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# Fast simultaneous spectrophotometric determination of naphazoline nitrate and methylparaben by sequential injection chromatography

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**Abstract**

Fast simultaneous determination of naphazoline nitrate and methylparaben in pharmaceuticals using separation method based on a novel reversed-phase sequential injection chromatography (SIC) is described in this contribution as an alternative to classical HPLC. A Chromolith™ Flash RP-18e (25 mm × 4.6 mm) column (Merck®, Germany) and a FIAlab® 3000 system (USA) with a six-port selection valve and 5.0 ml syringe pump were used for sequential injection chromatographic separations in our study. The mobile phase used was methanol/water (40:65, v/v), pH 5.2 adjusted with triethylamine 0.8 μl ml$^{-1}$ and acetic acid, at flow rate 0.9 ml min$^{-1}$. UV detection provided by DAD detector and two wavelengths were simultaneously monitored for increasing sensitivity of determination. Detector was set up at 220 nm for naphazoline nitrate and 256 nm for methylparaben and ethylparaben (IS). There is no necessity to use pre-adjustment of sample of nasal drops (only dilution with mobile phase) so the time of the whole analysis is very short. The validation parameters have shown good results: linearity of determination for both components (naphazoline nitrate and methylparaben), correlation coefficient >0.999; repeatability of determination (R.S.D.) in the range 0.5–1.6% at three different concentration levels, detection limits 0.02 μg ml$^{-1}$ (naphazoline nitrate) and 0.20 μg ml$^{-1}$ (methylparaben and ethylparaben), and recovery from the pharmaceutical preparations in the range 100.06–102.55%. The chromatographic resolution between peaks of compounds was more than 4.0 and analysis time was less than 4 min under the optimal conditions. The advantages and drawbacks of SIC against classical HPLC are discussed showing that SIC can be an advantageous alternative in many cases.


*Keywords:* Sequential injection chromatography; Monolithic column; Naphazoline nitrate; Methylparaben; Spectrophotometric determination

## 1. Introduction

In the last few years, special attention was given to sequential injection analysis (SIA), high versatile technique based on a programmable flow as an economical and expeditious alternative for the automation of analytical procedures [1]. SIA has been proposed by Růžička and Marshall as an efficient tool for automated liquid handling, especially performing of derivatisation reactions [2]. The technique is based on forward and reverse movement of a piston of syringe pump, which together with a multi-position selection valve enables precise sampling of chemicals into the system and propelling of the sequenced zones to the reactors and detector [3]. Automation, speed of the analysis and low consumption of sample and reagents are the most important features that favour the SIA technique for application in many fields of analysis, primarily by more complicated operations such as sample pre-treatment or monitoring of long lasting processes [4–6]. On the other side, SIA technique itself has generally one important drawback—it cannot primarily provide the separation procedure and analysis of multi-component samples.

This weak point was solved by coupling of short monolithic column [7] with SIA manifold. The new method called sequential injection chromatography (SIC) was recently successfully applied in the analysis of relatively simple multi-component samples like pharmaceuticals [8–11].

The use of monolithic columns (formed from a single piece of porous silica gel) enabling operation at high flow rates with lower back-pressure [12]. This feature can be used for integrating these columns into a SIA manifold and for extending the possibilities of SIA technique (the back-pressure limit range of the syringe pump in SIA apparatus is about 2.5 MPa).

The problem of determination of one analyte in the presence of other compounds or complex matrix using SIA method could be solved by using selective detectors or different analytical

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tools. There can be mentioned fluorescence for determination of complex formed between naproxen and β-cyclodextrin in sample without any previous separation, extraction or other sample preparation [13], chemiluminescence for monitoring of glucose and penicillin during cultivations using specific reactions [14], selective sensors – ion selective electrodes sensitive to penicillin-G antibiotics for pharmaceutical products analysis [15], selective extraction – anion exchange solid phase micro-column for simultaneous determination of benzophenone-4 and phenylbenzimidazole sulphonic acid in sunscreen sprays [16], determination of organic acids and sugars in soft drinks by Fourier transform infrared spectroscopy [17], solid phase C18 RAM for direct determination of furosemide in serum [18], liquid–liquid microextraction using lab-on-valve (LOV) and a separating chamber for determination of diphenhydramine hydrochloride in pharmaceutical preparations and anionic surfactant in water samples [19], reaction columns—reduction copperised cadmium column for the determination of nitrate and nitrite in water samples [20,21], gas-diffusion unit for determination of ammonium in environmental samples [22], dialysis through a cellulose membrane was used to enable sample dilution and matrix separation to quantify pH, chloride and nickel in electrolytic baths [23], LOV format for simultaneous spectrophotometric determination of copper and iron in wastewater [24], lab-on-valve system using chelating Sepharose beads as sorbent material for the determination of ultra-trace levels of $Cd^{2+}$, $Pb^{2+}$ and $Ni^{2+}$ by electrothermal atomic absorption spectrometry [25], selective reaction of sulphate with barium-dimethylsulphonazo(III) for sulphate determination in automotive fuel ethanol [26] or use of special mathematical models—multivariate curve resolution with alternating least squares for simultaneous determination of analytes in the presence of interferents without the need to pretreat the sample [27].

Naphazoline nitrate (NN: 2-(1-naphthylmethyl)-2-imidazoline nitrate) depicted in Fig. 1, is an imidazolic α-sympathomimetic drug used like relatively long-lasting action nasal decongestive substance to threat rhinitis. Methylparaben

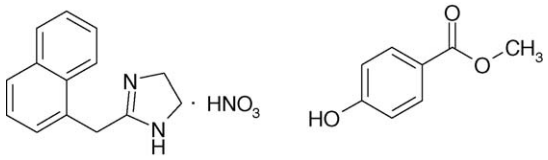


Fig. 1. Structure of naphazoline nitrate (A) and methylparaben (B).

(MP: methyl *p*-hydroxybenzoate) depicted in Fig. 1, is effective antibacterial and antifungal agent, which is commonly used as preservative in foods, beverages, cosmetics and pharmaceuticals.

Very recently, naphazoline salt was analysed by first-derivative UV spectrophotometry [28] and by chemometric assisted simultaneous spectrophotometric determination together with methyparaben, phenylephrine and diphenhydramine [29]. There has been no separation method found in the literature for simultaneous determination of NN and MP.

## 2. Experimental

### 2.1. Apparatus

#### 2.1.1. Sequential injection system and monolithic column

A commercially available instrument FIAlab® 3000 system (FIAlab® Instruments Inc., Bellevue, USA) with a syringe pump (syringe reservoir 5.0 ml) and a 6-port selection Cheminert® valve (Valco Instrument Co., Houston, USA) was used. The manifold was equipped with fiber-optic UV–vis diode array detector USB 2000 (Ocean Optics Inc., Dunedin, USA), 10 mm Z-flow cell (Avantes, CO, USA) and UV light source D-1000-CE (Analytical Instrument Systems Inc., Flemington, USA). The whole SIC system was controlled by the program FIAlab® for Windows 5.0. Flow lines were made of 0.75 mm i.d. PTFE tubing. Mobile phases and samples were aspirated through the 6-port multi-position valve and then delivered to the monolithic column and to the detector. On-line sample separation was per-

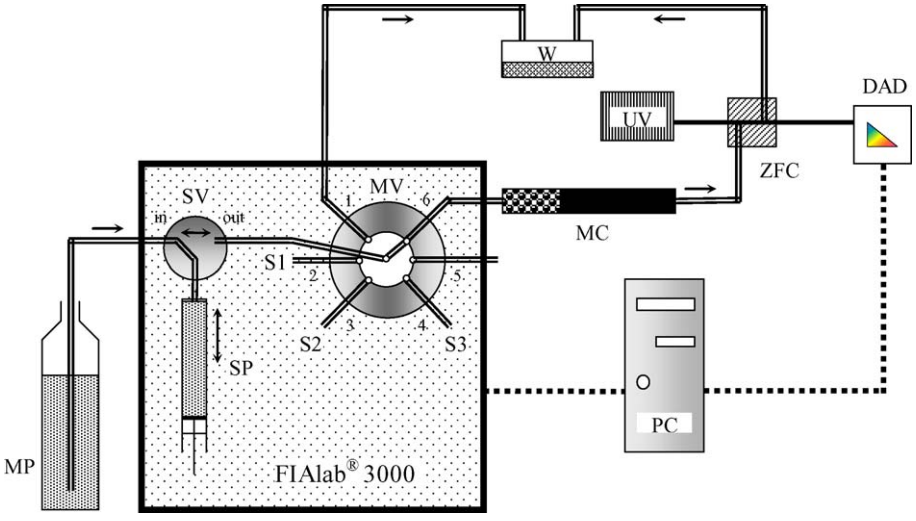


Fig. 2. Scheme of SIC set-up for determination of NN and MP. DAD, DAD detector; MC, monolithic column; MP, mobile phase; MV, 6-port multi-position valve; SP, syringe pump; SV, solenoid valve; S1–S3, Sample 1–3; PC, computer, UV, UV lamp, W, waste, ZFC, Z-flow cell.

formed on C-18 monolithic column Chromolith™ Flash RP-18 (25 mm × 4.6 mm) (Merck, Darmstadt, Germany) coupled with monolithic precolumn (5 mm × 4.6 mm) (Merck). The Monolithic column with precolumn was placed between the multiposition valve and flow cell of the detector. A scheme of the sequential injection chromatography system with the monolithic column is depicted in Fig. 2.

#### 2.1.2. HPLC apparatus

Preliminary experiments concerning the composition of mobile phase for precise separation were performed on HPLC system consisting of a pump (Ecom LCP 4100, Prague, Czech Republic), autosampler (Waters 717, Milford, USA), UV detector (Waters 486) and data processing software CSW v. 1.7 for Windows (Data Apex s.r.o., Prague, Czech Republic). Analyses were performed on the same above-mentioned column. Mobile phases of different composition were tested at flow rate 0.9 ml $min^{-1}$ and the detector was set on 220 nm.

### 2.2. Reagents

Naphazoline nitrate was obtained from IVAX Pharmaceuticals s.r.o. (Czech Republic, PhEur3 grade quality), methylparaben was obtained from Zentiva, a.s. (Czech Republic, PhEur3 grade quality), ethylparaben was obtained from Sigma–Aldrich (Czech Republic, PhEur3 grade quality) and organic modifiers for mobile phase preparation were obtained from Sigma–Aldrich. Methanol (Chromasolv, for LC) was obtained from Sigma–Aldrich. All other used chemicals were of analytical grade quality. Millipore Milli-Q RG (Millipore s.r.o., Czech Republic) ultra pure water was used for preparing the solutions. Mobile phases were degassed by helium before use. Stock standard solutions were prepared in water with addition of methanol (5%) and were stored at 5 °C for 1 month. The final concentrations of the sample working standard solutions or reference standards for pharmaceutical preparations analysis were prepared by diluting the stock solution in the mobile phase.

### 2.3. Method and sample preparation

#### 2.3.1. Mobile phase

The optimal mobile phase for separation of NN, MP and internal standard EP was methanol/water (40:65, v/v), pH 5.2 adjusted with triethylamine 0.8 μl $ml^{-1}$ and acetic acid; flow rate 0.9 ml $min^{-1}$ at ambient temperature. Volume of mobile phase used for one analysis was 3.5 ml. Mobile phase was degassed before application by means of helium.

#### 2.3.2. Solutions and sample preparation

The tested pharmaceutical preparation was Sanorin® 0.5‰ (IVAX, Czech Republic) containing 500 μg of NN and 1000 μg of MP in 1.0 ml of nasal drops. Determination of the active substances in pharmaceutical was done by the following procedure: 1.00 ml of Sanorin® 0.5‰ solution was transferred to 50.00 ml calibrated flask; then 5.00 ml methanol and 1.00 ml of stock solution of internal standard ethylparaben was added. The sample was homogenized and dissolved by 5 min sonication; the time period 15 min was let for temperature stabilization, then the flask was filled to the mark with mobile phase and mixed. The comparative standard solution was the same for all the analysis and it was prepared diluting stock standard solution in 50.00 ml calibrated flask with 5.00 ml methanol and then the flask was filled to the mark with mobile phase and mixed. The final concentrations of the analytes in comparative standard solution were 10 μg $ml^{-1}$ of NN, 20 μg $ml^{-1}$ of MP and 20 μg $ml^{-1}$ of EP. A volume of 10 μl of sample was analyzed by SIC system. Standards and samples were measured in triplicates and the mean peak height values were used for data acquisition.

## 3. Results and discussion

### 3.1. Method development and optimization

The incorporation of monolithic columns to SIA manifold has already been introduced in our previous works [7–11]. The main aim of the present study was to find optimal separation conditions of the sequential injection cycle for simple method of determination of NN and MP, and to explore practical suitability of this method for analysis in pharmaceutical solution. The optimization of mobile phase was started with Chromolith® Flash RP-18 column 25 mm × 4.6 mm and methanol/water (50:50, v/v) mobile phase. The mobile phases containing methanol as organic part have shown better separation of peaks and peak symmetry than acetonitrile containing mobile phases and the optimization was focused to make a proposal appropriate ratio of methanol/water mobile phase composition. In order to achieve a sufficient symmetry of the peaks together with a good separation of compounds and a short retention time, the optimal mobile phase for the separation of NN, MP was founded methanol/water (40:65, v/v), pH adjusted to 5.2 by means of triethylamine 0.8 μl $ml^{-1}$ and acetic acid and flow rate of it 0.9 ml $min^{-1}$. Ethylparaben (EP) was chosen as a suitable internal standard. The sample injection volume was 10 μl. The proposed system enabled successful separation of target analytes in the time less than 4 min and total volume of mobile phase for one analysis was 3.5 ml. Standards and samples were measured in triplicates and the mean peak height values were used for data acquisition. The typical sequence of particular steps of the program is mentioned in Table 1 (action description of all parts of system). From the UV spectra of NN and MP in mobile phase, the optimal detection wavelength of 220 nm for NN and 256 nm for MP and internal standard EP was chosen. Peak height evaluation was performed using the FIAlab® software. Representative sequential injection chromatogram showing successful separation of active substances of Sanorin® 0.5‰ including internal standard is shown in Fig. 3.

### 3.2. Parameters of sequential injection chromatography process

The target compounds were successfully separated using the proposed procedure and basic chromatographic parameters were calculated from experimental data, such as retention times, peak

Table 1
The sequence of particular steps of the SIC control program for Sanorin® 0.5‰ determination (a single cycle)

| Unit | Command | Parameter | Action |
|---|---|---|---|
| Solenoid valve | Valve in | | Set valve position |
| Syringe pump | Set flow rate (μl s$^{-1}$) | 100 | |
| Syringe pump | Aspirate (μl) | 3500 | Mobile phase aspirated |
| Solenoid valve | Valve out | | Set valve position |
| Multi-position valve | Valve port 2 | | |
| Syringe pump | Set flow rate (μl s$^{-1}$) | 10 | |
| Syringe pump | Aspirate (μl) | 10 | Sample aspirated |
| Multi-position valve | Valve port 6 | | |
| Syringe pump | Set flow rate (μl s$^{-1}$) | 15 | |
| Syringe pump | Dispense (μl) | 1200 | Elution of NN |
| Syringe pump | Set flow rate (μl s$^{-1}$) | 15 | |
| Syringe pump | Dispense (μl) | 900 | Elution of MP |
| Syringe pump | Set flow rate (μl s$^{-1}$) | 15 | |
| Syringe pump | Dispense (μl) | 1400 | Elution of EP |

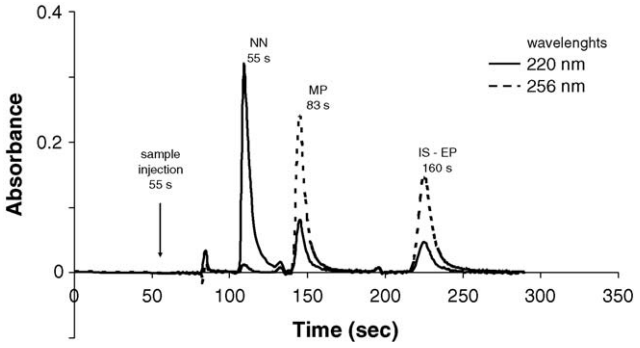


Fig. 3. SI chromatogram of the separation of active substances of Sanorin® 0.5‰ nasal drops. Mobile phase: methanol/water (40:65, v/v), pH 5.2 adjusted with triethylamine 0.8 μl ml$^{-1}$ and acetic acid, flow rate 0.9 ml min$^{-1}$ at ambient temperature, UV detection at 220 and 256 nm.

symmetry, number of theoretical plates and peak resolution; they are given in Table 2.

### 3.3. Validation and analytical parameters of the method

The developed method was validated in order to evaluate if adequate linearity, sensitivity, repeatability, recovery, selectivity, precision and accuracy had been achieved. Linearity was established with a series of working solutions prepared by diluting the stock solution with mobile phase to the final concentrations. Each concentration was injected in triplicate and the mean value of peak height was used for the calibration curve. The calibration graphs involved eight experimental points for NN (concentration range 0.065, 0.13, 0.26, 0.52, 1.04, 3.13, 6.25 and 12.50 μg ml$^{-1}$) and it is described by the following equation: $A = (0.0507 \pm 0.0004)c + (0.0019 \pm 0.0019)$ (where $A$ is the absorbance and $c$ the analyte concentration), the correlation coefficient was 0.9998; for MP and EP six experimental points (concentration range 1.30, 2.60, 5.20, 15.63, 31.25, 62.50 μg ml$^{-1}$) and they are described by following equations: MP $A = (0.0142 \pm 0.0002)c - (0.0179 \pm 0.0058)$, the correlation coefficient was 0.9996; and for internal standard EP: $A = (0.0088 \pm 0.0002)c - (0.0157 \pm 0.0047)$, the correlation coefficient was 0.9993. The limit of detection (LOD) was calculated by comparison of the three-fold variation of signal to noise ratio (3 S/N) obtained from analysis of the standards, and the limit of quantification (LOQ) was defined as the lowest measured quantity above which the analyte can be quantified at a given statistical level of (10 S/N). The system precision of the method was determined by preparing the standards of NN, MP and EP at three concentration levels (25, 50 and 250 times diluted drops) and peak heights for each compound were determined after processing each standard eight times. The method validation results obtained under the final conditions are shown in Table 3. The method was found to fulfill common requirements of accuracy, precision and linearity (calibration range with correlation coefficient >0.999, R.S.D. for repeated standard injections at three concentration levels ($n = 8$) less than 1.6%). To validate the precision of the method, a number of six different pharmaceutical sample solutions were used, which were prepared from the same batch and analyzed consecutively. This approach provides a means of covering the precision of the entire method, from sample preparation to data handling. The precision of the method calculated as R.S.D. of six sample determination, including sample preparation, was 1.45% for NN and 1.44% for MP. The mean values of found amount were average 99.41% of NN and 97.29% of MP. The accuracy of the method was carried out measuring of the pharmaceutical samples fortified with known quantity of the analytes (addition of 100% amount of the standards to pharmaceutical preparation). Spiked sample solutions and un-spiked sample solutions were compared for recovery evaluation. The method accuracy results—mean values of the

Table 2
Characterization of SIC process

| | Nafazoline nitrate | Methylparaben | Ethylparaben |
|---|---|---|---|
| Retention time (s) | 55 | 83 | 160 |
| Peak symmetry | 2.67 | 1.59 | 1.75 |
| Number of theoretical plates | 848.4 | 1418.3 | 2157.3 |
| Peak resolution | $R_{NN/MP} = 4.0$ | $R_{MP/EP} = 6.4$ | |

Table 3
Analytical parameters and method validation results

| | Nafazoline nitrate | Methylparaben | Ethylparaben |
|---|---|---|---|
| Calibration range ($\mu g\,ml^{-1}$) | 0.065–12.50 | 1.30–62.50 | 1.30–62.50 |
| Correlation coefficient | 0.9998 | 0.9996 | 0.9993 |
| Limit of detection ($\mu g\,ml^{-1}$) | 0.02 | 0.20 | 0.20 |
| Limit of quantification ($\mu g\,ml^{-1}$) | 0.06 | 0.60 | 0.60 |
| System precision—drops diluted 25× (%)[a] | 1.05 | 1.37 | 1.35 |
| System precision—drops diluted 50× (%)[a] | 1.36 | 0.87 | 0.52 |
| System precision—drops diluted 250× (%)[a] | 0.84 | 1.58 | 0.76 |
| Repeatability of $T_R$ (%)[a] | 0.53 | 1.01 | 0.66 |
| Method precision (%)[b] | 1.45 | 1.44 | |
| Accuracy—spike recovery (%)[c] | 102.55 | 100.06 | |

[a] Relative standard deviation (R.S.D.) values were calculated for repeated standard injections ($n = 8$).
[b] R.S.D. for repeated injections of multiple sample preparations ($n = 6$).
[c] Spiked sample solutions.

Table 4
Comparison of HPLC and SIC

| Characteristic | HPLC | SIC | Benefit SIC |
|---|---|---|---|
| Possibility of separation | Yes | Yes—simple mixtures[a] | No |
| Using of chromatographic columns | Yes | Only short monolithic[b] | No |
| Variability of detection | Yes | Yes | |
| Flow of mobile phase | Continual | Discontinual | Yes |
| Direction of flow of mobile phase | One way | Both ways + stop flow | Yes |
| Speed of mobile phase | Constant | Variable | |
| Consumption of mobile phase | High | Low (discontinual flow)[c] | Yes |
| Speed of the analysis | Average | Average | |
| Use of reagents (reactions) | Limited[d] | Yes | Yes |
| Pre-treatment of sample | Yes (restricted) | Yes | Yes |
| Automation of measurement | High | High | |
| Robustness of measurement | High | Average[e] | No |
| Data evaluation | Sophisticated | Simple | No |
| Reproducibility | High | High | |
| Cost of instrumentation | High | Low[f] | Yes |
| Portability of analyzer | No | Yes[g] | Yes |

[a] From two to five substances.
[b] At present.
[c] Mobile phase is flowing during the separation only.
[d] Post-column derivatization.
[e] Sometimes problems with higher pressure in system, restriction in column lengths.
[f] Two to three times cheaper.
[g] Small-sized box.

recoveries were found as 102.55% for NN and 100.06% for MP. Assay values of recoveries show that the method allows direct determination of NN and MP in commercial dosage forms in the presence of other adjuvants.

### *3.4. Determination in pharmaceutical product*

The method developed has been applied to the determination of NN and MP in nasal drops Sanorin® 0.5‰. The drops were commercially available on the Czech market. The interference effect of adjuvants (boric acid and ethylendiamine) was not observed. The samples were prepared by dilution 50 times with mobile phase containing IS. For analysis, a loop of three loads of comparative standard solution was programmed, three loads of first sample solution and three loads of second sample solution prepared from one pharmaceutical. The results of determination of samples (same batch) were in the range (96.78–101.59%) for NN and (95.37–99.26%) for MP of declared value. The procedure of sample preparation was simple, fast and achieving high precision and low sample and reagent consumption.

## 4. Conclusion

The proposed SIC system was proved to be a convenient and efficient tool for the separation and determination of naphazoline nitrate and methylparaben in pharmaceutical preparation (nasal drops). The simultaneous analysis of both compounds has never been described before. SIC technique shows several advantages as short time of analysis and possibility of on-line use of reagents in all steps of determination. The production of the waste and the consumption of solvents are lower than in HPLC methods (due to discontinual flow), this enable reduction of cost per analysis (at

least twice). Easy liquid manipulation not attainable by classical HPLC set up, dimensions of the SIC system and portability of analyzer provides the opportunity for analysis "on field".

On the other hand, SIC has several disadvantages like limited ability of separation due to short (only monolithic) column and limited amount of mobile phase available for one analysis due to the use of 5 ml syringe pump. Also robustness of SIC technique is not as high as in HPLC and data processing is rather elementary (only peak height at present). A comparison of different characteristics of HPLC and SIC together with their advantages/disadvantages is shown in Table 4.

The coupling of the commercial monolithic column with high separation performance at lower pressure to SIA manifold allows to carry out simple separations without an expensive instrumentation such as the HPLC. From this point of view, the low-pressure monolithic silica columns opened a new area offering separation analysis in highly flexible sequential injection systems. Moreover, the use of two wavelengths simultaneously in our method provides additional increasing of sensitivity of determination (measuring in wavelength of absorbance maximum of each compound). In summary, the SIC system can be an important tool for the rapid separation and quantification of several compounds in pharmaceutical analysis.

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