

Micellar extraction of cimetidine

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Introduction

The occurrence of pharmaceutical residues in the particular environmental components might harmfully influence on the growth of the aquatic ecosystem and human health. The used therapeutic compounds are not completely metabolized and are excreted in unchanged forms. Moreover, the progress of pharmaceutical industry and unsuitable utilization of the unused drugs increases probability of their getting into surface water. The pharmaceutically active compounds are not biodegradable and are not eliminated during wastewater treatment [1, 2].

The different groups of pharmaceuticals including antibiotics or analgesic and anticancer drugs are detected in the environmental components [3]. Nowadays, the histamine H_2 receptor antagonists are usually used for treatment of gastric diseases. These compounds enable decreasing of secretion of stomach acid by antagonizing effect of histamine H_2 receptors [4 – 6]. Cimetidine (CMT) as an antihistaminic drug contains heteroaromatic ring of imidazole, which is connected with 1-cyano-2-methylguanidine by polar group (Fig. 1.) [7]. Cimetidine is well soluble drug in water ($\log K_{ow} = 0.2$) and exhibits the basic chemical properties ($pK_a = 7.1$) [8]. The discussed analyte is able to form coordination compounds with metal ions due to the presence of amine groups in its structure [9]. Cimetidine creates four polymorphic forms (A-D). However, structure A of this drug is present in pharmaceutical dosage forms [10]. The little amount of applied CMT is metabolized in the human body and is excreted in 70% in unchanged forms [11].

The occurrence of cimetidine in environmental samples indicates on the wide applying of this compound. The discussed drug was detected in river and wastewater samples from Hungary and South Korea with using solid phase extraction (SPE) and chromatographic determination (LC-MS/MS) [12, 13]. The low level of the concentration of pharmaceuticals (ng/L up to the $\mu\text{g/L}$) in the environmental samples induces to developing of the new isolation methods to ensure sensitive and selective detection of these compounds. The micellar extraction realizes this requirement. The discussed technique is frequently used for isolation of metal ions and different organic analytes [14, 15]. The micellar extraction is performed with applying surface active agents. These compounds are enable to create micelles above their the critical micellar concentration (CMC). During extraction, the analytes from aqueous phase are connected with the micellar aggregates [16, 17].

In the presented studies, the micellar extraction was used for selective isolation of cimetidine and then for its spectrophotometric determination in aqueous samples. The extraction process was performed with using anionic surfactant: sodium dodecylsulfate (SDS) (Fig. 2). Moreover, the nonionic surface active agent Tween 80 (TW-80) was added to extractive samples. This surfactant is polyoxyethylene derivative of sorbitol and oleic acid. According to our best knowledge, the micellar extraction has not been applied for the analysis of cimetidine in the environmental samples.

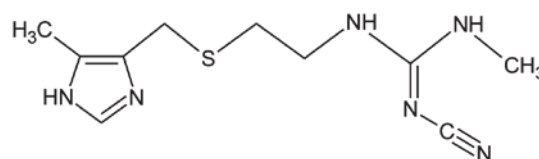


Fig. 1. Chemical structure of cimetidine (CMT)

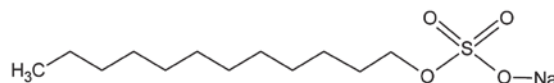


Fig. 2. Chemical structure of sodium dodecylsulfate (SDS)

Experimental

Apparatus and reagents

Micellar extraction of cimetidine was performed using a vortex mixer (Heidolph Vibramax 110, Germany) and a centrifuge (MPW-251, Poland). Spectral measurements were done on a spectrophotometer UV/VIS (200 V, U-1900, model 310–0003, Hitachi, Japan). The reagents for experiments were obtained from Sigma Aldrich (Germany).

The standard solutions of cimetidine (10^3 mol/L), sodium dodecylsulfate (0.2 mol/L) and sodium chloride (4 mol/L) were prepared by dissolving appropriate weighed amounts of these substances in 100 mL of doubly distilled water. The standard solution of TW-80 (10%) was prepared by diluting 100% solution of surfactant of doubly distilled water in 100 mL flask. The stock solution of TW-80 (1%) was prepared by next diluting of this surface active agent.

Micellar extraction procedure

For the micellar extraction of cimetidine, 3 mL of solution of SDS (0.2 mol/L), 0.5 mL of 10^3 mol/L solution of studied analyte and 3.5 mL of solution of sodium chloride (4 mol/L) were transferred into a 10 mL volumetric tube. Then the extractive samples were manually shaken for 30 seconds and were centrifuged for 5 min at 6000 rpm. Separation of the two phases was achieved. After removing aqueous phase, the micellar layer was dissolved in 4 mL of methanol.

The micellar extraction of studied analyte with using mixture of surfactants: SDS and TW-80 was performed following by above-mentioned procedure. However, 2.5 mL of solution of SDS (0.2 mol/L) and 0.3 mL of 1% solution of TW-80 were transferred into a 10 mL volumetric tube. The samples were shaken for 10 min (500 rpm) using vortex mixer. The surfactant-rich layer was dissolved in 3 mL of methanol. The absorbance of extracts was measured at 220 nm.

The extraction procedures were applied for surface water and wastewater analysis. The real samples were taken from regions of Podlaskie Voivodeship in Poland (Białystok, Suwałki).

3. Results and discussion

3.1. The optimal conditions of micellar extraction of cimetidine

Cimetidine exhibits the basic chemical properties and exists in the form of an organic cation in acidic and neutral aqueous solutions. Therefore, the anionic surface active agent: sodium dodecylsulfate was used for the process of micellar extraction of cimetidine. The discussed surfactant exists in the aqueous solution in the form of

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organic anion and is able to bind CMT following by electrostatic interaction with created micelles. The primary studies showed that micellar extraction using SDS makes possible effective isolation of analyte. Additionally, the nonionic surface active agent Tween 80 was applied in the isolation process to enhance efficiency of micellar extraction of cimetidine. However, the discussed surfactant enabled only increasing of coefficient of CMT preconcentration. The obtained micellar layers were dissolved in the less of amount of organic solvent in comparison to isolation process with using SDS. Cimetidine exhibits the characteristic band at 220 nm in methanolic solution (Fig. 3).

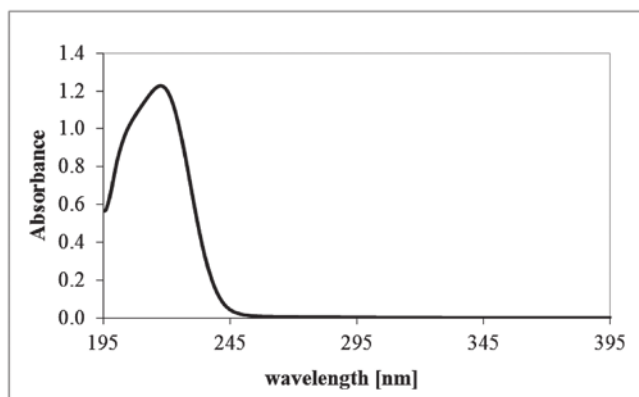


Fig. 3. Absorption spectrum of cimetidine ($5 \cdot 10^{-5}$ mol/L) in methanol ($\lambda_{\text{CMT}} = 220$ nm)

The extraction of cimetidine was performed with using surface active agents above their critical micellar concentration [18, 19]. It was visually observed that efficiency of isolation process is adequate while the concentration value of solutions of SDS and TW-80 is equal 0.05 mol/L and 0.03%, respectively. The optimized volumes of surfactants enable appropriate size and consistency of the creating micelles. Their aggregation number is increased by the addition of an electrolyte too. The fixed amounts of sodium chloride were introduced into the aqueous samples during micellar extraction of CMT. It was found that absorbance of the studied analyte in extracts is the highest while concentration of solution of NaCl is equal 1.4 mol/L (Fig. 4). The performed studies showed that the change of pH samples does not influence on the extraction process of cimetidine (Fig. 5). Therefore micellar extraction of analyte at pH: 7.0 was performed for further studies. The addition of a suitable volume of acid or base causes decreasing of absorption value of CMT. During performing studies it was observed, that the change of shaking time and rate does not influence for isolation process of cimetidine. The same results were obtained for centrifugation of extractive samples. The highest absorbance of CMT in methanolic extracts was received while the content of tubes were shaken for 1 min and 10 min (500 rpm) during extraction of cimetidine using SDS and SDS with TW-80, respectively. The extractive samples were centrifuged for 5 min at 6000 rpm.

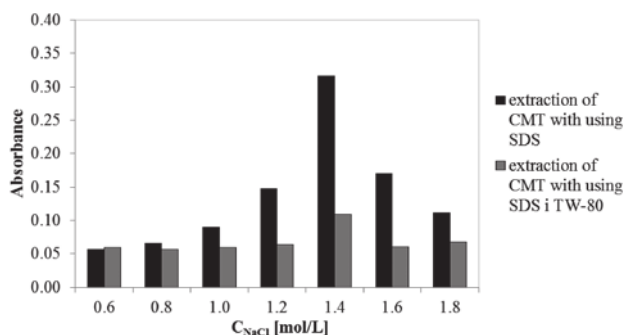


Fig. 4. The effect of sodium chloride concentration on the micellar extraction of CMT

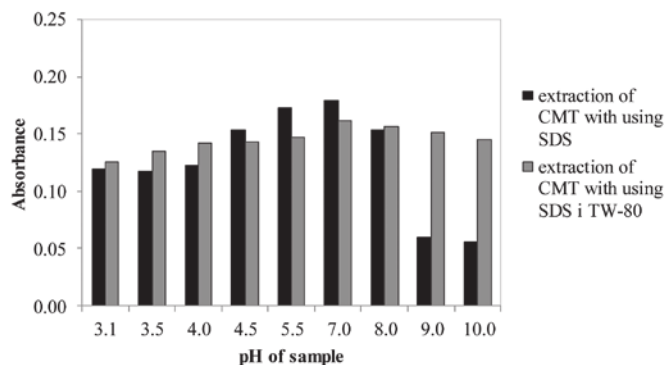


Fig. 5. The influence of pH aqueous samples on the absorbance of cimetidine in obtained extracts

The analytical parameters of methods for determination of CMT

The analytical parameters of determination methods of cimetidine after its isolation following by micellar extraction were estimated (Tab. 1). Precision of spectrophotometric method for determination of CMT was evaluated by repeatability and reproducibility of absorbance measurements of analyte. The micellar extraction of cimetidine ($5 \cdot 10^{-5}$ mol/L) was simultaneously performed for ten samples in one day to determine parameter of repeatability. Reproducibility of obtained results was estimated by measurements of absorbance of CMT in received extracts in five days. The analytical characteristic of elaborated methods showed that the extraction procedures can be interchangeably applied for spectrophotometric determination of cimetidine. It was found that limit of detection and sensitivity of elaborated methods are characterized by the similar values. Although, coefficient of preconcentration for studied analyte is a bit higher during extraction with mixture of surfactants in comparison to isolation process of cimetidine with using SDS.

Table 1

Analytical characteristic of methods for spectrophotometric determination of CMT after micellar extraction with using the appropriate surfactants

Analytical parameter	Extraction of CMT with using SDS	Extraction of CMT with using SDS and TW-80
equation of calibration curve	$y = 8091x + 0.010$	$y = 2362x + 0.050$
coefficient of determination	$R^2 = 0.999$	$R^2 = 0.999$
sensitivity	$8.1 \cdot 10^3$ L/mol · cm	$2.4 \cdot 10^3$ L/mol · cm
repeatability of measurement ($n = 10$)	7.3%	7.0%
reproducibility ($n = 5$)	6.6%	7.3%
linearity	$1.5 \cdot 10^{-5}$ mol/L – $1.0 \cdot 10^{-4}$ mol/L	$1.0 \cdot 10^{-5}$ mol/L – $3.5 \cdot 10^{-4}$ mol/L
limit of detection (LOD)	$2.9 \cdot 10^{-6}$ mol/L	$3.2 \cdot 10^{-6}$ mol/L
limit of quantification (LOQ)	$8.8 \cdot 10^{-6}$ mol/L	$9.2 \cdot 10^{-6}$ mol/L
coefficient of preconcentration	2.7	3.4
recovery of analite after extraction	99.1%	99.7%

Analysis of surface water and wastewater samples

The influence of interfering compounds on the extraction process and determination of cimetidine was investigated. It was observed that ions present in natural water samples: NO_3^- , SO_4^{2-} , CO_3^{2-} , Cl^- , $\text{C}_2\text{O}_4^{2-}$ and Fe^{2+} do not influence on the analysis of the studied drug. The elaborated procedures for isolation and determination of CMT (Chapter 2.2) were applied for studying presence of this analyte in wastewater and water samples from river Biala (Białystok) and Szeszuła (Suwałki). The analysis of the obtained results (Tab. 2) following by standard addition method indicated absence of cimetidine in the real samples in the studied range of concentration. The received values of extraction recovery amounted to about 100%.

Table 2

Spectrophotometric determination of cimetidine in river and wastewater samples after micellar extraction with using SDS and mixture of SDS and TW-80

Sample	Extraction of cimetidine with using SDS			
	Added amount of CMT [μg]	Found amount of CMT [μg]	Recovery [%] ($n = 3$)	RSD [%]
River Biala (Białystok)	37.85	35.33	90.2	7.5
	126.17	113.55	89.3	6.3
River Szeszuła (Suwałki)	37.85	35.33	93.8	7.2
	126.17	116.08	91.5	7.4
Wastewater after treatment	37.85	35.33	94.1	8.1
	126.17	118.6	93.3	6.0
River Biala (Białystok)	Extraction of cimetidine with using SDS and TW-80			
	25.23	23.97	95.4	7.9
River Szeszuła (Suwałki)	25.23	24.73	98.2	7.1
	126.17	123.65	97.3	6.4
Wastewater after treatment	25.23	23.72	94.0	6.4
	126.17	118.60	94.4	5.3

Conclusions

The elaborated methods enable effective isolation of cimetidine from aqueous samples. The recovery of analyte after extraction is equal 99%. The applying of the surface active agents during isolation process of the studied compound cause decreasing of volatile organic solvents amounts which are used in a classical extraction techniques. The spectrophotometric method for determination of CMT with using optimized procedures of isolation is characterizes by wide range of linearity, satisfactory precision and low limit of detection and quantification values. The elaborated methods with applying micellar extraction give possibility of determination of cimetidine in surface water samples at the low level concentrations.

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