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# Dissolution Profile of Calcium Supplements in Brazil: A Critical Analysis and Formulation Proposal

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## ABSTRACT

Low calcium intake is common worldwide and may lead to osteoporosis. Therefore, calcium supplementation is a vital resource to prevent fractures in patients with osteoporosis. The present study aims to assess whether the dissolution profiles of calcium tablets available in the Brazilian pharmaceutical market are equivalent and interchangeable. Seven commercial samples from the local pharmaceutical market and an experimental formulation containing calcium carbonate from seaweed *Lithothamnium calcareum* were evaluated. In addition to the dissolution test, the tablets were characterized according to average weight, hardness, disintegration time, and calcium content. Moreover, we determined the polymorphic forms of calcium present in the tablets by employing x-ray diffraction. We related the data of these quality attributes by applying principal component analysis (PCA). The results revealed that the formulation containing calcium carbonate from the seaweed *L. calcareum* outperformed the other products from the market, with a complete dissolution within 10 min. Statistically significant differences in dissolution efficiency were noted. The disintegration times for all samples varied greatly from 12 s to 14 min. Polymorphic forms were identified in two samples, and the calcium content of the commercial samples was out of pharmacopeial specification. Thus, the products cannot be considered equivalent. It is recommended to evaluate the manufacturing processes for these supplements.

**KEYWORDS:** dissolution profile, calcium carbonate, calcium citrate, *Lithothamnium calcareum*, osteoporosis

## INTRODUCTION

Intake of inadequate milk or milk derivates may lead to calcium deficiency, which may develop into osteoporosis, a medical condition in which the bones lose density and quality, becoming more prone to fractures. It affects one-third of women and one-fifth of men over the age of 50 worldwide (*1*). In Brazil, this number is about 10 million, causing pain and making daily life more challenging. After a hip fracture, 20–24% of patients with osteoporosis die within a year, and 60% of patients require assistance 1 year later; this illustrates the potential severity of osteoporosis. Estimates of emotional suffering and economic losses are around $200 million in Brazil. A healthy lifestyle should be pursued for prevention, including adequate calcium intake (*2*, *3*).

The average calcium intake in the diet is inadequate worldwide. In South America, the population consumes on average 400–600 mg/day, despite the recommended dose of 1000 mg/day for an adult (19–50 years old) (*1*, *4*).

Therapeutic options to combat osteoporosis have increased, including dietary calcium supplements in the pharmaceutical form of coated or chewable tablets (*5*, *6*). However, calcium in food supplementation can come from several sources, such as biogenic calcium carbonate ($CaCO_3$), such as *Lithothamnium calcareum* seaweed, $CaCO_3$ from oysters, and the mineral $CaCO_3$, which is the most traditional. In addition, $CaCO_3$ contains higher elemental calcium ($Ca^{++}$) content (40%) compared to other calcium salts (*7*, *8*).

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A daily calcium intake (700–1200 mg/day) with 800 IU or more of vitamin D is recommended to prevent fracture in adults over 50 years old. This combination is also important for patients at high risk for fractures and those who use medication to treat osteoporosis, such as bisphosphonates (*9*). Despite some controversy, there is a consensus that the calcium-vitamin D association is beneficial for patients with low calcium and/or osteoporosis (*10*).

Calcium dissolution from formulations containing calcium can be challenging due to its absorption by the body, regardless of dosage. This question was addressed by Brennan et al., who evaluated 27 commercial samples containing calcium in the USA and found that 67% of these did not present adequate dissolution (*11*). This is the only study addressing the dissolution profile of products containing calcium.

The dissolution of calcium carbonate formulations and its different salts can be affected by several factors, such as those related to quality attributes (hardness, disintegration, content, dissolution efficiency, among others) (*12–15*). A useful way to identify and relate characteristics, such as the quality attributes of pharmaceuticals formulations, is to apply principal component analysis (PCA). In addition to being an exploratory method, the PCA technique is capable of separating important information from the collected data. PCA can objectively detect several variables in a given set of data and group individuals according to their variation (*16*). A comparison of variance (ANOVA) was also performed with the dissolution efficiency (DE) data, and the formulations were grouped by Tukey's test to confirm significant differences in the calcium release of the analyzed samples.

The objective of the present study is to assess and evaluate the dissolution profile of calcium tablets available in the Brazilian pharmaceutical market and compare with a calcium carbonate formulation from the seaweed *L. calcareum*.

## METHODS

### Samples

Seven samples of calcium tablets from different manufacturers were acquired from pharmacies in the city of São Paulo, Brazil. The samples were identified by alphabetical letter, composition, calcium per tablet, and expiration date, respectively, as shown below:

- A - oyster calcium carbonate, 500 mg, Oct 2017
- B - calcium carbonate, 600 mg, Dec 2017
- C - oyster calcium carbonate, 500 mg, Feb 2018
- D - calcium citrate malate, 500 mg, Dec 2018
- E - calcium carbonate, 600 mg, Dec 2018
- F - calcium citrate, 600 mg, Feb 2019
- G - calcium citrate malate, 250 mg, Aug 2017

All products were evaluated prior to the expiration date.

In addition, an experimental calcium carbonate formulation (500 mg of elemental calcium) from the seaweed *L. calcareum* was produced. The *L. calcareum* used was previously characterized as described in da Silva et al. (*17*). The process used to prepare this formulation was wet granulation, with conditions established in a Mixer Torque Rheometer (*18*).

### Reagents

The analytical grade reagents used were hydrochloric acid (LabSynth, São Paulo, Brazil), sodium hydroxide (LabSynth), and edetate disodium (Merck, Darmstadt, Germany). Polyethylene cannula filters with 45-µ porous ultrahigh molecular weight (Quality Lab Accessories, PA, USA) were used to filter the aliquots during the dissolution tests. Other reagents included ultrapurified water (Merck Millipore, Darmstadt, Germany) and hydroxynaphthol blue (Dinâmica Química, São Paulo, Brazil).

### Physical Characterization of Tablets

The tablets were visually inspected (by the naked eye), and their external characteristics such as color, odor, tablet shape, surface aspects, whether coated or uncoated, were described. The samples were characterized according to the *Brazilian Pharmacopoeia* for tablet pharmaceutical forms, including average weight, hardness test, thickness, diameter, and disintegration time (*19*).

### X-Ray Diffraction

Powder x-ray diffraction analyses were conducted in a Panalytical Empyrean diffractometer (Malvern Instruments, Malvern, UK). Previously, the tablets were crushed in a mortar with a pestle until a homogeneous powder formed. A chrome-steel planetary spray container (dry) was selected. The instrumental parameters employed were Cu radiation obtained with a voltage of 45 kV and a current of 40 mA. Angular range analyzed from 2–65° (2θ) in the angular step of 0.02° (2θ), and time per step was 150 s. Data were collected in reflection mode in Bragg-Brentano geometry.

To identify polymorphs, the Cambridge Structural Database (CSD) and Inorganic Crystal Structure Database

(ICSD) were used to access structural models (i.e., Crystallographic Information Framework [CIF]). Rietveld refinement was used to confirm the polymorphic phase and quantify the present phases (*20*). The TOPAS-Academic V7 program was employed, in which network parameters of the unit cells, crystallite size, and adjusted background were refined using the Chebyshev polynomial function with eight terms (*21*). The structures used during refinement can be found in the mentioned databases with the ICSD codes 40109 (magnesian calcite), 252901 (aragonite), 150 (calcite), 21017 (talcum), and 248960 (brucite), and CSD code LACTOS01 (∝-lactose).

### Calcium Content

Calcium quantification in the tablets was performed as recommended by the *United States Pharmacopeia* (*22*). For the measurement, a digital burette (Bürette II, Gerbershausen, Germany) and quantitative filter of 18.50 ± 0.15 cm (Framex, Blumenau, Brazil) with average filtration speed of 140 s were used. The reagents were prepared as described in the *USP* method.

The quantification of dissolved calcium was performed using Flame Atomic Absorption Spectrometry (Varian SpectrAA 50B, CA, USA). The instrumental parameters applied were acetylene air pressure at 1.5 bar, compressed air pressure at 3 bar, current intensity (40 mA) of the cathode lamp (Photron Hollow-HAG0054, Victoria, Australia), manual burner height adjustments, slit opening of 1.0, and wavelength of 422 nm. For the calculation of calcium quantification, the linearity result was considered with the coefficient of determination (*R*) of 0.998. The solution was prepared at a concentration of 1000 µg/mL (in triplicate) and subsequently diluted to 25, 50, 75, 100, 150, and 200 µg/mL. A 99% content standard (Dinâmica Química) was used for this procedure.

### Dissolution Tests

The dissolution tests were conducted using USP apparatus 2 (paddle) and 708-DS Dissolution Apparatus equipment (Agilent Technologies Inc., Santa Clara, CA, USA) for 60 minutes. The dissolution medium was 750 mL of hydrochloric acid 0.01 N at 37 ± 0.5 °C and 75 rpm. Samples (5 mL aliquots, in triplicate) were collected at intervals of 5, 10, 15, 20, 30, 45, and 60 min, without medium replacement, and the aliquots were filtered through 45-µ porous cannula filters. Subsequently, calcium was quantified with dilutions from 4 to 30 times in an atomic absorption spectrometer.

The dissolution profiles were derived from the results obtained using Microsoft Excel software. DE was calculated with the aid of the Microsoft Excel DDSolver add-in (Simulations Plus), as described by Zhang and collaborators (*23*). The DE parameter was calculated using the following equation (*24*): $DE\% = \int 0ty \times dty_{100} \times t \times 100\%$, where **y** is the percentage of drug (*d*) dissolved at time *t*.

### Statistical Analysis

Cal Initially, PCA was performed using the data of hardness, disintegration, content, and the percentage of dissolved calcium at 15 ($Q\%_{15min}$) and 45 min ($Q\%_{45min}$), in addition to DE. Statistica (version 13.5.0.17, TIBCO Software Inc., Tulsa, OK, USA) was used for the analyses. After standardizing the data, new variables were created, and those with higher eigenvalues (CPA1 and CPA2) were selected for the construction of two-dimensional graphs.

For comparative effect, a one-way analysis of variance (ANOVA) was performed with the DE data, and the formulations were grouped using the Tukey test. Normality of the data was tested using the Anderson-Darling method, requiring the transformation of this method by applying the Johnson model. Action Stat (version 3.6.331.450 build 7 – 2019, Estatcamp, São Carlos, Brazil) was used for these analyses.

## RESULTS AND DISCUSSION

### Sample Characterization

The calcium tablets presented no apparent defects, with a varied shape, with or without coating. As shown in Table 1, the lowest weight corresponded to the tablet in the form of citrate (product F). The highest weight (product B) also presented the highest amount of calcium (600 mg). Interestingly, the weight of product G contained only 250 mg of calcium in citrate malate. Product G contains a high amount of excipients and the lowest calcium dose compared to other products studied here.

The weight, size, and consequently, the volume of the pill can represent considerable discomfort for the patient when ingested, impacting adherence to the treatment. Thus, immediate-release formulations are needed to disintegrate rapidly in the gastric fluid. The disintegration time varied from 12 s to 14 min, regardless of hardness values. Products C and D required a longer disintegration time, exceeding 9 min, while product G disintegrated in 14 min. In contrast, the formulation of *L. calcareum* $CaCO_3$ and products B and F stood out, disintegrating in under 1 min.

The calcium content of the tablets should be 90–115% of the label claim to comply with USP specifications (*22*).

*Table 1. Sample Characterization*

| Product | Weight, g (*n* = 20) | Hardness, Kgf (*n* = 10) | Thickness, cm (*n* = 20) | Diameter, cm (*n* = 20) | Disintegration Time, min:sec (*n* = 6) | $Ca^{++}$ Content, mg (%) (*n* = 9) |
|---|---|---|---|---|---|---|
| *L. calcareum* $CaCO_3$* | 1.77 ± 0.30 | 8.00 ± 0.20 | 0.61 | 1.20 | 0:39 ± 0:01 | 529.42 (106.01) |
| A* | 1.69 ± 0.05 | 25.67 ± 0.93 | 0.48 | 1.94 | 6:24 ± 0:12 | 538.65 (107.73) |
| B** | 1.92 ± 0.01 | 6.50 ± 0.11 | 0.51 | 1.99 | 0:12 ± 0:01 | 602.06 (100.34) |
| C* | 1.58 ± 0.03 | 20.50 ± 0.17 | 0.51 | 1.73 | 9:13 ± 0:12 | 562.82 (112.56) |
| D* | 1.59 ± 0.03 | 18.70 ± 0.79 | 0.76 | 2.16 | 9:63 ± 0:32 | 434.39 (86.87) |
| E** | 1.78 ± 0.03 | 13.20 ± 1.47 | 0.61 | 1.94 | 1:68 ± 0:61 | 605.87 (100.97) |
| F** | 1.26 ± 0.01 | 14.57 ± 1.06 | 0.58 | 1.68 | 0:27± 0:02 | 578.21 (96.36) |
| G*** | 1.88 ± 0.02 | 8.87 ± 1.35 | 0.47 | 1.72 | 14:00 ± 0:35 | 255.48 (102.19) |

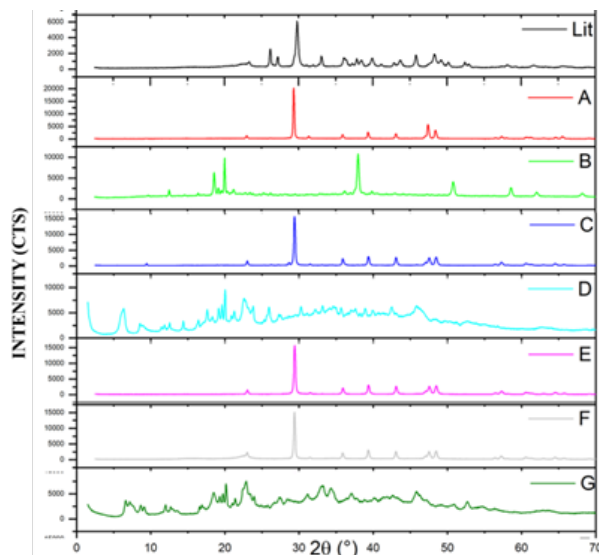
*Data are expressed as mean ± SD.*
**500 mg; **600 mg; ***250 mg*

Product D contained only 86.87% calcium. In these cases, the manufacturer should review their procedures to conform to the specifications.

### X-Ray Diffraction Analysis

Refinement of the crystalline structures and quantification of the crystalline phases was possible for all samples of *L. calcareum* $CaCO_3$, A, B, C, E, and F, because all were identified in the databases (Table 2). Samples D and G presented several phases with high peak overlap, which prevented their identification, but they contain a significant amount of amorphous phase. Both samples have broad peaks and undefined characteristics, such as the calcite peak or another polymorphic phase identified in the samples, which indicates the absence of crystallinity (*25*, *26*).

*Table 2. X-ray Diffraction Patterns, Calcium Type, and Distribution of Crystalline Phases*

| Comparison of XRD Patterns for Sample Standards | Product | Type of Calcium | Crystalline Phases and Mass Ratio (wt% ± SD) |
|---|---|---|---|
|  | *L. calcareum* $CaCO_3$ | Calcium carbonate | Aragonite (50.8 ± 6.0) and magnesian calcite (49.2 ± 6.0) |
| | A | Oyster calcium carbonate | Aragonite (1.83 ± 3.0) and calcite (98.20 ± 4.0) |
| | B | Calcium carbonate | Calcite (0.99 ± 2.0) and brucite (99.01 ± 2.0) |
| | C | Oyster calcium carbonate | Aragonite (2.82 ± 4.0) and calcite (96.82 ± 5.0) |
| | D* | Calcium citrate malate | Not determined |
| | E | Calcium carbonate | Aragonite (0.6 ± 3.0) and calcite (99.4 ± 3.0) |
| | F | Calcium citrate | Calcite (100%) |
| | G* | Calcium citrate malate | Not determined |



**Products D and G were not determined due to no crystalline phase found.*
*XRD: x-ray diffraction.*

The crystalline phases constituted by aragonite-calcite are typical of biogenic samples, i.e., samples from the ocean, which corresponds to that indicated in products A and C from oyster calcium carbonate and in the formulation of *L. calcareum* $CaCO_3$, which is from marine origin containing only calcium carbonate (*27*). However, the manufacturer of product E failed to indicate the marine origin of its product, because we could detect a small proportion of aragonite in the product. Interestingly, aragonite is the dominant phase in L. calcareum $CaCO_3$, representing an advantage, as this phase is metastable and much more soluble than magnesian calcite, which is thermodynamically stable (*28*). On the contrary, product F consists of 100% calcite, which is a disadvantage concerning calcium solubility, as can be seen from its behavior in the dissolution test.

**Dissolution Profiles**

Dissolution profiles were very different among the calcium tablets and *L. calcareum* $CaCO_3$ formulation (Fig. 1, Table 3). The formulation of L. calcareum CaCO3 stood out with a quick calcium release, dissolving entirely within 10 min, followed by product C, A, B, and E. In contrast, products D, F, and G presented slower dissolution, with D and F having a marked deficiency in calcium dissolution. For product D, the explanation can be linked to two aspects: the high disintegration time (9:63 ± 0:32) and low calcium content (86.87%). Product F, in contrast, exhibited a disintegration time of only 12 s; however, DE was only 68%, which is unfavorable. In this case, the tablet can break down very quickly, but its calcium content does not dissolve in the same proportion. This phenomenon can be attributed to the raw material characteristics, i.e., calcium citrate was included in the formulation (*12*, *13*).

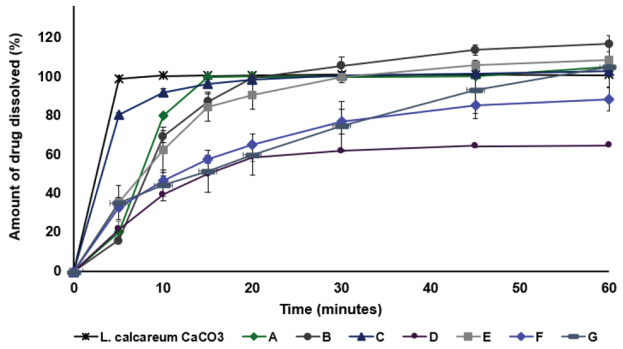



*Figure 1. Dissolution profiles of calcium and Lithothamnium calcareum $CaCO_3$ samples (n = 3).*

Product G presented an inadequate disintegration time (14 min), the highest of all samples studied here. The excipients used in the formulation development, especially the binder, likely influenced the tablet disintegration (*14*). The lack or insufficient amount of a disintegrant can also contribute to such inadequate performance (*15*).

It is important to highlight that the samples investigated contained different calcium salts, which influenced the dissolution profile. Cartensen et al. demonstrated that calcium salts do not have the same dissolution behavior; however, they concluded that the in vitro dissolution data for different calcium salts are similar to in vivo results (i.e., bioavailability) (*29*). Even though these data were for calcium salts and not for dosage, such findings corroborate the data presented here. Therefore, we can attribute the differences in dissolution profiles to different calcium salts.

As shown in Table 3, the tested products were not equivalent based on the average percentage of dissolved calcium. DE was greater than 90% in only three formulations. Therefore, the most similar formulations to $CaCO_3$ from *L. calcareum* were products B and C. In addition to having rapid calcium release, these products are different in their origin: B is calcium carbonate and C it is oyster calcium carbonate.

*Table 3. Dissolution of Calcium Within 60 Minutes*

| Product | Dissolved Calcium (%), mean ± SD | Dissolution Efficiency (%) |
|---|---|---|
| *L. calcareum* $CaCO_3$ | 101.05 ± 2.15 | 96.90 |
| A | 104.97 ± 3.16 | 88.36 |
| B | 116.98 ± 4.32 | 91.87 |
| C | 102.84 ± 2.42 | 93.86 |
| D | 64.73 ± 0.96 | 53.64 |
| E | 108.87 ± 0.16 | 87.42 |
| F | 88.56 ± 6.01 | 68.00 |
| G | 105.04 ± 10.77 | 70.44 |

**Statistical Analysis**

PCA results are shown in Table 4. In Figure 2, it is noticeable that the two new variables created from the distribution presented (PCA1 and PCA2) were able to retain 84.01% of the original information contained in the input factors (hardness, disintegration, content, $Q\%_{15min}$, $Q\%_{45min}$, and DE). Concerning PCA1, the samples approximated the results from the dissolution test (Fig. 1). The samples that had a slower release (F and D), as in the case of product G, were closer together. The type of salt used also influenced the grouping in PCA1. All samples on the left side contain calcium carbonate, and those on the right contain citrate

or citrate malate. The isolation of product D is most likely due to lower calcium content.

In the case of PCA2, hardness and disintegration showed a greater influence on the grouping of the samples. However, as shown in Table 4, the coating appears to influence disintegration time and hardness.

The Anderson-Darling test was performed to assess the normality of the DE data and analyze the ANOVA, obtaining a *P*-value of 0.0009. When considering a significance level of 0.05, the previous transformation of data was necessary. A new test was performed after applying the Johnson model, resulting in a higher *P*-value (0.536), thus attesting to normality. The *P*-value obtained with ANOVA ($p < 0.05$) confirmed statistically significant differences in calcium release from the samples analyzed. With the Tukey test, it was possible to perform the grouping and understand where this difference is located.

The results were similar to the PCA, the only difference being separation of *L. calcareum* $CaCO_3$ from the other samples. This was due to the responses adopted for each analysis (i.e., other data points were considered in the PCA, such as $Q\%_{15min}$).

According to the statistical analyses, the tested products cannot be considered equivalent or interchangeable due to products D, F, and G failing to meet USP specifications for calcium content (D and F) and dissolution of calcium (D, F, and G).

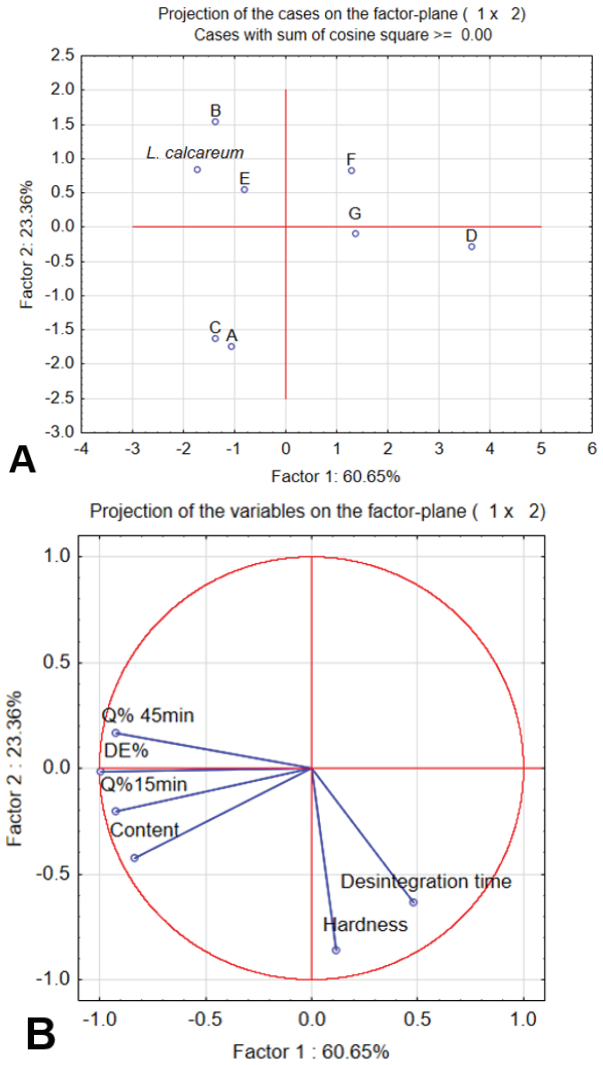



*Figure 2. Graphs of principal component analysis. (A) Distribution of samples for comparison. (B) 2D graph of principal components; both factors 1 and 2 correspond to 84.01% of the information contained in the original variables.*

*Table 4. Results for the Four Groups Suggested by PCA.*

| Product | Type of Salt | Dose (mg) | Coating | Hardness (Kgf) | Disintegration Time (s) | Content (%) | Cumulative Drug Release (%) | | DE% |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | 15 min | 45 min | |
| **Group 1** | | | | | | | | | |
| *L. calcareum* $CaCO_3$ | Carbonate | 500 | No | 8 | 39 | 106.01 | 100.94 | 101.26 | 96.90 |
| B | Carbonate | 600 | No | 6.5 | 12 | 100.34 | 87.23 | 113.78 | 91.87 |
| E | Carbonate | 600 | Yes | 13.2 | 128 | 100.97 | 84.63 | 106.17 | 87.42 |
| **Group 2** | | | | | | | | | |
| A | Carbonate | 500 | Yes | 25.87 | 384 | 107.73 | 100.06 | 100.49 | 88.36 |
| C | Carbonate | 500 | Yes | 20.5 | 553 | 112.56 | 96.15 | 101.56 | 93.86 |
| **Group 3** | | | | | | | | | |
| F | Citrate | 600 | No | 14.57 | 27 | 96.36 | 57.56 | 85.45 | 68.00 |
| G | Citrate | 250 | Yes | 8.87 | 840 | 102.19 | 51.40 | 93.30 | 70.44 |
| **Group 4** | | | | | | | | | |
| D | Citrate malate | 500 | Yes | 18.7 | 603 | 86.87 | 49.99 | 64.41 | 53.64 |

*PCA: principal component analysis; DE: dissolution efficiency.*

## CONCLUSION

The formulation of *L. calcareum* $CaCO_3$ exhibited a much higher dissolution rate, probably due to the presence of aragonite in high concentrations and low disintegration time. Statistical analysis of dissolution profiles revealed the existence of different groups, ranging from products with an outstanding profile to products with a marked deficiency in the release of calcium. Therefore, calcium supplements found in the Brazilian market are not equivalent. In some cases, manufacturers should review their formulations and manufacturing processes to improve relevant quality aspects.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## CONFLICT OF INTEREST

The authors disclosed no conflicts of interest related to this article.

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