Вісник Дніпропетровського університету. Серія хімія
Bulletin of Dnipropetrovsk University. Series Chemistry
ISSN 2306-871X (Print),
ISSN 2313-4984 (Online)
journal homepage: http://chemistry.dnu.dp.ua

UDC 543.422.3:54-328

SIMULTANEOUS DETERMINATION OF TWO ACTIVE COMPONENTS OF PHARMACEUTICAL PREPARATIONS BY SEQUENTIAL INJECTION METHOD USING HETEROPOLY COMPLEXES

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Received 12 November 2013; revised 15 November 2013; accepted 4 December 2013

A b s t r a c t

New approach has been proposed for the simultaneous determination of two reducing agents based on the dependence of their reaction rate with 18-molybdo-2-phosphate heteropoly complex on pH. The method was automated using the manifold typical for the sequential analysis method. Ascorbic acid and rutin were determined by successive injection of two samples acidified to different pH. The linear range for rutin determination was 0.6-20 mg/L and the detection limit was 0.2 mg/L (l = 1 cm). The determination of rutin was possible in the presence of up to a 20-fold excess of ascorbic acid. The method was successfully applied to the determination of ascorbic acid and rutin in ascorutin tablets. The applicability of the proposed method for the determination of total polyphenol content in natural plant samples was shown.

Keywords: spectrophotometric determination, rutin, ascorbic acid, 18-molybdo-2-phosphate heteropoly anion.

ОДНОЧАСНЕ ВИЗНАЧЕННЯ ДВОХ АКТИВНИХ КОМПОНЕНТІВ ФАРМАЦЕВТИЧНИХ ПРЕПАРАТІВ ПОСЛІДОВНО ІНЖЕКЦІЙНИМ МЕТОДОМ ІЗ ВИКОРИСТАННЯМ ГЕТЕРОПОЛІКОМПЛЕКСІВ

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А н о т а ц і я

Запропоновано новий підхід до одночасного визначення двох відновників, який ґрунтується на залежності швидкості їх реакції з 18-молібдо-2-фосфорним гетерополікомплексом від pH. Метод автоматизовано з використанням типового приладу методу послідовного інжекційного аналізу. Аскорбінову кислоту і рутин визначено при послідовній інжекції двох зразків, підкислених до різних pH. Інтервал лінійності під час визначення рутину складав 0.6-20 мг/л, а межа визначення була 0.2 мг/л (l = 1 см). Визначення рутину можливе у присутності 20-разового надлишку аскорбінової кислоти. Метод було успішно апробовано для визначення аскорбінової кислоти в таблетках «Аскорутину». Показано можливість застосування запропонованого методу для визначення загального вмісту поліфенолів у природних рослинних препаратах.

Ключові слова: спектрофотометричне визначення, рутин, аскорбінова кислота, 18-молібдо-2-фосфорний гетерополіаніон.

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doi: 10.15421/081408

ОДНОВРЕМЕННОЕ ОПРЕДЕЛЕНИЕ ДВУХ АКТИВНЫХ КОМПОНЕНТОВ ФАРМАЦЕВТИЧЕСКИХ ПРЕПАРАТОВ ПОСЛЕДОВАТЕЛЬНО ИНЖЕКЦИОННЫМ МЕТОДОМ С ИСПОЛЬЗОВАНИЕМ ГЕТЕРОПОЛИКОМПЛЕКСОВ

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Аннотация

Предложен новый подход к одновременному определению двух восстановителей, который основывается на зависимости скорости их реакции с 18-молибдо-2-фосфорным гетерополикомплексом от pH. Метод автоматизирован с использованием типичного прибора метода последовательного инжекционного анализа. Аскорбиновая кислота и рутин определены при последовательном инжектировании двух образцов, подкисленных до разных pH. Интервал линейности при определении рутина составил 0.6-20 мг/л, а предел обнаружения – 0.2 мг/л (l = 1 см). Определение рутина возможно в присутствии 20-кратного избытка аскорбиновой кислоты. Метод был успешно апробирован для определения аскорбиновой кислоты в таблетках «Аскорутина». Показана возможность применения предложенного метода для определения общего содержания полифенолов в природных растительных препаратах.

Ключевые слова: спектрофотометрическое определение, рутин, аскорбиновая кислота, 18-молибдо-2-фосфорный гетерополианион.

Introduction

The ever increasing demand for more and more rapidly obtained analytical information from clinical, environmental and industrial samples, in which a large number of analytes have to be determined at low concentrations, has strongly influenced the development of modern instrumental analytical chemistry. Therefore, the partial or complete elimination of human interaction is a clear trend in the analytical laboratory. Automated on-line procedures are independent of «operator error» and are highly repeatable [1].

Flow analysis methods are widely used to solve many problems of chemical analysis taking into account the possibility of full automation, high throughput, flexibility and relatively low cost for single analysis. As it follows from the new trends existing in flow methods, increasing attention is being paid to the multicomponent analysis. The review of the literature has shown that contrary to the situation with flow injection analysis only several papers devoted to the sequential injection analysis (SIA) have appeared in this field [2; 3].

Among the various detection techniques used in flow injection analysis (FIA), visible spectrophotometry has been the most predominant [4; 5]. FIA provides high sample throughput, high repeatability and easily automated operation. It is widely used for the determination of pharmaceuticals. Sequential injection analysis (SIA) based on principles similar to FIA, but with the possibility of universal flow manipulation, was introduced in 1990. Among the major benefits of SIA systems are reduced consumption of reagents by at least one order of magnitude, robust hardware and flexible control software which enables the convenient optimization and operation of the system [6].

The many of the existing procedures for the determination of reducing agents are based on the slow reactions. Therefore, their implementation into flow/sequential analysis can lead to the decrease of sample throughput and significant increase in dispersion thus worsening the sensitivity of the analysis. So far, batch and flow spectrophotometric methods based on the reduction of Fe(III) to Fe(II) or Cu(II) to Cu(I) with ascorbic acid (AsA), followed by the complexation of Fe(II) or Cu(I) with different reagents, have found extensive use for the determination of reducing agents [7]. The methods using heteropolyanions (HPAs) in spite of their simplicity, stability and high coloration of the reaction products are not so widespread. One of the main reasons for that was the slowness of the reactions between Keggin HPA and reducing agents [8].

As a result of the search for the more appropriate reagent, very fast reaction of 18-molybdo-2-phosphate HPA $P_2Mo_{18}O_{62}^{6-}$ (18-MPA) with reducing agents was proposed and several simple, fast, automated, sensitive and rather selective sequential injection methods have been developed by us for the determination of ascorbic acid, *p*-aminophenol, epinephrine and cysteine [4; 6; 8–12]. 18-molybdo-2-phosphate HPA has one of the highest reduction-oxidation potentials among other known HPAs. Comparing with Keggin's HPAs, reactions of this HPA with reducing agents are much more rapid, more selective, convenient in the realization. In addition, much more compounds can be determined by using this reagent.

Spectrophotometry as well as FIA/SIA methods usually allow determining only one compound

that significantly reduces their attractiveness. Simultaneous determination of two or more compounds comparatively seldom used in the flow methods of the analysis. The reactions between heteropoly anions and reducing agents have many useful properties which can be used for the development of the analytical methods for the simultaneous determination of two or more compounds.

In this work, the new approach has been presented for the simultaneous SIA determination of two active substances in pharmaceutical formulations by using 18-molybdo-2-phosphate HPA with Wells–Dawson structure as reagent. The method is based on the manifold typical for the SIA method. Ascorbic acid and rutin were determined by successive injection of two samples acidified to different pH.

Experimental

Reagents and apparatus. All used reagents were of «p.a» grade and distilled water was used throughout. 0.01 M solution of $(NH_4)_6P_2Mo_{18}O_{62}\cdot 14H_2O$ (18-MPA) [4] was prepared by dissolving 0.7855 g of the salt in a 25 ml flask. 66.4 mg of rutin $C_{27}H_{30}O_{16}\cdot 3H_2O$ were dissolved in ethanol and made up to 100 ml to make a 0.001 M stock solution. The concentrated acetate buffer solution of pH 4.7±0.2 was prepared by dissolving 10.1 g of sodium acetate in 50 mL of water, mixing in a 4.0 mL of glacial acetic acid and adjusting the resulting mixture to a volume of 100 ml. The phosphate buffer solution of pH 7.4±0.1 was prepared by dissolving 1.17 g of $NaH_2PO_4\cdot 2H_2O$ and 7.78 g of $Na_2HPO_4\cdot 12H_2O$ in water and making to a volume 500 ml.

Absorbance measurements were made using SF-26 spectrophotometer equipped with 10 and 50 mm light-path cells. The pH of the solutions was monitored using an EV-74 pH-meter with glass and silver/silver chloride reference electrodes.

Sequential injection system. A commercial FIAlab® 3500 system (FIAlab® Instruments, USA) with a syringe pump (syringe reservoir 5 mL) and an 8-port selection Cheminert valve (Valco Instrument Co., USA) was used. A tungsten light source and a USB 2000 UV-VIS fiber optic CCD detector (OceanOptics, USA) were connected to the flow system via 600 μm i.d. optical fibers with 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 from 0.75 mm i.d. PTFE tubing and a 10 mm optical Z-flow through-cell was used.

General SIA procedure. The configuration of the SIA manifold employed for the determination of ascorbic acid and rutin is shown in Fig. 1. At the first stage of the measurements, syringe pump was filled with 1000 μL of acetate buffer solution with pH 4.7 or phosphate buffer solution with pH 7.4 used as the carrier solution, the syringe pump valve was set out and 220 μL of sample through port 5 (sample acidified to pH 4.7) or 2 (sample acidified to pH 7.4) and 40 μL of $4\cdot 10^{-3}$ M 18-MPA through port 4. At the last measurement stage, the spectrometer reference scan was made, and then 320 μL of the colored solution were forced away through port 6 into the Z-flow cell at 30 μL s^{-1} (at higher flow rates probability of bubble detention on the walls of flow cell increased), the flow was stopped for 10 s. The measured absorbances were averaged during this time. At last, the remained solution and water containing in the system were displaced into the waste container by emptying the syringe pump. That amount of water was sufficient for the thorough washing of the system.

Procedure for the determination of total phenolic contents. 1 ml of sample was dissolved in 10 ml of ethanol and filtered. 1 ml of this sample was introduced into 25 ml volumetric flask and mixed with 1.25 ml of 0.001 M 18-MPA and 5 ml of phosphate buffer solution. The flask was then filled with water to the mark. Absorbance was measured after 10 min at 820 nm against water.

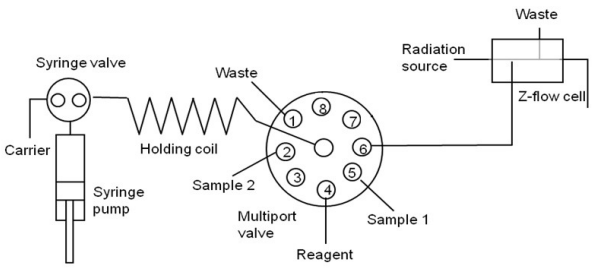

Fig. 1. SIA manifold for the simultaneous determination of ascorbic acid and rutin

Procedure for the determination of total flavonoids. 1 ml of sample was mixed with 0.2 ml of 10% $AlCl_3$ and 0.2 ml of 1 M CH_3COONa 10 ml in test tube and volume was made up. Absorbance was measured after 30 min at 424 nm against water.

Results and discussion

Sequential injection system. In a typical sequential injection system (Fig. 1), the multiport valve selects the sample, reagents and carrier/wash aliquots, which are sequentially aspirated towards the holding coil. A stack of reproducible unsegmented plugs is then assembled inside this coil. The flow is thereafter reversed and the valve is switched in order to direct these plugs towards the detector. During transport of this stack, the

sample and reagent plugs penetrate one another as a consequence of dispersion, and the interactions between their components give rise to one or more detectable species that can be monitored during passage of the processed sample through the detector.

In 1999, Honorato et al. [13] developed the flow-batch analyzer (FBA). The main component of this manifold was the mixing chamber [14]. Most FBA systems described in the literature employ peristaltic pumps for moving liquids and a multi-commutation system, usually three-way solenoid valves for directing the fluids towards the mixing chamber or continuing the loop flow.

One of the main distinctions between flow batch analysis and previously known FIA/SIA techniques consists in the change of diffusion mass transfer between sample and reagent zones to more effective convective stirring. Thus, an analytical signal is measured under conditions, when it reaches a maximum value in the given analytical procedure.

By using of a FBA method, the optimization of the flow variables of the manifold can be greatly simplified because the parameters of the analytical method found in batch conditions can be used almost without any changes. The combination of the FBA manifold with such modules as an auxiliary vessel or a sorption column allows effectively to preconcentrate the analyte. By the carrying out the extraction process or the absorption of the gaseous species in the reaction chamber, the configuration of the system is significantly simplified [5; 15; 16]. The configuration of the FBA system is in many situations more flexible than that for the FIA/SIA methods and shows greater analytical efficiency. New possibilities are given by the integration of the mixing chamber with a measurement cell. At the same time, FBA has lower throughput than that for known flow methods but this feature is not always asked for in real analysis.

In appropriate conditions, 18-molybdophosphate Dawson HPA reacts with most of reducing agents almost immediately, colour of the obtained blue is stable at least for one day. Obtained heteropoly blue is characterized by high molar absorptivity. High reactivity of the 18-MPA towards a variety of species such as paracetamol, many representatives of polyphenols, bears promising perspective towards the development of the appropriate analytical methods.

The range of pH in which the reaction goes between HPA and reducing agent considerably differs for various species. On this basis, a whole number of effective methods for the simultaneous determination of different species can be developed. Such examples can include the procedures for the determination of paracetamol and its degradation product p-aminophenol, ascorbic acid and rutin in ascorutin, ascorbic acid and flavonoids in plants, ascorbic acid and uric acid, epinephrine or other polyphenols in serum or urea. Many other combinations of analytes are possible, but the theory and practical implementation of such reactions has been not yet clarified up to now.

SIA procedure: Optimization of chemical and flow variables. The influence of the solution pH on the formation of the heteropoly blue produced during the reaction between rutin and ascorbic acid with 18-MPA was investigated (Fig. 2). At pH > 4.0 ascorbic acid is almost immediately oxidized by 18-MPA [8]. The reaction of rutin with 18-MPA is more continuous at any pH studied. First two OH groups of rutin are oxidized very rapidly for 1-2 min while about 10-15 min is necessary for the complete oxidation of other two hydroxyls. Subsequently, the colour of the solution remains unchanged for a long time. The stoichiometry of the reaction determined by the molar ratio method leads to the conclusion that 2 mol of 18-MPA is required for the oxidation of 1 mol of rutin. It can be concluded from the preceding that four electrons are lost by rutin because 18-MPA behaves as two-electron reducer in the excess of the reagent. Such process is responsible for the oxidation of four oxy groups of rutin to oxo groups (R-OH → R=O). Proposed scheme of the reaction is confirmed by the fact that molar absorptivity for the rutin determined from the slope of the calibration graph was equal to $2.2 \cdot 10^4$ $mol^{-1} \cdot l \cdot cm^{-1}$. Considering that molar absorptivity for two-electron heteropoly blue is of $1.1 \cdot 10^4$ $mol^{-1} \cdot l \cdot cm^{-1}$, this allows to suppose the participation of four electrons in the studied reaction.

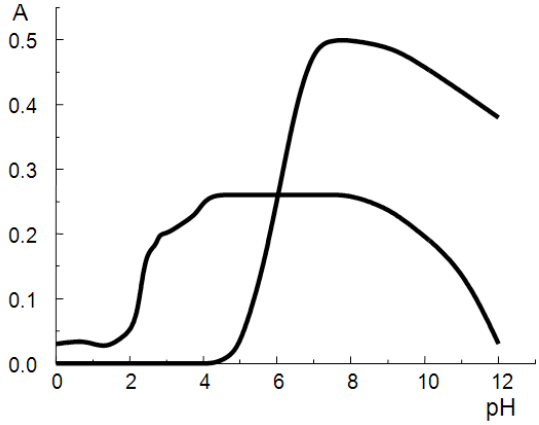

Fig. 2. Effect of the solution pH on the formation of heteropoly blue in the reaction between 18-MPA and ascorbic acid or rutin.
C(Rutin) = 0.02 mmol/L; C(Ascorbic acid) = 0.02 mmol/L;

C(18-MPA) = 1 mmol/L; λ = 820 nm; l = 1 cm

As can be seen from Fig. 2, in the pH range from 4 to 5 only ascorbic acid is capable of reducing 18-MPA. At the same time, in the pH range from 7 to 8 simultaneous and complete oxidation of both ascorbic acid and rutin occurs. Such behavior of these compounds allows to develop method for their simultaneous determination based on the difference of the results obtained for two injections of sample acidified to pH 4.7 and 7.4. The content of ascorbic acid and rutin in ascorutin tablets can be significantly greater than that of rutin. Therefore, very precise method was necessary to determine rutin in the presence of big amounts of ascorbic acid.

First, the optimal conditions were found for the determination of rutin by SIA method. By using $4 \cdot 10^{-3}$ M solution of 18-MPA as reagent, the maximum signal was observed when injected volumes for reagent and sample were 40 and 220 μL, respectively. The calibration curve was linear in the range of rutin concentrations from $1.6 \cdot 10^{-6}$ M to $8 \cdot 10^{-5}$ M. The dispersion of the sample in the reagent and carrier streams was comparatively low and intensity of the analytical signal was only two times lower than theoretically calculated. The reproducibility was also satisfactory about 1-2%.

However, the repetition of the SIA method for the determination of ascorbic acid at pH 4.7 with 18-MPA described in [9] has shown that significant and hardly eliminated Schlieren peak arises that strongly interferes to the determination of small amounts of ascorbic acid at its low concentrations. Using the flow-batch configuration instead of SIA manifold can allow to obtain significantly higher sensitivity and precision by the determination of both ascorbic acid and rutin.

Thus, the volume of reagent used in the proposed method was lower on two order of magnitude than in batch procedure – 40 μL instead of 2 mL. This volume as well as volume of waste can be even further reduced because the total volume of the reaction mixture was 260 μL that was considerably higher than it was required for the filling of the flow cell.

It was established that difference in molar absorptivities calculated for ascorbic acid at pH 4.7 and 7.4 was insignificant. This makes it possible to manage without the using the method of three calibration graphs and to limit the procedure by constructing only two calibration curves. Under the optimal pH value of 7.4, linear calibration curve was obtained over the range from $1 \cdot 10^{-6}$ to $3 \cdot 10^{-5}$ M (0.6–20 mg/l) of rutin ($r^2 = 0.995$). The relative standard deviation was 0.8–2.5% and the limit of detection ($3s_a$) was 0.2 mg/l. By using the cell with longer path length of 5 cm determination range was from $2 \cdot 10^{-7}$ to $1 \cdot 10^{-5}$ M (0.1–6 mg/L).

Application. The content of rutin or flavonoids (total polyphenol content) was determined in some medical and pharmaceutical formulations and was expressed as mg/l rutin equivalent. In addition, aluminium chloride colorimetric method was used for the determination of flavonoids (Table 1).

Table 1

Total phenolic or flavonoid contents in different tinctures

	$AlCl_3$		$P_2Mo_{18}O_{62}^{6-}$	
Sample	C, mg/l	S_r	C, mg/l	S_r
Tincture «Sofora»	40.6	0.03	52.9	0.04
Tincture «Gingko biloba»	28.9	0.05	30.9	0.013
Tincture «Solodka»	8.6	0.07	6.5	0.04
Tincture «Haw»	8.2	0.03	11.8	0.021

Literature data [18] as well as spectrum of complex with aluminium (λ_{max} = 390 nm) confirm that the main flavonoid (> 90%) present in the preparates of Sophora japonica is rutin. The higher value obtained can be explained by the presence of ascorbic acid which is not detectable by the aluminium chloride method. Quercetin and its glucoside derivatives dominate in the composition of tincture «Gingko biloba» [19]. Comparison of the results obtained by both methods in all the cases indicates that flavonoids are the main part of phenols present in sample. The content of ascorbic acid and rutin was simultaneously determined by the above described SIA method in ascorutin tablets (Table 2).

Table 2

Results for the determination of ascorbic acid and rutin in ascorutin tablets by the proposed and the reference methods (mg/tablet ± Δ, n = 5, 95% confidence level)

Sample, Producer	Claimed value		Found by the proposed method		Found by the reference method	
	Ascorbic acid	Rutin	Ascorbic acid	Rutin	Ascorbic acid[a]	Rutin[b]
«Ascorutin», Zentiva, Czech republic	100	20	100.7±1.7	21.5±1.4	101.4±1.5	20.7±0.4
«Аскорутинтаб», Kyiv vitamin factory, Ukraine	50	50	49.1±1.2	49.7±2.5	50.3±0.7	49.4±1.2

[a] Determination with 2,6-phenolindophenol [20]
[b] Determination with $AlCl_3$ [21]

The values given by producer and determined by the proposed method were in good accordance in all cases. In addition, the accuracy of the proposed method was evaluated by comparison with the results obtained by the reference methods. The confidence intervals of both the methods were overlapping. The method is characterized by good sensitivity of 1–2%.

Conclusions

Capability of 18-molybdo-2-phosphate heteropoly anion to the interaction with reducing agents in the wide range of pH and strong dependence of the reaction rate on the acidity are the basis for the development of the new methods for the simultaneous determination of several analytes. This approach was implemented in the procedure for the simultaneous determination of ascorbic acid and rutin. Even high excess of most interfering substances present in pharmaceutical preparations, including rutin, does not influence on the determination of ascorbic acid. In one's turn, rutin can be determined in the presence up to 20-fold excess of ascorbic acid. It is very important that by using the proposed reagent ascorbic acid and other phenols present in the sample can be determined separately and overall antioxidant activity can be evaluated.

The proposed configuration of the flow manifold combines the full automation and flexibility inherent to the sequential injection analysis. Reagent, sample consumption and volume of effluents are maintained at the lowest level in accordance with the principles of «Green chemistry». Volume of the reagent was reduced to 40 μL and its concentration was one order of magnitude less than for the corresponding batch method. Only water was used as carrier and solvent and no previous separation of the components was required.

Acknowledgements

This work was supported by Scientific Grant Agency of the Ministry of Education of the Slovak Republik and the Slovak Academy of Sciences (Project VEGA No. 1/1096/12).

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