ORIGINAL ARTICLE

ANALYTICAL VALIDATION OF THE DETERMINATION OF THE CONTENT OF CALCIUM CARBONATE IN CAPSULES BY COMPLEXOMETRIC TRITRATION

Dênis Gomes de Melo[1], Matheus da Silva Campelo[2]
Cristiani Lopes Capistrano Gonçalves de Oliveira[3], Maria Elenir Nobre Pinho Ribeiro[4]

Highlights: (1) The amount of indicator described in the norm had to be changed to ensure precision and accuracy. (2) Youden's method revealed the significant impact of the quantity of the indicator on robustness. (3) The content of various capsule formulations is determined, including those containing vitamin D.

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[1] Federal University of Ceará – UFC. Department of Organic and Inorganic Chemistry. Fortaleza, Ceará, Brazil. https://orcid.org/0000-0002-9540-4184

[2] Federal University of Ceará – UFC. Department of Organic and Inorganic Chemistry. Department of Clinical and Toxicological Analysis. Fortaleza, Ceará, Brazil. https://orcid.org/0000-0003-0286-1974

[3] Federal University of Ceará – UFC. Department of Pharmacy. Fortaleza, Ceará, Brazil. https://orcid.org/0000-0002-8120-2362

[4] Federal University of Ceará – UFC. Department of Organic and Inorganic Chemistry. Fortaleza, Ceará, Brazil. https://orcid.org/0000-0001-6896-7179

ANALYTICAL VALIDATION OF THE DETERMINATION OF THE CONTENT OF CALCIUM CARBONATE IN CAPSULES BY COMPLEXOMETRIC TRITRATION

ABSTRACT

People who suffer from calcium deficiency need supplementation to avoid diseases caused by low levels in the body, as this element performs several essential physiological functions in the human body. In this context, the present work aimed to validate a complexometric method for the determination of calcium carbonate in four different formulations, and the method validation followed the specifications of RDC 166/17 (ANVISA). The method proved to be selective, linear, accurate, precise and robust. The analytical curve showed a parametric and homoscedastic data distribution, with R2 > 0.99. In the analysis of precision and accuracy, relative standard deviation (RSD) values of less than 1.7% and recovery percentages above 98% were obtained, respectively, indicating that the method is precise and accurate. The application of the Youden method in the robustness study demonstrated the influence of the indicator on the methodology, while the other deliberate changes in the analytical method did not affect the response. In this way, a precise adjustment was made in the amount of the indicator to maintain the precision and accuracy of the methodology. The application of the validated classic method, as an environmentally friendly alternative, confirmed its potential for possible routine analysis applied to pharmaceutical forms in capsules.

Keywords: Calcium carbonate. EDTA. Validation. Titration. Quality control.

INTRODUTION

Calcium is a component of the human body that performs a range of important physiological functions. It plays a vital role in maintaining human life activities, such as preserving the skeletal system, regulating hormonal secretion, transmitting nerve impulses, and supporting vascular functions[1]. Calcium supplementation is indicated for pregnant women with mineral deficiencies to prevent risks caused by hypertension during pregnancy and for patients with renal failure in the treatment of hyperphosphatemia. Furthermore, when associated with vitamin D, it is recommended for the prevention of fractures in elderly people affected by bone decalcification (osteoporosis)[2,3].

Calcium carbonate is a source of calcium supplementation, containing 40% calcium by weight. Naturally, it occurs in ores (calcite and aragonite in crystalline form), eggshells, and

mollusk shells. However, in the pharmaceutical industry, precipitated calcium carbonate (PCC) stands out due to its high purity and small particle size, which enhance its absorption[4–6]. The most common process to obtain PCC is Calcination-Dissolution-Precipitation (CDP), which guarantees a purity above 99%. In this process, the mineral source undergoes calcination (1) to form calcium oxide, which is then hydrated (2) to form calcium hydroxide. In the third step, calcium hydroxide reacts with carbon dioxide to produce PCC (3). This process minimizes impurities such as magnesium salts, sulfates, and silicates[7].

$$CaCO_{3(s)} + \text{heat} \rightarrow CaO_{(s)} + CO_{2(g)} \quad (1)$$

$$CaO_{(s)} + H_2O_{(l)} \rightarrow Ca(OH)_{2(aq)} \quad (2)$$

$$Ca(OH)_{2(aq)} + CO_{2(g)} \rightarrow CaCO_{3(s)} + H_2O_{(l)} \quad (3)$$

For the quality control of calcium carbonate in raw materials, the complexometric titration method is used with the chelator ethylenediaminetetraacetic acid (EDTA) and the blue indicator hydroxynaphthol. Complexometric titration with EDTA is described in several pharmacopoeias with minor modifications. The Brazilian Pharmacopoeia (2019) and the International Pharmacopoeia (2020) include monographs that determine the content of the raw material using similar methodologies[8,9]. The Japanese Pharmacopoeia (2016) includes a monograph for tablets, fine granules, and raw material[10].

Although there are more sophisticated analytical methods for quality control, such as Inductively Coupled Plasma Atomic Emission Spectrometry (ICP-AES), Atomic Absorption Spectroscopy (AAS) and Inductively Coupled Plasma Atomic Emission Spectrometry (ICP-OES), volumetric methods remain viable alternatives[11,12]. Regardless of the analytical method used, prior chemical treatments are necessary to convert the crude and complex sample into a homogeneous solution with free ions, such as acid digestion, which promotes the complete decomposition of excipients or other added constituents, such as cholecalciferol. In this way, these preliminary treatments ensure that titrimetric methods present reliable results that are comparable to those obtained by more advanced analytical techniques, since they go through the same procedure to eliminate the matrix, reducing potential deviations in the analytical results[12,13]. In this context, titrimetric methods stand out as safe and economical alternatives to more modern techniques.

However, the literature on determining calcium carbonate content does not mention aspects related to the excipients in commercial formulations, nor does it evaluate the technique in vitamin D-enriched formulations. Additionally, any developed analytical method must be validated to ensure the procedure's suitability, thus ensuring excellent laboratory quality control[14]. The typical parameters considered for validating a dosage assay methodology are linearity, selectivity, precision, accuracy, robustness, and working range[8].

Therefore, the aim of this study was to validate the methodology for quantifying calcium carbonate in capsules for four different formulations, including those enriched with vitamin D, by complexometric titration using EDTA. For this purpose, the normative requirements of the Agência Nacional de Vigilância Sanitária (ANVISA), through RDC 166/17, and the procedures adopted by the Brazilian Pharmacopoeia in its 6th edition (2019) were followed, thus contributing validating data for dosing calcium in capsules.

MATERIAL AND METHODS

Materials

For the analytical tests, disodium edetate dihydrate EDTA (Dinâmica®), hydroxynaphthol blue (Dinâmica®), and calcium carbonate 99.8% (Êxodo®) were used as reagents. To validate the method, four different presentations of capsules containing calcium carbonate were used, as shown in **Table 1**.

Table 1: Description of the composition of the samples used to validate the analytical method for measuring calcium carbonate ($CaCO_3$) in capsules.

Sample	Composition
Formulation 1	500 mg of $CaCO_3$, 150 mg of corn starch and 1.5 mg of colloidal silicon dioxide
Formulation 2	500 mg $CaCO_3$, 150 mg corn starch, 1.5 mg colloidal silicon dioxide and vitamin D 200 IU
Formulation 3	500 mg $CaCO_3$, 150 mg corn starch, 1.5 mg colloidal silicon dioxide and vitamin D 400 IU
Formulation 4	600 mg $CaCO_3$, 150 mg corn starch, 1.5 mg colloidal silicon dioxide and vitamin D 400 IU

Methods

Determination of average weight with measurement uncertainty

To analyze the average weight of the content in the four pharmaceutical formulations, twenty capsules were individually weighed. The content of the empty capsules was then subtracted, and the variation limits were evaluated according to the official compendium[8].

The expanded measurement uncertainty (U_e) was calculated based on the obtained results. For this purpose, the uncertainties in the weights of the capsule contents inherent to the uncertainties generated by the balance (U_c = 0.38) and the standard errors due to the variability of the samples (U_v) were calculated through the quotient of the standard deviation of the capsule contents by the square root of the sample number. Equation 4 mathematically describes the calculation of expanded uncertainty, where the coverage factor K_a equals 2.09 for n = 20. Finally, the average weights with expanded uncertainty were calculated for each analyzed sample, as per Equation 5.

$$\text{Ue} = (\sqrt{Uc^2 + Uv^2}) \quad (4)$$

$$\text{Mean} \pm \text{Ue} \quad (5)$$

Preparation of the sample solution to determine the $CaCO_3$ content

After determining the average weight, a quantity of powder equivalent to 200 mg of $CaCO_3$ in different formulations was weighed according to Table 1. The weighed sample was transferred to a 250 mL erlenmeyer flask and 3 mL of 3 mol L^{-1} HCl was added to dissociate the $CaCO_3$. The system was then diluted with deionized water to a volume of 100 mL. After dilution, 15 mL of 1.0 mol L^{-1} NaOH and 10 mg of the blue indicator hydroxynaphthol were added (after this addition, the solution turned pink). The solution obtained was titrated with EDTA 0.05 mol L^{-1} until it turned blue. After the titrations, the $CaCO_3$ content was determined using equations 6 and 7.

$$Real\ mass\ (mg) = \frac{\text{Volume spent (mL)} * \text{Correction factor} * 5.004\ \text{mg mL}{-1} * \text{Average weight (mg)}}{\text{Sample mass (mg)}} \quad (6)$$

$$\text{Content (\%)} = \frac{\text{Real concentration}}{\text{Theoretical concentration}} \text{ x } 100 \quad (7)$$

Uniformity of dosage units

For the test, the first ten individual masses were weighed to determine the content of each of the 4 formulations. Afterward, the means and standard deviation of the obtained levels were calculated. Finally, the test described in the Brazilian Pharmacopoeia (6th, page 76) was applied, in which the result could not exceed the acceptance value (AV). Equation 8 describes the mathematical analysis, with (X) being the average of individual contents, (M) the reference value for the limits specified in the monograph, (k) the acceptability constant and (S) the sample standard deviation. Under the conditions of this work k = 2.4 (n = 10) and M ≤ 101.5% (with X > 101.5%). The AV value must be less than 15 for the samples to be considered uniform according to the Pharmacopoeia[8].

$$AV = (M - X) + kS \quad (8)$$

Validation of the analytical method

For the analysis of calcium carbonate in capsules with or without vitamin D, the pharmacopeial method for the analysis of raw calcium carbonate material was used. As this is a method already established in the literature, the robustness of this analysis was assessed using the Youden method to evaluate the interference parameters in the method, mainly related to the excipients and vitamin D present in the formulations[15].

Robustness

To assess robustness, the Youden method was used on samples containing calcium carbonate in 500 mg and 600 mg capsules, as well as 400 IU of vitamin D. This method involves applying a factorial design to evaluate the effect of the combination of factors under normal and altered conditions on the analytical response[8]. Table 2 describe the factors and combinations carried out. All experiments were performed in triplicate and results were calculated as averages.

Table 2: Parameters an factorial combination of parameters for evaluation using Youden method.

Conditions for robustness factors			Factorial combination							
Parameter / Conditions	Normal	Altered	1	2	3	4	5	6	7	8
A/a - Sample	200 mg	220 mg	A	A	A	A	a	a	a	a
B/b - Volume of NaOH	15 mL	14.5 mL	B	B	b	b	B	B	b	b
C/c - Theoretical equivalence point	38 mL	39 mL	C	c	C	c	C	c	C	c
D/d - Volume of water	100 mL	95 mL	D	D	d	d	d	d	D	D
E/e - Volume of HCl	3.0 mL	2.7 mL	E	e	E	e	e	E	e	E
F/f - Color charge	Light pink	Dark violet	F	f	f	F	F	f	f	F
Result			***s***	***t***	***u***	***v***	***w***	***x***	***y***	***z***

To determine the influence of the variations of each parameter on the final result, the means of the four assays corresponding to the capital letters (normal conditions) were compared to the means of the four other assays corresponding to lowercase letters (altered conditions) for each parameter, as described in Equation 9. The result is compared with that of Equation 10. The value found in equation 9 must be smaller than the value determined in equation 10 for the effect to be interpreted as not significant.

$$\text{Effect A/a} = \text{Normal parameters} - \text{Changed parameters} \quad (9)$$

$$\text{Reference value} = \text{SD}\sqrt{2} \quad (10)$$

Where,

Normal parameters: results of the samples indicated with capital letters for each parameter of the factorial combination;

Changed parameters: results of the samples indicated in lowercase letters for each parameter of the factorial combination;

SD: standard deviation of the results obtained (s, t, u, v, w, x, y, z).

Selectivity

In the selectivity evaluation, formulations similar to those presented in **Table 1** were prepared, distinguishing only $CaCO_3$, which in this case was used analytical standard. Furthermore, a fifth sample containing only analytical-grade $CaCO_3$ was prepared for comparison purposes. Quantifications were carried out following the methodology reported

above for $CaCO_3$ content determination. The experiment was performed in triplicate, using independent weighing for each sample analyzed.

After the titrations, the results were calculated based on the volumes of EDTA 0.05 mol L^{-1} used and the calcium carbonate masses used in the test (standard and samples). The calcium carbonate content was obtained by the ratio between the experimentally determined mass and the mass of each weighed sample, according to Equation 11. Finally, one-way analysis of variance (one-way ANOVA) was used as a statistical test for verifying the selectivity of the method, taking into account a 95% confidence interval and a p-value < 0.05 as significant.

$$\% = \frac{\text{Volume spent (mL)} * \text{Correction factor} * 5{,}004 \text{ mg mL}^{-1}}{\text{Sample mass (mg)}} * 100 \quad (11)$$

Linearity

The analytical curve was constructed using analytical-grade calcium carbonate with the following masses: 100, 150, 250, 350, 450 and 500 mg, in triplicate and on three different days. The data obtained were subjected to the linear regression model to obtain the angular coefficient, linear coefficient, and coefficient of determination (R^2). Residue dispersion was assessed using the Breusch-Pagan test, and data normality using the Shapiro-Wilk test.

Precision

Precision was determined by an analyst under the same analytical conditions, evaluating samples on the same day and different days[15]. Precision was evaluated in four different formulations using the sample solution, being analyzed on three different days and preparing 6 samples individually on each day with 100% of the concentration proposed by the method. The precision of the method was determined by analyzing the relative standard deviation (RSD) obtained for intra-day and inter-day assays.

Accuracy

In assessing accuracy, the recovery method was continued, through the addition of calcium carbonate to samples of different formulations. Determinations were carried out in triplicate. In this test, a mass of powder equivalent to 200 mg of $CaCO_3$ was used in the analyzed capsules. Standard addition was performed at three levels, considering a lower (50 mg), medium

(150 mg) and high (250 mg) mass. After this, titration of the different systems continued, as shown in Table 3. Finally, the recovery percentage was calculated using Equation 12. The result was expressed as mean ± RSD.

$$\text{Recovery (\%)} = \frac{\text{Added mass}}{\text{Experimentally determined mass}} * 100 \qquad (12)$$

Table 3: Amount of $CaCO_3$ added and total mass of the samples.

Level addition	Standard (mg)	$CaCO_3$ in capsules*	Final quantity (mg)
Sample (capsules)	*****	200	200
Low	50	200	250
Medium	150	200	350
High	250	200	450
Standard	200	*****	200

(*) - equivalent to 200 mg.

Statistical analysis

Data analysis was carried out using GraphPad Prism 8.0 software. Data normality was checked using the Shapiro-Wilk test. Statistical analysis was carried out using one-way ANOVA, followed by Tukey's multiple comparison test for data with normal distribution. The significance level adopted was 5% ($p < 0.05$), with a 95% confidence interval. Other information is described throughout the sections.

RESULTS AND DISCUSSION

Average weight determination

In the Brazilian Pharmacopoeia, 6th edition, Volume II - Monographs, which deals with Pharmaceutical Inputs and Specialties, it is mentioned that 150 mg of the hydroxynaphthol blue indicator is used for the volumetric assay of calcium carbonate[16]. However, this study found that this quantity is excessive, making it impossible to visually identify the endpoint, as it generates a dark violet solution. This visual perception of the color change occurs after the equivalence point, leading to inaccuracies and analytical errors. Therefore, a quantity of 10 mg of the indicator was established, resulting in a light pink solution that allows clear visual identification of the endpoint.

After adjusting the methodology, the determination of the average weights with their respective uncertainties were carried out during validation for the four the values were 682.18 mg, 670.93 mg, 679.47 mg and 671.84 mg for formulations 1, 2, 3, and 4, respectively. All formulations evaluated presented variation limits of ± 5%, all being within the pharmacopoeial specification. Therefore, with no capsule is out of range.

Robustness

The complexometric titrimetric method using EDTA for the determination of calcium carbonate is already well described in different Pharmacopeias, including the Brazilian one for raw material analysis. The validation of the method for determining calcium carbonate in capsules aimed to show the application and safety in this API (Active Pharmaceutical Ingredient) analysis by using a classic analysis method. For this, the pharmacopeial method was applied, first evaluating its robustness and also its interference in routine analysis. The Youden method was used, which consists of applying a factorial design to study the consequences of changes in the parameters of the analytical method based on the response obtained (Brazil, 2019; Brazil, 2020). To accomplish this, combinations are made between normal and altered conditions, and the effect of this change is evaluated by comparing it to the reference value. The results of comparing the A/a effect and the reference value are presented in Table 4 for formulations 1 and 2.

Table 4: Results obtained for robustness assessment using the Youden method.

Parameter	Effect A/a: Formulation 1	Effect A/a: Formulation 2
Sample	2.26	1.15
Volume of NaOH	1.85	-1.21
Theoretical equivalence point	-2.59	-1.03
Volume of water	-7.88	0.52
Volume of HCl	-3.29	0.19
Color charge	6.58	10.84
Reference value	2.46	2.20

When analyzing the results, it was observed that the amount of indicator used in the test influences the routine analysis, since the results obtained exceeded the reference values. As mentioned above and confirmed by the Youden method, it is clear that the amount of indicator in the pharmacopeial method significantly affects routine analysis and can lead to analytical

errors. By applying the Youden test to assess robustness, we demonstrated the interference of the indicator in the analysis and, consequently, in other validation parameters[17].

The interference of color (equivalence end point) is directly related to the analyst's visualization of the titration end point. It can be seen that Formulation 2 (effect of 10.84 and reference value 2.20) has a greater interference in the visualization of the titration end point than Formulation 1. For the titrimetric method, the determination of the end point is critical in the analysis and can lead to undesirable analytical results due to errors in the amount of indicator used in the technique.

For other parameters, the result obtained was lower than the reference value, demonstrating that variations applied in the analytical method are not significant from a statistical point of view, which denotes the ability of the analytical method to resist deliberate modifications, without compromising accuracy and precision[18].

Selectivity

The selectivity of quantitative methods must be demonstrated by proving that the analytical response is exclusively focused on the analyte of interest, without interference from the diluent, matrix or degradation products[19]. From its analysis, it appears that one-way ANOVA presented an F value (0.54) lower than the tabulated one (3.478), indicating that the results of the averages of the five samples (standard and the four formulations) are statistically similar. Furthermore, a p-value > 0.05 was obtained (0.71), indicating that the observed variations are not statistically significant (Table 5). Therefore, it is estimated that the method developed proved to be selective.

Table 5: Evaluation of the selectivity of calcium carbonate capsule samples.

Formulation	Sample 1 (%)	Sample 2 (%)	Sample 3 (%)	Mean ± SD (%)
Standard	99.67	99.28	99.81	99.59 ± 0.27
Formulation 1	99.54	99.56	99.86	99.65 ± 0.18
Formulation 2	99.64	99.68	99.16	99.49 ± 0.29
Formulation 3	99.72	99.04	99.46	99.47 ± 0.34
Formulation 4	98.83	99.65	99.41	99.29 ± 0.42
one-way ANOVA	$\alpha = 0.05$	$F_{tabulated} = 3.478$	$F_{calculated} = 0.54$	$p = 0.71$

SD = Standard deviation.

Linearity

Linearity must be assessed by determining the analyte covering the established working range and in five different concentrations in at least triplicates[15]. With data from triplicates in six concentrations and three different days, it was possible to construct the standard curve (a), as well as the scatter plot of residues (b) for $CaCO_3$ (Figure 1). After applying the linear regression model using the ordinary least squares method, the following equation was obtained: y = 0.1965x - 0.0910. Furthermore, it was observed that the coefficient of determination (R^2) was above that recommended (0.99) by RDC 166/17 with a value of 0.999[15]. In parallel, the dispersion of residues was studied using the Breush-Pagan test and the distribution of data using the Shapiro-Wilk test. It was found out that the data obtained presented a parametric distribution (p = 0.42) and homoscedastic behavior (p = 0.36), indicating that the variance of data is constant and is concentrated around the average value. Furthermore, the choice of concentration levels must be aligned with the desired working range to ensure adequate precision and accuracy, varying according to the purpose of the method and applicable guidelines. In general, for testing a substance, values between 80% and 120% of the expected value are acceptable, while content uniformity can range from 70% to 130% of the expected value[20]. As can be seen in Table 6, the precision and accuracy values are significantly above the standards accepted in the literature, which demonstrates the suitability of the working range chosen to achieve precise and accurate responses. In addition, the limit of quantification (LOQ) was calculated based on the standard deviation estimated by the curve (SD = 0.947) and the angular coefficient, resulting in a value of 48.31 mg. However, values lower than the lowest level of the curve (100 mg) are not considered, as established by the regulations, and this is the limit of quantification adopted[15].

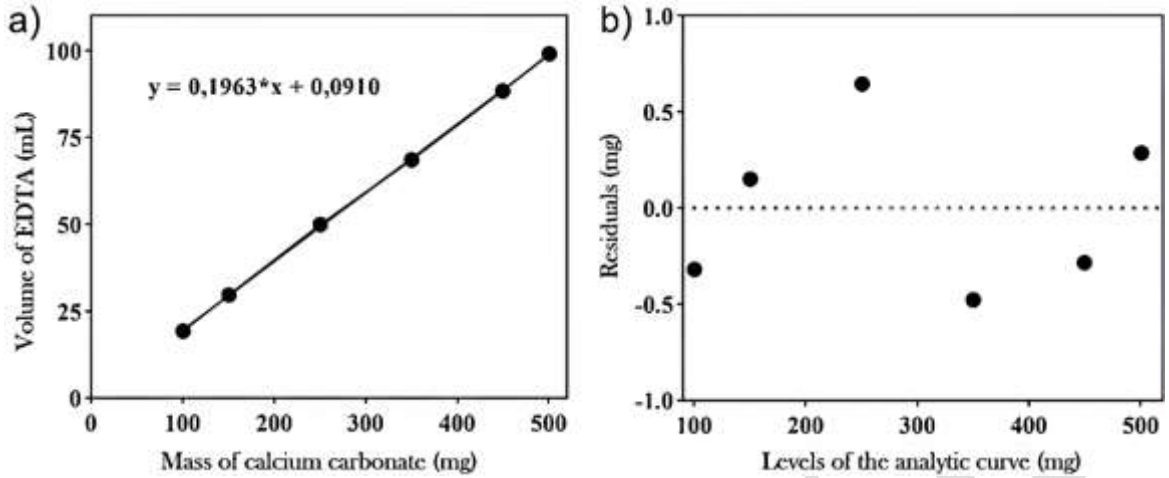

Figure 1. Standard curve (a) and residual scatter plot (b) obtained using the linearity parameter.

Precision and Accuracy

The results of the averages obtained over the three days in the evaluation of this parameter are presented in Table 6. In all analyses, the Relative Standard Deviation (RSD) values between 0.13 and 0.87% were obtained for all $CaCO_3$ samples in intra-day and inter-day assays. In general, it is assumed that to be accurate, a validated analytical method must present RSD results lower than 2.0% for the precision parameter in the concentration range analyzed [19]. Therefore, these results indicate that the developed method proved to be precise.

Regarding accuracy, it can be verified by independently preparing samples at three concentration levels (low, medium and high) with three replicates at each level[16]. The standard addition method was used to evaluate accuracy and results of the tests are shown in Table 6. Based on their analysis, it can be seen that the standard recovery averages ranged from 98.02 to 101.48%. Additionally, RSD values remained between 0.44 and 1.69% for all samples analyzed. For recovery accuracy tests, average recovery values must be between 98 and 102%, within the ranges analyzed[19,20]. Therefore, the developed method demonstrated good accuracy.

Table 6: Assessment of the Precision and Accuracy of the Titrimetric Method for Measuring $CaCO_3$ in Capsules: Intra-Day and Inter-Day Analyses and Results Using the Standard Addition Method.

Parameter	Condition	Formulation 1	Formulation 2	Formulation 3	Formulation 4
Precision[A]	Day 1	108.42 ± 0.42	104.05 ± 0.63	101.04 ± 0.66	104.35 ± 0.45
	Day 2	109.48 ± 0.16	104.57 ± 0.33	101.82 ± 0.33	104.69 ± 0.47
	Day 3	108.17 ± 0.46	104.61 ± 0.35	101.83 ± 0.87	104.48 ± 0.42
	Inter-day	108.85 ± 0.85	104.22 ± 0.23	101.57 ± 0.37	104.50 ± 0.13
Accuracy [B]	Low quantity	100.84	98.49	101.30	98.32
	Medium quantity	99.43	101.45	101.48	98.02
	High quantity	101.22	99.68	98.45	99.06
	Mean ± RSD	100.50 ± 0.94	99.87 ± 1.49	100.41 ± 1.69	98.47 ± 0.54

The results are presented as the mean percentage ± relative standard deviation (Mean ± RSD) of the content; ([A]) - Determining the content of commercial formulations with 6 repetitions (intra-day) and on 3 different days (inter-day); ([B]) - Commercial formulations enriched with 3 levels of analytical standard $CaCO_3$.

In Brazil, calcium carbonate is classified as a low-risk drug, according to RDC 576 of November 11, 2021. These are medicines with simplified registration, generally marketed by national companies that have a certificate of good manufacturing practices. In addition to these companies, compounding pharmacies also sell the product in capsule form[21]. Although there are more sophisticated methods recommended by official compendia to assess the calcium content of these products, there are few studies in the literature that determine the calcium content of food supplements. These methods are particularly recommended for situations in which formulations contain multiminerals, since titrimetric methods can have low selectivity. An example of this is the use of Graphite Furnace Atomic Absorption Spectrometry (GFAAS), applied by Soltyk et al. for calcium analysis in multivitamin/mineral formulations containing from 162 to 250 mg of calcium per tablet[12,22]. Titration, on the other hand, is a simple, easy-to-apply and low-cost technique. When proper precautions are taken with regard to possible interferents and considering the possibility of its use, it offers significant analytical safety, as demonstrated by the analysis of the set of results presented in this work.

Application of the developed analytical method to determine the $CaCO_3$ content in capsules

After validating the analytical method, it continued with its application in any routine analysis. Table 7 presents the results obtained in the different analyses. When determining the average weight of the capsules, there was a variation of 663.74 to 687.98 mg in the contents of

the samples under study. Furthermore, all samples presented a $CaCO_3$ content within the limit recommended by the pharmacopoeia (90-110%) and acceptance value below 15[16]. Thus, all $CaCO_3$ formulations with or without vitamin D presented average weight results, content and uniformity of dosage unit in accordance with pharmacopeial specifications.

Table 7: Average weight results with expanded uncertainty, dose, content in relation to the declared content and unit dose uniformity of $CaCO_3$ in capsules.

Formulation	Average weight (mg)	Dose found (mg)	Content (%)	Uniformity dosage units (AV)
1	687.98	542.34	108.47	12.93
2	675.93	522.94	104.59	8.90
3	671.45	508.27	101.24	5.43
4	663.74	628.89	101.58	5.81

Results presented as means of triplicates; (AV) - Acceptance value.

CONCLUSION

The developed analytical method proved to be selective, linear, precise, accurate and robust for the analysis of different formulations of calcium carbonate with or without vitamin D in capsules, following Pharmacopeial specifications. When analyzing the robustness of the method, the interference of the indicator in the final point of analysis was verified when the adequate quantity was not verified. Thus, checking the quantity of the indicator guarantees good precision and analytical accuracy. Therefore, it is estimated that the complexometric method developed has potential for quality control analyzes of pharmaceutical formulations or supplements containing $CaCO_3$ and It is also a classic method as an environmentally friendly alternative.

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ANALYTICAL VALIDATION OF THE DETERMINATION OF THE CONTENT OF CALCIUM CARBONATE IN CAPSULES BY COMPLEXOMETRIC TRITRATION

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Author contributions	
Dênis Gomes de Melo:	Data curation, Formal analysis, Investigation, Visualization, Writing – original draft.
Matheus da Silva Campelo:	Conceptualization, Visualization, Writing – review & editing.
Cristiani Lopes Capistrano Gonçalves de Oliveira:	Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing.
Maria Elenir Nobre Pinho Ribeiro:	Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing.
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Corresponding author:	Cristiani Lopes Capistrano Gonçalves de Oliveira Federal University of Ceará – UFC Department of Pharmacy Rua Pastor Samuel Munguba, 1210, Rodolfo Teófilo Zip code: 60430-372 Fortaleza, Ceará, Brazil
Editor-in-chief:	Adriane Cristina Bernat Kolankiewicz. PhD
Editor:	Christiane de Fátima Colet. PhD