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ORIGINAL ARTICLE / ÖZGÜN MAKALE

EXTRACTION-FREE SPECTROPHOTOMETRIC DETERMINATION OF MELOXICAM USING BROMOTHYMOL BLUE

BROMOTİMOL MAVİSİ KULLANILARAK EKSTRAKSİYON OLMADAN MELOKSİKAMIN SPEKTROFOTOMETRİK TAYİNİ

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ABSTRACT

Objective: *The purpose of the present work was to develop and validate a fast, simple and sensitive extraction-free spectrophotometric technique for the quantitative determination of meloxicam based on the reaction with bromothymol blue.*
Material and Method: *The reference standard of meloxicam, bromothymol blue and finished dosage forms of meloxicam were used in the study. Absorption measurements were performed on the Analytic Jena UV-visible spectrophotometer model Specord 200.*
Result and Discussion: *The developed method is based on the formation of the colored reaction product between meloxicam and bromothymol blue in acetone medium with absorption maximum at 348 nm. The method meets the requirements of the State Pharmacopoeia of Ukraine for such validation characteristics as specificity, linearity, precision, accuracy, robustness and range of application. The obedience to Beer's law is observed in the range of meloxicam concentrations 0.80-2.40 mg/100 ml, the correlation coefficient is 0.9998. The range of application of the method is 60-140%.*
Keywords: *Meloxicam, bromothymol blue, sulfonephthalein dyes, spectrophotometry, validation studies*

ÖZ

Amaç: *Mevcut çalışmanın amacı, bromotimol mavisi ile reaksiyona dayalı olarak meloksikamın kantitatif tayini için hızlı, basit ve hassas ekstraksiyon gerektirmeyen bir spektrofotometrik teknik geliştirmek ve doğrulamaktır.*
Gereç ve Yöntem: *Çalışmada meloksikamın referans standardı, bromotimol mavisi ve meloksikamın bitmiş dozaj formları kullanılmıştır. Absorpsiyon ölçümleri, Analitik Jena UV-*

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görünür spektrofotometre modeli Specord 200 üzerinde gerçekleştirilmiştir.
Sonuç ve Tartışma: *Geliştirilen yöntem, 348 nm'de maksimum absorpsiyon gözlenerek aseton ortamında meloksikam ve bromotimol mavisi arasındaki reaksiyonun boyalı ürününün oluşmasına dayanmaktadır. Geliştirilen teknik, özgüllük, doğrusallık, kesinlik, doğruluk, sağlamlık ve uygulama aralığı gibi validasyon özellikleri için Ukrayna Devlet Farmakopesi şartlarını karşılamaktadır. Beer yasasına uygunluk 0.80-2.40 mg/100 ml konsantrasyon aralığında gözlemlenir. Korelasyon katsayısı 0.9998'dir. Tekniğin uygulama aralığı %60-140'tır.*
Anahtar Kelimeler: *Meloksikam, bromotimol mavisi, sülfonatalein boyaları, spektrofotometri, validasyon çalışmaları*

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly used drug groups in medicine. Their advantage is their complex action (antipyretic, anti-inflammatory, analgesic) and a wide range of indications for use. NSAIDs are used for the symptomatic treatment of pain and inflammation of various etiologies, particularly in lesions of the musculoskeletal system [1,2]. According to statistics, NSAIDs are the most popular medications among doctors and the public for the treatment of musculo-articular pain and take the leading place in the world in terms of consumption [3]. One of the well-known representatives of NSAIDs is meloxicam.

Meloxicam (4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide) refers to the group of oxicams and shows selective inhibition of COX-2 isoenzyme, providing anti-inflammatory and analgesic effects. It is used as a drug for the symptomatic treatment of exacerbations of arthritis, chronic polyarthritis, rheumatoid arthritis. Meloxicam preparations are produced by leading pharmaceutical companies in the form of tablets, capsules and solutions for injection [4,5]. Therefore, the development of reliable and accessible methods of quantitative analysis of the drug is undoubtedly relevant.

The assay of meloxicam is listed in the European Pharmacopoeia, which describes non-aqueous titration with potentiometric fixation of the end-point [6]. The United States Pharmacopeia recommends HPLC method using a UV-Vis absorbance detector for the quantitative determination of the drug [7].

There is a wide choice of various analytical techniques for the assay of meloxicam in pharmaceuticals available in the literature [8-18]. Spectrophotometry is one of the most commonly used methods for the determination of this drug.

Thus, A. Chaplenko et al. proposed spectrophotometric and colorimetric determination of meloxicam, lornoxicam, tenoxicam in drugs using 7-chloro-4-nitrobenz-2-oxa-1,3-diazole (NBD chloride). The techniques are based on alkaline hydrolyses of oxicams with NBD chloride and the subsequent spectrophotometric and colorimetric determination of the colored products of the reaction [19].

Two sensitive and fast methods for determination of meloxicam using direct and indirect flow injection spectrophotometry are described in *Current Pharmaceutical Analysis*. The direct method depended on the coupling of meloxicam with diazotized procaine benzylpenicillin in alkaline medium. On the other hand, the indirect method involved a charge transfer reaction between the alkaline hydrolytic product of meloxicam as n-donor with metol (*p*-methylaminophenol sulfate) as a π- acceptor using sodium periodate as an oxidant [20].

In the literature, there are also data on the quantitative determination of meloxicam using sulfonephthalein dyes. Thus, Sane et al. recommend a method based on the formation of ion-pair complexes of the drug with three acid dyes, namely, bromothymol blue (BTB), bromocresol purple (BCP), bromophenol blue (BPB) in acidic buffer solutions followed by their extraction in organic solvents (chloroform and methylene chloride) [21].

Sulfonephthalein dyes are synthetic substances that are derivatives of triphenylmethane. Their water-soluble sodium salts, as well as acidic forms, are widely used in chemical analysis as pH indicators [22]. Sulfonephthalein dyes are known to form ionic associations when interacting with basic drugs, which are used to determine many pharmaceutical compounds by extraction spectrophotometry [23]. For example, bromothymol blue is used for the extraction spectrophotometric determination of

antifungal [24], antimicrobial [25], cardiovascular [26], and other drugs. Since extraction is a time-consuming procedure, a promising area of research is the development of non-extraction spectrophotometric methods based on ionic pairs in non-aqueous or aqueous solutions.

Therefore, the purpose of the work was to develop and validate a fast, simple and sensitive extraction-free spectrophotometric technique for the quantitative determination of meloxicam based on the reaction with bromothymol blue.

MATERIAL AND METHOD

Analytic Equipment

Absorption measurements were performed on the Analytic Jena UV-visible spectrophotometer model Specord 200 with 1 cm quartz cells. Kern electronic balance ABT-120-5DM was used to weigh the analyzed samples.

Materials and Reagents

All chemicals and reagents used were of analytical or pharmaceutical grade. Bromothymol blue, acetone, chloroform, 1,4-dioxane, ethanol were obtained from commercial sources. The reference standard of meloxicam was supplied by Derivados Quimicos, S.A., Spain (series No. 269001T01D).

Tablets “Meloxicam KV” 15 mg (JSC “Kyiv Vitamin Plant”, Ukraine, series No. UE20820), tablets “Meloxicam” 15 mg (PJSC "Lekhim-Kharkiv", Ukraine, series No. 93029004), tablets “Revmoxicam” 7.5 mg (JSC “Farmak”, Ukraine, series No. 80819), tablets “Meloxicam Teva” 7.5 mg (Merkle GmbH, Germany, series No. V23961A) were purchased from a local pharmacy.

0.15% solution of bromothymol blue was prepared by dissolving 0.15 g of bromothymol blue in 100 ml of acetone.

0.016% working standard solution was prepared by dissolving 0.0160 g of pure meloxicam in 100 ml of acetone.

General Method for the Assay of Meloxicam

The aliquots of the working standard solution containing 0.80-2.40 mg of meloxicam were transferred into 10 ml volumetric flasks. 1 ml of 0.15% bromothymol blue solution was added to each of the above flasks and brought to the mark with acetone. The absorption of the reaction product was measured at a wavelength of 348 nm against the reagent blank.

Method for the Assay of Meloxicam in Tablets

Twenty tablets were weighed and powdered. A portion of the powder containing 4 mg of meloxicam was weighed and transferred into a 25 ml calibrated flask. The volume was brought to the mark with acetone, mixed and filtered using “Blue ribbon” filter. Aliquots of the filtrate were analyzed according to the general method.

RESULT AND DISCUSSION

In order to develop a spectrophotometric method for the quantitative determination of meloxicam by reaction with bromothymol blue, the optimal conditions for the interaction of the components of the reaction were determined.

To establish the optimal reaction medium, the interaction of meloxicam with the reagent in such solvents as chloroform, 1,4-dioxane, acetone, and ethanol was studied (Figure 1). The maximum value of the absorption and satisfactory results when checking the stability of the reaction product in the selected solvent confirmed the feasibility of using acetone for further development of the method.

The effect of reagent concentration on the absorption value was also investigated. For this purpose, the absorption of solutions containing a fixed concentration of meloxicam and different amounts of bromothymol blue was measured. The graph shows that 1 ml of 0.15% reagent is the most acceptable. Further increase in the volume of the reagent does not lead to an increase in the absorption (Figure 2).

The product of the reaction was formed instantly at room temperature and was stable.

Thus, it was found that meloxicam reacts with bromothymol blue in an acetone medium. The maximum absorption of the reaction product is measured at a wavelength of 348 nm (Figure 3).

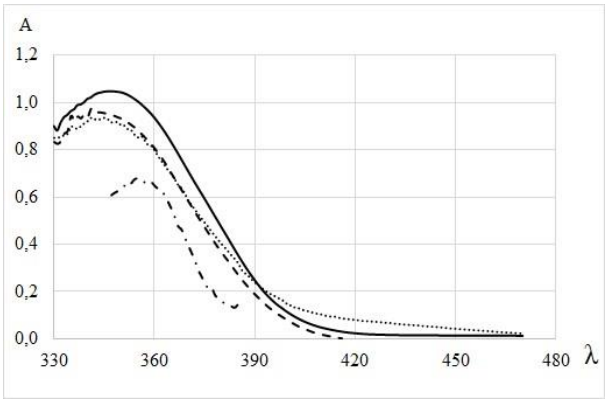

Figure 1. Absorption spectrum of reaction product of meloxicam (0.016%) with bromothymol blue (0.15%) in acetone (──), chloroform (- - - -), 1,4-dioxane (····), ethanol (-·-·-·-)

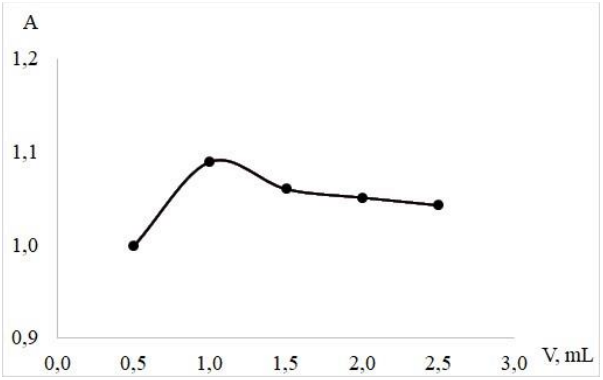

Figure 2. Dependence of the absorption value on the volume of the added reagent (0.15%)

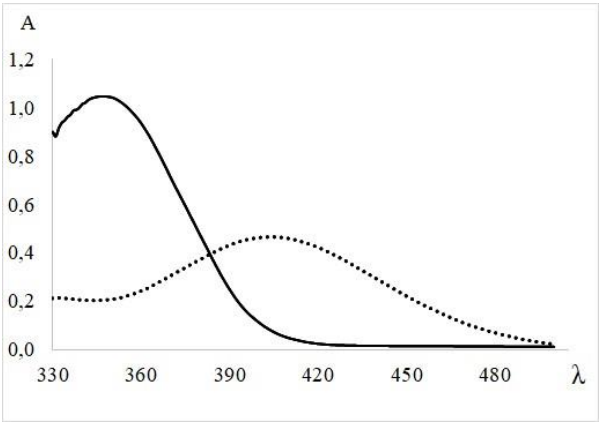

Figure 3. Absorption spectrum of reaction product of meloxicam (0.016%) with bromothymol blue against reagent blank (──); bromothymol blue (0.15%) reagent blank against acetone (····)

It is known that when sulfonephthalein dyes interact with nitrogen-containing compounds in organic solvents, ionic pairs are formed by the proton transfer mechanism [27, 28]. Thus, the secondary

aliphatic amino group of meloxicam attaches a proton to the phenolic group of the dye. The lactoid ring is opened, accompanied by the formation of a complex between protonated meloxicam and the dye anion (Figure 4).

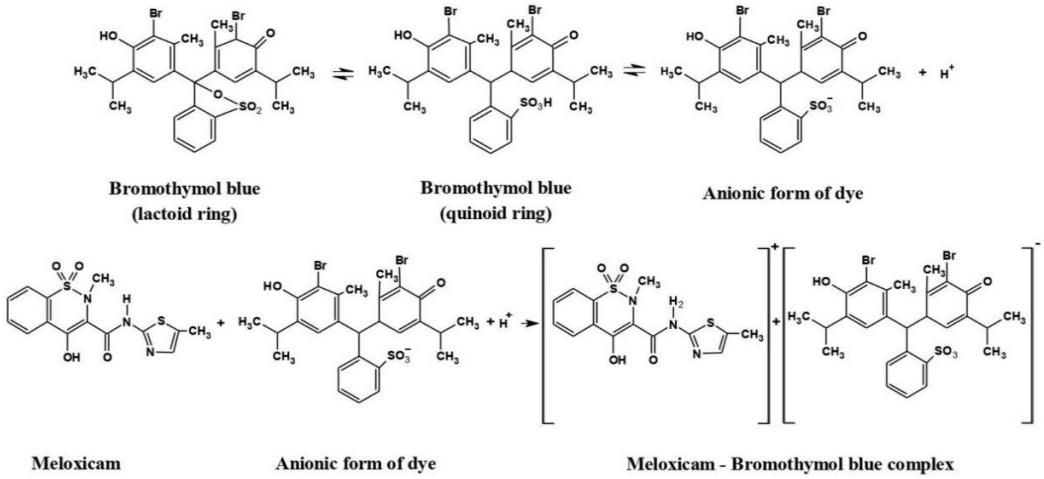

Figure 4. The possible reaction mechanism between meloxicam and bromothymol blue

Definition of Validation Characteristics

Validation was performed to confirm the suitability of the developed method for quality control of meloxicam. The selection and calculation of validation characteristics were performed in accordance with the requirements of the State Pharmacopoeia of Ukraine [29].

Specificity

In order to assess the specificity of the developed method, the contribution of excipients included in the dosage forms to the total absorption of the solution was determined. Tests with a placebo solution were conducted for this study. Model mixtures of excipients were prepared. Meloxicam of the concentration contained in the test drug was added to a part of each model mixture. Then all the stages of sample preparation were reproduced and the absorption of the "placebo" solution and the comparison solution containing the test drug was measured. It was found that contribution of placebo to the total background absorbance is insignificant for the investigated dosage forms (Figure 5).

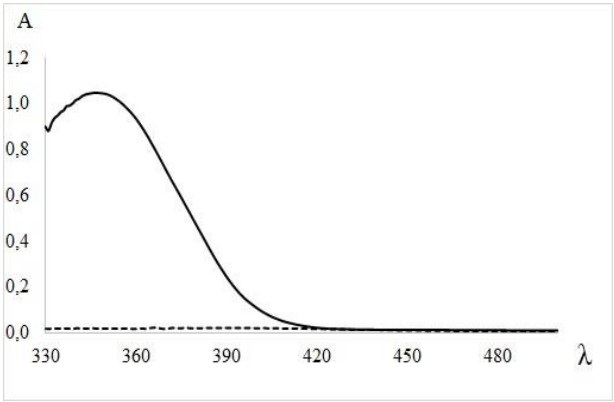

Figure 5. Absorption spectrum of placebo of tablets "Revmoxicam" 7.5 mg (- - -); reaction product of meloxicam (0.016%) with bromothymol blue (──)

Linearity

The linearity of the developed method was studied in the range of meloxicam concentrations of 0.80-2.40 mg/100 ml. A graph of the dependence of absorption (Y_i, %) on the concentration of the test substance (X_i, %) in normalized coordinates was plotted (Figure 6).

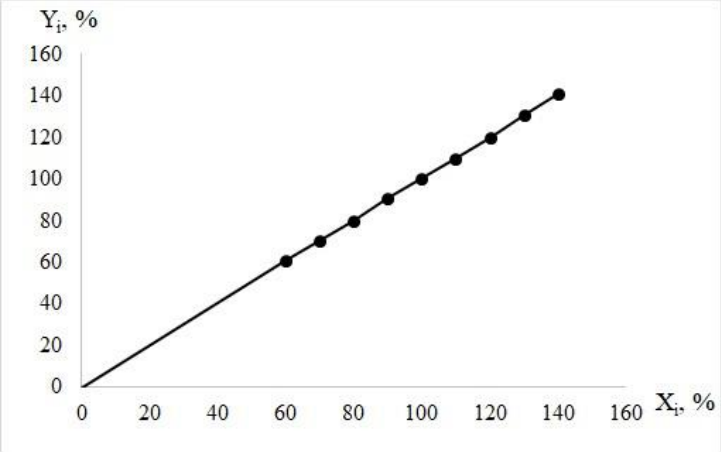

Figure 6. Graph of the absorption dependence on the concentration of meloxicam

The linear dependence parameters were calculated using the least squares method. It was found that the linearity parameters meet the requirements of the State Pharmacopoeia of Ukraine over the entire application range of the method (60-140%). The data are shown in Table 1.

Table 1. Optical characteristics and main parameters of linear dependence

Validation parameter	Results
Wavelength (nm)	348
Beer's law range (mg/100 ml)	0.80-2.40
Molar absorption coefficient, ε	21810
Sendell's coefficient, W_S	0.01611
Limit of detection (LOD), %	2.27
Limit of quantification (LOQ), %	6.89
Equation of linear regression	Y = bX + a
Slope, b±(S_b)	0.9986 ± (0.00667)
Intercept term, a±(S_a)	0.5022 ± (0.6888)
Residual standard deviation, $S_{x,o}$	0.5173
Correlation coefficient, r	0.9998

Precision

Precision was determined at the level of repeatability. Nine samples were analyzed, the concentrations of which are evenly distributed in the studied range of the method (plus a comparison solution, the concentration of which is close to the nominal). According to the requirements for precision of the State Pharmacopoeia of Ukraine, the method is accurate at the level of repeatability if the relative confidence interval (Δ_z) does not exceed the maximum permissible uncertainty of the analysis (Δ_{As}). The data in Table 2 confirm the precision of the developed method.

Table 2. Precision evaluation of the proposed method

Dosage form	Metrological characteristics			
	ΔZ	s_z	Δ_z	Δ_{As}
Tablets "Meloxicam" 15 mg	99.86	0.78	1.45	1.6
Tablets "Meloxicam KV" 15 mg	99.93	0.69	1.28	1.6
Tablets "Meloxicam Teva" 7.5 mg	100.37	0.72	1.34	1.6
Tablets "Revmoxicam" 7.5 mg	100.19	0.79	1.48	1.6

ΔZ - mean, %; S_Z – relative standard deviation; Δ_Z – relative confidence interval; Δ_{As} – maximum permissible uncertainty of the analysis

Accuracy

The accuracy of the developed method was established by the method of standard addition. In the course of the experiment, the absorption of the tested samples and the same samples with the addition of a working standard solution of meloxicam was compared. As shown by the calculations (Table 3), the value of the systematic error does not exceed the confidence interval of the mean value for the ratio "found/injected".

Table 3. Accuracy evaluation of the proposed method

Dosage form	Taken mg/100 ml	Additive mg/100ml	ΔZ	Δ_z	δ	$\Delta_Z/\sqrt{n}$
Tablets "Meloxicam" 15 mg	0.87	0.48	100.44	1.38	0.44	0.84
	0.87	0.64				
	0.87	0.80				
Tablets "Meloxicam KV" 15 mg	1.28	0.32	101.18	5.98	1.18	1.99
	1.28	0.48				
	1.28	0.64				
Tablets "Meloxicam Teva" 7.5 mg	1.52	0.32	99.88	3.92	0.12	1.31
	1.52	0.48				
	1.52	0.64				
Tablets "Revmoxicam" 7.5 mg	0.85	0.48	99.16	2.71	0.84	0.90
	0.85	0.64				
	0.85	0.80				

ΔZ – mean, %; Δ_Z – relative confidence interval; δ – systematic error

Robustness

In order to determine the robustness of the developed method, the stability of the reaction product was investigated. The absorption of the test solutions of the analyzed dosage forms (A_1 – A_4) and the working standard sample (A_0) of meloxicam was measured every 5 minutes for 30 minutes. The relative standard deviation (RSD_t%) and the confidence interval (Δ_t%) of the results obtained were calculated, which should not exceed the permissible systematic error (maxδ). The calculations confirm the stability of the analyzed solutions for at least 30 min (Table 4).

The results of the definition of validation characteristics (specificity, linearity, range of application, precision, accuracy, robustness) confirm the correctness of the proposed method. The simplicity of the experiment, the absence of extraction steps, satisfactory accuracy, and reproducibility make it possible to employ the method for routine pharmaceutical analysis of meloxicam tablets.

Table 4. Evaluation of the stability studies

t, min	0	5	10	15	20	25	30	Mean	RSD,%	Δ_t%	maxδ, %
A_0	1.0501	1.0512	1.0522	1.0528	1.0542	1.0554	1.0562	1.0531	0.210	0.41	0.51
A_1	0.9937	0.9957	0.9965	0.9971	0.9982	0.9987	1.0003	0.9972	0.218	0.42	
A_2	0.9874	0.9882	0.9901	0.9907	0.9925	0.9935	0.9931	0.9908	0.244	0.47	
A_3	1.0016	1.0026	1.0035	1.0038	1.0053	1.0068	1.0057	1.0042	0.183	0.35	
A_4	0.9917	0.9929	0.9941	0.9948	0.9958	0.9973	0.9981	0.9949	0.234	0.45	

RSD,% – relative standard deviation; Δ_t% – confidence interval; maxδ,% – critical value of the systematic error

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AUTHOR CONTRIBUTIONS

Concept: A.D., S.V., N.N.; Design: A.D., S.V., N.N.; Control: A.D., S.V.; Sources: A.D., S.V.; Materials: A.D., S.V.; Data Collection and/or Processing: A.D., S.V.; Analysis and/or Interpretation: A.D., S.V.; Literature Review: A.D., N.N.; Manuscript Writing: A.D., N.N.; Critical Review: S.V.; Other: -

CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The authors declare that the ethics committee approval is not required for this study.

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