QUANTITATIVE ANALYSIS OF IBUPROFEN IN PHARMACEUTICAL FORMULATIONS THROUGH FTIR SPECTROSCOPY

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Abstract. **The quantification of ibuprofen through infrared spectroscopy was developed and validated for pharmaceuticals in tablet form. The method involves the extraction of the active ingredient with chloroform and the measurement of the area of the infrared band corresponding to the carbonyl group centered at 1721.5 cm^{-1}. The specificity, linearity, detection limits, precision and accuracy of the calibration curve, ibuprofen extraction, infrared analysis and data manipulation were determined in order to validate the method. Moreover, the statistical results were compared with the quantification of ibuprofen through UV detection.**

The recovery values obtained in the analysis of pharmaceuticals are within the 98-110 % range.

Keywords**. Ibuprofen quantification, FTIR analysis, UV analysis, pharmaceuticals.**

I. INTRODUCTION

Ibuprofen [(+/-) 2-(*p*-isobutylphenil propanoic acid, $(CH_3)_2CHCH_2C_6H_4CH_3CHCO_2H$] is well known as a non-steroidal anti-inflammatory (NSAID), analgesic and antipyretic agent (Adams *et al.*, 1969). This pharmaceutical is the active ingredient of a variety of oral medicines in tablets, gel pellets and syrup forms that are used worldwide due to the higher efficiency and tolerance, lower adverse effects and toxicity than other substances such as, aspirin, indomethacin and pirazolonic derivatives (Gasco López *et al.*, 1999).

The literature shows a variety of methods (approved and non-approved by health government agencies) to analyze raw ibuprofen (IBU for brevity) and pharmaceutical preparations, such as: direct titration with sodium hydroxide in methanol, potentiometric titration, high performance liquid chromatography, UV spectroscopy and flow injection infrared analysis. More recently, capillary electrophoresis and isotachophoresis have also been used to analyze ibuprofen and other NSAID pharmaceuticals (Sádecká *et al.*, 2001; Veraart *et al.*, 1998; Cherkaoui and Veuthey, 2000; Fanali, 2000; Donato *et al.*, 1994; Persson-Stubberud and Astrom, 1998).

The direct titration with sodium hydroxide is economical, easily applicable and is described in the European Pharmacopoeia for the quantification of raw IBU (Pharmacopèe Europèenne, 2002). However, colored or non-soluble excipients contained in tablets might interfere in the observation of the completion of the reaction through a chemical acid-base indicator.

Potentiometric titrations avoid the interference of the excipients since the completion of the reaction is detected through the slope change of the electromotive force emf (or pH) versus volume of titrant. This method is suitable to analyze raw IBU and tablets using tetrabutylammonium in acetonitrile (ANMAT monograph, 2003; Cakirer *et al.*, 1999).

The analysis of IBU through high performance liquid chromatography is used worldwide for quality control of pharmaceuticals. This method allows to analyze both IBU and products of degradation such as, 4-isobutylacetophenone (Pharmacopèe Europèenne, 2002; ANMAT monograph, 2003; Ravisankar *et al.*, 1998; Lampert and Stewart, 1990; US Pharmacopoeia, 2002). However, the pretreatment of the sample might be difficult if the excipients or the active ingredient are non-soluble in the mobile phase.

Capillary electrophoresis and isotachophoresis are economic, easily applicable and accurate methods to analyze IBU (Donato *et al.*, 1994; Persson-Stubberud and Astrom, 1998). Moreover, non-ionic species such as those involves in the excipients, do not interfere in the analysis. However, the technique requires qualified technicians and is not accepted by the government agencies (Sádecká *et al.*, 2001).

Although, infrared spectroscopy is the method described by the pharmacopoeias to identify IBU, the literature shows only one investigation concerning the quantification of IBU through IR (Pharmacopèe Europèenne, 2002; ANMAT monograph,

2003; US Pharmacopoeia, 2002).

Garrigues *et al*. developed the quantification of IBU measuring the infrared absorption of the carbonyl species of the acid through an FTIR spectrometer on-line with a flow injection device (Garrigues *et al*., 1993). The authors pointed out that the device is not commercially available and was specially built for that application which is a disadvantage of the method. Moreover, the flow rate fluctuations of the mobile phase and the volume of sample might diminish the reproducibility of the assays.

The present investigation shows the development and validation, according to the US Pharmacopoeia recommendation, of the quantitative analysis of IBU in tablets through infrared spectroscopy. The results allowed to demonstrate that a standard FTIR spectrometer is suitable to be used both to identify and quantify active ingredients of pharmaceuticals. Additionally, the technique was compared with the results obtained with UV spectroscopy.

II. METHODS

A. Chemicals and Pharmaceuticals

IBU (99.8%) used as standard for physico-chemical assays of medicines was provided by the National Agency of Medicines, Food and Medical Technology A.N.M.A.T of Argentina.

4-isobutylacetophenone (Lancaster, 97%) was also used in the identification of degradation products.

The following local pharmaceuticals containing different amounts of IBU in tablet form were analyzed: Ibuzidine 400 mg (Hexa S.A.), Ibu-evanol 200 mg (Smith Kline Beecham Argentina S.A.), Sindol 600 mg (Ahimsa S.A.), Ibupirac 400 mg (Searle-Monsanto Argentina S.A.I.C.).

B. Infrared Spectroscopy

The IR analyses were performed in a Bruker FTIR IFS 68 equipment. Quantitative analyses of solutions of ibuprofen in chloroform were performed in a cell with CaF_2 windows and variable optic pathway (Wilks).

Qualitative analyses of solid samples were performed through thin wafers with KBr (Spectranal Riedel-de Haën P.A.).

C. UV-VIS Spectroscopy

The analyses were performed in a Varian SuperScan 3 equipment with quartz cells.

III. RESULTS AND DISCUSSION

A. Extraction of ibuprofen from pharmaceutical formulations in tablet from

The extraction of ibuprofen from pharmaceuticals in tablet form was achieved through the selective dissolution of the active ingredient with chloroform according to the indications of the USP for the identification of IBU (US Pharmacopoeia, 2002).

Six tablets of a pharmaceutical (Sindol 600 mg) were weighed, finely powdered and homogenized. An accurately weighed quantity of the powder was dissolved in 10.00 ml of chloroform (Merck P.A.), maintained under stirring for 5 min and centrifuged in order to separate the excipients. The supernatant solution was further diluted to 25.0 ml with chloroform in a standard flask.

Figure 1 shows the IR spectra of the pharmaceutical (solid) before the extraction, and the excipients (solid) and the active ingredient (solution in chloroform) recovered after the extraction. The infrared spectra of the excipients correspond to SiO_2 that is not dissolved in chloroform. The spectra show that the excipient is free of IBU after the treatment with the solvent.

The recovered ibuprofen possesses an intense, well defined infrared band at 1721.5 cm^{-1} attributed to the stretching of the carbonyl C=O group that is in agreement with the infrared spectra of the standard chemical provided by ANMAT (Silverstein *et al.*, 1991*).*

B. Linearity

Is well known that the fundamental relationship between the concentration of a substance and its absorbance of radiation at a certain frequency is given by the Beer-Lambert Law,

$$D(\nu) = \log [I_o(\nu)/I(\nu)] = \varepsilon(\nu) \times b \times c, \qquad (1)$$

where $D(\nu)$ is the absorbance; $I_o(\nu)/I(\nu)$ is the ratio between the intensities of the incident and transmitted radiation of ν frequency that goes through a substance with c concentration contained in a cell of width b. The parameter $\varepsilon(\nu)$, known as molar absorptivity, is a property of the substance and varies with the wavelength of the radiation.

The range of linearity of absorbance versus concentration of IBU and the molar absorptivity (at constant b and ν) was determined through a series of solutions of different concentrations of IBU in chloroform. Each of them were analyzed through infrared spectroscopy and the area of the signal corresponding to the carbonyl species (typically in the 1648-1783 cm^{-1} range) was determined.

The limits of detection and the parameters of

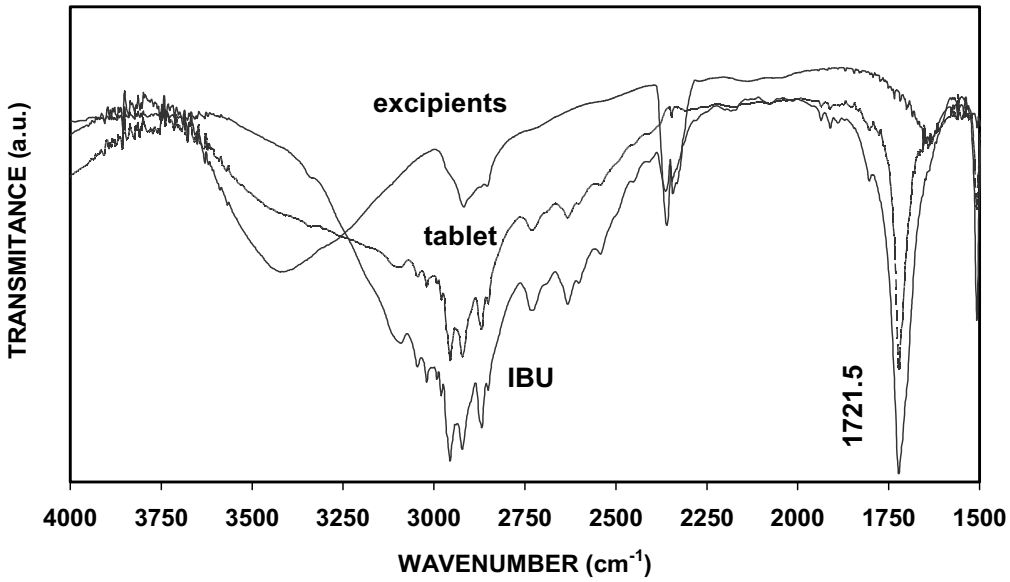

Figure 1. Infrared spectra of a pharmaceutical (tablet) containing IBU as the active ingredient, the excipients and ibuprofen after extraction with chloroform.

the linear regression are presented in Table 1.

C. Precision and Accuracy

The precision and accuracy were determined over the following key steps of the analytical method: the preparation of standard solutions of IBU, the determination of the IR spectra of the solutions along with the data processing for area calculation and the extraction of IBU from the tablets.

The precision and accuracy of the preparation of standard solutions (key step in the calibration process) was investigated through the preparation of six solutions containing 0.300 % p/v of standard IBU in chloroform that were further analyzed through IR spectroscopy.

The IR analysis and data processing involve, transferring a solution to the cell, digitalize the infrared spectra and the mathematical manipulation of the data for area calculation. The statistical study of those steps was performed through the preparation of three solutions containing concentrations of IBU that correspond to the limits (0.056 % p/v and 0.500 % p/v) and center of the calibration curve (0.300 % p/v) obtained in Section B. Each of those solutions was analyzed six times through IR spectroscopy and the area of the infrared signal of the carbonyl species was determined.

Finally, the precision and accuracy of IBU extraction was determined treating six tablets of the same commercial pharmaceutical with chloroform as described in Section A.

Table 2 shows the theoretical concentration of IBU, the relative standard deviation (RSD %) of peak areas, the relative error and the recovery values, obtained on the experiments described above. The experiments were performed by only one operator within one day.

The RSD values are an indication of the repeatability (precision) and reproducibility of an experiment and the error and recovery values show the accuracy of the analytical determination (US Pharmacopoeia, 2002). The RSD values presented in Table 2 indicate that the extraction of IBU from the pharmaceuticals possesses the lowest repeatability (3.8 %). However, the recovery values demonstrate that the quantification of the active ingredient is highly accurate at concentrations of ~0.300

Table 1. Linear regression equations ($y = A + B\,x$)[1] for IBU quantified through IR and UV spectroscopy.

method	detection limits (% p/v)	A	B	correlation coefficient r^2
IR spectroscopy	0.000-0.609	0.00	168.38	0.998
UV spectroscopy	0.000-0.200	0.00	10.61	0.993

[1] y, peak area of the infrared band at 1721.5 cm^{-1} and Absorbance at 273 nm for UV detection.
x, concentration of IBU in chloroform expressed as weight of IBU in 100 ml of solution (% p/v).

Table 2. Precision and accuracy of the different key steps of the quantitative analysis of IBU in tablets through infrared spectroscopy.

Step	theoretical concentration of IBU (% p/v)	RSD[1] (%)	accuracy[2] (%)	recovery[3] (%)
preparation of solutions of standard	0.300	2.0	0.7	99.0
spectroscopic analysis and data manipulation	0.056	1.9	34.0	68.0
	0.300	1.0	0.3	100.0
	0.500	0.2	2.4	98.0
quantification of IBU in pharmaceuticals	0.400	3.8	10.2[4]	110.2

[1] RSD, relative standard deviation of the peak areas of the IR signal at 1721.5 cm^{-1}.
[2] Relative error between the peak area of theoretical concentration (from calibration curve) and the experimental value.
[3] Percentage ratio between the experimental and theoretical concentration values.
[4] Relative error between the nominal concentration (indicated by the vendor) and the experimental value.

% p/v (center of the calibration curve) and above. These results were compared with the quantification of IBU through UV spectroscopy. The quantification of IBU through UV detection is regularly used in the HPLC methods described in the Pharmacopoeias and is also recommended by the National Agency of Medicines, Food and Medical Technology of Argentina (ANMAT monograph, 2003).

A calibration curve was determined by measuring the UV absorbance at 273 nm of several solutions containing different concentrations of IBU in chloroform (US Pharmacopoeia, 2002). The limits of detection and the parameters of the linear regression are presented in Table 1.

The accuracy and precision of the determination of absorbance of a series of solutions of standard IBU in chloroform along with the data processing, and the quantification of IBU in pharmaceuticals are presented in Table 3.

Again the extraction of IBU from the pharmaceutical possesses the lowest repeatability (~5 %) as observed previously (see Table 2 for comparison). The UV detection allows a more accurate quantification of lower concentrations of IBU compared with the IR analysis. The relative error and the recovery values indicate that the UV quantification is highly accurate at concentrations below 0.160 % p/v while the FTIR analysis possesses a high accuracy even at concentrations of 0.500 % p/v. This is an important observation considering that most of the IBU based pharmaceutical possess 200 mg or more of the active ingredient therefore, the IR analysis avoids further dilutions that diminish the accuracy of the quantification.

D. Specificity

The ability to assess unequivocally the analyte in the presence of 4-isobutylacetophenone (IKP), a

Table 3. Precision and accuracy of the different key steps of the quantitative analysis of IBU in tablets through UV spectroscopy.

Steps	theoretical concentration of IBU (% p/v)	RSD[1] (%)	accuracy[2] (%)	recovery[3] (%)
spectroscopic analysis and data manipulation	0.020	0.9	~1[4]	100.0
	0.100	1.1	~1[4]	100.0
	0.200	0.4	6.5	93.5
quantification of IBU in pharmaceuticals	0.160	5.4	5.0	95.0

[1] RSD, relative standard deviation of the absorbance at 273 nm.
[2] Relative error between the absorbance of the theoretical concentration (from calibration curve) and the experimental value.
[3] Percentage ratio between the experimental and theoretical concentration values.
[4] Nominal accuracy of the equipment provided by the vendor.

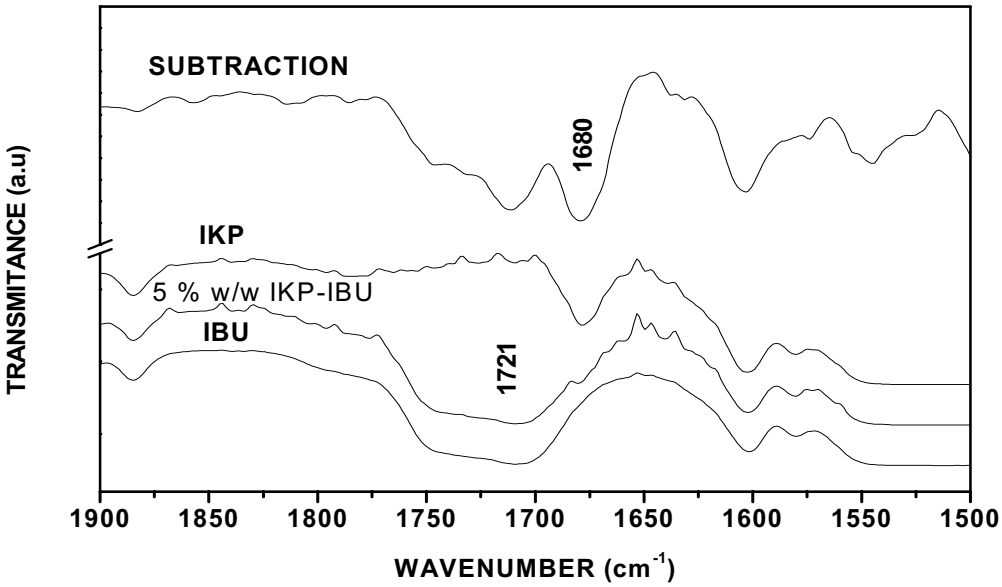

Figure 2. Infrared spectra of a solution of ibuprofen (IBU) 0.462 % p/v, 4-isobutylacetophenone (IKP) $4.62x10^{-3}$ % p/v, a mixture containing 5 % weight IKP/weight IBU and the subtraction of a mixture containing 1 % weight IKP/weight IBU minus the spectra of pure ibuprofen.

typical impurity of ibuprofen, was also tested.

The specificity of the method was established through the analysis of 0.231 % p/v and 0.462 % p/v of ibuprofen spiked with 0.00231 % p/v IKP (1% weight IKP/weight IBU) and 0.0231 % p/v IKP (5% weight IKP/weight IBU), respectively. Figure 2 shows the infrared spectra of a solution of 0.00462 % p/v IKP, 0.462 % p/v IBU, a mixture of IBU containing 5% of IKP, and the resulting spectra of the subtraction of the spectra corresponding to a mixture containing 1% of IKP and a solution of similar concentration of pure IBU.

The infrared analysis of solutions containing different concentrations of 4-isobutyl acetophenone in chloroform allowed to establish that the limit of detection corresponds to $4.62x10^{-3}$ % p/v (only the spectra corresponding to the lowest concentration is shown). Figure 2 demonstrates that the characteristic band of carbonyl species of IKP (1680 cm^{-1}) is shifted from the signal of IBU (1721 cm^{-1}) which makes the impurity easily identifiable. Although, the presence of the impurity is distinguishable when the amount of IBU is about 5%, further subtraction of spectra allows to identify the ketone at lower concentrations.

E. Comparison with other methods and quantification of IBU in pharmaceuticals

Table 4 compares the precision, accuracy and recovery of the present method with other techniques reported in the literature such as, flow injection infrared spectroscopy FIA-FTIR, high performance liquid chromatography, titrimetric, isotachophoresis and UV spectroscopy.

The quantification of IBU through infrared spectroscopy either with a conventional cell for liquid analysis or a flow injection device possesses similar accuracy and recovery values. Although the FTIR method presents lower precision than the non-official assays, is similar to HPLC which is the most frequently used for quality control of pharmaceutical formulations.

The low precision of both HPLC and FTIR methods might be attributed to the extraction of the active ingredient from the pharmaceuticals that is required in order to perform the assay.

Table 5 shows nominal amounts of the active ingredient and the recovery values obtained in the IR quantification of IBU of a series of commercial pharmaceutical products. The recovery values are within the limits recommended by the Pharmacopoeias (~90.0 % to ~110.0 % in BP, USP and EUP).

IV. CONCLUSIONS

The quantification of IBU through infrared spectroscopy accomplishes with the requirements of specificity, precision and accuracy in order to be used as a method for the quality control of pharmaceuticals. Moreover, the method might be classified within the Category I of analytical methods since is suitable for the quantitation of major components of bulk drug substances or active ingredient in finished pharmaceutical products, according to the US

Table 4. Comparison of precision, accuracy and recovery of the quantification of ibuprofen through IR and other reported methods.

method	reference	precision[1] (%)	accuracy (%)	recovery (%)
FIA-FT-IR	Garrigues *et al.*, 1993	0.8	4.0	97.8-104.5
HPLC	Ravisankar *et al.*, 1998	3.2	1.6	98.6
HPLC	Gasco-Lopez *et al.*, 1999	0.89-1.61	2.8	100.4
titrimetric	Cakirer *et al.*, 1999	< 1	0.4	99.5
isotachophoresis	Sádecká *et al.*, 2001	0.6-1.0	0.7-2.9	96.2-101-5
FTIR spectroscopy	*this work*	3.8	0.3-2.4	98.0-100.0
UV spectroscopy	*this work*	5.4	5.0	95.0

[1] RSD, relative standard deviation values.

Table 5. Quantification of IBU in commercial pharmaceutical products through infrared spectroscopy.

product	nominal amount of IBU[1] (mg)	recovery %
Ibu Evanol	200	103.5
Ibupirac	400	100.5
Ibuzidine	400	110.2
Sindol	600	97.8

[1]Amount of IBU per tablet as indicated in the package.

Pharmacopoeia (US Pharmacopoeia, 2002).

This technique extends the use of a standard IR spectrophotometer, typically used for identification purposes, to the reliable quantification of ibuprofen. The present method opens the possibility of applying IR spectroscopy to quantify other active ingredients than IBU.

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REFERENCES

Adams, S.S., K.F. McCullough and J.S. Nicholson, "The pharmacological properties of ibuprofen, an anti-inflamatory analgesic and antipyretic agent", *Arch. Int. Pharmacodyn*. **178**, 115-129 (1969).

A.N.M.A.T National Agency of Medicines, Food and Medical Technology. Ibuprophen monograph (control number: 197038). Ministerio de Salud y Acción Social of Argentina. A.N.M.A.T.- I.N.A.M.E (2003).

Cakirer, O., E. Kilic, O. Atakol and A. Kenar, "The non-aqueous titrimetric assay of the selected anti-inflamatory agents using tetra-n-butylammonium hydroxide as titrant", *J. Pharm. Biomed. Anal*. **20**, 19-26 (1999).

Cherkaoui, S. and J.L. Veuthey, "Development and robustness testing of a nonaqueous capillary electrophoresis method for the analysis of non-steroidal anti-inflammatory drugs", *J. Chromatogr. A* **874**, 121-129 (2000).

Donato, M.G., W. Baeyens, W. Van den Bossche and P. Sandra, "The determination of non-steroidal antiinflammatory drugs in pharmaceuticals by capillary zone electrophoresis and micellar electrokinetic capillary chromatography", *J. Pharm. Biomed. Anal*. **12**, 21-26 (1994).

Fanali, S., "Enantioselective determination by capillary electrophoresis with cyclodextrins as chiral selectors", *J. Chromatrogr. A* **875**, 89-122 (2000).

Garrigues, S., M. Gallignani and M. De La Guardia, "FIA-FT-IR determination of ibuprofen in pharmaceuticals", *Talanta* **40**, 89-93 (1993).

Gasco López, A.I., R. Izquierdo-Hornillos and A. Jiménez., "LC method development for ibuprophen and validation in different pharmaceuticals", *J. Pharm. Biomed. Anal*. **21** 143-149 (1999).

Lampert, B.M. and J.T. Stewart, "Determination of

non-steroidal anti-inflammatory analgesics in solid dosage forms by high-performance liquid chromatography on underivatized silica with aqueous mobile phase", *J. Cromatogr*. A **504**, 381-389 (1990).

Persson-Stubberud and K.O. Astrom, "Separation of ibuprofen, codeine phosphate, their degradation products and impurities by capillary electrophoresis: I. Method development and optimization with fractional factorial design", *J. Chromatogr. A* **798**, 307-314 (1998).

Pharmacopèe Europèenne, 4th ed., pp. 1471-1472 (2002).

Ravisankar, S., M. Vasudervan, M. Gandhimathi and B. Suresh, "Reversed-phase HPLC method for the estimation of acetaminophen, ibuprofen and chlorzoxazone in formulations", *Talanta* **46**, 1577-1581 (1998).

Sádecká, J., M. Čakrt, A. Hercegorá, J. Polonskŷ and I. Skačáni, "Determination of ibuprofen and naproxen in tablets", *J. Pharm. Biomed. Anal*. **25**, 881-891 (2001).

Silverstein, R.M., G.C. Bassler and T.C. Morrill, *Spectrometric Identification of Organic Compounds*, 5th edition, J. Wiley & Son Inc., New York, pp. 117-123 (1991).

United States Pharmacopeia. The National Formulary USP XXV, US Pharmacopeial Convention Inc., p.p. 885-887 and Validation of Compendial Methods, pp. 2256-2259 (2002).

Veraart, J.R., C. Gooijer, H. Lingeman, N.H. Velthorst and U.A.Th. Brinkman, "At-line solid-phase extraction for capillary electrophoresis: application to negatively charged solutes", *J. Chromatogr. B* **719**, 199-208 (1998).

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