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Quantification by the Spectrophotometric Method of Triclosan in Personal Care Products through Experimental Design

Quantificação pelo Método Espectrofotométrico de Triclosan em Produtos de Cuidados Pessoais através de um Planejamento Fatorial

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The factorial design was used for optimization of the spectrophotometer method for determining the best conditions to produce an azo compound with higher molar absorptivity and stability. The diazotization reaction of sulphanilamide with triclosan was optimized for the determination of triclosan in samples of personal care products. The diazotization reaction occurs in two steps: (1) reaction of sulphanilamide with sodium nitrite in an acidic medium to form diazonium ion and (2) reaction of diazonium ion and (2) reaction of diazonium ion with triclosan to form a yellowish-orange azo compound in an alkaline medium. The concentration of hydrochloric acid, sulphanilamide and the volume of sodium nitrite were optimized through factorial design of experiments and response surface methodology. The resulting yellowish-orange product showed maximum absorption at 452 nm, which allowed the determination of triclosan in a concentration range of 0.50 mg L^{-1} to 10 mg L^{-1} with a correlation coefficient of 0.9994. The limits of detection (LD) and quantification (LQ) were 0.018 mg L^{-1} and 0.060 mg L^{-1}, respectively. The optimum conditions established by multivariate method produced an azo compound with high optical stability which was successfully applied in the quantification of triclosan in samples of personal care products. This method might be used as an alternative less expensive, easy and simple way to determine triclosan in several personal care products such as toothpaste, body cream and deodorants.

Keywords: Triclosan; spectrophotometry; experimental factorial design

1. Introduction

Personal care products such as soaps, toothpaste and mouthwashes usually contain between 0.1 and 1% (v/v) triclosan (5-chloride-2-(2,4-dichlorophenoxy)phenol in their formulation.[1,2,3] In Brazil, according to the Resolution RDC 528/2021 by ANVISA (Sanitary Vigilance National Agency)[4] the triclosan maximum concentration allowed to be added to personal care products composition is 0.3%. Triclosan has been used for over four decades and is extensively employed worldwide. The annual use of triclosan is estimated to be between 300 and 450t in the United States and Europe, respectively.[5] Literature has shown that these compounds are found in domestic sewage treatment stations effluents in the following concentrations: μg L^{-1} and ng L^{-1}.[6,7] Lv *et al.*,[8] reported that in 57.6% water bodies evaluated in 30 States in the United States the maximum level of 2.3 mg mL^{-1} triclosan was found.

Triclosan is also known as endocrine disruptor and its presence in the environment might be harmful to the human health as a consequence of the development of a generation of resistant micro-organisms.[9,10] In addition, it might cause toxicity to water organisms such as fish and algae, in low concentrations, that is, when in the μg L^{-1} concentration range.[11,12] Therefore, it is necessary to control triclosan in formulations since its indiscriminate and uncontrolled use in several products along with the disposal without proper treatment might cause severe damage to the environment and people's health due to the development of resistant microorganisms.

The most used analytical technique to determine triclosan in personal care products and environmental samples is the high performance liquid chromatography (HPLC)[13-16], but despite its possibility of quantifying triclosan in low concentrations (ng mL^{-1}), this technique requires expensive instruments, which are not usually available in many research laboratories. Also, it requires specifically trained people, since chromatographic runs are long and the solvents are expensive and harmful to the human health.[16] In such context, the need for techniques to enable proper quantification which are at the same time simpler, cheaper, fast and generate less residue using environmentally safer reagents is recognized.

Spectrophotometric methods have been widely used for the quantitative determination of the different types of analytes and has significantly increase the interest due to their simplicity, versatility, speed, accuracy, precision, low cost and due be an environmental friendly method.[17-23] In general, to increase sensitivity and selectivity in the spectrophotometric determination of species in the UV-vis region, the analyte transformation is used in order to obtain higher molar absorptivity and wavelength in the visible region.[24] This process usually involves the generation of an azo compound which can be obtained through a diazo coupling reaction. This reaction involves the formation of an arenediazonium cation (electrophile) and another aromatic ring activated by an electron donating substituting group (nucleophile), for example, a primary amine.[25]

Besides, one of the most important steps in the development of a new analytical method is its optimization, for instance, the study of those factors which have an influence on the analytical signal, and selection of the values that produce the best results for the analytical method. Furthermore, the number of experiments necessary is large and consequently, the time required is high and with high consumption of reagent and materials. In this context, the chemometric techniques have been used for optimization of analytical methods. The use of design experiments (DOE) is the most efficient way to estimate effects of simultaneous variables, it maximizes the number of useful information with a minimum number of tests, which in routine analytical laboratories is a way to reduce time, material and reagent costs.

As already mentioned, the spectrophotometric methods have been reported for determination triclosan in personal care products[17,19] and environmental samples.[21,22,23] As can be seen for personal care products, there are few methods described. Among these, the method described by Jin et al.,[19] triclosan is determined at 282 nm. However, samples of personal care products most often contain fragrances and other compounds that can interfere with the quantification of triclosan, because these compounds exhibit ultraviolet absorption due to their chemical structure. Therefore, the authors propose the use of the derivative spectrophotometry method to eliminate the interference of impurities after extraction with chloroform of the triclosan from the analyzed samples. Already the method proposed by Lu et al.,[17] is based on the diazotization reaction, however, in this work the reaction conditions were realized by univariate optimization. The one variable at a time method is inefficient and might generate false results. Therefore, to use a systematic and statistical way of optimizing the reaction variables might produce best results. For this reason, this study proposes use the optimization by factorial design for determination the best conditions to produce an azo compound with higher absorptivity via spectrophotometry method which might be applied as routine quality control for determination triclosan (TCS) in personal care products.

2. Methodology

2.1. Chemicals

For the preparation of the solutions and samples, deionized water (Milli-Q Gradient system) and grade A glassware were used. All reagents used in this study were of analytical grade and the solutions prepared daily. A triclosan stock solution 200 mg L^{-1} (Merck) was prepared, weighing 0.020 g TCS, dissolved in 20 mL NaOH 0.50 mol L^{-1} and obtaining 100 mL final volume with deionized water. A 50 mg L^{-1} working solution was prepared by dilution in deionized water. A 0.09 % sulphanilamide solution (Vetec) was prepared by the dissolution of 0.090 g solid in HCl solution (Vetec) 4.00 x 10^{-2} mol L^{-1} (previously standardized by volumetric procedure) in a 100 mL volumetric flask. The 10 % sodium carbonate solutions (Vetec) and 0.50 mol L^{-1} sodium nitrate (Nuclear) were prepared with deionized water.

2.2. Analytical curve construction

Analytical curve was constructed by transferring 0.80 mL $NaNO_2$ 0.50 mol L^{-1} and 1.00 mL sulphanilamide 0.09 % prepared in HCl 4.00 x 10^{-2} mol L^{-1} into each series of 10.0 mL standard flasks and leave to stand at the 5 °C for 5 min. It was added to each standard flask aliquots of 0.10 to 2.00 mL triclosan 50 mg L^{-1} working solution, so that its final concentration was from 0.50 to 10.0 mg L^{-1} and 2.00 mL Na_2CO_3 10 %. The volume was completed with deionized water. After 10 minutes the absorbance measurements were carried out in 452 nm against a blank solution prepared in a similar way, but without the addition of triclosan.

2.3. Equipment

Absorbance measurements were carried out using a UV-vis spectrophotometer, Shimadzu model MultiSpec 1501, monitoring the region around 200 and 700 nm. All the measurements were carried out in quartz cuvette with 1 cm optical path length.

2.4. Sample preparation

The personal care products (toothpaste, cream deodorant (for the feet and armpit) and body cream) were bought at the local commerce and analyzed by the method proposed. Around 0.15 g was weighed and submitted to agitation with 10 mL sodium hydroxide 0.01 mol L^{-1} using ultrasound bath for 10 minutes and centrifuged for 30 minutes. The supernatant solution was filtered in a 0.45 µm millipore filter and transferred to a 25 mL volumetric flask and the volume completed with deionized water. Then, 3.00 mL portion was taken and derivatization of triclosan present

in the sample was carried out using optimum reaction conditions. The colored solution so obtained was analyzed spectrophotometrically at 452 nm and triclosan content was determined with the calibration curve equation.

3. Results and Discussion

3.1. Optical Stability of azo compound

The molecular absorption spectrophotometric methods are the ones most widely used among the quantitative analysis techniques in chemistry and clinical laboratories around the world.[26] The literature commonly presents several proposals of diazotation reaction, and the sulphanilamide[27-29] is widely employed to form diazonium salt in the first phase and the use of sodium carbonate or an alkaline glycine buffer[17,22,23] of pH 12 is indicated to make the medium alkaline for the coupling reaction. The literature[27,29] describes the development of a colorimetric method to quantify 17β-estradiol in medicine using sulphanilamide and to determine triclosan in personal care products by employing the sulphanilic acid[17]. However, those reports present univariate optimization studies which might not observe interactions between variables or neglect an important region to obtain a better response. It is well known that the diazonium salts are stable at 0-5 °C and undergo decomposition at high temperatures.[30] In our study, the diazonium salt formation step was carried out at low temperatures, which favored the optical stability of the colored product formed. When we reproduced the method employing the sulphanilic acid[17] with the indicated conditions the results were not reproducible. The published work does not mention the optical stability of the colored product formed and in tests carried out in our laboratory we verified that the product was not stable at the beginning of the reaction, and this must be the reason for the lack of reproducibility. The studies reported do not report that they performed this temperature control, which may explain the low reproducibility of the method described in the literature.

Therefore, based on the literature, a preliminary study was carried out to verify the viability of using sulphanilamide and sodium carbonate as precursor reagents to form an azo compound. By following this reaction kinetics, the results presented in Figure 1 were obtained.

The reagents used in this study enabled the formation of a yellow product which absorbs at 452 nm and presents good optical stability; therefore, these results indicate that it is possible to use these reagents to propose the development of an analytical methodology to determine triclosan. Also, Figure 1 shows that with the use of sulphanilamide the reaction occurs quickly and reaches equilibrium after 8 minutes. In the time interval between 8 and 60 minutes, the absorbance intensity at 452 nm remains practically constant and there is enough time to carry out the reaction

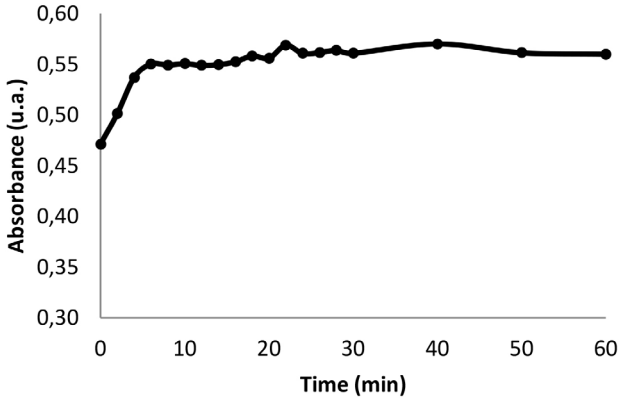

Figure 1. Optical stability of the product formed after diazotization and coupling reaction with triclosan. Absorbance measurements (λ = 452 nm)

and read the absorbance of the product formed. In this work, all absorbance measurements were taken after 10 minutes.

3.2. Optimization of the methodology proposed

The traditional procedure for a univariate optimization, in which each factor is evaluated separately, requires a large number of experiments but is not able to establish how each factor behaves in relation to the others.

The use of statistical tools such as experiment planning is a more efficient way of extracting higher amounts of information about certain system with fewer tests. In practice that means the reduction of time consumed and reagent costs and greater speed in the development of new products, processes or methods, in addition to better understanding of the system, better control and consequently, more reliable results, among other advantages.[31-33]

Experiment planning cannot be the only route to be followed, but it directs the experiments toward the previously determined target. Therefore, it is necessary to select the independent variables to be evaluated, selecting the level at which each variable will be evaluated and project the experiment plan so that it obtains exactly the information desired.[31-33]

First, a selection of variables was carried out through a complete factorial design. Next, the response surface methodology (RSM) was adopted to evaluate the existing relation between the system main variables and the measurement of the colorful product absorbance.

A complete 2^3 factorial design was employed in the initial studies to determine how the factors sodium nitrite volume, sulphanilamide and chloridric acid concentrations influence the formation of a colorful product. The objective was to obtain the best experimental condition, in which an optimal value is obtained for the response variable (absorbance measured at 452 nm), that is, to obtain the best analytical sensitivity. The factors considered with the levels examined (real and coded) and the experimental matrix with the results obtained are shown in Table 1. The triclosan concentration was 10 mg L^{-1} in all experiments.

Table 1. Experimental matrix of 2^3 factorial design conducted to study the experimental conditions for analysis of triclosan

Experiment	Uncoded factors			Coded factors			$A_{452\ nm}$ [c]
	V $NaNO_2$ (mL) [a]	[sulphanilamide] % m/v [b]	[HCl] mol L^{-1}	V $NaNO_2$ (mL)	[sulphanilamide] % m/v [b]	[HCl] mol L^{-1}	
1	0.40	0.20	0.10	-1	-1	-1	$0.9117 \pm 0.52 \times 10^{-2}$
2	0.80	0.20	0.10	1	-1	-1	$0.9222 \pm 1.94 \times 10^{-2}$
3	0.40	0.40	0.10	-1	1	-1	$0.8026 \pm 0.55 \times 10^{-2}$
4	0.80	0.40	0.10	1	1	-1	$0.8372 \pm 1.59 \times 10^{-2}$
5	0.40	0.20	0.20	-1	-1	1	$0.6786 \pm 2.11 \times 10^{-2}$
6	0.80	0.20	0.20	1	-1	1	$0.8220 \pm 4.90 \times 10^{-2}$
7	0.40	0.40	0.20	-1	1	1	$0.5731 \pm 1.29 \times 10^{-2}$
8	0.80	0.40	0.20	1	1	1	$0.6013 \pm 0.26 \times 10^{-2}$

[a] $NaNO_2$ 0.5 mol L^{-1}; [b] 1.00 mL de sulphanilamide prepared with HCl at the concentrations indicated in the table; [c] Average ± standard deviation (SD) of two determinations.

This study required 8 experiments, which were replicated to estimate experimental error and the data was analyzed using the program Statistica 12.6.

Figure 2 presents the Pareto graph for estimated effects of the factors under investigation and their interactions. In this graph, horizontal bars indicate the degree of importance that the factors under study have on the colorimetric reaction. The length of each bar on the chart is proportional to the absolute value of its associated estimated effect or the standardized effect. The chart includes a vertical line that corresponds to the 95% limit indicating statistical significance. An effect is therefore significant if its corresponding bar crosses this vertical line. The most significant effects were sulphanilamide and chloridric acid concentrations, obtaining better response when both are adjusted at a lower level (-1). The nitrite volume factor in the conditions evaluated was significant, however, it presented smaller influence and when adjusted at its high level (+1) the best response is obtained. Therefore, to continue the optimization process, the nitrite volume was fixed at the highest level in the following experiments.

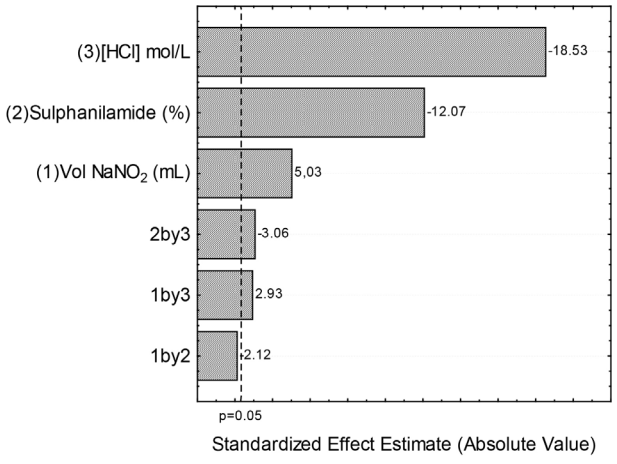

Figure 2. Standardized effects of $NaNO_2$ volume, sulphanilamide and HCl concentrations, and their interaction effects on the absorbance measurements (λ = 452 nm)

In order to develop the optimization procedure, the response surface methodology was adopted. Through the response surface it was possible to analyze how the relevant response (colorful product absorbance measurement) was simultaneously influenced by the factors selected. In this study, the factors sulphanilamide and chloridric acid concentration were evaluated at five different levels, totaling 11 experiments. The factors under study and their respective levels (coded and non-coded), the experimental matrix and the results obtained are in Table 2. The central point experiments were carried out with replications (n=3) to estimate experimental error. In all experiments, the triclosan concentration was 10 mg mL^{-1}. The results were analyzed by using the program Statistica, version 12.6.

The analysis of variance (ANOVA) of the central composite design of the results was carried out to verify the significance of the mathematical model obtained. A statistically significant quadratic model accounting for 90 % of the variance was fitted to the data at a 95% confidence level.

The response surface (Figure 3) shows the relation between dependent variables. In this Figure, the darker region presents the best absorbance responses. The equation of the quadratic model generated for this planning is in the same Figure 3, and through this equation it is possible to predict the optimal condition to carry out the reaction proposed. For this study, optimal conditions should provide a 0.8537 (±0.0427) maximum absorbance value when the sulphanilamide concentration is 0.088% and the chloridric acid is 0.038 mol L^{-1}.

Experiments were performed in triplicate in optimal conditions determined by the mathematical model to verify the agreement between the result obtained experimentally with that calculated by the program. It was seen that the result provided by the mathematical model (0.8537) for the absorbance measure in optimal conditions, agrees with those obtained experimentally ($0.8268 \pm 4.84 \times 10^{-3}$ (R.S.D = 0.6%), with 95% reliability.

Table 2. Central composite design matrix with the absorbance measurements

Experiment	Uncoded factors		Coded factors		A_{452nm} [c]
	[HCl] mol L^{-1}	Sulphanilamide[a] (%)	[HCl] mol L^{-1}	Sulphanilamide[a] (%)	
1	0.020	0.05	-1	-1	0.7447
2	0.050	0.05	1	-1	0.8352
3	0.020	0.15	-1	1	0.7591
4	0.050	0.15	1	1	0.7340
5 [b]	0.035	0.10	0	0	0.8548
6 [b]	0.035	0.10	0	0	0.8603
7 [b]	0.035	0.10	0	0	0.8378
8	0.014	0.10	-1.41	0	0.7789
9	0.056	0.10	1.41	0	0.7810
10	0.035	0.17	0	1.41	0.7861
11	0.035	0.03	0	-1.41	0.7889

[a] 1 mL of sulphanilamide prepared with HCl at the concentrations indicated in the table was added; [b] Central point replicate (n = 3); [c] In all experiments the triclosan concentration was 10 mg mL^{-1}.

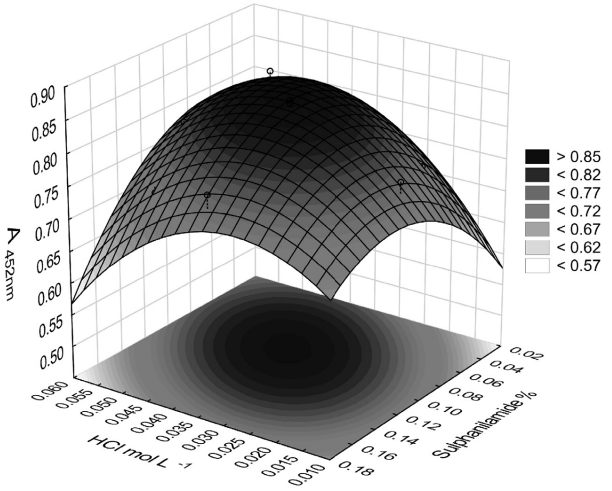

Figure 3. Three-dimensional plot of the optimized surface response of absorbance measurements (λ = 452 nm) at variable sulphanilamide and HCl concentrations

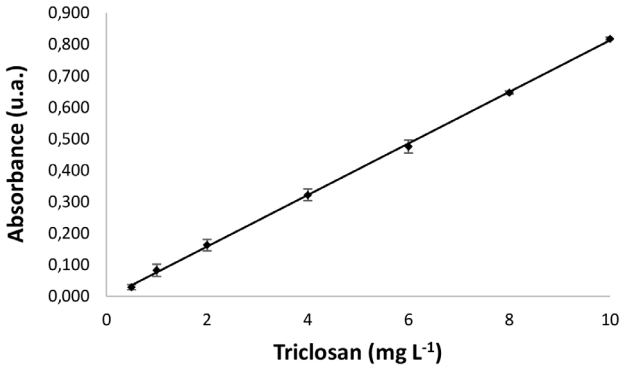

Figure 4. Analytical curve. Absorbance measurements (λ = 452 nm)

3.3. Method validation

The parameters evaluated in order to validate the method proposed were: linearity, accuracy, precision, repeatability, detection limit, quantification limit and recovery percentage, according to the Resolution n° 166/2017 (ANVISA)[34].

After optimizing the experimental conditions, a working band was verified in which a linear relation between the absorbance value and the triclosan concentration was obtained. The analytical curve was built, in triplicate, representing the A_{452nm} values as a function of the triclosan concentration. Figure 4 represents the linear relation observed at the concentration band from 10 mg L^{-1} to 0.5 mg L^{-1}. For concentrations below 0.5 mg L^{-1} or above 10 mg L^{-1}, linearity deviations were observed.

The mathematical equation which describes the linear relation existing between A_{452nm} and the triclosan concentration is: $A_{452nm} = 0.0864 \times C - 7.63 \times 10\text{-}3$, where C = triclosan concentration in mg L^{-1}, with a 0.9994 correlation coefficient. According to the Resolution 166/2017 by ANVISA (Sanitary Surveillance National Agency)[34] the minimum acceptable criterion for the correlation coefficient must be 0.99. Therefore, the correlation coefficient obtained in this study demonstrates excellent correlation between absorbance and the relevant analyte concentration. The detection and quantification limits were determined according to the same resolution by ANVISA, obtaining the values 0.018 mg L^{-1} and 0.06 mg L^{-1}, respectively, indicating that the method is highly sensitive.

The intraday precision (repeatability) was evaluated through the analyses of six sample solutions with the concentration 5 mg L^{-1} at different times of the day. The intermediary precision was obtained through the analyses of six solutions of the same concentration carried out on different days and by two different analysts. The repeatability and intermediate precision were evaluated regarding relative standard deviation. The results of such parameters are presented in Table 3 and indicate that the method can be considered precise since the values are below

Table 3. Figures of merit assessed by spectrophotometric method proposed for the determination of triclosan

Parameter	Values
Linearity	0.5 a 10 mg L^{-1}
Equation of regression	$y = 0.0864x + 7.63 \times 10^{-3}$
Correlation coefficient (r)	0.9994
λ nm	452
Detection limit	0.018 mg L^{-1}
Quantification limit	0.06 mg L^{-1}
Intermediate precision (5.0 µg mL^{-1})	1.90% (4 days; 2 analysts, n=6)
Accuracy intraday (5.0 µg mL^{-1})	1.92% (n=6)
Accuracy	99.3 – 104.0 %

5% for relative standard deviation. These values are also determined by ANVISA.[34]

According to the literature,[35,36] specificity and accuracy can be evaluated through the standard addition and recovery tests. In order to evaluate recovery rates, known amounts (1.5; 3.5; 5.5 and 7.5 mg L^{-1}) of triclosan (analytical pattern) were added to eight pre-analyzed samples (toothpaste, body deodorant cream, moisturizer cream, feet deodorant cream) containing 1.5 mg L^{-1}. According to the results obtained and presented in Table 4, it was seen that the triclosan recovery average percentage was around 99.3 – 104.0 %, suggesting again the good accuracy of the method proposed.

In order to apply the method to determine triclosan in the samples without the need of a previous chromatographic separation phase, the matrix potential effect must be evaluated.[36] In this sense, the external calibration curve angular coefficient was compared to the standard addition angular coefficients of each sample (Table 5) and the results demonstrated that the values were really close, indicating that there was no matrix interference.

3.4. Triclosan determination in personal care products

The method proposed was applied to determine the percentage of triclosan in eight commercial samples of toothpaste, the samples comprised four kinds of toothpaste (whitening, sensitive, professional and gel). In Brazil, the maximum percentage of triclosan allowed in personal care products is 0.3%, and according to the results obtained when applying the method proposed, the percentage of triclosan found was within the limits provided by the regulation (Table 6).

4. Conclusion

The optimization of a method to determine triclosan employing the response surface methodology enabled the determination of optimal conditions for the production of a colorful product which absorbs strongly at 452 nm by diazotation reaction. The validation was realized considering

Table 4. Recovery data for triclosan spiked samples

Samples	TCS added (mg L^{-1})	TCS found (mg L^{-1})	Recovery [d] %
A[a]	----	1.46	
	1.5	2.98	101.3
	3.5	5.04	102.3
	5.5	7.18	104.0
	7.5	9.08	101.6
			µ = 102.3 ± 1.2
B[a]	----	1.52	
	1.5	3.03	100.7
	3.5	5.07	101.4
	5.5	7.15	102.4
	7.5	9.23	102.8
			µ = 101.8 ± 1.0
C[b]	----	1.48	
	1.5	2.99	100.7
	3.5	5.06	102.3
	5.5	7.18	103.6
	7.5	9.10	101.6
			µ = 102.0 ± 1.2
D[b]	----	1.52	
	1.5	3.01	99.3
	3.5	5.08	101.7
	5.5	7.22	103.6
	7.5	9.00	99.7
			µ = 101.1 ± 2.0
	----	1.54	
E[c]	1.5	3.09	100.0
	3.5	5.14	102.9
	5.5	7.19	102.7
	7.5	9.30	103.5
			µ = 102.3 ± 1.6
F[c]	----	1.52	
	1.5	3.05	10.,0
	3.5	5.10	102.3
	5.5	7.19	103.1
	7.5	9.19	102.3
			µ = 102.4 ± 0.5
G[c]	----	1.54	
	1.5	3.03	99.3
	3.5	5.13	102.6
	5.5	7.19	102.7
	7.5	9.14	101.3
			µ = 101.5 ± 1.6
H[c]	----	1.48	
	1.5	3.01	102.0
	3.5	4.99	100.3
	5.5	7.02	100.7
	7.5	9.00	100.3
			µ = 100.8 ± 0.8

[a] body cream; [b] deodorants; [c] toothpaste; [d] Average ± standard deviation (SD) of three determinations.

Table 5. Compare angular coefficients obtained by standard addition to the slope obtained by external calibration

	External calibration	Standard addition / samples							
		A[a]	B[a]	C[b]	D[b]	E[c]	F[c]	G[c]	H[c]
Angular coef.	0.0864	0.0883	0.0889	0.0836	0.0895	0.0901	0.0831	0.0852	0.0886
SD(Angular coef.)	0.00763	0.0032	0.0035	0.0026	0.0038	0.0041	0.0007	0.0023	0.0034
Variation angular coef.	-	2.2	2.9	-3.2	3.6	4.2	-3.8	-1.4	2.6

[a] body cream; [b] deodorants; [c] toothpaste.

Table 6. Determination of triclosan in personal care products

Sample	% found TCS [d] (w/w)	RSD (%)
A[a]	$0.30 \pm 1.0 \times 10^{-2}$	3.3
B[a]	$0.29 \pm 7.6 \times 10^{-3}$	2.6
C[a]	$0.30 \pm 6.4 \times 10^{-3}$	2.1
D[a]	$0.28 \pm 1.1 \times 10^{-2}$	3.9
E[b]	$0.29 \pm 7.8 \times 10^{-3}$	2.7
F[b]	$0.28 \pm 2.5 \times 10^{-3}$	0.9
G[c]	$0.29 \pm 1.1 \times 10^{-2}$	3.8
H[c]	$0.29 \pm 9.9 \times 10^{-3}$	3.4

[a] body cream; [b] deodorants; [c] toothpaste; [d] Average ± standard deviation (SD) of three independent analyses.

the merit parameters recommended by ANVISA. These merit parameters evaluated permitted to verify that the spectrophotometric method proposed to determine triclosan in personal care products was safe and reliable considering the band 0.5 to 10 mg L^{-1}. Therefore, the studies carried out presented a simple, low cost and fast alternative to applied in routine control quality to determine TCS in personal care products.

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