АНАЛІТИЧНА ХІМІЯ / ANALYTICAL CHEMISTRY

UDC 543.422.3+546.18:546.28

M. K. E. A. Al-Shwaiyat,[1] A. B. Vishnikin,[2,*] L. P. Tsiganok,[2] E. V. Kabashnaya,[2] S. A. Khmelovskaya,[2] V. Andruch,[3] Ya. R. Bazel,[3] H. Sklenářová,[4] P. Solich[4]

[1]Zarka University college, Al-Balqa' Apllied University, Zarka Amman Highway, Zarka 13110, Jordan

[2]Oles Honchar Dnipropetrovsk National University, 72, Gagarin Ave., Dnipropetrovsk 49010, Ukraine

[3]P.J. Šafarik University, SK-01454 Košice, Slovak Republic

[4]Charles University, CZ-50005 Hradec Králové, Czech Republic

SEQUENTIAL INJECTION SPECTROPHOTOMETRIC DETERMINATION OF ANALGINE IN PHARMACEUTICAL FORMULATIONS USING 18-MOLYBDO-2-PHOSPHATE HETEROPOLY ANION AS CHROMOGENIC REAGENT

Simple, sensitive and selective sequential injection analysis (SIA) method for the analgine determination has been developed on the basis of fast reaction between analgine and 18-molybdo-2-phosphate heteropoly anion (18-MPA). Under found optimal conditions (0.01 M HCl, C(18-MPA) = 2 mmol/L) linear calibration curve was obtained over the range from 0.5 to 80 mg/L of analgine, and detection limit (S/N = 3) was 0.2 mg/L. The proposed SIA method has high sample throughput of 45 h^{-1} and small reagent consumption (0.08 mL). The procedure was successfully applied to the analysis of pharmaceuticals.

Keywords: analgine, 18-molybdo-2-phosphate, sequential injection analysis.

Analgine (dipyrone, novalgin, metamizole), the sodium salt of 1-phenyl-2,3-dimethyl-4-methylaminomethanesulfonate-5-pyrazolone, is a water-soluble pyrazolone derivative available in oral, rectal, and injectable forms. Since its introduction in 1922 it has been widely used as an effective analgesic, antipyretic, and antispasmodic drug in several European, South American, and Asian countries [1]. Being an effective painkiller in situations of severe pain its administration is sometimes associated with serious adverse effects like an increased risk of agranulocytosis and shock [2]. Its therapeutic relevance and the importance of the side effects have prompted the development of several methods for its determination both in pharmaceutical preparations and biological samples.

Various methods have been established for the quantitative determination of analgine in pharmaceutical preparations and biological fluids, including titrimetry [3], spectrophotometry [2; 4-7], sorption-spectrophotometry [8], multivariate spectroscopy [9], chemiluminescence [10; 11], fluorometry [12], voltammetry [13-17], chromatography [18], as well as spot test [19]. The iodometric titration of dipyrone is recommended by the many national Pharmacopoeias but this procedure is very slow and laborious, thus less applicable to large-scale analysis.

Flow injection analysis (FIA) arises ad a consequence of the growing trend towards automation in chemical analysis, and as a natural evolution of the so-called continuous flow analysis which had revolutionized the conception of chemical analysis, especially in

*Correspoding author: Tel.: +380567765834; fax: +380563749841; *e-mail address: vishnikin@hotmail.com*

the field of clinical analysis and sample manipulation. FIA belongs to a family of analytical methods based on the injection of a sample (containing the analyte or its reaction products) into a non-segmented carrier stream, which in turn carries it through a chemical or physical modulator towards the detector. FIA is characterized by its simplicity, speed, and accuracy of results. It is an alternative to other analytical methods, with clear advantages in terms of the short time required for each assay [20].

Sequential injection analysis (SIA) has been introduced by Ruzicka and Marshall in 1990 [21] as a following generation in the development of the flow injection technique. The principles upon which SIA is based are similar to those of FIA, namely controlled partial dispersion and reproducible sample handling. Normally FIA uses a multi-channel pump and unidirectional forward flow; in contrast SIA uses a single-channel pump to move the fluid zones in forward and reverse steps through a system consisting of a holding coil (HC), a multiposition valve and a detector. The multi-position valve acts as a central distributor through which required volumes of liquid segments are sequenced by aspiration into the HC and then flushed by a flow reversal into the detector. As only one pump is used to move the composite zone through the system, the sampling frequency of SIA is generally lower than the multi-channel pump FIA method. However, the SI system uses a smaller number of moving parts than a comparable FIA system and uses at least an order of magnitude less of reagents, on the order of microliters. Manipulation of solutions in an SIA system can be made via a computer keyboard using appropriate software. FIA, being a continuous flow system, presents several disadvantages such as high consumption of samples and reagents, a need for constant supervision of the peristaltic pumps, frequent recalibration and manual adjustment of the system. Characteristic advantages of SIA thus include its versatility, full computer compatibility, high sample throughput, and low sample and reagent consumption. Therefore, its application to routine pharmaceutical analysis has been proved to be very useful and of great potential [22].

Flow injection techniques employing amperometric [14; 15; 23], chemiluminescent [10; 24], fluorometric [12], ionometric [25; 26], and spectrophotometric [1; 2; 7; 27] detection have been successfully applied for analgine analysis in pharmaceuticals. No SIA method has been reported up to now for the determination of analgine.

Iso- and heteropoly anions were among few analytical reagents proposed for the spectrophotometric determination of analgine. Lately, the significance of the Wells-Dawson heteropoly anion (HPA) 18-molybdo-2-phosphate $P_2Mo_{18}O_{62}^{6-}$ (18-MPA) for the determination of a number of reducing agents in batch and sequential or stepwise injection systems was shown [28-31]. It should be noted that the history of the application of HPAs in analysis began with intensive use of complexes having Wells-Dawson structure in biochemical analysis [30].

Analgine can reduce molybdate in acid medium with formation of isopoly molybdenum blue. Reaction is fast but the intensity of the color obtained is small and strongly depends on the conditions used. Thus, the FIA method proposed on this basis had low sensitivity. The calibration curve obtained was linear in the range from 0.16 to 2.7 g L^{-1} of analgine [1]. Formation of heteropoly blue in the reaction between analgine and 12-molybdophosphate leads to the high molar absorptivity for the analgine (3.8×10^{-4} mol^{-1} l cm^{-1}). Nevertheless, the reaction is very slow and heating on boiling water bath for 20 minutes is necessary for the completion of the reduction [32].

As a result of the search for the more appropriate reagent, very fast reaction of 18-MPA with analgine was proposed and studied in this paper. On this basis, the simple,

fast, automated, sensitive, and rather selective sequential injection method for the determination of analgine has been developed. The advantages of the proposed procedure when applied to the analysis of pharmaceuticals were shown.

Experimental

Materials and Instrumentation. Ammonium salt of 18-molybdo-2-phosphate HPA $(NH_4)_6P_2Mo_{18}O_{62}\times14H_2O$ was synthesized according to the procedure described in [29]. 0.01 M solution of 18-MPA was prepared by dissolving 0.7855 g of the synthesized salt and diluting to 25 mL with 0.01 M HCl. The stock solutions of 0.01 M metamizole sodium mononhydrate (Sigma, p.a.) was daily prepared by dissolving accurately weighed amounts in 0.01 M HCl solution and stored in a refrigerator. The acetate buffer solution of pH 5.0 was used for adjusting the pH of the samples. All chemicals were of analytical-reagent grade.

Sequential injection system. A commercial FIAlab® 3500 system (FIAlab® Instruments, USA) with a syringe pump (syringe reservoir 5 mL) and an 6-port selection Cheminert valve (Valco Instrument Co., USA) was used. A tungsten light source and a USB 2000 UV-VIS fibre optic CCD detector (Ocean Optics, USA) were connected to the flow system via 600 μm i.d. optical fibres having SMA connectors (FIAlab® Inc., Bellevue, USA). The entire SIA system was controlled using the latest version of the FIAlab program for Windows. Flow lines were made of 0.75 mm i.d. PTFE tubing. 10 mm optical Z-flow through cells was used.

General SIA procedure. The configuration of the SIA manifold employed for the determination of analgine is shown in Fig. 1. The analytical cycle began by filling the piston pump syringe with 1000 μL of the carrier solution (0.01 M HCl), which was drawn into the syringe at a flow rate of 80 μL s^{-1}. This was followed by 40 μL of reagent (2 mmol L^{-1} M solution of 18-MPA in 0.01 M HCl), 160 μL sample or analgine standard, and again 40 μL of reagent which were aspirated sequentially into the holding coil at 30 μL s^{-1} through separate ports (ports no. 5 and no. 4, respectively) of the multi-position valve. The entire volume was then propelled at 30 μL s^{-1} through the Z-flow cell using port no. 6. A spectrometer reference scan was made, and absorbance scanning began immediately.

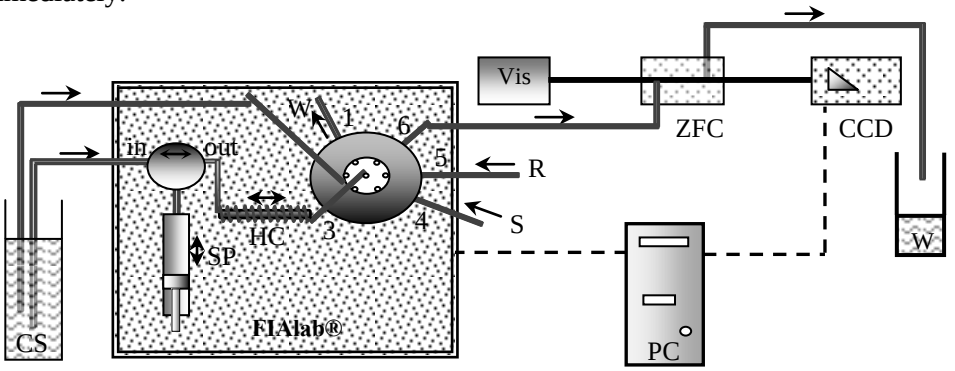


Fig. 1. Scheme of SIA manifold for the determination of analgine. CCD: charge-coupled detector; ZFC: Z-flow cell; Vis–tungsten lump; MV: 6-port multi-position valve; HC: holding coil; SP: syringe pump; SV: syringe valve; PC: computer; CS: carrier solution; W: waste; R: reagent; S: sample

Determination of analgine in pharmaceutical formulations. Five analgine tablets were accurately weighed and crushed into a powder. An amount equivalent to one tablet (500 mg) was weighed, dissolved in water and transferred to a 100-ml volumetric flask. The mixture was placed into an ultrasonic bath for 5 min, and the volume was filled up.

The solution was then centrifuged at 5000 rpm for 15 min and filtered through a 0.45 μm membrane filter. An appropriate aliquot of this solution was used for the analysis.

Results and discussion

Color reaction of 18-MPA with analgine. 18-MPA has certain chemical properties which markedly distinguish it among other heteropoly anions used for the determination of reducing agents. These are its comparatively high oxidation potential, rapid rate of reaction with the reducing agents and strong coloration of the reduced forms. It can be easily obtained in its pure form.

The completeness and the rate of the reaction between 18-MPA and analgine strongly depend on the solution pH (Fig. 2). Analgine reduces 18-MPA in very wide range of pH. In the given conditions, response was constant and maximal in the pH range from 1 to 4. At pH < 1 rate of reduction of 18-MPA with analgine becomes very slow. Decrease of absorbance at pH > 4 and especially at pH>8 is explained by growing extent of 18-MPA destruction in basic medium. In such conditions, the concentration of the 18-MPA left in the solution is already insufficient for the complete oxidation of the analgine. As can be seen from Fig. 2b, the main part of heteropoly blue is formed very quickly during first minute of reaction, after that the absorbance increases only slowly. pH 2.0 was chosen as optimal because in this case the reaction rate is the highest.

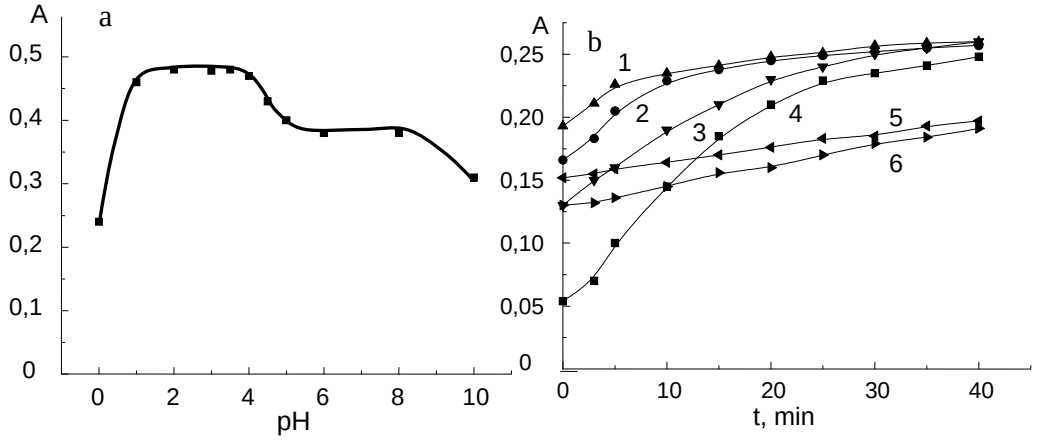
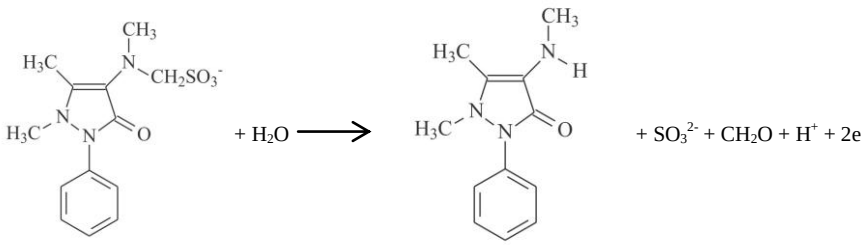


Fig. 2. Dependence of heteropoly blue absorbance on the pH and reaction time in the reaction between analgine and 18-MPA. C(18-MPA) = 1×10^{-3} M, l = 1 cm; λ = 790 nm; a: C(Analgine) = 5×10^{-5} M; b: C(Analgine) = 2.5×10^{-5}, pH = 2 (1), 1 (2), 3.5 (3), 0(4), 6 (5), 10 (6)

The spectrum of the heteropoly blue obtained for the oxidation of analgine by the excess of 18-MPA is identical with that for the 2-e heteropoly blue formed in the reaction between ascorbic acid and 18-MPA [30]. The absorption band maximum for this substance is situated at 760 nm at pH 2.0 with a molar absorptivity of 1.1×10^4 $mol^{-1}\cdot L\cdot cm^{-1}$.

Stoichiometry of the reaction was studied using the molar ratio method. The change in the absorbance of heteropoly blue was measured using constant concentration of 18-MPA and varying concentration of analgine, and vice versa. In both cases, only one intersection point was found on the experimental saturation curve at the ratio of 1 mol 18-MPA to 1 mol analgine. The absorbance remained constant even in the big excess of analgine. Such stoichoimetry of the reaction is consistent with generally accepted scheme for the reaction of analgine with most of oxidizing agents [17]. It is based on the methanesulphonate group oxidation and can be formulated by the following equation.



The various chemical and SI variables of the SI system shown in Fig. 1 were optimized using the univariate method at a fixed analgine mass concentration of 50 mg/L.

SIA procedure: Optimization of manifold parameters. Typical feature of the optimization process used in the flow methods is the fact that the optimization of the chemical variables should be repeated again even if such parameters were found previously by the development of the corresponding manual spectrophotometric procedure. In addition, the search of optimal values is as a rule more complex than for the batch methods, often needing the multivariate optimization to be carried out. The found optimal ranges of the variables are usually narrower.

In the first place, the order in which reactants are mixed in the holding coil has to be found out. It was found that it is much better initially to inject the reagent and only after that the sample. Even more better results were obtained when the sample was sandwiched between two zones of the reagent. Observed increase in the intensity of the signal may be explained if we take into account that relatively small volume of reagent is mixed with big volume of sample in holding coil. Therefore, repeated addition of the reagent allows to extend the zone in which reactants are effectively mixed.

Under the optimized conditions, the effect of the reagent volume on the analytical signal was studied at different concentrations of 18-MPA in the range of 5–50 μL. Increasing the concentration of the reagent increased the signal intensity, which had a maximum at a volume of 25 μL for 4 mmol/L concentration of 18-MPA (Fig. 3a, curve 3). A plateau is observed on the dependence of absorbance on the reagent volume by using 2 mmol/L solution of 18-MPA from a volume of 40 μL. By using more diluted reagent solutions it is difficult to obtain so high signal (Fig. 3a, curve 1).

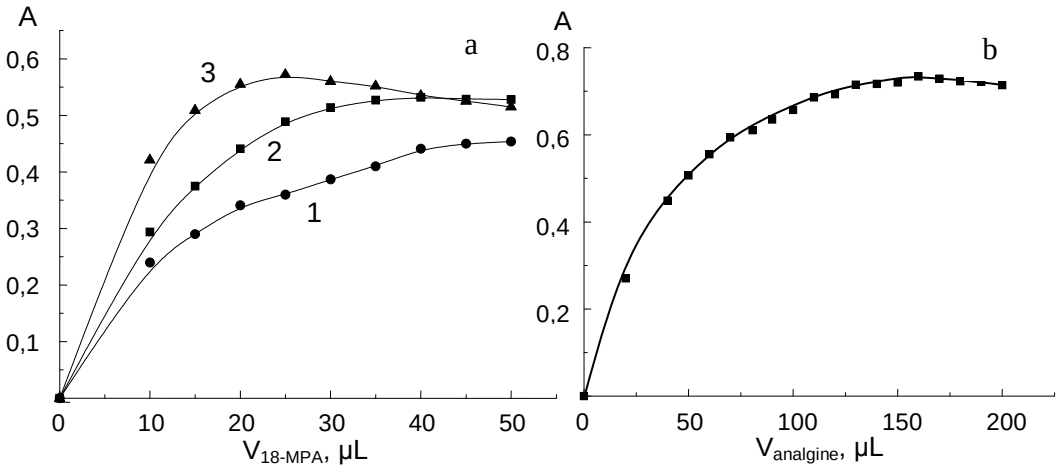


Fig. 3. Influence of reagent (a) and sample (b) injected volume on product absorbance at different concentrations of 18-MPA: 1 mmol/L (a1), 2 mmol/L (a2), 4 mmol/L (a3), 2 mmol/L (b), C(An) =50 mg/L

A comparatively high concentration of 18-MPC should be created in the solution to ensure a broad range of linearity for the analyte and its complete transformation into the

colored product. Taking into account the high molar weight of the ammonium salt of 18-MPA (3142 g mol^{-1}), a considerable mass concentration of the heteropoly complex is present in the solution. This may lead to a significant difference in the refractive indices between the mixed liquid zones and consequently to high Schlieren effect [31]. Hence, the concentration of 18-MPA of 2 mmol/L was chosen as optimal to keep good sensitivity and simultaneously to reduce the Schlieren effect.

The influence of the sample volume was investigated by injecting volumes in the range of 20–200 μL (Fig. 3b). A sample volume of 160 μL was then chosen as optimal, considering sample consumption and the fact that maximum absorbance was achieved at this value.

The effect of variation in the flow rate during the measurement stage with respect to the shape and intensity of the recorded peak was investigated. The signal intensity was independent on the flow rate in the range from 5 to 30 μL/s (Fig. 4b). Absorbance was slightly decreased when using faster flow rates. Thus, a flow rate of 30 μL/s was chosen as optimal to ensure a higher throughput value.

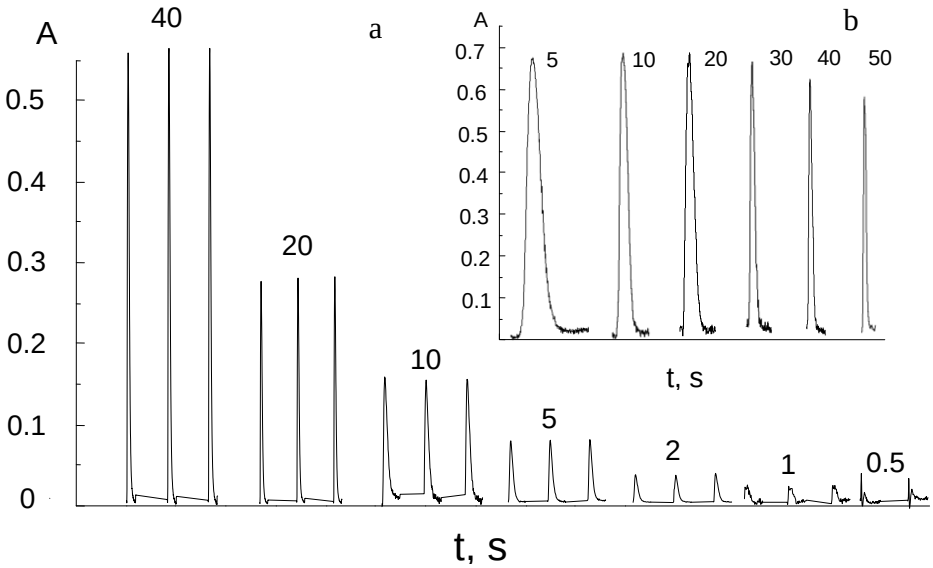


Fig. 4. a: Typical SIA signals measured in triplicate which were obtained for a calibration graph for the determination of analgine (concentration of analgine is given in mg/L); b: Influence of variation of flow rate (in μL s^{-1}) on the peak shape. C(analgine) = 50 mg L^{-1}

Investigation of the influence of the delay time of reactants in holding coil on the absorbance of the heteropoly blue formed showed that the response reached a plateau at 90 s, and the decrease in the absorbance due to the dispersion became significant after 200 s. But considering the fact that improvement in signal intensity was low, the delay time of 0 s was chosen to retain the high throughput.

Aspiration of a series of standard analgine solutions resulted in the flow signals shown in Fig. 4a. The equation of the calibration plot in the analgine concentration range from 0.5 to 80 mg/L was as follows: $A_{760} = (0.015 \pm 0.036) + [(0.0141 \pm 0.0008)] \times C_{Analgine}$, ($R^2 = 0.9988$). The precision of the proposed method was checked by repeated aspiration of the same standard analgine solutions. The relative standard deviations (R.S.D.) of 20 aspirations of each solution containing 2, 5, and 40 mg/L of analgine were 4.0%, 1.8% and 0.4%, respectively. The limit of detection obtained with a peak height by three-times of the signal-to-noise ratio (S/N = 3) was 0.2 mg/L. Under the SIA optimized conditions, the throughput was calculated as 45 h^{-1}, with negligible carryover.

Interference study. In order to assess the possible analytical applications of the SIA method described above, the effect of interfering species on the determination of analgine in real samples was studied by analyzing a model sample solution containing analgine and various excess amounts of common interferents. The tolerance limit was set as the maximum amount causing an error of $\leq\pm$ 5% in the absorbance.

No interferences were found for saccharose, acetylsalicylic acid, paracetamol, nicotinic acid, caffeine, citric acid, glucose, talc, starch, and other excipients at ratios [interferent]=[analgine] much higher than those found commonly in pharmaceuticals. At least ten-fold excess of inorganic reducers or oxidants such as Fe(II), Fe(III), Cu(II), hydrazine, and sulfite had no influence on the determination of analgine. Reaction of 18-MPA with cysteine is fast and quantitative. The 18-MPA reacts with polyphenols but under experimental conditions used in this study the reaction goes rather slowly. Thus, analgine can be determined in the presence of comparatively big excess of polyphenols.

Table 1

Results for the determination of analgine in pharmaceutical preparations by the proposed method (mg/tablet ± Δ, n = 5,95% confidence level)

Sample	Composition	Found analgine, mg $X_{сер}\pm\Delta$
Analgine-Darnitsa	500 mg of analgine, excipients	495±15
Pentalgine-IC	Sodium metamizole – 300 mg; paracetamol – 200 mg; caffeine – 20 mg; phenobarbital – 10 mg; codeine phosphate – 9,5 mg	304±8
Tempalgine	Tempidon – 20 mg; analgine – 500 мг	496±12
Belalgine	Analgine – 250 мг; anesthesin – 250 mg; $NaHCO_3$ – 100 mg	252±6
Phenalgine	Analgine – 125 mg; amidopyrine – 125 mg; phenacetine – 125 mg	123±3

Application. The determination results of the analgine content in some pharmaceuticals obtained by the proposed method based have been presented in Table 1 and were in good agreement with the claimed value of producers in all instances, thus confirming the accuracy of the developed method. Based on these results, it could be concluded that no interference was found in the presence of complex matrices such as common excipients and additives used in pharmaceutical preparations. It is thus possible to use this method for the direct determination of analgine in pharmaceuticals without separating potentially interfering materials.

Conclusions. Thus, a first example of SIA method for analgine assay in pharmaceutical formulations was developed. The developed SIA method proved to be more rapid, more selective and sufficiently sensitive when compared with most of the reported spectrophotometric and FIA methods. The reaction of analgine with 18-MPA is simple and direct. Unlike electrochemical procedures, the proposed method is robust and relatively low cost in terms of equipment and operations when compared with methods involving enzymes and chromatography.

It is very simple, direct, precise, notable for high sample throughput of 45 h^{-1} and a broad calibration range of 0.5-80 mg/L. Only small quantity of the reagent (80 μL of 2 mmol/L 18-MPA) is consumed during one analysis. So, 100 mL of reagent solution is wholly sufficient to work during one week. The reagent solution is stable and does not need to be standardized before use.

The development of the presented method for analgine determination took advantages of versatility from the sequential injection system. Optimization procedure was simple and quick and enabled to study reaction conditions in detail. High dispersion leading to high mixing quality speeded up reaction process and resulted in high sample

throughput. The developed method was successfully applied for the analysis of real samples with different matrix.

Compared to analgine determinations using HPLC separations the presented method is suitable for quick screening of analgine content in a large amount of samples that could be followed by detailed HPLC analysis of individual samples where higher or lower concentrations were found. In the sequential injection systems, the volumes of spent chemicals are significantly decreased and, thus, the term of ‘‘green analysis’’ is applicable.

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М. К. Е. А. Аль-Швейят,[1] А. Б. Вишникин,[2] Л. П. Цыганок,[2] Е. В. Кабашная,[2] С. А. Хмеловская,[2] В. Андрух,[3] Я. Р. Базель,[3] Х. Скленарова,[4] П. Солих[4]

[1]Университетский колледж г. Зарка, Прикладной университет Аль-Балка, Хайвей Зарка Амман, Зарка 13110, Иордания

[2]Днепропетровский национальный университет имени Олеся Гончара, пр. Гагарина, 72, Днепропетровск 49010, Украина

[3]Университет П.Й. Шафарика, SK-01454 Кошице, Словацкая республика

[4]Карлов университет, CZ-50005 Градец Кралове, Чешская республика

СПЕКТРОФОТОМЕТРИЧЕСКОЕ ОПРЕДЕЛЕНИЕ АНАЛЬГИНА МЕТОДОМ ПОСЛЕДОВАТЕЛЬНОГО ИНЖЕКЦИОННОГО АНАЛИЗА В ФАРМАЦЕВТИЧЕСКИХ ПРЕПАРАТАХ С ИСПОЛЬЗОВАНИЕМ В КАЧЕСТВЕ ХРОМОГЕННОГО РЕАГЕНТА 18-МОЛИБДО-2-ФОСФОРНОГО ГЕТЕРОПОЛИАНИОНА

На основе быстрой реакции между анальгином и 18-молибдо-2-фосфорным гетерополианионом (18-МФК) разработан простой, высокочувствительный и селективный метод определения анальгина методом последовательного инжекционного анализа. Соотношение 18-МФК и анальгина, найденное методом молярных отношений, равнялось 1 : 1 и соответствовало общепринятой схеме реакции анальгина с большинством окислителей, включающей окисление метансульфоновой группы. В оптимальных условиях (0,01 М HCl, С(18-МФК) = 2 ммоль/л) градуировочный график был линеен в интервале концентраций анальгина от 0,5 до 80 мг/л (предел обнаружения 0,2 мг/л). Относительное стандартное отклонение, рассчитанной для 20 инжекций растворов, содержащих 2, 5 и 40 мг/л анальгина, было равным, соответственно, 4.0%, 1.8% и 0.4%. Селективность по отношению к типичным компонентам фармацевтических препаратов была высокой. Предложенный метод обладает высокой производительностью (45 анализов/час) и малым потреблением реактивов (0,08 мл). Метод был успешно применен для анализа фармацевтических препаратов.

Ключевые слова: анальгин, 18-молибдо-2-фосфат, последовательный инжекционный анализ.

М. К. Е. А. Аль-Швейят,[1] А. Б. Вишнікін,[2] Л. П. Циганок,[2] К. В. Кабашна,[2] С. О. Хмеловська,[2] В. Андрух,[3] Я. Р. Базель,[3] Х. Скленарова,[4] П. Соліх[4]

[1]*Університетський коледж м. Зарка, Прикладний університет Аль-Балка, Хайвей Зарка Амман, Зарка 13110, Йорданія*

[2]*Дніпропетровський національний університет імені Олеся Гончара, пр. Гагаріна, 72, Дніпропетровськ 49010, Україна*

[3]*Університет П.Й. Шафарика, SK-01454 Кошице, Словацька республіка*

[4]*Карлів університет, CZ-50005 Градец Кралове, Чеська республіка*

СПЕКТРОФОТОМЕТРИЧНЕ ВИЗНАЧЕННЯ АНАЛЬГІНУ МЕТОДОМ ПОСЛІДОВНОГО ІНЖЕКЦІЙНОГО АНАЛІЗУ В ФАРМАЦЕВТИЧНИХ ПРЕПАРАТАХ З ВИКОРИСТАННЯМ ЯК ХРОМОГЕННОГО РЕАГЕНТУ 18-МОЛІБДО-2-ФОСФОРНОГО ГЕТЕРОПОЛІАНІОНУ

Ґрунтуючись на швидкій реакції між анальгіном і 18-молібдо-2-фосфорним гетерополіаніоном (18-МФК) розроблений простий, високочутливий і селективний метод визначення анальгіну методом послідовного інжекційного аналізу. Співвідношення 18-МФК і анальгіну, знайдене методом молярних відношень, дорівнювало 1 : 1 і відповідало загальноприйнятій схемі реакції анальгіну з більшістю окисників, яка включає окислення метансульфонової групи. В оптимальних умовах (0,01 М HCl, С(18-МФК) = 2 ммоль/л) градуювальний графік був лінійним в інтервалі концентрацій анальгіну від 0,5 до 80 мг/л (межа визначення 0,2 мг/л). Відносне стандартне відхилення, розраховане для 20 інжекцій розчинів, які містили 2, 5 і 40 мг/л анальгіну, дорівнювало, відповідно, 4.0%, 1.8% і 0.4%. Селективність по відношенню до типових компонентів фармацевтичних препаратів була високою. Запропонований метод має високу продуктивність (45 аналізів/годину) і малі витрати реактивів (0,08 мл). Метод був успішно застосований для аналізу фармацевтичних препаратів.

Ключові слова: анальгін, 18-молібдо-2-фосфат, послідовний інжекційний аналіз.

Надійшла до редколегії 20.02.13

UDC 543.6

O. V. Gurtova,[1] L. Ye,[2] F. A. Chmilenko[1,*]

[1]*Oles Honchar Dnipropetrovsk National University, 72, Gagarin Ave., Dnipropetrovsk 49010, Ukraine*

[2]*Chemical Center, Lund University, P.O. Box 124, SE-22100 Lund, Sweden*

EFFECT OF PLASTICIZER ON THE CHARACTERISTICS OF MOLECULARLY IMPRINTED POLYMER BASED POTENTIOMETRIC SENSOR FOR PROPRANOLOL

The effect of different plasticizers on the performance and selectivity coefficient of molecularly imprinted polymer (MIP) based potentiometric sensor in mixed non-aqueous mediums was first investigated. The research was undertaken for propanolol imprinted MIP. Plasticizers (di-n-octyl phthalate (DOP), dibutyl phthalate (DBP) and dioctyl sebacate (DOS)) were used in MIP based sensors for potentiometric determination of propranolol, as well as to change the resistance of the sensing polyvinylchloride membrane and to improve the detection limit and selectivity of the electrodes. For propranolol-selective sensors, the nature of plasticizer influences distribution of MIP particles in polyvinylchloride, slope of electrode function, linear range and selectivity coefficients. The applicability of the proposed sensors was tested by potentiometric propranolol determination in aqueous modeling solution with the use of tablets of pharmaceutical formulation.

Keywords: Plasticizer, Molecular imprinted polymer; Propranolol; Potentiometric sensor; MIP-based sensor; MIP microspheres.

* Correspoding author: Tel.: +380567765934; fax: +380563749841; *e-mail address: analyticdnu@mail.ru*