



Brief Report

Integral UV Spectrophotometric Methods for Determination of Clopidogrel Bisulphate and Metamizole Sodium in Rinse Waters from Industrial Equipment

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Abstract: In this paper, methods for the determination of clopidogrel bisulphate and metamizole sodium in rinse waters from industrial equipment, using multiwavelength UV spectrometry and the calculation of areas under curves, are proposed. Spectra were recorded in an aqueous medium without preliminary pH adjustment. A numerical integration of the spectra was performed in the wavelength range of 210 to 290 nm for clopidogrel bisulphate, and 220 to 320 nm for metamizole sodium. The methods enable the determination of clopidogrel bisulphate and metamizole sodium in solution in the concentration range of 1–100 mg/L, do not require lengthy sample preparation and complex analytical equipment, and are suitable for the routine determination of these drugs in rinse waters from industrial equipment.

Keywords: clopidogrel bisulphate; metamizole sodium; aqueous medium; integral spectrophotometric determination; area under the curve method; rinse waters from industrial equipment



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1. Introduction

When different drugs are produced on a single production line, an integral part of pharmaceutical production is the cleaning of industrial equipment after each change in the drug produced, and the determination of microgram amounts of manufactured products on the equipment's surface and in the rinse water. In this case, the determination method should be as express and simple as possible, so that the determination can be made directly in the production area, and so that lengthy sample preparation does not slow down the production process. Therefore, UV spectrometry is the preferred method for analysing industrial equipment rinse water.

Clopidogrel bisulphate (IUPAC name: (+)-(S)-methyl-2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)acetate), CAS number 113665-84-2) (see Figure 1) is an antiplatelet drug used to prevent heart disease and stroke in people at high risk, and is used with aspirin in heart attacks and after coronary artery stent placement. It is included in the WHO list of essential medicines.

Metamizole sodium (IUPAC name: sodium salt of ((2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazol-4-yl)-methylamino)-methanesulfonic acid, CAS number 68-89-3) (see Figure 2) is an analgesic, antispasmodic, and antipyretic agent, and one of the strongest non-opioid analgesics. Both drugs are produced worldwide by several pharmaceutical companies on an industrial scale, so the development of a method for analysing their microgram amounts in industrial equipment rinse waters is an important practical task.

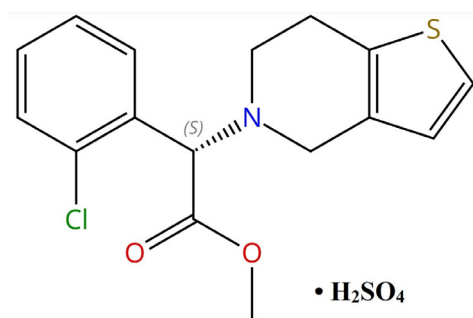


Figure 1. The structural formula of clopidogrel bisulphate.

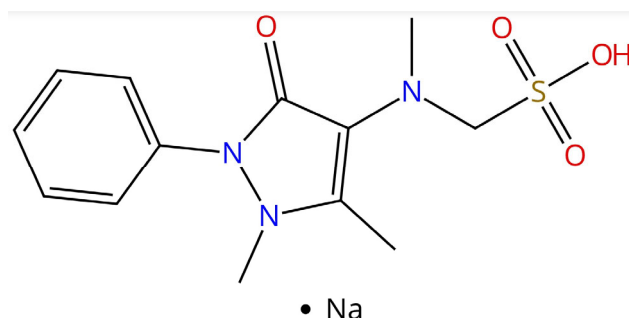


Figure 2. The structural formula of metamizole sodium.

Existing spectrophotometric methods for the analysis of clopidogrel bisulphate are summarised in Table 1. The UV spectra of clopidogrel bisulphate are shown in Figure 3. As can be seen from the figure, the absorption maxima at 270 and 276 nm have too low absorbance, so the sensitivity of direct spectrophotometric determination at these wavelengths is low. In a number of studies [1–9], differential spectrophotometry is used for determination, but the usage of organic solvents or preliminary adjustment of the pH of the solution is not applicable for the analysis of rinse waters. Other methods [7,10–15] employ different reactions of clopidogrel bisulphate with various reagents to form coloured products, but this complicates and lengthens the analysis.

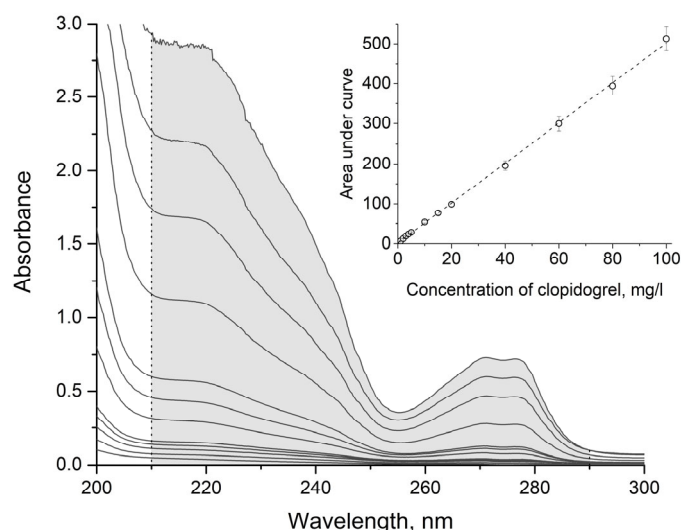


Figure 3. UV spectra of aqueous solutions of clopidogrel bisulphate of different concentrations, with the range for calculation of the areas under the curves, and the calibration dependence of the area under the curve (with the corresponding confidence intervals) on the concentration of clopidogrel bisulphate.

Table 1. Overview of spectrophotometric methods for analysis of clopidogrel bisulphate.

Medium	Used Reagents	Wavelength, nm	Linearity Range, mg/L	Accuracy, %	Precision, %	Ref.
Acetonitrile	No	220, 270, 274, 278	4–37	0.9	0.5	[1]
Acetonitrile	No	218, 229	5–38	0.9	0.5	[1]
Acetonitrile	No	210, 225	5–38	1.2	0.8	[1]
Methanol	No	203	10–26	2.9	4.1	[2]
Water	0.1 M HCl	271	42–336	1.3	1.9	[3]
Water	0.1 M HCl	280	42–336	2.5	0.8	[3]
Water	0.1 M HCl	269	42–336	0.5	1.2	[3]
Water	0.1 M HCl	276	42–336	0.5	1.2	[3]
Methanol + 1,4-dioxane	2,3-dichloro-5,6-dicyano-1,4-benzoquinone	450	5–35	1.5	1.3	[10]
Methanol	Citric acid, acetic anhydride	560	10–20	1.3	1.2	[10]
Water	N-bromosuccinimide, sulphanilamide	520	4–16	1.8	1.6	[10]
Water	Fe ³⁺ , 1,10-phenanthroline	510	10–50	0.4	0.4	[10]
Water/chloroform	Orange G	Not specified	50–250	Not specified	Not specified	[11]
Water/nitrobenzene	Cobalt thiocyanate	Not specified	100–500	Not specified	Not specified	[11]
Methanol + acetonitrile	No	202	1.25–25	3.6	3.8	[4]
Water	0.1 M HCl	222	40–70	1.2	0.9	[12,13]
Ethanol + water/chloroform	Bromophenol blue	407	15–80	0.8	0.8	[14]
Ethanol + water/chloroform	Bromocresol purple	407	25–115	0.9	1.0	[14]
Water	0.1 M HCl	219	10–30	1.7	0.5	[5]
Water/chloroform	Bromothymol blue	440	2.5–25	Not specified	Not specified	[15]
Water/chloroform	Orange II	490	2.5–20	Not specified	Not specified	[15]
Water/chloroform	Metanil yellow	410	2.5–15	Not specified	Not specified	[15]
Methanol + water	No	217	2.5–20	1.1	1.6	[6]
Water	Vanillin	517	5–40	Not specified	Not specified	[7]
Water	No	235	5–40	Not specified	Not specified	[7]
Water	0.1 M HCl	220	25–50	0.9	0.5	[8]
Ethanol	No	218	2–12	1.1	0.6	[9]
Water	No	210–290	1–100	3.8	4.1	This work

Existing spectrophotometric methods for the analysis of metamizole sodium are summarised in Table 2, and its UV spectra are shown in Figure 4. As can be seen from the figure, the spectra lack absorption maxima, and direct spectrophotometric determination is

difficult. Moreover, differential spectroscopy methods [16,17] are insensitive, and methods involving the formation of coloured reaction products [18–29] are time-consuming.

Table 2. Review of spectrophotometric methods for the analysis of metamizole sodium.

Medium	Used Reagents	Wavelength, nm	Linearity Range, mg/L	Accuracy, %	Precision, %	Ref.
Water	(NH ₄) ₂ MoO ₄	690	1–40	1.9	1.6	[18,19]
Water	Pb ²⁺ , pyrogallol red	520	2–16	2.9	0.8	[20]
Water	(NH ₄) ₆ P ₂ Mo ₁₈ O ₆₂	760	0.5–80	Not specified	4.0	[21]
Water	Chromotropic acid	575	0.57–5.7	1.3	1.7	[22]
Water	Nitrous acid	403	32–96	0.8	Not specified	[23]
Water	Fe ³⁺	642	3.5–281	4.0	0.8	[24]
Water	<i>p</i> -dimethylaminobenzaldehyde	430	10–400	1.0	2.2	[25]
Water	No	244	10–70	2.0	2.5	[16]
Water	No	285	10–70	2.0	3.4	[16]
Water	No	296	10–70	2.0	3.2	[16]
Water	0.05 M H ₂ SO ₄ , 0.025 M Na ₂ CO ₃	236–278	80–320	1.2	Not specified	[26]
Methanol	Bromine	232	40–320	3.7	Not specified	[26]
Water	(NH ₄) ₂ MoO ₄	620	155–2490	4.7	5.0	[27]
Water	No	258	8–40	7.0	8.3	[17]
	Cu ₃ (PO ₄) ₂ , alizarin red	540	16–125	4.0	4.0	[28]
Water	<i>m</i> -toluidine, K ₃ [Fe(CN) ₆]	530	0.4–10	2.0	0.7	[29]
Water	No	220–320	1–100	4.2	5.0	This work

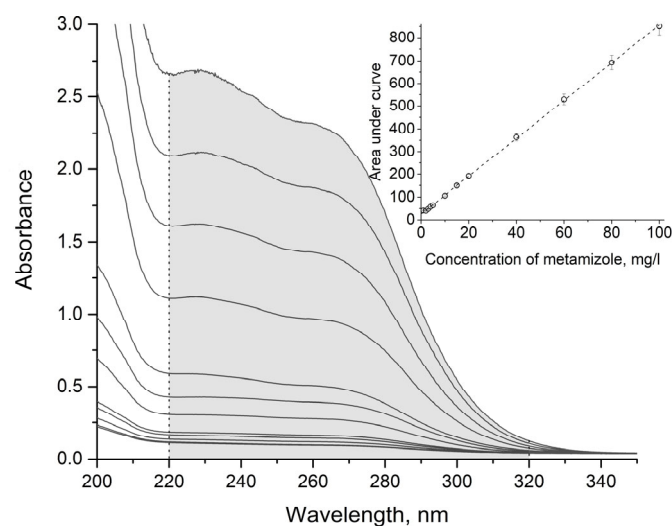


Figure 4. UV spectra of aqueous solutions of metamizole sodium of different concentrations, with the range for calculation of the areas under the curves, and the calibration dependence of the area under the curve (with the corresponding confidence intervals) on the concentration of metamizole sodium.

At the same time, integral spectroscopy has never been examined as a method for the determination of clopidogrel bisulphate or metamizole sodium in an aqueous solution. The

UV spectra of the aqueous solutions of both clopidogrel bisulphate and metamizole sodium do not depend on the solution pH. Therefore, the aim of this work is to develop integral UV spectrophotometric methods for determining clopidogrel bisulphate and metamizole sodium directly in rinse waters from cleaning industrial equipment, without using organic solvents and monitoring the solution pH.

2. Materials and Methods

2.1. Reagents and Equipment

Clopidogrel bisulphate and metamizole sodium were purchased from *Sigma-Aldrich* (Burlington, MA, USA). Tablets containing these substances were purchased from local pharmacies. Flat plates made from 12X12H10T steel were used to simulate rinses from industrial equipment. The analytical balance *Sartorius Cubis MSA 225P-ICE-DI* (Göttingen, Germany) was used for weighing. Various micropipettes manufactured by *Thermo Fisher Scientific* (Waltham, MA, USA) were used for taking the aliquots. The spectrophotometer *Agilent Cary 60* (Santa Clara, CA, USA) was used for all the spectrophotometric measurements. All the laboratory glassware used was of the second accuracy grade. The water for the preparation of the solutions was pre-purified by the *Sartorius Arium Pro VF Ultrapure Water* (Göttingen, Germany) deioniser.

2.2. Preparation of Solutions from Pharmaceutical Substances

Calibration and working solutions with different concentrations were prepared from the corresponding pharmaceutical substances by dissolving the corresponding weighed amounts in distilled water. The solutions were prepared anew daily.

2.3. Preparation of Solutions from Tablets

The tablets available in pharmacies contained 75 mg of clopidogrel bisulphate. The contents of ten tablets were thoroughly ground in a porcelain mortar, collected in a beaker, and dissolved in 800 mL of water; the solution was then filtered through a filter with a pore diameter of 12 μm , transferred to a 1000 mL volumetric flask, and its volume was brought up to the mark with water. Working solutions of various concentrations were prepared from the resulting solution.

The tablets available in pharmacies contained 500 mg of metamizole sodium. This solution was prepared in a similar way from ten tablets, and from this, working solutions of various concentrations are prepared.

2.4. Preparation of Model Rinse Waters

Aliquots of 10 mL of various working solutions, prepared from pharmaceutical substances or from tablets of clopidogrel bisulphate or metamizole sodium, were placed on flat plates made from 12X12H10T stainless steel, and dried in a fume hood. Test tubes containing 10.0 mL of distilled water were prepared. A cotton swab on a wire was immersed in water, and with its help, the dry residue was washed off the plates for 2 min. Used cotton swabs were immersed in the corresponding test tubes with water and mixed for 5 min. The resulting solutions were transferred to 10 mL measuring flasks, and the volume of the solution was brought up to the mark with water.

2.5. Construction of Calibration Graphs

Series of calibration solutions of clopidogrel bisulphate or metamizole sodium with concentrations equal to 1, 2, 3, 4, 5, 10, 15, 20, 40, 60, 80, and 100 mg/L were prepared. The solutions were placed in quartz cuvettes with an optical path length of 1 cm, and their UV

spectra were recorded in the wavelength range from 200 to 350 nm with a step of 0.2 nm relative to distilled water.

2.6. General Procedure for Determination

The test solution was placed in a quartz cuvette with an optical path length of 1 cm, and its UV spectrum was recorded in the wavelength range from 200 to 350 nm, with a step of 0.2 nm relative to distilled water.

2.7. Processing of Experimental Results

Numerical integration of the calibration spectra and spectra of the test solutions was performed in the wavelength range from 210 to 290 nm for clopidogrel bisulphate (see Figure 3) and from 220 to 320 nm for metamizole sodium (see Figure 4). Integration was performed using the Simpson formula. Then, the dependences of the areas under the curves on concentration were constructed. The dependence for clopidogrel bisulphate is shown in Figure 3, and that for metamizole sodium is shown in Figure 4. The experiments were repeated three times, and the corresponding confidence intervals for the areas under the curves are shown in the figures. The concentration of clopidogrel bisulphate or metamizole sodium in the test solution was determined using the obtained calibration dependence.

3. Results

3.1. Analytical Performance

The analytical performance of the method was determined in accordance with the regulations of the State Pharmacopoeia of the Russian Federation. The method was tested for linearity, selectivity, accuracy, and intra- and inter-day precision.

3.2. Linearity

According to Figures 3 and 4, the shapes of the UV spectra of aqueous solutions of clopidogrel bisulphate and metamizole sodium remain the same, and the areas under the curves are directly proportional to the concentrations of the corresponding substances in the concentration range from 1 to 100 mg/L. At lower concentrations, the values of the absorbances of the solutions become comparable with the spectrophotometer hardware error, and at higher concentrations, the shapes of the spectra begin to alter, which also significantly increases the error of the spectrophotometric measurements. The parameters of the regression dependence are given in Table 3.

Table 3. Parameters of regression dependencies of areas under curves on concentrations of pharmaceutical substances.

Parameter	Value	
	Clopidogrel bisulphate	Metamizole sodium
Substance being determined		
Slope of regression line and its confidence interval ($f = 10, p = 95\%$) (L/mg)	5.00 ± 0.04	8.32 ± 0.04
Intercept and its confidence interval ($f = 10, p = 95\%$)	1.7 ± 0.1	26 ± 1
R^2 value	0.9992	0.9998
Linearity range (mg/L)	1–100	1–100
Limit of detection (mg/L)	0.62	0.67
Limit of quantification (mg/L)	1.89	2.21

3.3. Interfering Effect of Commonly Used Excipients

According to the State Registry of Medicines of the Russian Federation, common excipients in tablets containing clopidogrel bisulphate are lactose, microcrystalline cellulose, talc, crosspovidone, and sodium starch glycolate, and in tablets containing metamizole sodium, common excipients are sucrose, talc, starch, and magnesium stearate. The possible interfering effect of these substances has been studied. Most of the excipients, except for lactose and sucrose, are insoluble in water at room temperature; therefore, after filtration of the solution, they do not affect the UV spectra. In turn, lactose and sucrose solutions in the quantities in which they are present in the tablets do not have an interfering effect in the used wavelength range of 210–320 nm.

3.4. Accuracy and Precision

Ten working solutions with concentrations equal to 30 mg/L were prepared from the bulk pharmaceutical ingredients clopidogrel bisulphate and metamizole sodium. Ten solutions with concentrations equal to 75 mg/L were prepared from the tablets of clopidogrel bisulphate, and ten solutions with concentrations equal to 50 mg/L were prepared from the tablets of metamizole sodium. The concentrations of the solution components were determined according to the described general procedure, and the relative uncertainties and relative standard deviations were determined. The results are summarised in Table 4. More details are given in the Supplementary Materials (see Figures S1 and S2, and Tables S1–S5).

Table 4. Accuracy and precision of method.

Test Solution	Relative Uncertainty, %	Relative Standard Deviation Within One Day, %	Relative Standard Deviation Within Several Days, %
Clopidogrel bisulphate working solution, 30 mg/L	3.1	4.1	5.4
Clopidogrel bisulphate solution from tablets, 75 mg/L	4.1	4.9	5.8
Metamizole sodium working solution, 30 mg/L	4.5	5.4	5.9
Metamizole sodium solution from tablets, 50 mg/L	5.8	5.8	6.4

3.5. Accuracy and Precision for Model Rinse Waters

Ten model rinse water solutions were prepared from the working solutions with concentrations equal to 30 mg/L that were prepared from the pharmaceutical ingredients clopidogrel bisulphate and metamizole sodium. Ten model rinse water solutions were prepared from the solutions with concentrations equal to 75 mg/L that were prepared from the tablets of clopidogrel bisulphate, and ten model rinse water solutions were prepared from the solutions with concentrations equal to 50 mg/L that were prepared from the tablets of metamizole sodium. The concentrations of the solution components were determined according to the described general procedure, and their relative uncertainties and relative standard deviations were determined. The results are summarised in Table 5. More details are given in the Supplementary Materials (see Figures S3 and S4, and Tables S6–S10).

Table 5. Accuracy and precision in analysis of model rinse waters.

Test Solution	Relative Uncertainty, %	Relative Standard Deviation, %
Model rinse water from working solution of clopidogrel bisulphate, 30 mg/L	8.7	9.4
Model rinse water from clopidogrel bisulphate solution from tablets, 75 mg/L	10.2	10.9
Model rinse water from working solution of metamizole sodium, 30 mg/L	8.7	10.2
Model rinse water from solution of metamizole sodium from tablets, 50 mg/L	10.0	10.9

4. Discussion

The experiments showed that the proposed integral spectrophotometric methods are suitable for the determination of clopidogrel bisulphate and metamizole sodium in rinse waters from cleaning industrial equipment. The methods are fast and simple, and do not require additional reagents, lengthy sample preparation, or complex equipment. The determination can be performed in the aqueous medium without the necessity of pH adjustment. Commonly used excipients do not interfere. Relative uncertainties and relative standard deviations did not exceed 7% in the analysis of the pharmaceutical ingredients, and did not exceed 11% in the analysis of the model rinse waters. These values are somewhat higher than those of the other methods presented in Tables 1 and 2; however, both the accuracy and the precision of the proposed methods are acceptable for the analysis of the residual quantities of pharmaceutical ingredients in rinse waters from cleaning industrial equipment. The calibration graphs of the dependence of the area under the curve on concentration retain linearity over a wide concentration range, from 1 to 100 mg/L. The linearity range of the proposed method usually exceeds those of the other methods presented in Tables 1 and 2. The limits of detection and limits of quantification of the proposed methods are sufficiently low, and allow the detection of the residual quantities of both clopidogrel and metamizole down to 1 ppm, which is suitable for the efficient control of the removal of these ingredients from the equipment's surface during cleaning. These methods are recommended for the routine analysis of clopidogrel bisulphate and metamizole sodium in rinse waters from cleaning industrial equipment.

5. Conclusions

Simple integral spectrophotometric methods for the determination of clopidogrel bisulphate and metamizole sodium in rinse waters from cleaning industrial equipment are proposed. The analytical performance of both methods is acceptable for rinse water analysis. The linearity range, limit of detection, and limit of quantification of the methods are comparable with those of other existing methods for the spectrophotometric determination of these pharmaceutical ingredients. The determination is performed in an aqueous medium, it is not expensive, and no environmentally harmful reagents and solvents are needed. The methods are fast and easy, do not require lengthy sample preparation, complex laboratory equipment, or highly trained personnel, and are suitable for routine analysis.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/spectroscj3010002/s1>, **Figure S1:** UV spectra of working solutions of clopidogrel bisulphate with concentration of 30 mg/L used for accuracy test; **Figure S2:** UV spectra of solutions from tablets of clopidogrel bisulphate with concentration of 75 mg/L used for accuracy test; **Figure S3:** UV spectra of working solutions of metamizole sodium with concentration of 30 mg/L

used for accuracy test; **Figure S4**: UV spectra of solutions from tablets of metamizole sodium with concentration of 50 mg/L used for accuracy test; **Table S1**: Accuracy test of method of determination of clopidogrel bisulphate; **Table S2**: Intra-day precision test of method of determination of clopidogrel bisulphate; **Table S3**: Inter-day precision test of method of determination of clopidogrel bisulphate; **Table S4**: Accuracy test for determination of clopidogrel bisulphate in model rinse water solutions; **Table S5**: Precision test for determination of clopidogrel bisulphate in model rinse water solutions; **Table S6**: Accuracy test of method of determination of metamizole sodium; **Table S7**: Intra-day precision test of method of determination of metamizole sodium; **Table S8**: Inter-day precision test of method of determination of metamizole sodium; **Table S9**: Accuracy test for determination of metamizole sodium in model rinse water solutions; **Table S10**: Precision test for determination of metamizole sodium in model rinse water solutions.

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