Technology Transfer in Vaccine Production: Implementation of Physical-Chemical Quality Control and Sodium Hydroxide Purity Analysis

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The transfer of technology for vaccine production is crucial to ensuring the fight against infectious diseases on a global scale. Thus, among the various requirements for this production to be carried out safely, the implementation of quality control stands out, which involves everything from acquiring raw materials and qualifying suppliers to carrying out microbiological and physical-chemical tests. The objective of this work was to demonstrate the purity test used in the quality control of sodium hydroxide, one of the inputs acquired for the production of the RNA MCTI CIMATEC HDT vaccine. The limit of carbonates present in the sample under study was determined as described in the official compendium, obtaining results compatible with current specifications.
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Introduction

The development of vaccines is one of the objectives of medicine, considering it as a strategy for reducing the global incidence of infectious diseases [1]. Vaccine innovation requires expertise, which initially includes demand from society, investment in research, intellectual property, and production, as well as the need to guarantee quality and compliance with regulatory standards [1]. From this perspective, technology transfer is one of the fastest ways to achieve the technology necessary for vaccine production [2]. In this sense, HDT BioCorp, in partnership with SENAI-CIMATEC and the Ministry of Health, developed the RNA MCTI CIMATEC HDT vaccine, which is under investigation for COVID-19 and in the process of technology transfer to Brazil.

In this context, many steps must be followed to carry out this process, guaranteeing the product's safety. Among them, the physical-chemical quality control of raw materials and the finished product is a primary requirement, recommended by RDC 658/2022 on good drug manufacturing practices [3]. This stage includes the literature review and development of all tests for the sample of interest to prove the raw material's compliance with current quality specifications. The present work aimed to implement quality tests, as purity test for the quantification of carbonates.

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Materials and Methods

The analyses were occurred at the Pharmaceutical Formulations Laboratory of SENAI-CIMATEC, and the tests were carried out in the sodium hydroxide monograph, IF224-00, of the Brazilian Pharmacopoeia 6th edition [4].

Sample Description

We analyzed the appearance and color of the sample with 1mg of sodium hydroxide (exodo®) added to a test tube

pH Determination

A 0.01% (w/v) aqueous solution was prepared to determine the pH. The sample was diluted with carbon dioxide-free water. The pH reading used the FP20 Five Easy Plus Mettler Toledo® pH meter.

Carbonate Limit

The solutions used in the test were prepared as described below:

Hydrochloric Acid M SV

The volumetric solution (VS) was prepared by slowly adding 85mL of hydrochloric acid to carbon dioxide-free water to obtain 1,000 mL of aqueous solution. The solution was standardized in duplicate, and each sample of 1.5g of anhydrous sodium carbonate was subjected to drying in an oven at 120°C for 1 hour. 100 mL of water and two drops of methyl red indicator solution (SI) were added. Hydrochloric acid M SV was slowly added from a burette until a faint pink color. The solution was heated, and when boiling began, the solution was removed from heating and cooled to room temperature to continue the titration. This sequence of operations was repeated until heating no longer affected the pink color. The molarity calculation was carried out considering that every 52.99 mg of sodium carbonate (Na_2CO_3) equals 1 mL of M hydrochloric acid.

Methyl Red SI

The indicator solution was prepared from a mixture of 0.1g of methyl red, 1.85 mL of 0.2 M sodium hydroxide and 5 mL of 90% (v/v) ethyl alcohol. The solution was heated at 40°C for 15 minutes. After solubilization, the volume was up to 250 mL with 50% (v/v) ethyl alcohol. For the sensitivity test of the indicator solution, 0.1 mL of SI methyl red, 100 mL of carbon dioxide-free water, and 0.05 mL of 0.02 M hydrochloric acid were used, and the addition of 0.1 mL of 0.02 M sodium hydroxide changed the color to yellow.

Phenolphthalein SI

The indicator solution was prepared by dissolving 0.1 g in 100 mL of 80% (v/v) ethyl alcohol. For the sensitivity test, a solution of 0.1 ml of SI phenolphthalein was prepared in 1000 mLof carbon dioxide-free water, and a change in color from colorless to pink was observed after adding 0.2 mL of 0.02M sodium hydroxide.

SI Methyl Orange

The indicator solution was prepared by dissolving 0.1 g of methyl orange in 100 mL of 20% (v/v) ethyl alcohol. For the sensitivity test, 0.1 mL of indicator solution was used with 100 mL of carbon dioxide-free water, and a change from yellow to red color was observed after adding 1 mL of 0.1 M hydrochloric acid.

Procedure for Determining Carbonate Limits

The purity test was carried out in two stages, as described below:

1st stage: 2 g of the sample was dissolved in 80 mL of carbon dioxide-free water. Immediately afterward, 0.3ml of SI phenolphthalein was added, and titration was carried out with hydrochloric acid M SV until the color changed.

2nd stage: 0.3 mL of SI methyl orange solution was added, and the titration was carried out again with hydrochloric acid M SV until the color changed.

The calculations were carried out considering that each mL of hydrochloric acid M SV used in step 2 of the titration is equivalent to 0.1060 g of Na_2CO_3, and each mL of hydrochloric acid M SV used in the total titration (steps 1 and 2) is equivalent to 40 mg of the total base, in the form of NaOH. The experiments were carried out in duplicate, and the average of the analyses was used to calculate the percentage of carbonate.

Results and Discussion

Sodium hydroxide appeared as a white crystalline mass in the shape of spheres. The sample solution presented pH 11, which describes a primary medium following current specifications.

Carbonate Limit

Sodium hydroxide (NaOH) is classified as a base and can easily react with an acidic oxide

such as carbon dioxide [5] (CO_2), forming sodium carbonate (Na_2CO_3) and water (H_2O), according to the equation described below:

$$2\ NaOH(s) + CO_2(g) \rightarrow Na_2CO_3(s) + H_2O(l)$$
(Equation 1)

Therefore, we need to verify the occurrence of this reaction and whether the carbonate content is within the limits established by legislation to guarantee the quality of the sample used in the vaccine production stages.

Quantification was based on acid-base volumetry with the addition of phenolphthalein and methyl orange indicator solutions, proceeding in two stages, with previously standardized hydrochloric acid being used as a titrating agent. In the 1st stage of titrating sodium hydroxide with hydrochloric acid (Equation 2), the turning point was observed after adding 49.5 mL of HCl, evidenced by the change from pink to colorless. In the 2nd stage of the titration, with the addition of methyl orange, an orange-yellow color was observed with a turning point after titration of 0.1mL of HCl.

For the first titration stage, the sodium hydroxide is completely neutralized (Equation 2). In the second stage, with methyl orange, the carbonate present in the sample is neutralized (Equation 3), as shown below:

$$NaOH(s) + HCl(l) \rightarrow NaCl(s) + H2O(l)$$
(Equation 2)
$$Na_2CO_3(s) + HCl(l) \rightarrow NaHCO_3(s) + NaCl(s)$$
(Equation 3)

The acceptance limit for carbonates is a maximum of 2.0%, and the percentage obtained in the analysis was 0.4% (±0.019), showing that the sample complies with the specifications for the purity test described.

Final Considerations

The present work described the purity test for the physical-chemical quality control of sodium hydroxide and demonstrated compliance with current specifications. The analyses are part of implementing physical-chemical quality control of the LION formulation, an adjuvant for the RNA MCTI CIMATEC HDT vaccine, and are in the process of technology transfer. New assays are under development and will be carried out to complete the quality analysis of the sample of interest.

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