IIAT Instituto Internacional de Análise Térmica

Available online at www.bjta.com.br
Braz. J. Therm. Anal. Vol. 2 No. 1 (2013) 17 - 22

Brazilian Journal of Thermal Analysis BJTA

Determination of calcium in tablets containing calcium citrate using thermogravimetry (TG)

S. P. M. C. Souza[1], E. G. Araújo[1], F. E. Morais[1], E. V. Santos[1], M. L. Silva[1], C. A. Martinez-Huitle[1], N. S. Fernandes[1*]

[1]*Institute of Chemistry, Federal University of Rio Grande do Norte, CP 1524, CEP 59.072-970, Natal-RN, Brazil.*

Received 23/04/2013; accepted 20/12/2013
Available online 27/12/2013

Abstract

The present study utilized thermogravimetry (TG) and optical emission spectroscopy with inductively coupled plasma (ICP/OES) to determine the amount of calcium in calcium citrate tablets, which are used for the treatment of osteoporosis. The samples were characterized using Fourier transform infrared spectroscopy (FTIR), termogravimetry/derivative thermogravimetry (TG/DTG), differential thermal analysis (DTA), differential scanning calorimetry (DSC) and X-ray diffraction (XRD). In the DTA and DSC curves obtained, both endo- and exothermic events were observed, which are indicative of dehydration and decomposition, respectively. The X-ray diffractograms showed that the samples present crystallinity. Additionally, peaks observed in the X-ray diffractograms indicate the presence of a calcium hydroxide residue due to the reaction between calcium oxide with moisture in the air. The calcium content obtained by TG from the tablet sample (17.77%) was similar to that obtained using ICP-OES (16.84%).

Keywords: Thermogravimetry, calcium citrate, thermal decomposition, drug, osteoporosis.

1. Introduction

Osteoporosis is defined as a reduction in bone mass accompanied by the deterioration of bone quality. These factors result in a reduction of bone strength and an increase the risk of fractures [1]. Two nutrients, calcium and vitamin D, are especially necessary for strong bones. Calcium is essential for the maintenance of bones, while vitamin D aids in the absorption of calcium [2].

Calcium citrate (Figure 1) is the calcium salt of citric acid. It is generally used as a food additive, but it can also be used as a dietary calcium supplement. Calcium citrate is a white powder and is odorless and soluble in cold water [3,4].

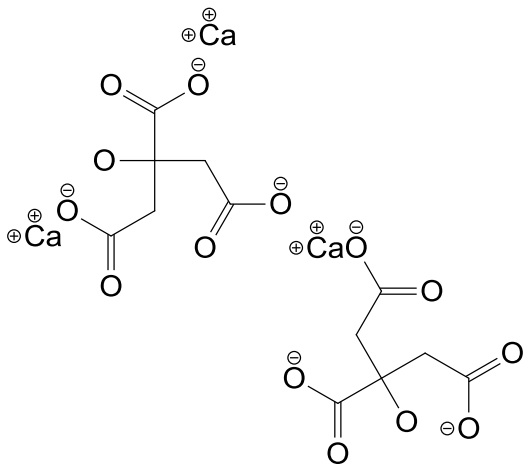

Figure 1 - Chemical structure of calcium citrate**.**

The determination of active ingredients using conventional procedures is difficult in some cases, as the active ingredients must be isolated. New techniques that provide information more quickly and more efficiently are needed to supplement or displace the analytical procedures that are currently used in drug analysis [5]. Thus, thermoanalytical techniques including TG, DTA and DSC have been characterized as important and effective tools in pharmaceutical analysis.

Studies on the thermal properties of zinc, bismuth and calcium citrate have been previously conducted [6]. The results indicated that the thermal decomposition of calcium citrate undergoes two dehydration steps with the elimination of 3 H_2O, which is followed by a formation stage of the anhydrous compound. Subsequently, the formation step of calcium carbonate is followed by the formation of CaO at approximately 800 ^{o}C. All intermediates of thermal decomposition were characterized using absorption spectroscopy in the infrared region, and the data obtained were confirmed using thermogravimetry.

The thermal decomposition of calcium citrate tetrahydrate in both synthetic air and under a nitrogen atmosphere has been previously studied [7]. The results indicated that the decomposition occurred in five steps: two dehydration steps associated with the formation of the anhydrous compound; the thermal decomposition of calcium citrate with the formation of calcium carbonate; and finally, the decomposition step with the formation of calcium oxide.

The calcium content in chicken and quail egg shells was determined using thermogravimetry [8]. The final residues obtained by thermogravimetry were characterized using Fourier transform infrared (FTIR) absorption spectra, which indicated that they were composed of calcium oxide.

*** Corresponding author:** Tel.: +55 84-3215-3828 Fax: +55 84-3211-9224
E-mail address: nedja@ufrnet.br (N. S. Fernandes)

doi: s/n

These results were confirmed using flame photometry and by a complexometric titration [8].

Therefore, in this study, an analysis of the thermal behavior of a medication used in the treatment of osteoporosis by thermogravimetry (TG), Differential Thermal Analysis (DTA) and Differential Scanning Calorimetry (DSC) was completed. Additionally, the obtained results from the medication analysis were compared to the calcium content determined using thermogravimetry and optical emission spectroscopy with inductively coupled plasma (ICP-OES).

2. Experimental

2.1. Materials

The calcium citrate and the pharmaceutical formulation were purchased from a drugstore. Subsequently, the samples were weighed, pulverized in an agate mortar, packed in glass jars and placed in a desiccator.

For the analysis of calcium using ICP-OES, approximately 500 mg of the tablet was weighed in a porcelain capsule and calcined up to 600 ^{o}C for 4 hours. Concentrated nitric acid was added until the sample was completely dissolved and was subsequently diluted to 100 mL using deionized water. Analyses were performed in triplicate. Table 1 lists the drug, excipients and theoretical percentage of calcium in the pharmaceutical formulation.

Table 1. Drug and excipients utilized in the tablet

Sample	Active Ingredient	Excipients	Average of the mass of tablets (mg) / Standard Deviation	Calcium average theoretical percentage (%)
Tablets	Calcium citrate (200mg of elemental calcium)	Magnesium sterate, microcrystalline cellulose, silicon dioxide and croscarmellose sodium	1119.3 ± 13.30	17.87

2.2. Methods

Fourier transform infrared spectroscopy (FTIR)

The infrared spectra were recorded on a Thermo Nicolet, Nexus 470 model FTIR spectrophotometer in the spectral range of 4000-400 cm^{-1} using KBr pellets.

Thermogravimetry-Differential Thermal Analysis (TG-DTA)

The TG-DTA curves were recorded on a model DTG 60 thermal analysis system from Shimadzu. The purge gas air operated at a flow rate of 50 mL min^{-1}. The samples, in triplicate, were heated from room temperature to 900 °C. A heating rate of 10 ºC min^{-1} was utilized, with samples weighing approximately 7 mg. Alumina crucibles were used for obtaining the TG and DTA curves.

Differential Scanning Calorimetry (DSC)

The DCS curves were recorded on a model DSC 50H thermal analysis system from Shimadzu. Purge gas was nitrogen gas at a flow rate of 50 mL min^{-1}. The samples were heated from room temperature to 500 °C. A heating rate of 10 ºC min^{-1} was utilized, with samples weighing approximately 2 mg and closed aluminum crucibles were used during sample analysis.

X-ray diffraction

The X-ray powder patterns were obtained using a diffractometer XDR model - 6000 Shimadzu with a proportion counter and pulse height discriminator. The Bragg-Brentano arrangement was adopted using Cu Kα radiation (λ=1.541 A), set at 38 kV and 20 mA, at a scanning speed of 2θ min^{-1} and using the powder method.

Inductively coupled plasma - optical emission spectroscopy (ICP – OES)

The calcium content in the samples was determined using inductively coupled plasma - optical emission spectroscopy (ICP – OES) on a 6300 model Shimadzu ICAP.

3. Results and Discussion

The FTIR spectra of the calcium citrate and the tablet samples are shown in Figure 2.

The spectrum of the calcium citrate sample (Figure 2a) presents a broad band at 3482 cm^{-1} that is assigned to the stretching of the OH group (ν OH), which results from hydration by water. These data are in agreement with the obtained TG curve (Figure 3). The spectrum also shows peaks at 1583 and 1441 cm^{-1} due the anti-symmetrical and symmetrical vibrations of the COO^{-} group, respectively.

The FTIR spectrum of the tablet sample (Figure 2b) presents at 3451 cm^{-1} a band assigned to the stretching of the OH group (ν OH), which results from hydration by water. These data are in agreement with the obtained TG curve (Figure 3). A band observed at 2929 cm^{-1} indicates the stretching of the C-H bond, which is probably due to the

croscarmellose sodium present as excipient in the pharmaceutical formulation [2]. The spectrum also shows peaks at 1583 and 1441 cm^{-1}, which are due the anti-symmetrical and symmetrical vibrations of the COO^- group, respectively.

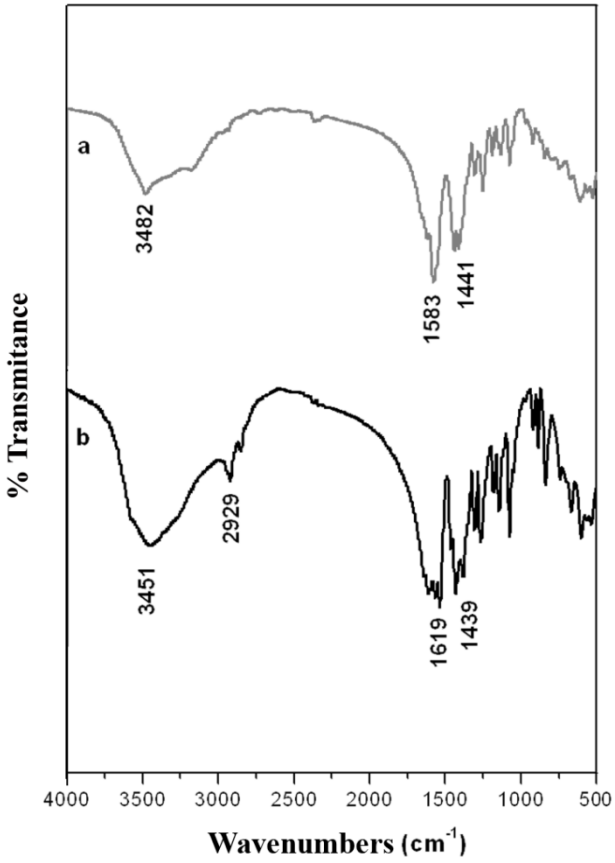

Figure 2. FTIR Spectra (a) calcium citrate (b) tablet sample**.**

The TG/DTG curves of the calcium citrate and the tablet samples are shown in Figures 3 and 4. The TG curve for the calcium citrate sample exhibited four mass losses. The first step occurred between 37.9 and 89.7 ^oC (T_p = 73.8 ^oC) and is attributed to the dehydration and elimination of 4 H_2O, which correspond to 8.2% of the mass loss and the formation of anhydrous calcium citrate. The second stage of mass loss occurs slowly between 89.7 and 463.3 ^oC (not shown in the DTG curve) (T_p = 452.9 ^oC), which represents 38.9% of the mass loss and is attributed to the thermal decomposition of calcium citrate associated with the formation of $CaCO_3$. The TG curve showed thermal stability between 463.3 and 619.6 ^oC. After this point, the thermal decomposition of the $CaCO_3$ occurs between 619.6 and 748.2 ^oC (T_p = 735.7 ^oC), which corresponds to 22.2% of the mass loss and results in the release of CO_2 and the formation of CaO as the final residue.

Similar results have been previously reported when the formation of solid calcium ferrites from the thermal decomposition of mixtures of calcium citrate tetrahydrate and iron oxalate hexahydrated was studied [9]. The calculation performed using the TG curves revealed that 20.2% of elemental calcium was present in the sample of calcium citrate.

The TG/DTG curve of the tablet sample showed five steps of mass losses. The first and second steps are attributed to the dehydration of the calcium citrate contained in the sample. The first occurred of the 35.4 at 100.9 ^oC (Tp = 88.3 ^oC), which represented 5.2% of the total mass loss. The second mass loss occurred between 100.9 and 151.7 ^oC (Tp = 137.2 ^oC), which corresponds to 5.9% of the total mass loss. The TG curve showed thermal stability between 151.5 and 273.1 ^oC. The third and fourth step occur consecutively in the range of 273.0 at 437.8 ^oC (Tp = 348.1 ^oC) with the 18.8% mass loss most likely assigned to the thermal decomposition of the calcium citrate and excipients such as microcrystalline cellulose, magnesium stearate and croscarmellose sodium. According to [10], the thermal decomposition of the croscarmellose sodium occurs between 180.0 and 600.0 ^oC with formation of Na_2CO_3, which is thermally stable up to 990.0 ^oC.

Additionally, [11] proved that the microcrystalline cellulose undergoes decomposition between 285.0 to 350.0 ^oC, with a mass loss of 76.0%.

The formation of $CaCO_3$ occurs by the decomposition of calcium citrate between 437.8 and 466.9 ^oC (Tp = 452.9 ^oC) and corresponds to 20.0% mass loss. The last event is due the thermal decomposition of $CaCO_3$ and occurs between 609.4 and 733.5 ^oC (T_p = 715.0 ^oC), which corresponds to 19.4 % mass loss. This loss is attributed to the release of CO_2 and the formation of 27.1% of the final residue, which consists of CaO, SiO_2 used as excipient and Na_2CO_3 and MgO obtained from the decomposition of croscarmellose sodium and magnesium stearate also utilized as excipients. The DTG curve is consistent with information obtained by the thermogravimetric curve.

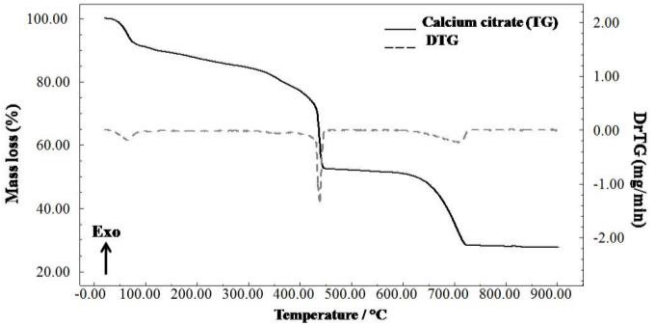

Figure 3. TG/DTG curves of the calcium citrate and tablet sample.

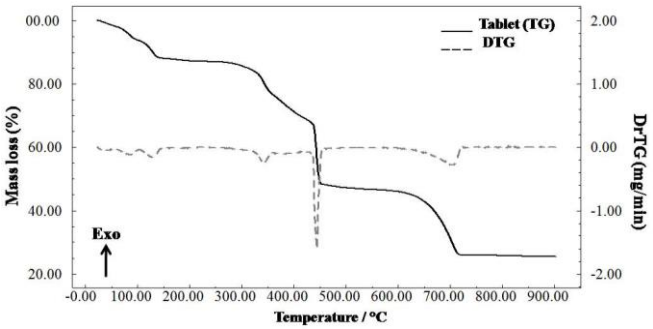

Figure 4 - TG/DTG curves of the tablet sample.

The DTA curves of the calcium citrate and the tablet samples are shown in Figure 5.

DTA curve of the calcium citrate sample three events are observed. The first endothermic peak observed between 37.9 and 89.7 ^{o}C and corresponds to dehydration, which was also observed in the TG curve. An exothermic peak is verified between 361.7 and 483.9 ^{o}C due the thermal decomposition of calcium citrate. Finally, an endotherm is observed when $CaCO_3$ decomposes in the range of 641.6 to 733.2 °C, which results in the formation of CaO. Similar results have been obtained previously when the thermal decomposition of calcium citrate tetrahydrate was studied [7].

Initially, the DTA curve of the tablet sample shows two endothermic events. The first is observed between 64.7 and 108.6 ^{o}C and the second between 108.6 and 160.6 ^{o}C, and both events are due to dehydration. This information is in agreement with the mass losses observed in the TG curve. The exotherm that occurs in the range 313.3 at 382.3 ^{o}C can be attributed the thermal decomposition of the croscarmellose sodium present in the pharmaceutical formulation. There is also an exothermic peak observed between 419.9 and 502.3 ^{o}C, which is a result of the thermal decomposition of calcium citrate. Finally, the $CaCO_3$ is decomposed in the range of 674.7 to 729.3 °C with formation of CaO corresponding to an endothermic peak.

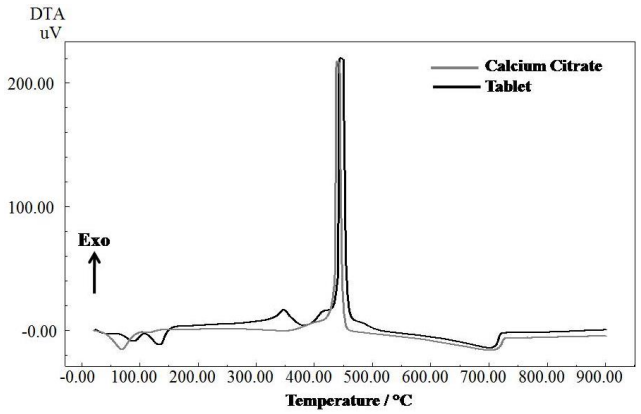

Figure 5. DTA curves of calcium citrate and tablet sample.

The DSC curves of the calcium citrate and the tablet samples are shown in Figure 6.

DSC curve of the calcium citrate sample, two endothermic peaks are observed. The first between 34.6 and 75.3 ^{o}C (ΔH = 43.3 Kj mol^{-1}) corresponding to dehydration, which was also observed in both TG and DTA curves. Another endothermic peak is verified between 320.6 and 352.7 ^{o}C (ΔH = 0.95 Kj mol^{-1}), which is due the thermal decomposition of calcium citrate.

The DSC curve of the tablet sample shows initially two endothermic events. The first between 65.0 and 111.7 ^{o}C (ΔH = 49.9 Kj mol^{-1}) and the second between 111.7 and 154.9 ^{o}C (ΔH = 83.0 Kj mol^{-1}), which are both related to the dehydration step of the calcium citrate. This information is in agreement with the events observed in the TG and DTA curves. Another endothermic peak observed between 325.5 and 402.7 ^{o}C (ΔH = 107.7 Kj mol^{-1}) is due to the thermal decomposition of the calcium citrate present in the pharmaceutical formulation as the active ingredient.

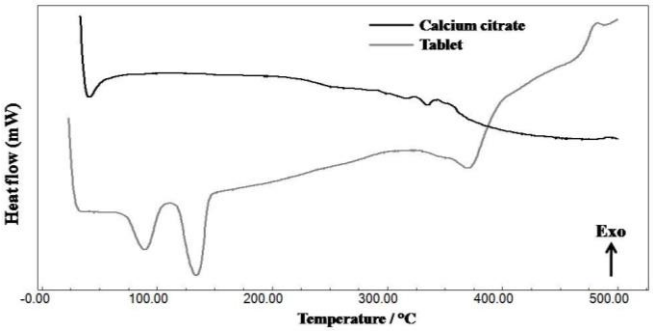

Figure 6 - DSC curves of calcium citrate and tablet sample.

The X-ray powder patterns (Figure 7) show that the compounds presented crystalline structure, with peaks characteristic of calcium citrate (JCPDF:01-0008). Although the tablet sample contains silicon dioxide as an excipient, no peaks were observed, indicating the presence of this compound.

Figure 8 shows the X-ray powder patterns of the intermediate compounds obtained by thermogravimetry at 550 °C from both the calcium citrate and the tablet samples. The diffractogram shows peaks indicative of calcium carbonate (JCPDF: 85-0849). This result is in agreement with the mass loss obtained from the TG curve, which indicates the thermal decomposition of anhydrous calcium citrate and the formation of $CaCO_3$.

The diffractogram of the final residue obtained at 900 °C is shown in Figure 9, and peaks are observed that are indicative of CaO (JCPDF: 77-2376) and $Ca(OH)_2$ (JCPDF: 76-0571). The formation of CaO is due to the thermal decomposition of calcium carbonate ($CaCO_{3(s)} \rightarrow CO_{2(g)} + CaO_{(s)}$), and the presence of the calcium hydroxide is attributed to reaction between calcium oxide and water ($CaO_{(s)} + H_2O_{(g)} \rightarrow Ca(OH)_{2(s)}$) as verified by [8].

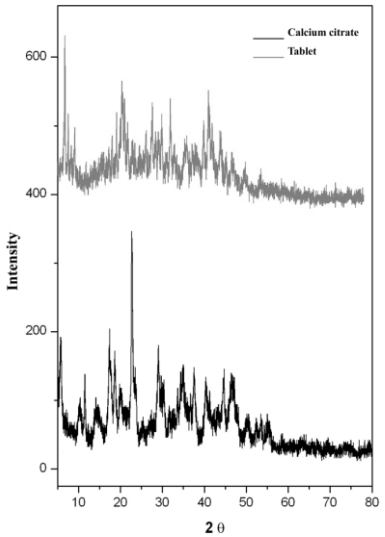

Figure 7. X-ray diffractogram of the calcium citrate and tablet sample.

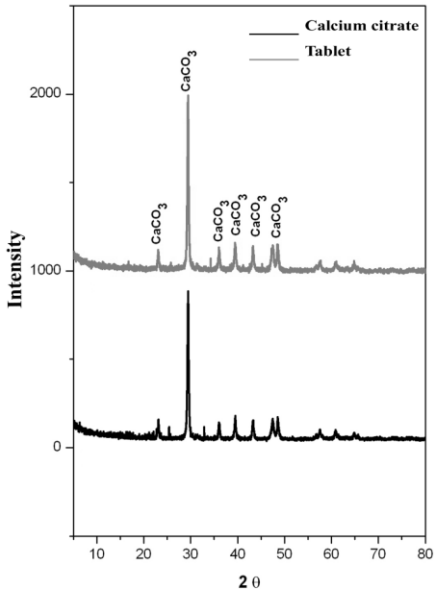

Figure 8. X-Ray diffractogram of residue obtained at 550 °C by Thermogravimetry of the calcium citrate and tablet sample.

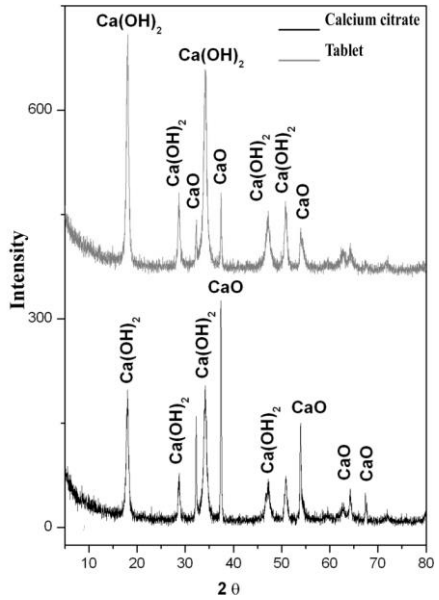

Figure 9. X-Ray diffractogram of the final residue obtained at 900 °C by Thermogravimetry of the calcium citrate and tablet sample.

The calcium content of the tablet samples with calcium citrate is provided in Table 2, and this value can be determined from the loss of CO_2 observed in the last thermal event of the thermogravimetric curve.

There is an observed similarity between the results obtained by thermogravimetry and ICP-OES, which can be used to determine the percentage of calcium in the pharmaceutical formulations.

The calcium content obtained by TG for the tablet sample (17.77%) was similar to the result obtained by ICP-OES (16.84%). The theoretical value obtained from the pharmaceutical formulation was 17.87%, which demonstrates the agreement between the different instrumental techniques.

These results show that thermogravimetry can be used to determine the level of calcium in pharmaceutical formulations while offering speed and minimal sample consumption.

Table 2. Percentage of calcium in tablets of calcium citrate determined using Thermogravimetry and Inductively Coupled Plasma – Optical Emission Spectroscopy

	% Calcium tablets								
Tablets	Thermogravimetry			Theoretical			ICP-OES		
	Ca (%)	SD	CV.	Ca (%)	SD	CV	Ca (%)	SD	CV
	17.77	0.31	1.70	17.87	0.22	1.20	16.82	0.52	3.10

SD = Standard Deviation, CV = Coefficient of Variation

4. Conclusion

The TG and DTG curves provided information concerning the thermal behavior of these pharmaceutical formulations. The TG curves showed that the decomposition temperature of calcium citrate is lower than that of the tablet samples, which is due to the presence of different excipients in the pharmaceutical formulation. Both the DSC and DTA curves showed endothermic events, which are attributed to dehydration and decomposition, and exothermic peaks, which are the result of thermal decomposition of the calcium citrate and excipients. The X-ray powder patterns showed similarities, and the samples studied in this work present a crystalline phase. The results for the calcium content obtained by thermogravimetry are consistent with the data obtained by ICP-OES, which indicate the possibility of using these techniques to determine calcium in drugs containing calcium carbonate. Thermogravimetry offers advantages over other techniques that are currently used, including speed, operational simplicity and consumption of small amounts of sample.

Acknolwledgments

The authors are grateful to CAPES and PETROBRAS for financial support and to the Institute of Chemistry for analysis.

References

[1] Fardellone P. Cotté F.E., Roux C., Lespessailles E., Mercier F., Gaudin A.F. Calcium Intake and the Risk of Osteoporosis and Fractures in French Women. Joint Bone Spine 2010:77(2):154-158. [Google Scholar] [Visualizar item] [PubMed] [CrossRef]

[2] Campos LMA, Liphaus BL, Silva CAA, Pereira RMR. Osteoporosis in childhood and adolescence. J Pediatr. 2003:79(6):481-8. [Google Scholar] [Visualizar item] [CrossRef]

[3] Rowe RC, Sheskey PJ, Owen SC. Handbook of Pharmaceuticals Excipients. Chicago: Pharmaceutical Press; 2006. [Google Scholar]

[4] Heaney R. P., Dowell M.S., Bierman J., Hale C.A., Bendich A. Absorbability and cost effectiveness in calcium supplementation. J. Am. Coll. Nutr. 2001:20(3)239-46. [Google Scholar] [CrossRef]

[5] Parisotto G, Souza JS, Ferrão MF, Furtado JC, Molz RF. Exploratory analysis applied in study of pharmaceutical formulations with piroxicam. Braz. J. Pharm. Sci. 2005:41-4. [Google Scholar]

[6] Srivastava A, Gunjikar VG, Sinha APB. Thermoanalytical studies of zinc citrate, bismuth citrate and calcium. Thermochim. Acta 1987:117:201-217. [Google Scholar] [CrossRef]

[7] Mansour SAA. Thermal decomposition of calcium citrate tetrahydrate. Thermochim. Acta 1994:233:243-256. [Google Scholar] [CrossRef]

[8] Pereira JG, Okumura F, Ramos LA, Cavalheiro ETG, Nóbrega JA. Termogravimetry: A new approach for the classic determination of calcium in eggshells. Quím. Nova: 2009:32(6):1661-6. [Google Scholar] [CrossRef]

[9] Berbenni V, Marini A, Bruni G, Milanese C. Solid state formation of calcium ferrites from thermal decomposition of mixtures $Ca_3(C_6H_5O_7)24H_2O$–$Fe_2(C_2O_4)36H_2O$ the role of mechanical activation on the mechanism of the thermal decomposition and the temperature of the ferrites formation. J. Anal. Appl. Pyrolysis 2008:82(2):255-9. [Google Scholar] [CrossRef]

[10] Alves, R. "Estudo termoanalítico e de compatibilidade fármaco-excipiente de rifampicina e alguns medicamentos utilizados na terapêutica da tuberculose". Dissertação de Mestrado. Universidade de São Paulo. Faculdade de Ciências Farmacêuticas, Produção e Controle Farmacêuticos Brasil (2007). [Visualizar Item]

[11] Filho ROC, Franco PIBM, Conceição EC, Leles MIG. Stability studies on nifedipine tablets using thermogravimetry and differential scanning calorimetry. J. Therm. Anal. Calorim. 2009:97(1):343-7. [Google Scholar] [CrossRef]