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Quantitative determination of dimethicone in commercial tablets and capsules by Fourier transform infrared spectroscopy and antifoaming activity test

G. Torrado [a], A. García-Arieta [b], F. de los Ríos [b], J.C. Menéndez [c], Santiago Torrado [b,*]

[a] *Department of Pharmaceutical Technology, Faculty of Pharmacy, Alcalá de Henares University, Campus Universitario, Alcalá de Henares, 28871, Madrid, Spain*

[b] *Department of Pharmaceutical Technology, Faculty of Pharmacy, Complutense University, Av. Complutense S/N, 28040, Madrid, Spain*

[c] *Department of Organic and Pharmaceutical Chemistry, Faculty of Pharmacy, Complutense University, Av. Complutense S/N, 28040, Madrid, Spain*

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Abstract

Fourier transform infrared (FTIR) spectroscopy and antifoaming activity test have been employed for the quantitative analysis of dimethicone. Linearity, accuracy and precision are presented for both methods. These methods have been also used to compare different dimethicone-containing proprietary medicines. FTIR spectroscopy has shown to be adequate for quantitation of dimethicone in commercial tablets and capsules in order to comply with USP requirements. The antifoaming activity test is able to detect incompatibilities between dimethicone and other constituents. The presence of certain enzymes in some medicinal products increases the defoaming properties of these formulations. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: FTIR spectroscopy; Antifoaming activity; Dimethicone; Quantitative analysis; Validation; Comparison

1. Introduction

Dimethicones are poly(dimethylsiloxanes) of different grades that are distinguished by a number after the name indicating the declared viscosity which, in terms of kinematic viscosity, is between 20 and 1000 $mm^2\ s^{-1}$ [1]. Simethicone is a mixture of liquid dimethicones containing finely divided silicon dioxide to enhance the defoaming properties of the silicone [2].

Silicones are water-repellent and have a low surface tension. Dimethicone and simethicone lower surface tension and when administered by mouth cause bubbles of gas in the gastrointestinal tract to coalesce, thus aiding their dispersion. They are used to relieve flatulence and abdominal discomfort due to excess of gastrointestinal gas in usual doses of 100–200 mg three or four times

* Corresponding author. Fax +34 1 3941727.

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daily as required. Doses of 20–40 mg of simethicone have been given with feeds to relieve colic in infants. For many gastrointestinal disorders, it is given in conjunction with an antiacid, although there is no good evidence that it provides additional benefit [3].

The British Pharmacopoeia (BP) does not contain a monograph of simethicone and its dimethicone monograph does not contain a quantitation assay. On the contrary, The United States Pharmacopeia (USP) does not contain a dimethicone monograph, but its simethicone monograph presents an assay that can be used to quantify dimethicone. This infrared spectroscopy assay quantifies the amount of poly(dimethylsiloxane), and two additional tests are required to determine the silicon dioxide content and the defoaming activity. However, the monographs of simethicone tablets and simethicone capsules do not contain the silicon dioxide assay.

We have selected Fourier Transform Infrared (FTIR) spectroscopy to quantify the amount of poly(dimethylsiloxane) and a variation of the defoaming activity test to determine the antifoaming properties of dimethicone in order to be validated.

Infrared spectroscopy applications include identification testing, moisture content determination [4] and qualitative detection method in thin-layer chromatography [5]. Quantitative assays by FTIR spectrometry of active ingredients in the pure compound or in the dosage form, have been also published by several authors [4,6–8].

This paper also compares the results obtained by both methods with different commercial tablets and capsules.

2. Experimental

2.1. Materials

Dimethicone was purchased from Rhone Poulenc (Spain). Sodium laurylethersulfate (Texapon N40) was purchased from Henkel (Germany). Hydrochloric acid, carbon tetrachloride and anhydrous sodium sulphate were purchased from Panreac PRS (Spain). Distilled de-ionised water was used in the preparation of all aqueous solutions.

2.2. Formulations

A: 'Clanzoflat' (Batch: K-07, Exp: 2001). Dimethicone 200 mg capsule^{-1}.

B: 'Aero Plus' (Batch: K-13, Exp: 2001). Dimethicone 100 mg capsule^{-1} and metoclopramide hydrochloride 5 mg capsule^{-1}.

C: 'Aero Red Eupéptico' (Batch: I-01, Exp: 1999). Dimethicone 100 mg capsule^{-1}. Amylase 6000 U, lipase 6000 U and protease 400 U.

D: 'Pankreoflat' (Batch: K-026, Exp:1999). Dimethicone 80 mg tablet^{-1}. Amylase 6000 U, lipase 6000 U and protease 400 U.

E: 'Alucol Silicona' (Batch: K-2, Exp: 2001). Dimethicone 100 mg capsule^{-1}. Aluminium hydroxide dried gel: 375 mg capsule^{-1}. Magnesium hydroxide: 125 mg capsule^{-1}.

2.3. Infrared spectroscopy

A Perkin Elmer FTIR Paragon 1000 infrared spectrometer was used in the 500–4000 cm^{-1} scan range. Each spectrum was automatically averaged over 16 scans obtained at a spectral resolution of 4 cm^{-1}.

The assay preparation of the USP method requires the addition of 50 ml of dilute hydrochloric acid to the 25 ml of carbon tetrachloride and, after extraction of the organic layer, addition of 0.5 g of anhydrous sodium sulphate is necessary. The method employed in this work has omitted the addition of an aqueous phase to the carbon tetrachloride and the posterior addition of anhydrous sodium sulphate. However, a sonication period to obtain the complete dissolution of the dimethicone contained in a powdered solid has been necessary.

2.3.1. Sample assay

For each formulation, not less than ten tablets or capsules were weighed and finely powdered. An accurately weighed portion of the powder, equivalent to about 50 mg of dimethicone, was transferred to a glass-capped 50 ml conical flask, 25 ml of carbon tetrachloride were added and the mixture was sonicated for 30 min in a sonication bath (h.f. 35 kHz) to induce dispersion and filtered (Millipore HV 0.45 μm). A blank was prepared

with carbon tetrachloride. Concomitantly, the absorbances of the solutions were determined in 0.5 mm cells at the wavelength of maximum absorbance, 7.9 μm, using the blank to set the instrument.

2.4. Antifoaming activity

The USP Defoaming Activity Test (DAT) of Simethicone employs 1 g of octoxynol 9 in 100 ml of water to prepare the foaming solution. The alternate method described in this paper was carried out with 13 g of sodium laurylether-sulphate, dissolved in 100 ml of distilled water.

2.4.1. Procedure

For each formulation, ten tablets or capsules were weighed and finely powdered. An accurately weighed portion of the powder, equivalent about 50 mg of dimethicone was added to a clean unused cylindrical 250 ml glass jar, fitted with a 50 mm cap, containing 100 ml of foaming solution. This suspension was sonicated for 5 min in a sonication bath (h.f. 35 kHz). The jar was capped and clamped in an upright position on a wrist-action shaker. Employing a radius of 13.3 ± 0.4 cm (measured from centre of shaft to centre of bottle), the jar was shaken through an arc of 10° at a frequency of 300 ± 30 strokes min^{-1} until the foam reached the level of 250 ml.

The USP method Defoaming Activity Text produces foam during a defined time (10 s) and measures the time for foam collapse. The higher antifoaming activity the lower volume of foam and the quicker decrease of volume of foam. Then, in the compendial method the time to collapse is affected by both parameters, volume of foam and velocity of decrease. The method presented in this paper evaluates the time to collapse a constant volume of foam, in order to keep constant one of these parameters. Therefore, the time to collapse only depends on the velocity of decrease of the foam volume. A direct correlation between time to collapse and antifoaming activity of different doses of dimethicone can be observed with this method. The time, in s, required for the foam to collapse, measured from the end of the shaking period, was recorded and determined at the instant the first portion of foam-free liquid surface appears.

2.5. Methods for the determination of analytical parameters

Linearity was evaluated by preparing nine standards of dimethicone of different concentrations in the range from 1.5 to 3.0 mg ml^{-1} in FTIR and from 20 to 50 mg ml^{-1} in the defoaming activity test. The relationship between concentration of dimethicone and the measured variable, absorbance in FTIR and the defoaming activity time in the defoaming activity test was adjusted by means of least squares regression.

Additionally, linearity was evaluated by calculation of the relative standard deviation of the slope ($Sb_{rel}\%$) according to the following equation.

$$Sb_{rel}\% = \frac{Sb}{b} 100$$

where Sb is the standard deviation of the slope (b).

2.5.1. Recovery

The accuracy of the assay was assessed by fortifying the samples in triplicate with known amounts of dimethicone at 75, 100 and 125% of the sample solution concentration.

2.5.2. Precision

Repeatability was calculated by assaying six sample preparations of a 100% standard concentration. Reproducibility was calculated by comparing the results obtained from three different dimethicone concentrations in triplicate on three different days.

2.6. Statistical analysis of results

The results of the content of dimethicone in six samples of an standard of dimethicone and different proprietary medicines were statistically analysed by means of an analysis of variance (two-way ANOVA, Statgraphics 6.0) to determine whether these techniques provide similar results.

The assignation of the cause of significance to some of the different proprietary medicines was carried out with an Student Newman–Keuls Multiple Range Test. A 95% confidence level ($p \leq 5\%$) was considered satisfactory for indicating significant differences.

3. Results and discussion

3.1. FTIR analysis of dimethicone

The IR spectrum in the mid-IR region is divided into the functional-group region, 4000–1300 cm^{-1} (2.5–7.7 μm), the fingerprint region, 1300–909 cm^{-1} (7.7–11.00 μm) and the 909–650 cm^{-1} (11.0–15.4 μm) region. The fingerprint region is characteristic of each molecule and provides positive identification of certain functional groups. The quantitative FTIR analytical method of the USP 23 simethicone monograph employs the wavelength of maximum absorbance, 7.9 μm. BP disregards the region of the spectrum from 750 to 850 cm^{-1} since slight differences may be observed depending on the degree of polymerisation [1].

Dimethicone dissolved in carbon tetrachloride shows a characteristic peak at 7.9 μm. This peak is attributed to the symmetrical deformation vibration of the methyl group attached to the silicon atom, and its position is remarkably constant in methylsilanes. It is the peak used in USP 23 for quantitative studies. The symmetric and antisymmetric stretching vibrations of the Si–O–Si system are responsible for the two strong bands at 1098 and 1015 cm^{-1}.

3.1.1. Linearity

The linearity of the method for dimethicone assay was evaluated for the range of concentrations between 1.5 and 3.0 mg ml^{-1}. The correlation coefficient was 0.9976, the slope and the intercept values were 0.1802 A.U. ml mg^{-1} (A.U.: Absorbance Units) and -0.0136 A.U., respectively. The intercept value was not statistically different from zero ($P < 0.05$) $a = -0.0136 \pm 0.0250$. The linearity was 2.61%, calculated by the R.S.D. of the slope ($Sb_{rel}\%$) [9]. This linearity value is considered acceptable in routine analysis [10].

3.1.2. Recovery

Accuracy of the assay was assessed at three different concentrations. Mean recoveries were $98.72 \pm 1.96\%$ R.S.D., 100.92 ± 1.60 and 100.37 ± 0.40, respectively. Since the recovery was within one standard deviation of 100%, the method is capable of accurately quantitating dimethicone at these concentrations [11].

3.1.3. Precision

3.1.3.1. Repeatability. Dimethicone results ranged from 94.27 to 106.31% of the label claim, with a mean of 99.70 and 4.41% R.S.D.

3.1.3.2. Reproducibility. The inter-day reproducibility of the assay method was evaluated from three different dimethicone concentrations (1.5, 2.0 and 2.5 mg ml^{-1}) on three separated days. This method gave R.S.D. values 5.34, 6.01 and 5.07%, respectively.

3.2. Antifoaming activity

3.2.1. Linearity

The defoaming activity test was linear in the concentration range between 20 and 50 mg ml^{-1}. The correlation coefficient obtained with this method was 0.9981. The slope and the intercept were -2.673 s ml mg^{-1} and 212.13 s, respectively. The relationship between defoaming activity and concentration is:

$$C = \frac{212.13 - \mathrm{DAT}}{2.673}$$

Where C is concentration in mg ml^{-1} and DAT is defoaming activity time in s.

3.2.2. Recovery

Accuracy was assessed at 75, 100 and 125% of the sample solution concentration. Mean recoveries were 100.90 ± 1.92, 101.68 ± 3.48 and 100.10 ± 0.53 R.S.D., respectively. As above, the

recovery is within one standard deviation of 100%, therefore the method is capable of accurately quantitating dimethicone at these concentrations.

3.2.3. Precision

3.2.3.1. Repeatability. Dimethicone results ranged from 95.67 to 103.45%, with a mean of 99.55 and 2.81% R.S.D.

3.2.3.2. Reproducibility. The inter-day reproducibility of this method was determinated by the R.S.D. obtained at different dimethicone concentrations (25, 32.5 and 40 mg ml^{-1}). This method was reproducible with R.S.D. values 2.20, 1.40 and 2.05%, respectively. Similar result were obtained by Torrado et al. for phenolphthalein tablets [10].

3.2.4. Comparative study of commercial tablets and capsules

Fourier transform Infrared (FTIR) spectroscopy was carried out for different commercial tablets and capsules. All formulations showed a spectrum similar to the one obtained with standard dimethicone, as can be seen in Fig. 1 for formulations B and D, except for formulation E where a different spectrum was obtained (Fig. 2).

Dimethicone release from commercial tablets and capsules was influenced by sonication time in the FTIR method. Fig. 3 shows that a sonication time of 5 min has produced the complete release of the dimethicone contained in formulations E and D. However, complete release of formulation A is achieved after 10 min of sonication, whereas formulation C requires 20 min and formulation B requires 30 min for complete release. The sonication time has been established at 30 min in order to standardise the analytical procedure. In the

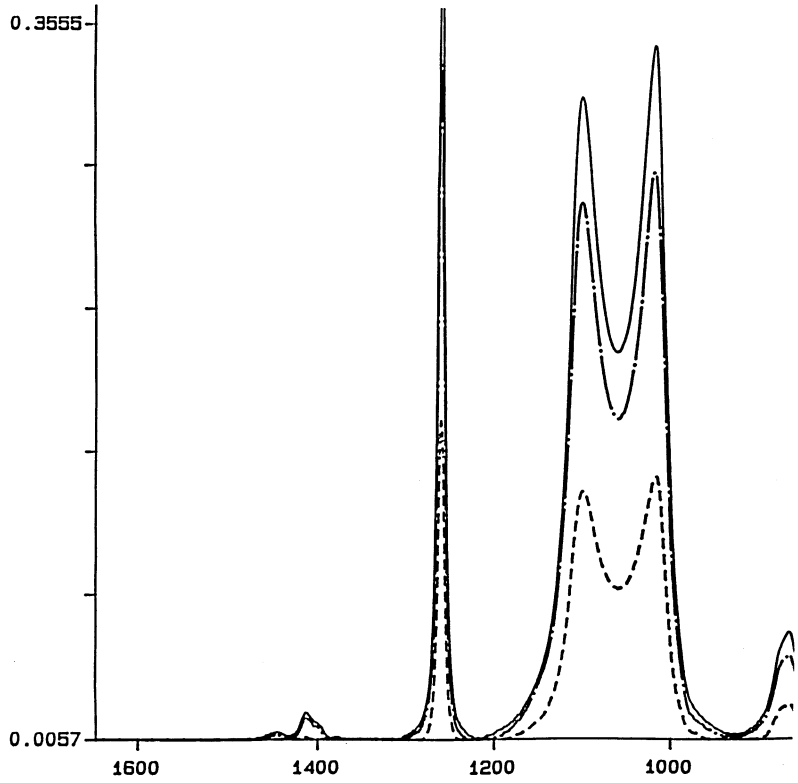

Fig. 1. FTIR spectroscopy of standard dimethicone (——), formulation B (– · –) and formulation D (– – –).

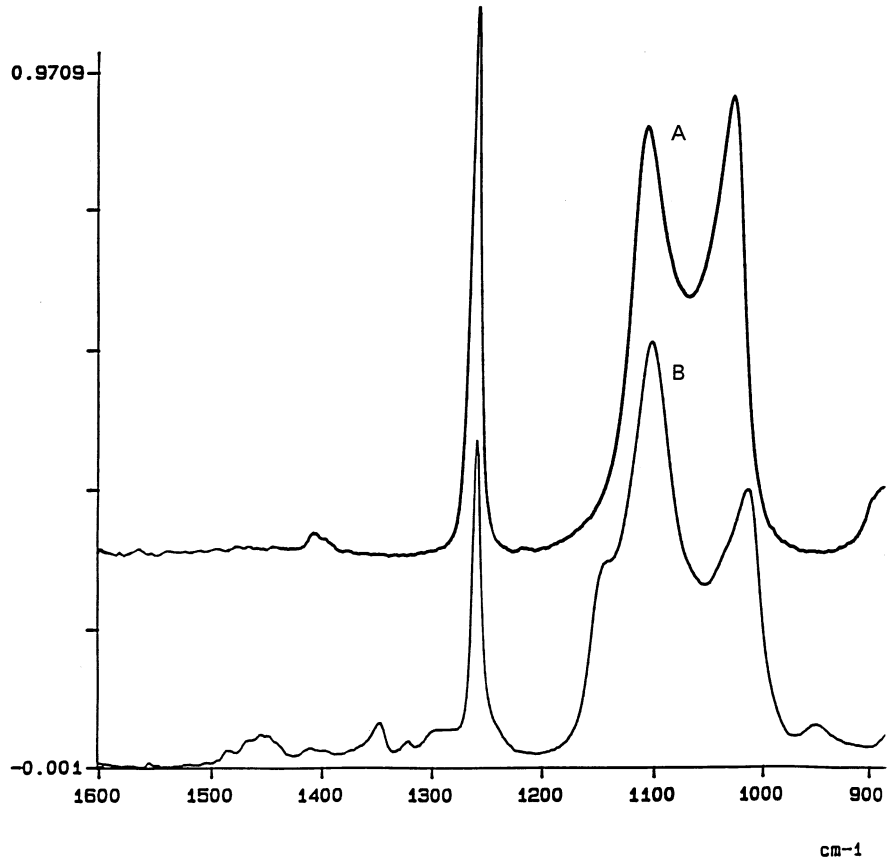

Fig. 2. FTIR spectroscopy of standard dimethicone (A) and formulation E (B).

defoaming activity test a sonication time of 5 min produced similar times to collapse to that obtained with sonication times of 30 min with all tested formulations.

Table 1 shows the dimethicone content obtained in these proprietary medicines by FTIR spectroscopy and defoaming activity test. The results were statistically analysed in order to determine the existence of differences between methods.

Formulations A and E presented a defoaming activity time greater than 5 min, indicative of a very limited antifoaming activity. These results showed clearly that FTIR and DAT do not provide similar results and, therefore, were not employed in the statistical analysis. The results of the content of an standard of dimethicone and formulations B, C and D were found to be statistically different by means of analysis of variance (two-way ANOVA). The formulations C and D were responsible of significance as can be seen in Table 1, where P values of an Student Newman–Keuls Multiple Range Test are presented.

No statistically significant differences at the 95% confidence level were found between the results obtained by FTIR spectrometry and those by defoaming activity for the determination of dimethicone in the standard of dimethicone and formulation B.

Formulation E presents a very high content of dimethicone (119%) by FTIR spectroscopy, but it presents a low defoaming activity (>5 min). Besides, its differences in IR spectrum (Fig. 2) suggest that the dimethicone of these capsules presents structural differences with respect to standard dimethicone.

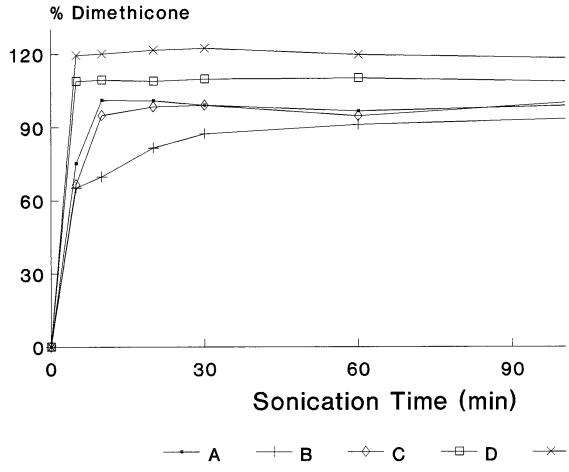

Fig. 3. Percentage of dimethicone released in the different proprietary medicines vs. sonication time in the FTIR method. Formulation A (A); formulation B (B); formulation C (C); formulation D (D) and formulation E (E).

The defoaming activity of the different proprietary medicines (equivalent to 40 mg of dimethicone) in decreasing order and in increasing order of antifoaming times was: D (Pankreoflat, $t = 63$ s) > C (Aero Red Eupéptico, $t = 70.2$ s) > B (Aero Plus, $t = 115.8$ s) ≫ E (Alucon Silicona) = A (Clanzoflat, $t > 300$ s).

Defoaming activity is not complete in formulations A (Clanzoflat) and E (Alucon Silicona) and do not increase with higher sonication times. Formulation A (Clanzoflat) has shown adequate results in the FTIR analysis, therefore the antifoaming activity decrease may be due to the presence of other excipients in the formulation, which are able to diminish the antifoaming activity of dimethicone. In the case of formulation E (Alucon Silicona), its decrease of activity is possibly due to the structural differences in the raw material and to the existence of aluminium and magnesium salts, substances whose ability to adsorb dimethicone is well documented [3].

Formulations D (Pankreoflat) and C (Aero Red Eupéptico) presented an antifoaming activity higher than that of 50 mg of standard dimethicone, 63 and 70.2 s, respectively. This superior activity can be attributed to the presence of certain enzymes in the formulation, some of which can also have antifoaming activity.

Table 1
Mean dimethicone content (%) of different proprietary medicines determined by FTIR Spectroscopy and Defoaming Activity Test (DAT).

Formulation	% FTIR	% DAT	Difference
Standard	100.00	99.10	NSS[a] ($P = 0.58$)
A[b]	99.09	—	—
B	87.42	90.10	NSS ($P = 0.15$)
C	99.00	132.75	SS[c] ($P = 2.35 \times 10^{-4}$)
D	108.86	139.50	SS ($P = 1.35 \times 10^{-4}$)
E[b]	119.42	—	—

[a] NSS: difference not statistically significant ($P > 0.05$).
[b] Apparently, formulations A and E did not present antifoaming activity. Defoaming Activity Test was unable to detect any content of dimethicone. These results were not included in the statistical analysis.
[c] SS: difference statistically significant ($P \leq 0.05$).

4. Conclusions

The infrared spectroscopy and the defoaming activity tests were shown to be linear, with good accuracy and precision (repeatability and interday reproducibility) in the analysis of dimethicone. However, the defoaming activity test was influenced by other ingredients of the formulations (salts and enzymes) and therefore it does not possess the necessary selectivity for the quantitation of dimethicone in commercial preparations.

The content of dimethicone, determined by FTIR spectroscopy, in the commercial tablets and capsules were within the USP 23 limits for simethicone (85–115%), except in the case of formulation E, that presented a higher value (119%).

The defoaming activity of dimethicone is reduced in conjunction with some excipients and some common antiacids, particularly aluminium hydroxide and magnesium hydroxide, due to its adsorption on these particles from where dimethicone is not completely released [3]. On the contrary, the addition of some enzymes in the formulation produces a higher defoaming activity.

References

[1] British Pharmacopoeia, vol. 1, HMSO, London, 1993, pp. 229–230.
[2] USP 23–NF 18, United States Pharmacopeia Convention, Rockville, MD, 1995, pp. 1409–1411.
[3] J.E.F. Reinolds (Ed.), Martindale The Extra Pharmacopoeia, 31th ed., The Pharmaceutical Press, London, 1996, pp. 1241.
[4] W. Plugge, C. Van Der Vlies, J. Pharm. Biomed. Anal. 6 (1993) 435–442.
[5] E.W. Ciurezak, W.R. Murphy, D.M. Mustillo, Spectrosc. Int. 3 (1987) 39–44.
[6] S. Lonardi, R. Viviani, L. Mosconi, M. Bernuzzi, P. Corti, E. Dreassi, C. Murratzu, G. Corbini, J. Pharm. Biomed. Anal. 7 (1989) 303–308.
[7] P. Corti, E. Dreassi, C. Murratzu, G. Corbini, L. Ballerini, S. Gravina, Pharm. Acta Helv. 64 (1989) 140–145.
[8] R.A. Forbes, M.L. Persinger, D.R. Smith, J. Pharm. Biomed. Anal. 15 (1996) 315–327.
[9] S. Torrado, S. Torrado, R. Cadórniga, J. Pharm. Biomed. Anal. 12 (1994) 383–387.
[10] S. Torrado, S. Fraile, J.J. Torrado, V.E. Sellés, J. Pharm. Biomed. Anal. 13 (1995) 1167–1172.
[11] E.R. Montgomery, S. Taylor, J. Secretario, E. Engler, D. Sebastian, J. Pharm. Biomed. Anal. 15 (1996) 73–82.