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Automated in-tube solid-phase microextraction–liquid chromatography–electrospray ionization mass spectrometry for the determination of ranitidine

Hiroyuki Kataoka, Heather L. Lord, Janusz Pawliszyn*

Department of Chemistry, University of Waterloo, Waterloo, Ontario N2L 3G1, Canada

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Abstract

The technique of automated in-tube solid-phase microextraction (SPME) coupled with liquid chromatography–electrospray ionization mass spectrometry (LC–ESI-MS) was evaluated for the determination of ranitidine. In-tube SPME is an extraction technique for organic compounds in aqueous samples, in which analytes are extracted from the sample directly into an open tubular capillary column by repeated aspirate/dispense steps. In order to optimize the extraction of ranitidine, several in-tube SPME parameters such as capillary column stationary phase, extraction pH and number and volume of aspirate/dispense steps were investigated. The optimum extraction conditions for ranitidine from aqueous samples were 10 aspirate/dispense steps of 30 μl of sample in 25 m*M* Tris–HCl (pH 8.5) with an Omegawax 250 capillary column (60 cm×0.25 mm I.D., 0.25 μm film thickness). The ranitidine extracted on the capillary column was easily desorbed with methanol, and then transported to the Supelcosil LC-CN column with the mobile phase methanol–2-propanol–5 *M* ammonium acetate (50:50:1). The ranitidine eluted from the column was determined by ESI-MS in selected ion monitoring mode. In-tube SPME followed by LC–ESI-MS was performed automatically using the HP 1100 autosampler. Each analysis required 16 min, and carryover of ranitidine in this system was below 1%. The calibration curve of ranitidine in the range of 5–1000 ng/ml was linear with a correlation coefficient of 0.9997 ($n=24$), and a detection limit at a signal-to-noise ratio of three was ca. 1.4 ng/ml. The within-day and between-day variations in ranitidine analysis were 2.5 and 6.2% ($n=5$), respectively. This method was also applied for the analyses of tablet and urine samples.

Keywords: Automated in-tube solid-phase microextraction; Mass spectrometry; Solid-phase microextraction; Ranitidine

1. Introduction

Drug analyses are important for the quality control of pharmaceutical preparations and the continuing development of more effective drugs. Furthermore, confirmation and determination of drugs in biological fluids are important for pharmacokinetic studies and clarification of therapeutic and toxic effects. Drugs are generally present at low concentration in these complex matrices. Therefore, it is not an exaggeration to say that the clean-up procedures for these samples greatly influences the reliable and accurate analysis of drugs. In order to achieve an efficient isolation and pre-concentration of drugs, several

*Corresponding author. Tel.: +1-519-8884-641; fax: +1-519-7460-435.
E-mail address: janusz@sciborg.uwaterloo.ca (J. Pawliszyn)

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methods for sample preparation have been developed including liquid–liquid extraction, solid-phase extraction and other techniques. However, these methods are time-consuming, and require large volumes of sample and solvent. Solid-phase microextraction (SPME), recently developed by Pawliszyn and coworkers [1,2], is an extraction technique using a fused-silica fiber that is coated on the outside with an appropriate stationary phase. The method saves preparation time, solvent purchase and disposal cost, and can improve the detection limits [1–4]. It has been used routinely in combination with gas chromatography (GC) and GC–mass spectrometry (MS), and successfully applied to a wide variety of compounds [2–5] including several drugs [6–17]. However, these methods are not suitable for weakly volatile or thermally labile compounds such as most drugs. In order to solve these problems, SPME was recently introduced for direct coupling with high-performance liquid chromatography (HPLC) [17–24] and LC–MS [25–29]. The SPME–LC interface equipped with a special desorption chamber is utilized for solvent desorption prior to LC analysis instead of thermal desorption in the injection port of the GC instrument. Moreover, a new SPME–LC system known as in-tube SPME, was recently developed using an open tubular fused-silica capillary column as the SPME device instead of an SPME fiber [30]. In this paper we report on the automation of this method. This has been facilitated by the Hewlett-Packard 1100 LC–MS system, as the standard autosampler for this system (ALS 1100) is ideally suited for in-tube SPME. In this technique organic compounds in aqueous samples are extracted directly from the sample into the internally coated stationary phase of a capillary column. The capillary column is placed between the injection loop and the injection needle of an HPLC autosampler. While the injection syringe under computer control, repeatedly aspirates and dispenses sample from the vial, the analytes partition from the sample matrix into the stationary phase until equilibrium is reached. The extracted analytes are directly desorbed from the capillary coating into desorption solvent, transported to the HPLC column with mobile phase flow, and then detected with UV or mass-selective detection (MSD).

Ranitidine is a histamine H_2 receptor antagonist and is used for the treatment of duodenal and stomach ulcers [31–33]. Ranitidine is selected here as a model compound to demonstrate the feasibility of the method. Ranitidine ($pK_a=8.2$) is very stable at room temperature, in the refrigerator and in the freezer, but this compound is slightly unstable for heating and is degraded under strong alkaline and acidic conditions [34]. Furthermore, it is reported that ranitidine is metabolized in the liver to its N-oxide, S-oxide and desmethyl forms, and approximately 70% of dose of the drug is excreted in urine as the uncharged form [35]. HPLC [36–47], LC–MS [48,49] and capillary electrophoresis [50] have been used for the separation and determination of ranitidine in pharmaceutical and biological samples. However, these methods require laborious and time-consuming clean-up of the sample, and are not easy to automate. In this study, an automated in-tube SPME method coupled with LC–electrospray ionization (ESI)-MS was investigated for the determination of ranitidine. Using this method, ranitidine in tablet and urine samples were also analyzed.

2. Experimental

2.1. Materials

Ranitidine hydrochloride (Sigma, St. Louis, MO, USA) was dissolved in water to make a stock solution at a concentration of 1 mg/ml as ranitidine, and used after dilution with water to the required concentration. Zantac 75 (ca. 150 mg/tablet, Glaxo Wellcome) was purchased from a local drug store. All solvents used in this study were of HPLC grade. Water was obtained from a Barnstead/Thermodyne NANO-pure ultrapure water system (Dubuque, IA, USA).

2.2. Instrument and analytical conditions

The LC–MS system used was a Model 1100 series LC coupled with an atmospheric pressure (AP)-ESI mass spectrometer (Hewlett-Packard, Palo Alto, CA, USA). A Supelcosil LC-CN column (3.3 cm×4.6 mm I.D., 3 μm particle size) from Supelco (Bellefonte, PA, USA) was used for the LC separation. LC conditions were as follows: column temperature,

25°C; mobile phase, methanol–2-propanol–5 *M* ammonium acetate (50:50:1); flow-rate, 0.5 ml/min. ESI-MS conditions were as follows: nebulizer gas, N_2 (40 p.s.i.; 1 p.s.i.=6894.76 Pa); drying gas, N_2 (10 l/min, 350°C); fragmentor voltage, 70 V; capillary voltage, 3500 V; ionization mode, positive; mass scan range, 100–400 u; scan time, 0.68 s/cycle; selected ion monitoring (SIM), *m/z* 270, 315 and 337 (identified ions); dwell-times for the ions in SIM, 132 ms.

2.3. In-tube solid-phase microextraction

The schematic diagram of the in-tube SPME system is illustrated in Fig. 1. GC capillary column (60 cm×0.25 mm I.D., 0.25 μm film thickness) was used as the in-tube SPME device, and placed between the injection loop and injection needle of the autosampler. The injection loop was retained in the system to avoid fouling of the metering pump. Capillary connections were facilitated by the use of a 2.5 cm sleeve of 1/16 in. polyether ether ketone (PEEK) tubing at each end of the capillary (1 in.= 2.54 cm). A PEEK tubing internal diameter of 330 μm was found to be suitable to accommodate the capillary used. Normal 1/16 in. stainless steel nuts, ferrules and connectors were then used to complete the connections. Omegawax 250, SPB-5, SPB-1 and retention gap capillary (no coating) (Supelco) were tested for comparison of extraction efficiency. The total internal volume of each capillary was 29.4 μl. The autosampler software was programmed to control the SPME extraction, desorption and injection. An aliquot of sample and 0.05 ml of 0.5 *M* Tris–HCl (pH 8.5) were pipetted into a 2-ml vial, total volume was made up to 1 ml with water, and the vials were then set on the autosampler. In addition, each of 1.5 ml of methanol and mobile phase in the 2-ml vial was set on the autosampler, the capillary column was washed by two aspirate/dispense steps of 40 μl of these solvents prior to extraction. The extraction of ranitidine onto the capillary coating was performed using 10 aspirate/dispense steps of 30 μl of sample at a flow-rate of 100 μl/min, with the six-port valve in the LOAD position. After washing the injection syringe by aspirate/dispense of 2 μl of methanol, the extracted ranitidine was desorbed from the capillary coating by aspiration of 40 μl of methanol, and then transported to the LC column with mobile phase flow with the six-port valve in the INJECT position.

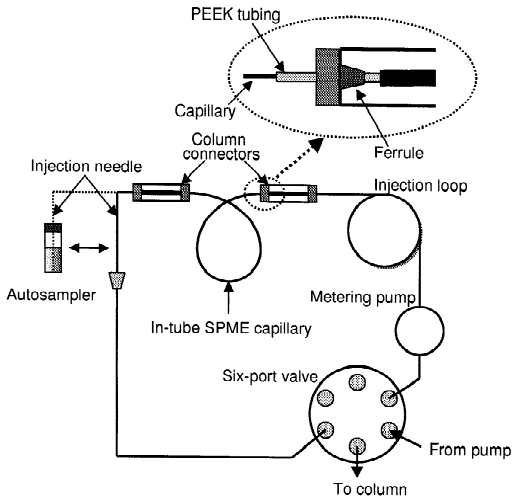

Fig. 1. Schematic diagram of the in-tube SPME system for LC–MS.

2.4. Pharmaceutical and biological samples

Zantac 75 tablets were ground with a mortar and pestle, and dissolved in water at a concentration of 40 μg/ml (containing 20 μg/ml ranitidine). The solution was then filtered with syringe microfilter (0.45 μm, Gelman Science), and used after dilution with water to the required concentration. Urine samples were diluted 10 times with water and used after filtration. An aliquot of each sample was pipetted into the 2-ml vial and 0.05 ml of 0.5 *M* Tris–HCl buffer (pH 8.5) was added. After the total volume was made to 1 ml with water, the vials were set on the autosampler.

3. Results and discussion

Although SPME fibers have been used for the analysis of several organic compounds in combination with LC or LC–MS [18–29], a general problem with the fiber SPME method is that there are limited commercially available SPME fibers for polar analytes such as drugs. On the other hand, GC capillary columns with a vast array of stationary phases are

commercially available. Some of these are appropriate for the extraction of drugs with the in-tube SPME method. The other limitation of fiber SPME–LC analysis is the absence of a commercial autosampler. In-tube SPME addresses this deficiency. Although the theories of fiber and in-tube SPME are similar, important differences between these methods are that the extraction of analytes is performed on the outer surface of fiber for fiber SPME and in the inner surface of capillary column for in-tube SPME, and that in-tube SPME can continuously perform extraction, desorption and injection using an autosampler.

In preliminary studies, ranitidine gave a very simple ESI mass spectrum under typical operation conditions (see Experimental), and a strong signal corresponding to m/z 315 $[M+H]^+$ was observed (Fig. 2). Other minor peaks appeared at m/z 270 $[M+H-NH(CH_3)_2]^+$ and m/z 176 $[SCH_2CH_2NHC(CHNO_2)NHCH_3]^+$. However, the adduct ion m/z 337 $[M+Na]^+$ was also observed as the major ion instead of $[M+H]^+$ when the sodium ion was present in the sample. The ratio of $[M+H]^+$ and $[M+Na]^+$ ions was dependent on the sodium ion concentration in the sample. In this study, the sum of all three ions (m/z 270, 315 and 337) was used for quantifications in the SIM mode, because biological samples contain sodium ions.

In order to optimize the extraction of ranitidine by in-tube SPME, several parameters such as stationary phase of capillary column, extraction pH, number and volume in aspirate/dispense steps were investigated by monitoring of total ion current of m/z 270, 315 and 337. In this work, four different capillary columns were evaluated for ranitidine analysis using in-tube SPME–LC–MS-SIM. As expected, the relatively polar Omegawax 250 column gave superior extraction efficiency as compared to the less polar SPB-5, SPB-1 and no coating columns (Fig. 3). A capillary column 50 to 60 cm long was optimal for extraction [30]. Below this level, extraction efficiency was reduced, and above this level, peak broadening was observed. The effect of sample pH on the extraction of ranitidine by in-tube SPME was examined using several buffer solutions. As shown in Fig. 4, Tris–HCl, pH 8.5 was most effective, and the optimal concentration of this buffer was 25 to 50 m*M*. These results clearly indicated that the sample pH and ionic strength considerably affect the extraction efficiency. In order to monitor the extrac-

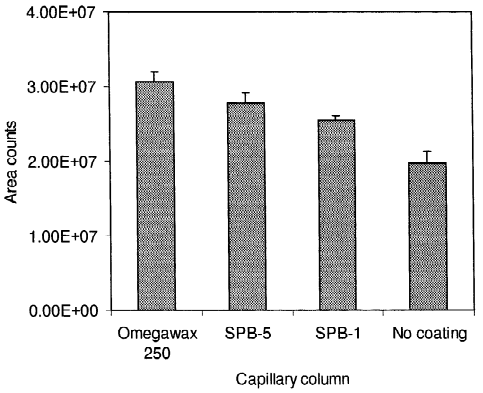

Fig. 3. Evaluation of four capillary columns for the in-tube SPME–LC–MS analysis of ranitidine.

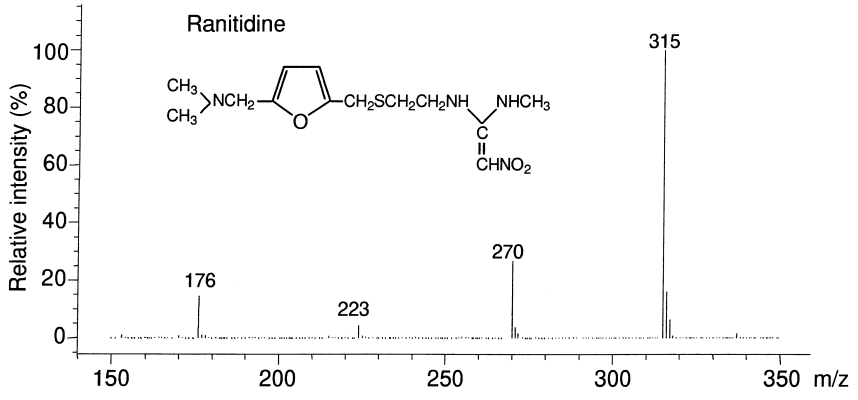

Fig. 2. ESI^+ spectra obtained by in-tube SPME–LC–MS of 0.5 μg/ml ranitidine.

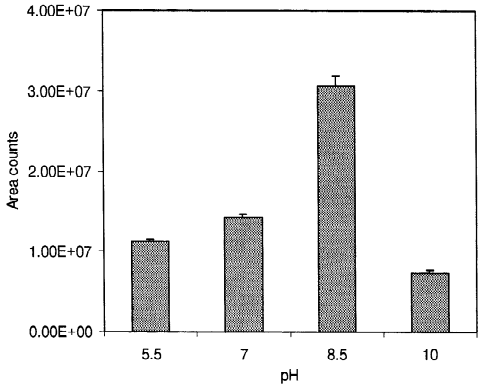

Fig. 4. Effect of sample pH on ranitidine extraction efficiency with Omegawax 250. Buffer: pH 5.5, sodium acetate buffer; pH 7.0, sodium phosphate buffer; pH 8.5, Tris–HCl buffer; pH 10.0, sodium carbonate buffer. Buffer concentration in all samples was 25 m*M*.

tion–time profile of ranitidine by in-tube SPME, the number of aspirate/dispense steps was varied from 0 to 20 steps. As shown in Fig. 5, the extraction of ranitidine using Omegawax 250 reached equilibrium after 10 aspirate/dispense steps of 30 μl of sample. Above 35 μl, peak splitting was observed due to the overload of the capillary column volume (29.4 μl). Furthermore, an aspirate/dispense rate of 50 to 100 μl/min was optimal for extraction [30]. Below this level, extraction required an inconveniently long time, and above this level, bubbles formed inside of the capillary and extraction efficiency was reduced. The absolute amount of ranitidine extracted on the capillary column under optimal conditions was

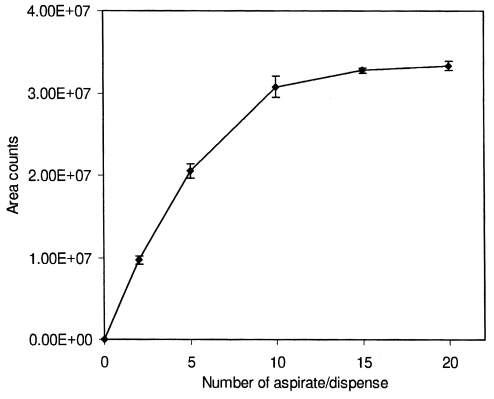

Fig. 5. Extraction–time profile of ranitidine with Omegawax 250.

calculated from comparison with the corresponding direct injection of the sample solution onto the LC column. By in-tube SPME of ranitidine at 1 μg/ml, ca. 50 ng (2.5%) was extracted onto the Omegawax 250 column.

Static desorption of ranitidine from the capillary was achieved by aspiration of 40 μl of methanol into the capillary column. The desorbed ranitidine was easily transported to the LC column with mobile phase flow. The carryover, which is the ratio of the amount of analyte remaining on the capillary after the first desorption to the amount of the total analyte, was examined. The remaining ranitidine was $<1\%$ under typical operating conditions, and could be removed by washing the capillary with methanol and mobile phase prior to the next analysis. All operations including column washing, sample extraction, desorption and LC–MS analysis were performed continuously and automatically, and accomplished within 16 min per sample.

Fig. 6 shows the total ion chromatograms obtained from aqueous samples of 20, 100 and 200 ng/ml ranitidine. Ranitidine gave an excellent response in this system and the detection limit ($S/N=3$) under our LC–MS conditions was 1.4 ng/ml. In order to test the linearity of the calibration curve, various

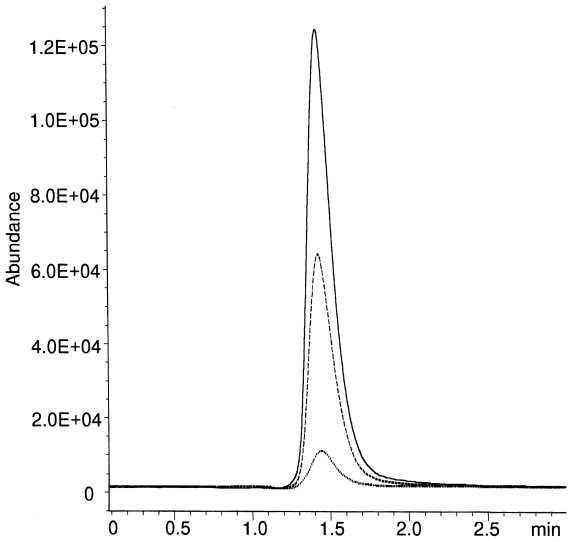

Fig. 6. Total ion chromatograms obtained from ranitidine by in-tube SPME–LC–MS-SIM. LC–MS conditions: see Experimental. Dotted line, 20 ng/ml; dashed line, 100 ng/ml; solid line, 200 ng/ml.

concentrations of ranitidine ranging from 5 to 1000 ng/ml (eight points) were analyzed by three repeats at each point. The calibration curve was constructed from the peak area counts of a sum of the ions at m/z 270, 315 and 337 analyzed in SIM mode. A linear relationship was obtained with correlation coefficient being 0.9997 ($n=24$), and the relative standard deviations for each point were 0.2 to 3.4% ($n=3$). In addition, the within-day and between-day variations for standard ranitidine analysis by in-tube SPME–LC–MS method were 2.5 and 6.2% ($n=5$), respectively.

In order to demonstrate the applicability of this method to pharmaceutical preparations and biological samples, ranitidine was analyzed from tablet and urine samples. Although the extraction of ranitidine in these samples has been performed by liquid–liquid extraction [36–42], column chromatography [48] and solid-phase extraction [43–45], these methods are laborious, time-consuming and not easy to automate. The in-tube SPME–LC–MS method was successfully applied to these samples with minimal prior clean-up procedure (filtering only). Fig. 7 shows the typical total ion chromatograms obtained from tablet and urine samples. Ranitidine in tablet gave a good peak shape (dotted line). On the other hand, some unknown peaks were observed in front of the ranitidine peak in urine sample, but the ranitidine in this sample could be analyzed without any influence from coeluting substances. To confirm the validity of this method, known concentrations of ranitidine were spiked to tablet and urine samples and their relative recoveries were calculated. As shown in Table 1, the overall recoveries of ranitidine were above 92% for tablet and above 58% for urine. The lower recoveries in urine samples are likely caused by binding of ranitidine to urine components. However, good reproducibilities were obtained using the autosampler. Furthermore, the detection limit of ranitidine in the analysis of urine samples was ca. 10 ng/ml, the relative standard deviations for the analyses of tablet and urine samples were 0.7 to 3.4% ($n=3$).

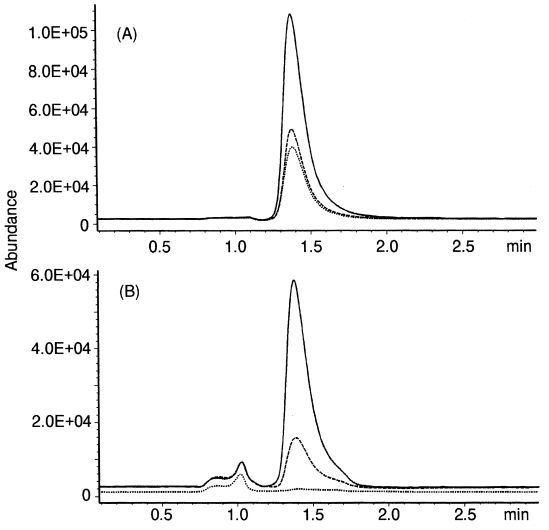

Fig. 7. Total ion chromatograms obtained from ranitidine in tablet and urine samples by in-tube SPME–LC–MS-SIM. (A) Tablet sample (Zantac 75) containing 0.1 μg/ml ranitidine, (B) normal human urine sample. LC–MS conditions: see Experimental. Solid line: spiked at 200 ng/ml; dashed line: spiked at 20 ng/ml; dotted line: non-spiked.

Table 1
Recoveries of ranitidine spiked to tablet and urine samples

Sample	Spiked (ng/ml)	Amount found[a] (ng/ml)	Recovery (%)
Tablet[b]	0	97.3±2.6	
	20	116.4±4.0	95.5
	200	282.6±2.0	92.7
Urine[c]	0	ND[d]	
	20	11.7±0.4	58.5
	200	127.1±2.8	63.6

[a] Mean±SD ($n=3$).
[b] Tablet was dissolved to 2 μg/ml tablet powder in water, and 0.1 ml of this solution was used for the analysis.
[c] Urine was diluted 10 times with water and 0.1 ml of this solution was used for the analysis.
[d] Not detectable.

4. Conclusion

These experiments have conclusively demonstrated that the automated in-tube SPME–LC–MS method can continuously perform analyte extraction from sample followed by LC–MS analysis. This method is simple, rapid, selective and sensitive, and can be directly applied to ranitidine analysis in tablet and urine samples. We believe that this method provides a useful tool in biomedical and clinical research, and

the application range of automated in-tube SPME–LC–MS can be easily increased for non-volatile and thermally labile compounds, by selection of appropriate capillary coatings. The general concept described is readily applicable for direct introduction of compounds to MS, without chromatography, with the benefit that interferences from matrix salt ions for example, are eliminated [17].

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