixed with 4.0 ml of working or sample solution of norepinephrine bitartrate in a test tube. The blank solution was prepared by mixing 2.0 ml of the color reagent with 4.0 ml of water in another test tube. The contents of the test tubes were mixed, placed in the water bath and incubated at 25 °C for 10 minutes. Then, the

absorbance of the formed silver nanoparticles at the wavelength of 450 nm in the glass cuvette with the optical path length of 1 cm was measured against the blank solution.

3.2.7. *Construction of the calibration curve.* Working solutions of norepinephrine bitartrate with concentrations ranging from 10  $\mu\text{g/l}$  to 10  $\text{mg/l}$  were prepared and treated as described in the general procedure. The absorbances of formed silver nanoparticles at the wavelength of 450 nm in the glass cuvette with an optical path length of 1 cm were measured against the corresponding blank solutions. The results are shown in Figure 5.

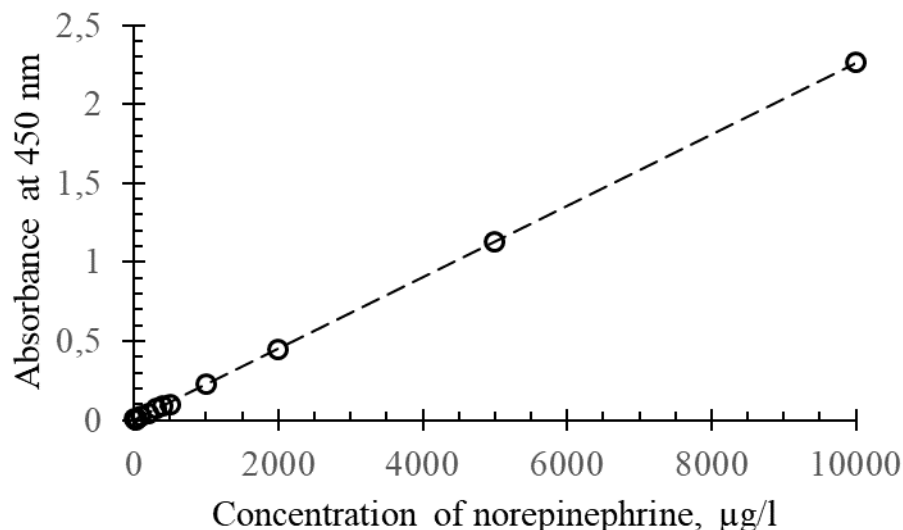


Figure 5. The dependence of the absorbance of the silver nanoparticles on the concentration of norepinephrine bitartrate.

3.2.8. *Linearity.* According to Figure 5, the dependence of the absorbance of formed silver nanoparticles at 450 nm on the concentration of norepinephrine bitartrate is linear in the range from 25  $\mu\text{g/l}$  to 10  $\text{mg/l}$ . The regression analysis was performed using the least-squares technique [106]. Additionally, the Ringbom's optimum range [107–109], the molar attenuation coefficient, and the Sandell's sensitivity coefficient [110] were calculated. The parameters of the regression equation are listed in Table 9.

TABLE IX. The parameters of the linear regression of the dependence of the absorbance of the silver nanoparticles on the concentration of norepinephrine, and the analytical parameters of the method.

Parameter	Value
Slope and its confidence interval ( $f = 10$ , $p = 95\%$ ), $l/\mu\text{g}$	$0,227 \pm 0,001$
Intercept and its confidence interval ( $f = 10$ , $p = 95\%$ )	$-0.0003 \pm 0.0002$
$R^2$ value	0.9998
Linearity range, $\mu\text{g/l}$	25 – 10000
Ringbom's optimum range, $\mu\text{g/l}$	200 – 5000
Molar attenuation coefficient and its confidence interval ( $f = 10$ , $p = 95\%$ ), $\text{m}^2/\text{mol}$	$7650 \pm 30$
Sandell's sensitivity coefficient and its confidence interval ( $f = 10$ , $p = 95\%$ ), $\mu\text{g}/\text{cm}^2$	$0.00440 \pm 0.00002$
Limit of detection, $\mu\text{g/l}$	3.1
Limit of quantification, $\mu\text{g/l}$	9.4

3.2.9. *Limit of detection and limit of quantification.* The limit of detection and the limit of quantification of the method were calculated according to [111–113]. The values are presented in Table 9.

3.2.10. *Selectivity with respect to common excipients.* The possible interference of the excipients was studied. The 50 mg/l solutions of sodium chloride, sodium bisulphite, sodium tartrate and tartaric acid, and the 1% solution of acetic acid were prepared. In a series of test tubes, the aliquots of 4.0 ml of these prepared solutions were mixed with a total of 2.0 ml of the color reagent, and the test tubes were incubated at 25 °C for 60 minutes. No color development indicating the formation of silver nanoparticles was observed, which means that the considered excipients do not interfere with this determination.

3.2.11. *Accuracy.* Four series of experiments were conducted. In the first two series, ten working solutions with concentrations of norepinephrine equal to 25 µg/l and 1 mg/l, and in the other two series, ten solutions from injections with the concentration of norepinephrine equal to 100 µg/l and 500 µg/l were prepared and treated as described in the general procedure. The absorbance of the silver nanoparticles was recorded. The concentrations of the solutions were calculated according to the regression equation, and the relative uncertainties were determined. The results are collected in Table 10.

TABLE X. The accuracy test of the method of determination of norepinephrine with the Tollens' reagent.

	Sample number	Absorbance at 450 nm	Concentration of norepinephrine bitartrate, µg/l	Relative uncertainty, %
Working solution, 25 µg/l	1	0.0053	23.28	6.89
	2	0.0052	22.96	8.16
	3	0.0057	24.93	0.28
	4	0.0056	24.89	0.44
	5	0.0059	25.88	3.53
	6	0.0058	25.43	1.72
	7	0.0056	24.88	0.47
	8	0.0058	25.78	3.12
	9	0.0058	25.47	1.90
	10	0.0062	27.16	8.64
	Mean value	0.0057	25.07	3.51
Working solution, 1 mg/l	1	0.2267	998.78	0.12
	2	0.2283	1005.89	0.59
	3	0.2284	1006.14	0.61
	4	0.2313	1018.82	1.88
	5	0.2276	1002.72	0.27
	6	0.2228	981.68	1.83
	7	0.2280	1004.20	0.42
	8	0.2293	1010.30	1.03
	9	0.2265	998.00	0.20
	10	0.2278	1003.44	0.34
	Mean value	0.2277	1003.00	0.73
Solution from injections, 100 µg/l	1	0.0233	102.82	2.82
	2	0.0220	96.93	3.07
	3	0.0217	95.71	4.29
	4	0.0219	96.51	3.49

	5	0.0227	99.81	0.19
	6	0.0220	96.75	3.25
	7	0.0233	102.67	2.67
	8	0.0231	101.94	1.94
	9	0.0226	99.51	0.49
	10	0.0231	101.70	1.70
	Mean value	0.1154	508.21	1.64
Solution from injections, 500 µg/l	1	0.1154	508.60	1.72
	2	0.1135	499.87	0.03
	3	0.1112	490.04	1.99
	4	0.1115	491.30	1.74
	5	0.1147	505.19	1.04
	6	0.1139	501.66	0.33
	7	0.1154	508.30	1.66
	8	0.1115	491.25	1.75
	9	0.1151	507.13	1.43
	10	0.1138	501.16	1.33
	Mean value	0.1154	508.21	1.64

3.2.12. *Intra-day precision.* Four experiments were conducted similarly to those described in Section 3.2.11. The relative standard deviations were determined. The results are collected in Table 11.

TABLE XI. The intra-day precision test of the method of determination of norepinephrine with the Tollens' reagent.

Sample number	Working solution				Solution from injections			
	25 µg/l		1 mg/l		100 µg/l		500 µg/l	
	Abs. at 450 nm	Conc. of NB, µg/l	Abs. at 450 nm	Conc. of NB, µg/l	Abs. at 450 nm	Conc. of NB, µg/l	Abs. at 450 nm	Conc. of NB, µg/l
1	0.0054	23.76	0.2254	992.89	0.0227	99.93	0.1115	491.17
2	0.0054	23.97	0.2289	1008.60	0.0231	101.64	0.1127	496.46
3	0.0057	25.00	0.2270	1000.08	0.0235	103.36	0.1134	499.79
4	0.0061	26.81	0.2295	1010.81	0.0233	102.45	0.1160	510.84
5	0.0058	25.39	0.2291	1009.17	0.0229	100.77	0.1157	509.72
6	0.0057	25.30	0.2253	992.52	0.0218	96.23	0.1159	510.55
7	0.0054	23.78	0.2251	991.67	0.0236	104.11	0.1136	500.62
8	0.0058	25.72	0.2230	982.45	0.0223	98.23	0.1117	492.12
9	0.0058	25.47	0.2278	1003.61	0.0234	103.00	0.1125	495.69
10	0.0058	25.78	0.2245	989.20	0.0221	97.22	0.1130	498.01
Mean value	0.0057	25.10	0.2266	998.10	0.0229	100.69	0.1136	500.50
SD	0.0002	0.99	0.0022	9.73	0.0006	2.72	0.0017	7.43
RSD, %	3.96	3.98	0.97	0.99	2.70	2.71	1.48	1.49

3.2.13. *Inter-day precision.* Four series of experiments were conducted similarly to those described in Section 3.2.11. The solutions were prepared each day for five consecutive days. The relative standard deviations were determined. The results are collected in Table 12.

TABLE XII. The inter-day precision test of the method of determination of norepinephrine with the Tollens' reagent.

Sample number	Working solution				Solution from injections			
	25 µg/l		1 mg/l		100 µg/l		500 µg/l	
	Abs. at 450 nm	Conc. of NB, µg/l	Abs. at 450 nm	Conc. of NB, µg/l	Abs. at 450 nm	Conc. of NB, µg/l	Abs. at 450 nm	Conc. of NB, µg/l
1	0.0056	24.51	0.2264	997.17	0.0213	93.67	0.1105	487.00
2	0.0055	24.36	0.2281	1004.70	0.0223	98.19	0.1156	509.45
3	0.0058	25.51	0.2262	996.66	0.0225	99.34	0.1119	492.89
4	0.0061	26.84	0.2331	1027.11	0.0233	102.71	0.1168	514.37
5	0.0053	23.25	0.2300	1013.30	0.0225	99.09	0.1137	500.76
Mean value	0.0056	24.89	0.2288	1007.79	0.0224	98.60	0.1137	500.89
SD	0.0003	1.35	0.0029	12.74	0.0007	3.24	0.0026	11.31
RSD, %	5.43	5.43	1.26	1.26	3.29	3.29	2.26	2.26

3.2.14. Accuracy for the determination of model rinse water samples. Four series of experiments were conducted. In the first two series five model rinse water samples prepared from the working solutions with the concentrations of norepinephrine equal to 25 µg/l and 1 mg/l, and in the other two series five model rinse water samples prepared from the solutions from injections with the concentration of norepinephrine equal to 100 µg/l and 500 µg/l were prepared and treated as described in the general procedure. The absorbance of the solutions was recorded. The concentrations of the solutions were calculated according to the regression equation, and the relative uncertainties were determined. The results are collected in Table 13.

TABLE XIII. The accuracy test of the method of determination of model rinse water samples of norepinephrine with the Tollens' reagent.

	Sample number	Absorbance at 450 nm	Concentration of norepinephrine bitartrate, mg/l	Relative uncertainty, %
Rinse water from the working solution, 25 µg/l	1	0.0052	22.81	8.75
	2	0.0054	23.71	5.15
	3	0.0052	23.05	7.80
	4	0.0058	25.71	2.83
	5	0.0052	22.80	8.80
	Mean value		0.0054	23.62
Rinse water from the working solution, 1 mg/l	1	0.2232	983.13	1.69
	2	0.2227	981.24	1.88
	3	0.2231	983.01	1.70
	4	0.2235	984.76	1.52
	5	0.2240	986.74	1.33
	Mean value		0.2233	983.77
Rinse water from the solution from injections, 100 µg/l	1	0.0213	94.01	5.99
	2	0.0224	98.50	1.50
	3	0.0220	97.04	2.96
	4	0.0240	105.55	5.55
	5	0.0215	94.67	5.33
	Mean value		0.0222	97.95



Rinse water from the solution from injections, 500 µg/l	1	0.1105	486.60	2.68
	2	0.1102	485.49	2.90
	3	0.1132	498.72	0.26
	4	0.1102	485.53	2.89
	5	0.1095	482.38	3.52
	Mean value	0.1107	487.74	2.45

3.2.15. *Precision for the determination of model rinse water samples.* Four series of experiments were conducted similarly to those described in Section 3.2.14. The relative standard deviations were determined, and the results are collected in Table 14.

TABLE XIV. The precision test of the method of determination of model rinse water samples of norepinephrine with the Tollens' reagent.

Sample number	Rinse water from the working solution				Rinse water of the injection's solution			
	25 µg/l		1 mg/l		100 µg/l		500 µg/l	
	Abs. at 450 nm	Conc. of NB, µg/l	Abs. at 450 nm	Conc. of NB, µg/l	Abs. at 450 nm	Conc. of NB, µg/l	Abs. at 450 nm	Conc. of NB, µg/l
1	0.0052	22.97	0.2240	986.78	0.0221	97.16	0.1120	493.21
2	0.0061	26.87	0.2216	976.30	0.0222	97.85	0.1095	482.46
3	0.0053	23.38	0.2301	1013.60	0.0214	94.11	0.1099	484.15
4	0.0054	23.71	0.2198	968.18	0.0230	101.44	0.1117	492.27
5	0.0053	23.26	0.2247	989.75	0.0214	94.23	0.1152	507.59
Mean value	0.0055	24.04	0.2240	986.92	0.0220	96.96	0.1117	491.93
SD	0.0004	1.60	0.0039	17.20	0.0007	3.02	0.0023	9.96
RSD, %	6.68	6.70	1.74	1.75	3.11	3.13	2.03	2.04

3.2.16. *Comparison of the results of titrimetric and spectrophotometric determinations.* A total of 1.000 g of norepinephrine bitartrate was weighed and dissolved in glacial acetic acid; the solution was transferred to the 100 ml volumetric flask, and the volume of the solution was adjusted by glacial acetic acid. The exact concentration of the solution was determined by titration. For this, ten aliquots of 5.0 ml of the prepared solution were transferred to the titration flask, and the solutions were mixed and titrated with the solution of 0.1 M perchloric acid using 0.05 ml of the solution of crystal violet as an indicator. Then, the aliquot of 5.0 ml of the prepared solution with the determined concentration was taken, transferred to the 2000 ml volumetric flask, and the volume of the solution was adjusted by water; the next aliquot of 5.0 ml of the diluted solution was taken, transferred to the 500 ml volumetric flask, and the volume of the solution was adjusted by water. The diluted solution was treated as described in the general procedure. The absorbance of ten portions of the silver nanoparticle suspension was recorded, and the concentrations were calculated according to the regression equation. The content of norepinephrine in the weighting was calculated using both methods, and the F-test of equality of variances and the t-test of equality of means were performed. The results are shown in Table 15.

TABLE XV. The comparison of titrimetric method of determination of norepinephrine and spectrophotometric method of determination of norepinephrine with the Tollens' reagent.

Sample number	Titrimetric method			Spectrophotometric method		
	Volume of the titrant, ml	Amount of NB in the aliquot, mg	Amount of NB in the weighting, mg	Absorbance at 279 nm	Concentration of NB in the aliquot, µg/l	Amount of NB in the weighting, mg

1	1.54	49.17	983.44	0.0569	250.54	1002.15
2	1.56	49.81	996.22	0.0553	243.69	974.76
3	1.60	51.09	1021.76	0.0567	249.62	998.47
4	1.62	51.73	1034.53	0.0587	258.50	1034.01
5	1.58	50.45	1008.99	0.0571	251.52	1006.06
6	1.60	51.09	1021.76	0.0559	246.13	984.50
7	1.58	50.45	1008.99	0.0555	244.57	978.27
8	1.56	49.81	996.22	0.0570	251.26	1005.04
9	1.60	51.09	1021.76	0.0552	243.11	972.44
10	1.62	51.73	1034.53	0.0584	257.23	1028.92
Mean value	1.59	50.64	1012.82	0.0567	249.62	998.46
Sample variance	0.0007	0.73	291.81	0.000001	28.80	460.82
F-value ( $f_1 = 9, f_2 = 9, p = 95\%$ )			1.58	Critical F-value ( $f_1 = 9, f_2 = 9, p = 95\%$ )		3.18
t-value ( $f = 18, p = 95\%$ )			1.655	Critical t-value ( $f = 18, p = 95\%$ )		1.734

### 3.3. Discussion

The method of determining the residues of pharmaceutical ingredients on the industrial equipment surface after the equipment cleaning should be as rapid and as simple as possible so that it can be performed directly in the production area after the cleaning procedure. The simplicity and rapidity of the UV and visible spectrophotometry method make it a good choice. It is also advantageous if the method utilizes only the reagents that are common for pharmaceutical laboratories. A comprehensive review of the available spectrophotometric methods of determination of different catecholamines was conducted, ensuring the reliability of the findings. The simplicity, analysis time, needed reagents and linearity ranges of available methods were compared. Based on this review, the simplest method of determination of norepinephrine at the ppm level is one utilizing its own absorption band at 279 nm. The common excipients present in the norepinephrine injections do not interfere. The linearity range is relatively broad, and the method has satisfactory accuracy and precision for the determination of model rinse water samples. However, the insoluble excipients and impurities should be pre-filtered and removed because their presence may affect the absorbance. The method is also not suitable for the determination of norepinephrine in complex matrices and in the mixtures of pharmaceutical ingredients. Suppose the analysis of norepinephrine in the rinse waters at the ppb level is required. In that case, the method utilizing the reduction of ammoniacal silver nitrate by norepinephrine to the colloidal silver and the measurement of the absorbance of the surface plasmon resonance band of silver nanoparticles is the most promising. In the previous work [103], this method needed to be properly validated, and therefore, in the present study, the analytical performance of this method was carefully studied. It was found that the method is simple and rapid, with only one-color reagent needed to initiate the reaction; the common excipients also do not interfere, and the accuracy and precision of the method for determining model rinse waters are also satisfactory. However, other reducing substances that may reduce silver nitrate to elemental silver might interfere. Therefore, the method may not be suitable for determining norepinephrine in mixtures of pharmaceutical preparations and complex matrices. Both methods were compared with the official titrimetric method of determination of norepinephrine proposed in the European Pharmacopoeia. As could be seen, both the calculated F- and t-values do not exceed the critical values for the given degrees of freedom and p-value, which means that these titrimetric and spectrophotometric methods give statistically equal results for the tested sample. Both methods are recommended for routine and quick analysis of norepinephrine in industrial intermediate goods during intermediate quality control, pharmaceutical formulations, and industrial equipment cleaning rinse water.

## 4. CONCLUSIONS

Two simple spectrophotometric methods for the determination of norepinephrine were validated to analyze the pharmaceutical ingredient in industrial equipment cleaning rinse water. The first method utilizes the absorbance of norepinephrine, and the second is based on the reduction of the Tollens' reagent by norepinephrine and the colorimetric determination of the formed silver nanoparticles. Both methods show suitable linearity ranges (0.02 to 10 and 1 to 150 mg/l, respectively), accuracy (4 and 7%, respectively), and precision (4 and 7%, respectively) do not require lengthy sample preparation and sophisticated laboratory equipment and are suitable for routine analysis of the pure pharmaceutical formulations and industrial equipment cleaning rinse waters. The applicability of this method for the analysis of complex mixtures containing norepinephrine and various catecholamines might be the subject of further studies.

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