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# A selective volatilization method for determination of chloride and sulfate in calcium carbonate pharmaceutical raw material and commercial tablets

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ABSTRACT

In this work a feasible method for chloride and sulfate determination in calcium carbonate pharmaceutical raw material and commercial tablets by ion chromatography after microwave-induced combustion was developed. The analytes were released from matrix by combustion in closed system pressurized with oxygen. Starch as volatilization aid, 100 mmol $L^{-1}$ $HNO_3$ as absorbing solution and 5 min of microwave irradiation time were used. Recovery tests using standard solutions were performed for the accuracy evaluation. A mixture of calcium carbonate pharmaceutical raw material or commercial tablets, starch and a certified reference material was also used as a type of recovery test. Recoveries ranging from 88% to 103% were obtained in both spike tests. Limits of detection ($Cl^-$: 40 μg $g^{-1}$ and $SO_4^{2-}$: 140 μg $g^{-1}$) were up to eighteen times lower than the maximum limits established for the analytes by Brazilian, British, European and Indian Pharmacopoeias. The limit tests recommended by the European Pharmacopoeia for $Cl^-$ and $SO_4^{2-}$ in $CaCO_3$ were carried out to compare the results. Chloride and $SO_4^{2-}$ concentrations in the samples analyzed by proposed method were in agreement with those results obtained using the tests recommended by the European Pharmacopoeia. However, the proposed method presents several advantages for the routine analysis when compared to pharmacopoeial methods, such as the quantitative simultaneous determination, high sample preparation throughput (up to eight samples per run in less than 30 min), reduced volume of reagents and waste generation. Thus, the proposed method is indicated as an excellent alternative for $Cl^-$ and $SO_4^{2-}$ determination in $CaCO_3$ pharmaceutical raw material and commercial tablets.

## 1. Introduction

Calcium carbonate is widely used as a mineral supplement indicated for preventative or adjuvant treatment of pre- and post-menopausal bone demineralization [1,2]. It is used in the treatment of hyperphosphatemia in patients with advanced renal insufficiency or hyperparathyroidism, gastric hyperacidity and the prevention of pre-eclampsia [1–4]. Calcium carbonate is an inert raw material and is also used as filler and diluent with desirable flow and compression properties in capsules and tablets [5]. However, it should be emphasized that the therapeutic activity and safety of the final product are directly related to the quality of the raw material and therefore depend on the impurities that it may contain [6]. In this way, it is of paramount importance the control of impurities in $CaCO_3$ pharmaceutical raw material as well as in commercial tablets.

Determination of anions in pharmaceutical raw materials is mainly carried out to control the appropriate amount of the anionic counterion in the salt, which is an important step in characterization of the raw material [7]. In addition, it is also performed to assess amounts of anionic synthetic impurities and the degradation products [8,9]. The nature and concentration of these impurities depend on the synthesis conditions and raw material quality used. In other words, it will also depend on the reagents, solvents, purification steps, and storage conditions of the pharmaceutical raw material and/or the final product [10,11]. Chloride and sulfate are common impurities contained in $CaCO_3$ in view of the use of hydrochloric acid and sulfuric acid in its synthesis process [12,13]. To ensure the quality of the final product, the official compendiums, such as the Brazilian Pharmacopoeia [14], British Pharmacopoeia [15], European Pharmacopoeia [16] and Indian Pharmacopoeia [17] determine maximum concentration for $Cl^-$ and $SO_4^{2-}$ in $CaCO_3$. Therefore, it is essential to evaluate the impurities in $CaCO_3$ in order to meet several regulatory requirements and ensure the quality of the final product.

In general, $Cl^-$ and $SO_4^{2-}$ limit tests in $CaCO_3$ are performed by sample dissolution in an acid medium under or without conventional heating in open system. Subsequently, a reaction with precipitating reagents, in order to form insoluble compounds with the analytes, is performed [14–17]. Then, a visual comparison with a standard solution

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is performed to verify if the opalescence is within the limits established. These visual comparison tests are also recommended by United States Pharmacopoeia (USP) as general methods for determination of $Cl^-$ and $SO_4^{2-}$ in several pharmaceutical raw materials [18]. Although they are conventional methods that require simple equipment and glassware, the $Cl^-$ and $SO_4^{2-}$ limit tests are not quantitative and allow the semi-quantitative determination of only one analyte by analysis, besides being unsuitable for the analysis the final pharmaceutical products. The precision and accuracy of the results are dependent on the visual acuity of the analyst, workplace brightness and other factors. Moreover, the use of metals such as $Ag^+$ and $Ba^{2+}$ – precipitating reagents used in the $Cl^-$ and $SO_4^{2-}$ limit tests are $AgNO_3$ and $BaCl_2$, respectively – hinders the waste treatment step and adds more costs for analysis.

Currently, in order to overcome the mentioned limitations related to the conventional limit tests, the USP has recommended the use of ion chromatography (IC) as an alternative for $Cl^-$ and $SO_4^{2-}$ determination [19]. Ion chromatography has been one of the most widely used to develop important analytical methods in various applications for the pharmaceuticals industries [20,21]. Moreover, several studies have been carried out to optimize the IC parameters for determination of anionic constituents in different pharmaceutical raw materials [21–23]. However, analysis by IC requires the analytes in a suitable solution, which makes the sample preparation an indispensable step since it is very susceptible to physical and chemical interferences when the sample is not efficiently prepared [24,25]. Thus, only sample dissolution in an acid medium is not considered suitable for analysis by IC.

Sample preparation methods based on dissolution in acid medium, extraction or fusion should be mentioned in view of their simplicity and low cost [26]. However, these methods can present several drawbacks such as the high number of steps involved, the use of a large amount of reagents, the possibility of losses of the analytes as volatile compounds (such as HCl, $Cl_2$, $SO_2$ and $SO_3$) and the low sample throughput. Moreover, $CaCO_3$ is practically insoluble in water and the presence of matrix compounds, high acid content or fluxes, usually used on the conventional sample preparation step, may not be supported by some techniques, as occurs in IC analysis [20]. This may lead to damage to the chromatographic system and/or interferences during the determination step [20,21,27]. Thus, a suitable sample preparation method for solid matrices should be recommended to avoid interferences during the IC analysis and ensure accurate results.

Microwave-induced combustion (MIC) emerges as an interesting alternative for sample preparation of $CaCO_3$ and subsequent $Cl^-$ and $SO_4^{2-}$ determination by IC. The combustion occurs in a closed quartz vessel pressurized with oxygen, and the ignition step is performed using microwave radiation and an ammonium nitrate solution. After combustion, the analytes are absorbed in a suitable solution, which can be compatible with the analytes and the determination technique [28]. Microwave-induced combustion has usually been applied for the digestion of organic samples, including raw materials, active substances and drugs, and subsequent determination of metals and non-metals using different analytical techniques [29–34]. In the sample preparation of noncombustible inorganic matrices, it is necessary to use a volatilization aid in order to provide enough energy to promote the analytes volatilization from the sample matrix [25,35–38]. This approach has been successfully applied for sample preparation of partial or total inorganic matrices, such as soil [35–37], high-purity magnesium [38], and cement [25] for subsequent determination of metals and non-metals using spectrometric and chromatographic analytical techniques.

Recently, MIC was reported by the Brazilian Pharmacopoeia [39] and by USP [40] as a suitable sample preparation method for difficult-to-digest organic pharmaceutical products and subsequent determination of halogens, sulfur and metals. However, MIC was still not recommended for sample preparation of inorganic pharmaceutical substances for the subsequent determination of their impurities. In the volatilization by MIC method, the analytes are separated from inorganic matrix and there is still the possibility of choosing a suitable absorbing solution, which results in less interference during the determination step even using techniques more susceptible to interferences, such as IC.

Thus, the main goal of this study was to develop a method for $Cl^-$ and $SO_4^{2-}$ determination in $CaCO_3$ pharmaceutical raw material and commercial tablets using IC after volatilization by MIC. The feasibility of MIC for the volatilization of impurities from an inorganic pharmaceutical substance is demonstrated for the first time. Ion chromatography was selected as the determination technique in view of the USP recommendation as well as its suitability for routine analysis in pharmaceuticals industries. Microcrystalline cellulose, graphite or starch were evaluated as volatilization aids, and the type and concentration of absorbing solutions were also studied. Recovery tests using standard solutions and certified reference material (CRM) were carried out in order to evaluate the accuracy of the proposed method. The limit tests recommended by European Pharmacopoeia for $Cl^-$ and $SO_4^{2-}$ in $CaCO_3$ were carried out to compare the results. Finally, powder $CaCO_3$ raw material and commercial tablets containing $CaCO_3$ as active substance were selected to demonstrate the applicability of the proposed method for an inorganic pharmaceutical substance as well as for the final product.

## 2. Experimental

### 2.1. Instrumentation

A microwave sample preparation system (Multiwave 3000, Anton Paar, Austria) equipped with eight high pressure quartz vessels with an internal volume of 80 mL was used for the MIC method. The maximum operating temperature and pressure were 280 °C and 80 bar, respectively. Quartz holders were inserted inside the vessels as support for the samples during the combustion process.

Chloride and $SO_4^{2-}$ determination was carried out using an ion chromatograph (861 Advanced Compact IC, Metrohm, Switzerland) equipped with a pump (IC liquid handling unit), a chemical suppressor module and a conductivity detector. The ion chromatograph was equipped with an anion-exchange column (Metrosep A Supp 5, polyvinylalcohol with quaternary ammonium groups, 250 mm x 4 mm i.d., Metrohm) and a guard column (Metrosep A Supp 4/5 Guard, 5 mm x 4 mm i.d., Metrohm). A sample loop of 20 µL was used and the mobile phase flow rate was 0.7 mL $min^{-1}$. Additionally, to compare the results, a potentiometer (HI 3221 pH/ORP/ISE meter, Hanna Instruments, USA) equipped with a selective electrode for $Cl^-$ (HI 4107, Hanna Instruments) was used. In the same way, an ultraviolet-visible spectrophotometer (IL – 592, Kasuaki, Brazil) was used for $SO_4^{2-}$ determination.

### 2.2. Reagents and solutions

All solutions were prepared in ultrapure water (resistivity of 18.2 MΩ cm) obtained from a purification system (Mega UP, MegaPurity, South Korea) and all chemical reagents utilized in this experiment were of analytical grade. Nitric acid (65%, Merck, Germany) was previously distillated below its boiling temperature using a sub-boiling system (Duopor, Milestone, Italy).

The solutions of $NH_4OH$ (25%, Merck), $HNO_3$ (65%, Merck), $H_2O_2$ (50%, Sigma-Aldrich, USA) and solid $(NH_4)_2CO_3$ (Merck) were used to prepare the evaluated absorbing solution in the MIC method. Ammonium nitrate solution (6 mol $L^{-1}$) was used as a combustion igniter, and it was prepared by dissolving the solid reagent (Merck) in water. Small discs of filter paper (12 mg, 15 mm diameter) with low ash content (Qualy, J Prolab, Brazil) were used as a combustion aid for the MIC method, and polyethylene (PE) films with $8 \times 8$ $cm^2$ were used to wrap the samples. The paper discs and PE films were previously cleaned with 20% (v/v) absolute ethanol (Synth, Brazil) solution in an ultrasonic bath (USC-1800 A, Unique, 40 kHz, 155 W, Brazil) for 20 min,