Determination of p-toluenesulfonic acid in n-butyl-2-cyanoacrylate monomer by liquid-liquid extraction and UV detection

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Determinación del ácido p-toluensulfónico en el monómero 2-cianoacrilato de n-butilo por extracción líquido-líquido y detección UV

Determinació de l'àcid p-toluènsulfónic en el monòmer 2-cianoacrilat de n-butil per l'extracció líquid-líquid i la detecció UV

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SUMMARY

A simple standard addition method was developed for determination of the anionic inhibitor p-toluenesulfonic acid in n-butyl-2-cyanoacrylate monomer. Aqueous extraction (pH 10) of the monomer samples diluted in chloroform was performed, and the analyte was estimated by means of UV absorption in the range of 0.15 to 1.50 g/l. The method developed provides acceptable precision and linearity and is suitable for use in the routine quality control analysis.

Keywords: Liquid extraction; n-butyl-2-cyanoacrylate; p-toluenesulfonic acid; standard addition.

RESUMEN

Se desarrolló un método sencillo por adición de patrón para la determinación de inhibidor aniónico ácido p-toluensulfónico en el monómero 2-cianoacrilato de n-butilo. Se realizó una extracción acuosa (pH 10) de las muestras del monómero diluidas en cloroformo y el analito fue determinado por su absorción UV en el intervalo de concentraciones entre 0.15 y 1.50 g/l. El método desarrollado brinda una precisión y linealidad aceptables y es adecuado para su uso en los análisis de rutina de control de calidad del monómero.

Palabras clave: Extracción líquido-líquido; 2-cianoacrilato de n-butilo; ácido p-toluensulfónico; método de adición de patrón.

RESUM

Es va desenvolupar un mètode senzill que consistia en la addició de patró per a la determinació del inhibidor aniònic, el àcid p-toluènsulfónic al monòmer 2-cianoacrilat de n-butil. Es va realitzar una extracció aquosa (pH 10) de les mostres del monòmer diluïdes en cloroform, i l'analit va ser determinat per la seva absorció UV en l'interval de concentracions entre 0.15 i 1.50 g/l. El mètode desenvolupat ofereix una precisió i linealitat acceptables i és adequat per al seu ús en les anàlisis de rutina de control de la qualitat del monòmer.

Paraules clau: Extracció líquid-líquid; 2-cianoacrilat de n-butil; àcid p-toluènsulfónic; mètode d'addició de patró.

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INTRODUCTION

Alkyl-2-cyanoacrylate (ACA) monomers are widely used as industrial and domestic adhesives because of their fast cure time and high bond strength of the resulting polymers[1]. Longer chain ACAs, such as n-butyl-2-cyanoacrylate (Fig. 1) or n-octyl cyanoacrylate, have been developed for biomedical uses such as tissues adhesives and embolic agents[2,3]. Novel applications of the alkyl-2-cyanoacrylate polymers (PACA) include their use as nanoparticulate drug delivery matrices[4] and composite materials[5]. Therefore, much attention has been paid to the synthesis, properties and polymerization of the ACA and degradation of the PACA[6,7].

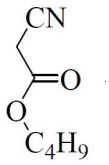

Fig. 1. *N-butyl-2-cyanoacrylate monomer*

The synthesis of cyanoacrylate monomers has been described in the literature since their discovery by Ardis in 1949[8] and has undergone several modifications[9,10,11]. The method consists of two stages. The first stage entails the Knoevenagel condensation reaction of the corresponding alkyl cyanoacetate with paraformaldehyde in the presence of a basic catalyst to form the cyanoacrylate polymer. In the second stage, the PACA is depolymerized at high temperatures and reduced pressure and the monomer is distilled in presence of suitable stabilizers.

The ACA monomers are highly reactive, clear and colorless liquids, with a low viscosity. Because of their high reactivity even at room temperature they have a strong tendency to polymerize and for this reason the presence of inhibitors in adhesive formulations are essential to maintain their storage stability. They are able to polymerize instantly in the presence of moisture or traces of basic components by an anionic polymerization mechanism due to the electron withdrawing CN and COOR groups. Therefore, acidic substances such as acidic gases (e.g. SO_2), organic sulfur compounds (e.g. sulfones) and protonic acids (e.g. sulfonic acids) are used as anionic polymerization inhibitors. ACAs also can polymerize by zwitterionic and free-radical mechanism, by exposition to high temperature or radiation. For this reason, free-radical stabilizers such as hydroquinone are also added to adhesive formulations. Nevertheless, because the polymerization is essential to the adhesive action of cyanoacrylates, the concentration of stabilizers has to be controlled. High content of stabilizers can make polymerization slow and reduce adhesive performance. Low content of inhibitors reduces the storage stability of the final products.

The purpose of this investigation was to develop a simple method for determination of the anionic inhibitor p-toluenesulfonic acid (PTSA) in n-butyl-2-cyanoacrylate (BCA) monomer, which can be used for routine quality control of the adhesive formulations.

MATERIALS AND METHODS

Materials

N-butyl-2-cyanoacrylate (BCA, $C_8H_{11}NO_2$, >99% purity) was synthesized in the Manufacturing Group of the Center of Biomaterials of the University of Havana, using the classic method previously described. Chloroform (UNI-CHEM, 99 %), p-toluenesulfonic acid (Sigma Aldrich, 98.5 %) and butyl cyanoacetate (Aldrich, 95%), acetone (BDH p.a.) and sodium hydroxide solution 1 N (UNI-CHEM) were used as received. Sodium hydroxide solution 1 N was dripped in 1.5 L of distilled water until a pH 10 (water pH 10) was obtained. The working standard solution of p-toluenesulfonic acid (10 g/l) was prepared by dissolving 0.25 g of PTSA in 25 ml of acetone in a volumetric flask. The solution is kept refrigerated until the utilization in a period less than three months.

METHODS

Determination of p-toluenesulfonic acid in n-butyl 2-cyanoacrylate is performed by aqueous extraction (pH 10) of the samples diluted in chloroform, using the method of standard addition and detection of the analyte by UV. In this method, the addition of several different equally-spaced amounts of analyte to separate equal aliquots of test solution is performed. Then, the signal is plotted on the y-axis; and the x-axis is graduated in terms of the amounts of analyte added. The regression line is calculated in the normal way, and it is extrapolated to the point on the x-axis at which y = 0. This negative intercept on the x-axis corresponds to the amount of the analyte in the test sample.

Sample extraction and calibration curve preparation

Three replicates of the blank solution and four calibration points were prepared.

Point 0: Chloroform (15 ml) and 0.5 ml of the BCA sample were poured in a separation funnel and gently mixed. 30 ml of the extraction solution (water pH 10) was added and gently shake for 1 min. After the layers separation, the bottom layer (chloroform + sample) was drained into a conic flask. The upper layer containing the interesting analyte was collected in a 100 ml sample bottle. The extraction procedure was repeated two more times collecting the extracts in the same sample bottle. Ten milliliters of the homogenized sample was centrifuged at 5000 rpm for 10 min.

Point 1: Chloroform (15 ml), 0.5 ml of the BCA sample and 25 µl of the PTSA working standard were poured in a separation funnel and gently mixed. The extraction was carried out as described for the Point 0.

Point 2: Chloroform (15 ml), 0.5 ml of the BCA sample and 50 µl of the PTSA working standard were poured in a separation funnel and gently mixed. The extraction was carried out as described for the Point 0.

Point 3: Chloroform (15 ml), 0.5 ml of the BCA sample and 75 µl of the PTSA working standard were

poured in a separation funnel and gently mixed. The extraction was carried out as described for the Point 0.

Blank solution: Chloroform (15 ml) was poured in a separation funnel and the extraction is carried out as described for the Point 0.

Apparatus

CINTRA 10e double beam UV-VIS was used for spectra recording and absorbance measurements at 228 nm in 1 cm quartz cells.

pH measurements for water solutions were taken on a potentiometer CRISON Basic 20, with combined glass electrode, that was calibrated at pH 4, 7 and 9 with buffer standards.

SACCS T51.1 centrifuge and SARTORIUS 210S analytic balance were used.

CALCULATIONS

Internal quality control

The range ($R = A_{max} - A_{min}$) of the absorbance values obtained was evaluated for each point and compared with the Critical Range ($CR_{0,95}$) for three replicas. If the calculated R was equal or less than the $CR_{0,95}$ the values were accepted and the mean value was calculated. If $R > CR_{0,95}$, the median value was taken because in this case it is a more realistic measure of central tendency than the arithmetic mean[12]. If the correlation coefficient of the calibration curve is less than 0.97 the assay was repeated.

Determination of the PTSA concentration in BCA samples

For each point, the mean (or median) of the absorbance values (Ap) versus the concentration of the added PTSA in the sample in g/l was plotted. The concentration of PTSA in the sample was calculated by the following equation[13]:

$$PTSA\ \% = \frac{Intercept\ (a)}{Slope\ (b)} \qquad (1)$$

All calculations were done in an Excel sheet as shown in the Fig. 2.

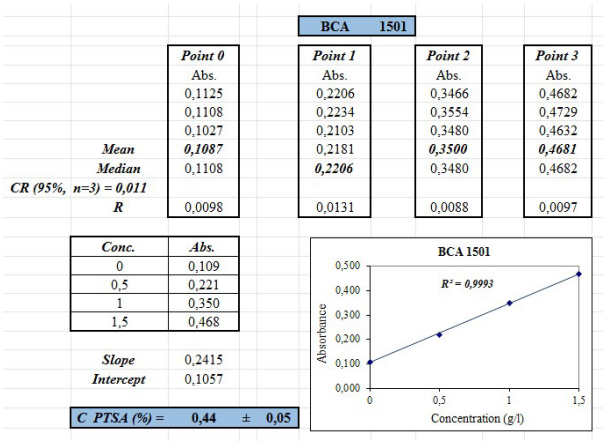

Fig. 2. Example of the calculations of p-toluenesulfonic acid (PTSA) concentration in the n-butyl-2-cyanoacrylate (BCA) monomer. The error (± 0,05) was calculated as $2S_x$.

The formula for the standard deviation of the extrapolated x-value is given by the following equation:

$$S_x = \frac{S_{y/x}}{b}\sqrt{\left(\frac{1}{n} + \frac{\bar{y}^2}{b^2 \sum_i (x_i - \bar{x})^2}\right)} \qquad (2)$$

where
b is the slope of the line,
n is the number of data points for the calibration curve,
$\bar{y}$ is the mean value of y for the points on the calibration curve,
$\bar{x}$ is the mean value of x for the points on the calibration curve,
$S_{y/x}$ estimates the random errors in the y-direction and is calculated by the equation (3).

$$S_{y/x} = \sqrt{\left(\frac{\sum_i (y_i - \hat{y}_i)^2}{n-2}\right)} \qquad (3)$$

where
$\hat{y}_i$ values are the points on the calculated regression line corresponding to the individual x_i values.

The error (E) was calculated as $2S_x$ because of the small value of n and the little concentration interval covered by the calibration line. The limit of quantification was calculated as 3E.

RESULTS AND DISCUSSION

The aim of this work was to find a fast, reliable and little complicated method to quantify the anionic polymerization inhibitor PTSA in BCA samples. This was done by a combination of liquid-liquid extraction and standard addition calibration method, using an UV detector for the quantification of the analyte concentrations.

Due to the strong reactivity of the BCA it is impossible to get the pure monomer to obtain an external calibration curve. A first approach was to use de butyl cyanoacetate as a substitute matrix for the calibration curve taking advantage from the chemical similarities between these two compounds. However, to obtain higher production yields it was necessary to increase the amount of the free-radical inhibitor (hydroquinone) in the depolymerization step and the obtained BCA also has small quantities of this compound remaining from the manufacturing. As shown in Fig. 3, the hydroquinone has an UV signal that interfere at 228 nm with the signal of the PTSA. This matrix effect makes it impossible to measure the analytical signal using the traditional external calibration curve approach even using a substitute matrix.

During this work, the experimental parameters were studied and optimized to achieve better extraction recoveries. Utilizing the acidic character of the inhibitors, the extractions were done with water at pH 9.5-10. Using cyanoacetate as experimental matrix, four extraction procedures were tested, with the conditions listed below. In these experiments the PTSA concentration was quantified employing the traditional external calibration curve.

A Dilution of 0.5 ml of the sample in 10 ml of chloroform; five extractions with 5 ml of water (pH 9.5) each; five replicates; 0.1 cm quartz cells.

B Dilution of 0.5 ml of the sample in 10 ml of chloroform; five extractions with 8 ml of water (pH 9.5) each; five replicates; 0.1 cm quartz cells.

C Dilution of 0.5 ml of the sample in 10 ml of chloroform; four extractions with 25 ml of water (pH 10) each; four replicates; 1 cm quartz cells.

D Dilution of 0.5 ml of the sample in 15 ml of chloroform; three extractions with 30 ml of water (pH 10) each; three replicates; 1 cm quartz cells.

The results obtained in the extraction experiments are shown in Table 1. The high dispersion of the results is due to the extensive sample manipulation. As the result of these initial experiments the chosen method was the D.

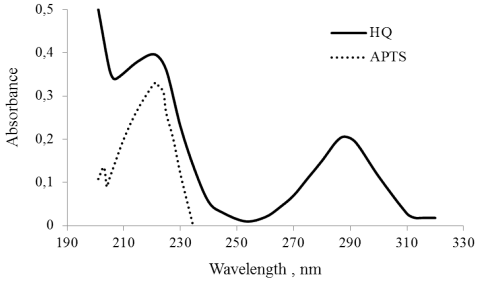

Fig. 3. *UV spectra of hydroquinone (HQ) and p-toluenesulfonic acid (PTSA)*

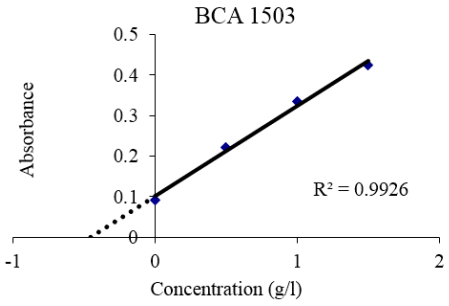

Fig. 4. *Linearity of the standard addition calibration curve for determination of PTSA in BCA.*

Table 1. *Extraction results using butyl cyanoacetate as sample matrix with 0.03 % of p-toluenesulfonic acid (PTSA); t: t-Student, S: standard deviation.*

Methods	PTSA concentration ± tS (%)	Recovery ± tS (%)
A	0.016 ± 0.002	53 ± 6
B	0.027 ± 0.003	90 ± 10
C	0.025 ± 0.002	83 ± 7
D	0.028 ± 0.002	93 ± 7

To establish the Critical Range for absorbance values, the average standard deviation was calculated from the results of the first five batches analyzed in 2015 (Table 2). Then the $CR_{0,95}$ was calculated by the following equation[12]:

$$CR_{0,95}(n) = f(n)S_r, \quad (4)$$

where is a tabulated factor for the Critical Rank and is the standard deviation in repeatability conditions.

Table 2. *Determination of the average value of the standard deviation for absorbance in repeatability conditions*

Batch	Standard deviations (n=3)				
	Point 0	Point 1	Point 2	Point 3	Average
1501	0.002	0.002	0.003	0.003	
1502	0.002	0.003	0.003	0.003	
1503	0.003	0.005	0.004	0.005	
1504	0.002	0.002	0.002	0.004	
1505	0.005	0.003	0.003	0.004	
Average	0.0028	0.0031	0.0030	0.0037	0.003

To assess the linearity of the calibration curve, four concentration points were measured in g/l: x, x+0.5, x+1.0, x+1.5 (Figure 4). The limit of quantification was found to be 0.15 g/l.

Once the linearity was verified, the calibration slope can obtain confining the measurements to the ends of the range. In the Table 3, calibration parameters and concentration results were obtained using four-points and two-points calibration curve for the same data. The differences between both results are smaller than the measurement error for the four-point calibration and furthermore this strategy requires a smaller number of operations per measurement result. If better precision is required, more replicas of each point could be done and the concentration of the added analyte could be five times the mean expected concentration of analyte (2 g/l)[14].

The specification for anionic inhibitor concentration established for the BCA monomer in the Manufacturing Group lays in the interval from 0.2 g/l to 0.6 g/l and the method was found to be appropriate for estimation of the analyte concentrations in this interval. The two-points method gave lower dispersion of the production batches results than the four-points method.

Table 3. *Comparison of the linear regression parameters and concentration results for calibration using four and two points.*

Batch	Four-points calibration			Two-points calibration			ΔX (g/l) (X4-X2)
	a	b	X4 (g/l)	a	b	X2(g/l)	
1501	0.2415	0.1057	0.438	0.2396	0.1087	0.453	-0.015
1502	0.1929	0.0733	0.380	0.1933	0.0808	0.418	-0.038
1503	0.2219	0.1013	0.457	0.2212	0.0912	0.412	0.045
1504	0.1934	0.0755	0.390	0.1920	0.0828	0.431	-0.041
1505	0.1937	0.0730	0.377	0.19487	0.0785	0.403	-0.026
Mean			0,408			0,423	-0.015
Standard deviation			0,033			0,017	0.031

CONCLUSIONS

In conclusion, the research shown here demonstrated that the method of standard addition employed for the determination of p-toluenesulfonic acid in cyanoacrylate monomer provides acceptable precision and linearity. The method could be simplified

using two-points calibration curve. This method is suitable for use in the routine quality control analysis.

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