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Quality of Drugs Based on Ferrous Sulfate Dispensed in a Basic Health and Commercial Pharmacy in a City in the Amazon Region

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Abstract

Background: For the WHO, anemia is a serious public health problem, with an emphasis on deprivation anemia, which has socioeconomic conditions as determining factors for its development. Among nutritional anemias, the most relevant is iron deficiency, whose main form of prevention and treatment is supplementation with ferrous sulfate dispensed in the public health system, with the need to periodically check whether the drug has the quality required by regulatory health agencies. Thus, the objective of this study was to analyze the quality of the ferrous sulfate medication, from the same laboratory, and dispensed in a basic health unit (BHU) and a commercial pharmacy (CF). **Materials and Methods**: An analytical, qualitative and quantitative study of ferrous sulfate heptahydrate (25 mg/mL in 100 mL syrup), carried out on 20 BHU and 10 from CF, both from the same laboratory, but in different batches. Samples were subjected to organoleptic analysis and verification of iron content, pH, volume and density. Data were compared with values recommended by the Brazilian pharmacopoeia 5th edition. **Results**: Three batches were evaluated: 4659 of from the CF; 4574 from the BHU1, and 4576 from the BHU2, stored in accordance with RDC 304/19 of ANVISA. All showed compliance with some organoleptic characteristics; and stable values in pH (3.61 - CF; 3.67 - BHU1; 3.65 - BHU2), density (1.079 - CF; 1.088 - BHU1; 1.086 - BHU2) and individual volume (not less than 95% of the declared value). However, it was not possible to detect the odor of herbs; the average volume of batch BHU1 was below the declared value, and the iron content of

both BHUs was above the maximum value of pharmacopoeia standards. **Conclusion**: Samples did not show full compliance with the physical and chemical parameters evaluated, suggesting deviation in the quality of the medication.

Keywords

Physical and Chemical Quality Control, Ferrous Sulfate Heptahydrate, Syrup

1. Introduction

Estimates indicate that almost two billion people are affected by anemia worldwide, in which iron-deficiency anemia ranges from 27% to 50% of that population [1]. And, Brazil, as a developing country, presents high rates of this condition [2], which are routinely observed in the Basic Health Units (BHUs) of the country, especially in the North and Northeast regions, which present the higher rates of this disease [3].

A measure to combat iron deficiency anemia is supplementation with iron salts [4], which was instituted in Brazil in 2005 through the National Iron Supplementation Program. The program aims to prevent and control anemia through the prophylactic or curative distribution of iron supplements, in BHU, to risk groups or to individuals who need it [5]. The antianemic medication most widely dispensed to users of the Unified Health System (SUS) is ferrous sulfate, which is preferably administered orally, with several oral formulations [5] [6].

Thus, these drugs should have their pharmaceutical quality periodically assessed, in which not only those with notification of suspected quality deviation, but also those that are most dispensed, marketed and consumed [7], since they are subjected to variations in transportation and storage and other factors, which can cause, even in small proportions, changes in their pharmaceutical formulations, which can bring risks to the safety of the medication and the effectiveness of the treatment, requiring corrective actions [8].

In order to ensure the effectiveness of the treatment of most of the population's health problems, the Ministry of Health, through GM Ordinance 3916/98, approved the National Medicines Policy whose essential proposal is to guarantee the population access to medications with safety, efficacy and quality, requirements that must obey laws and regulations, including Law 6360/76 and RDC 301/19 of the National Health Surveillance Agency (ANVISA) [9].

However, even with all the regulations, a study showed a high rate (more than 50% samples) of failure of a drug dispensed by the public sector, which highlights the importance of tests to monitor the quality of the drugs purchased in this local [10]. Therefore, the present study aimed to check the quality of liquid pharmaceutical formulations of the drug based on ferrous sulfate produced by the same laboratory and dispensed both in a basic health unit and in a commercial pharmacy in the city of Belém, state of Pará.

2. Material and Methods

This was a qualitative and quantitative analytical study with 30 samples of liquid formulations of a drug based on ferrous sulfate, which were collected at the Basic Health Unit (BHU) in the Jurunas neighborhood and in a commercial pharmacy (CF), located in the same neighborhood, both in the city of Belém, state of Pará. Collection at BHU was authorized by the Teaching and Research Center (NEP) of the Municipal Health Secretariat and carried out in October 2019. In the same month of October, commercial pharmacy samples were acquired through purchase. Tests were carried out in the physical-chemical quality control laboratory of the FIBRA University Center.

Study Design: qualitative and quantitative analytical study.

Study Location: Basic Health Unit (BHU) in the Jurunas neighborhood and in a commercial pharmacy (CF), located in the same neighborhood, both in the city of Belém, state of Pará.

Study Duration: October 2019.

Sample size: 30 samples of liquid formulations of a drug based on ferrous sulfate, due to BHU release limitations. The samples had different batches (4659 of from the CF batch; 4574 from the BHU1 batch, and 4576 from the BHU2 batch), but same pharmaceutical laboratory.

Sample size calculation: Samples were acquired at random.

Procedure methodology

The acquired samples were analyzed for organoleptic characteristics with regard to appearance, color and odor, according to the protocol of Ferreira [11]. To determine the potential of hydrogen (pH), the GEhaka pH meter, PG 1800, was used, following the Brazilian Pharmacopeia (volume 1, 5th edition). The equipment was calibrated with the buffer solutions provided by the manufacturer. The electrode was washed with distilled water and dried with paper towels, then immersed in the buffer solution (pH 7.00 ± 0.02), proceeding with the reading. It was washed again and immersed in the second buffer solution (pH 4.00 ± 0.02), checking the temperature at which it was going to operate and adjusting the pH value in accordance with the calibration table [9]. After this, the electrode was immersed in the ferrous sulphate samples to measure pH and record data by the potentiometer reading.

Values of relative density of the samples were quantified by determining the mass of the pycnometer, according to the Brazilian Pharmacopoeia [9], in which a clean and dry pycnometer with a capacity of 10 mL, previously calibrated, was used (determination of the mass of the empty pycnometer) and the mass of its content with water recently distilled and heated at 20˚C). Samples were transferred to the glassware, adjusting the temperature to 20˚C and removing excess sample, then weighing. The weight of the sample was obtained by the difference in mass of the filled and empty pycnometer. The relative density $\left(d_{20}^{20}\right)$ was calculated, determining the ratio of the mass of the liquid sample to the mass of the water, both at 20˚C. And this value was used to calculate the mass density (ρ)

[9].

The Brazilian Pharmacopoeia sets the mass density (ρ) of a substance as the ratio of its mass to its volume at 20˚C. The mass density of the substance (ρt) at a given temperature (t) is calculated from its relative density $\left(d_t^t\right)$ by the formula below, expressed in g/mL or kg/L [9].

$$\rho t = d\left(\text{water}\right) \times d_t^t + 0.0012$$

To determine the volume, each sample was weighed individually. The contents in an Erlenmeyer flask were homogenized, removed and collected, reserving for the determination of mass density. The vials and lids were washed with water and then with ethanol, drying at room temperature (25˚C). Afterwards, the lids and other corresponding parts were replaced and then weighed again. The difference between the two weighings represents the weight of the content. With that, the corresponding individual volumes in milliliters (mL) were determined, using the equation:

$$V = \frac{m}{\rho}$$

m = weight of the content, in g;

ρ = mass density of the product, in g/mL, determined at 20˚C.

From the values obtained, the average volume of the tested units was calculated, which should not be less than 95% of the declared volume and individual volume of any of the units [9].

The methodology adapted from Yano *et al.* [12] and the Brazilian Pharmacopeia [9] were used to determine the iron content of the samples. The protocol started with the transfer of the volume equivalent to 125 mg ferrous sulfate heptahydrate, as stated on the label, to an Erlenmeyer flask containing 15 mL sulfuric acid solution (1 M) and 75 mL previously boiled and cooled water. SI ferroin was added and the titrations were performed using the ceric sulfate solution (0.1 M).

Statistical Analysis

The collected data were tabulated in the Excel 2007 software and presented as mean and standard deviation. The results were compared with the values referenced by the Brazilian pharmacopoeia 5th edition, which determines for pH 1.8 to 5.3, and for ferrous sulfate heptahydrate content, the percentage equivalent to: minimum of 94.0% and maximum of 106.0% the declared amount of elemental iron (Fe).

3. Result

During the collection of samples at the BHU, it was observed that the storage of the medication was done on plastic pallets away from the floor and wall, protected from direct sunlight and at a constant temperature of 23˚C at the time of collection. As for the commercial pharmacy, the drug was stored on a glass shelf,

without contact with the floor or wall and under refrigeration. In both places, floor, walls and ceiling had adequate conditions of conservation, in accordance with RDC 304/19 of ANVISA.

Regarding the organoleptic characteristics, the color of the dark brown liquid and the odor of caramel were compatible with the descriptions in the manufacturer's package insert, however it was not possible to observe the odor of herbs as was also reported in the document. All samples were within the standard pH range recommended by the Brazilian pharmacopoeia (**Figure 1**).

From the results of density, using the pycnometer method, the mass density of the ferrous sulfate solution was calculated (**Figure 2**).

Regarding the volume, the results confirm that the Batch CF and UBS2 are within the acceptance limits recommended by the pharmacopoeia (**Table 1**), that is, the individual volume of none of the units is less than 95%, and the average volume of the samples was not less than stated on the label by the manufacturer, which is 100 mL. However, Batch UBS1 showed non-compliance with legal specifications, as the average volume was lower than declared, although the individual volume is within the standards.

In determining iron content, the sample acquired at the commercial pharmacy (CF) was within the standards defined by the Brazilian Pharmacopoeia. However, in the samples that were collected in the basic health unit (UBS1 and UBS2), the values found were above the maximum recommended value, but without significant difference (p = 0.4593/t = 0.1156; **Figure 3**).

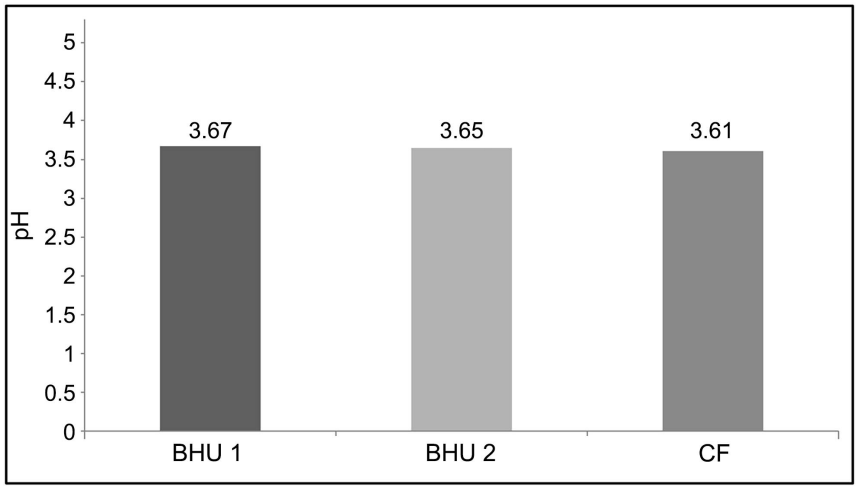

Figure 1. Values of pH of the samples analyzed.

Table 1. Weight, Percentage and Average Volume of the analyzed samples.

	Weight of the filled flask (g)	Weight of content (g)	Weight of the empty flask (g)	Individual volume (mL)	%
BHU 1	124.49 (±0.2641)	107.54 (±0.019)	16.95 (±0.2651)	98.85 (±0.2432)	98.6 (±0.2431)
BHU 2	126.29 (±0.5694)	109.33 (±0.5698)	16.96 (±0.023)	100.7 (±0.5272)	100.7 (±0.5272)
CF	125.63 (±0.3656)	108.53 (±0.3669)	17.10 (±0.0754)	100.59 (±0.3406)	100.59 (±0.3406)

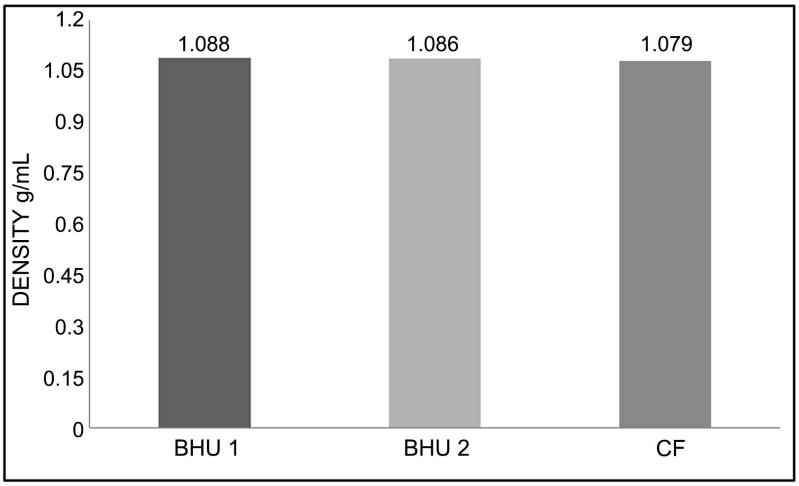

Figure 2. Mass density values of the analyzed samples.

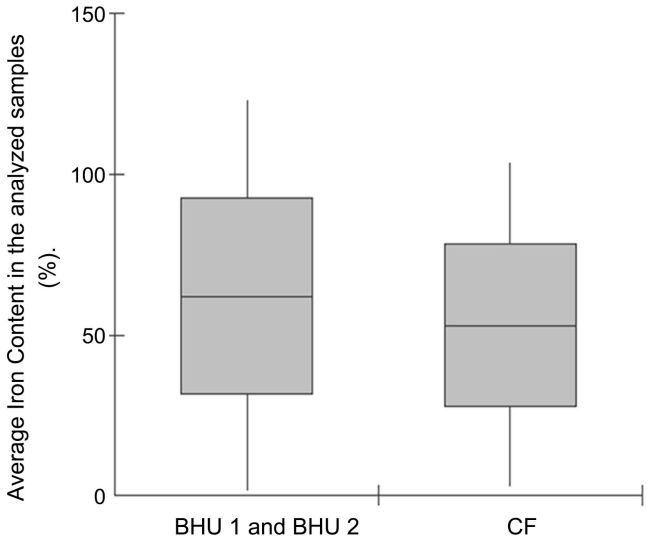

Figure 3. Dosing of the analyzed samples.

4. Discussion

Both the storage and the organoleptic characteristics showed compliance with the RDC 304/19 and the descriptions in the manufacturer's package insert. However, it was not possible to observe the odor of herbs as was also reported in the document. This was also reported by Alvarenga *et al.* [13], in which all samples analyzed exhibited their own aromatic odor, with divergence of aspects and colors. Nevertheless, Dutra *et al.* [14] presented negative evaluations for physical structure, such as lack of method for maintaining adequate room temperature, and lack of protection against the incidence of sunlight.

In another study on medication storage conditions in basic health units, Simão and Batista [15] found that of the BHUs inspected, 68.2% had electrical installations in an appropriate state of conservation, safety and use and, in 72.8% had floor, wall and ceiling conservation conditions.

Regarding the pH, the samples showed satisfactory values in accordance with the standards described in the Brazilian Pharmacopoeia (**Figure 1**), which sets a pH range of 1.8 to 5.3 for such formulations, which significantly contributes to the stability of the medication, which corroborates Yano *et al.* [12]. However, Baumer *et al.* [16] found that increasing the pH of captopril in aqueous solution favored microbial growth as well as increasing the sensitivity of the active ingredient to the oxidation process, also stating that liquid formulations need to have their pH adjusted for safe administration and maintenance of stability of the drug.

There is no data in the literature on density values for the syrup of ferrous sulfate heptahydrate. However, there was no significant variation between the samples. Compared with another drug, it was noted that the hydrochlorothiazide suspension had density values between 1.0050 and 1.0200 g/mL, that is, it did not present a relevant degree, being similar to the data of the present study [17].

With respect to the volume, the Brazilian Pharmacopoeia 5th edition reports that for each milliliter of 0.1 M ammonia ceric sulfate equals to 27.8 mg ferrous sulfate heptahydrate or 5.585 mg elemental iron, containing at least 94% and a maximum of 106% of the declared dose. Errors regarding the content of active ingredients can have consequences for the patient, as the correct dose would not be administered, which could lead to the worsening of a pathological condition or the appearance of others.

In fact, Solon [18], in a comparative study of naproxen suspensions, found that out of the samples analyzed, only one showed a significant volume difference. In another study, Yano *et al.* [12] noticed a significant deviation of quality in pharmaceutical formulations containing ferrous sulfate dispensed in the public network of São Paulo, observing values below the permitted level. Another result in which the required quality parameters were not met was reported by Ferreira *et al.* [19], who had 35.8% failure in samples of dipyrone drops for the specification of content, which were collected in the homes of Goiânia, under different storage conditions

The samples analyzed by the present study were kept in the same storage conditions after collection at BHU and CF. Another fact that can be observed and questioned is the existence of only one batch for the evaluation of the drug dispensed in the commercial pharmacy and two batches for the BHU. This is justified by the lack of availability of another batch in the commercial pharmacy.

In view of the results found and presented herein, it is interesting to note that the laboratory of the samples analyzed is the main supplier of this drug to the municipality of Belém. However, in 2013, it already had two batches of the medicine based on ferrous sulfate heptahydrate in the presentation of 125 mg/mL oral solution with suspension of distribution, trade and use, for presenting unsatisfactory results in terms of active ingredient content, through a counterproof report issued by the Adolf Lutz Institute [5].

Notoriously, it is necessary to effectively implement the manufacturing and

quality control processes of the medicine, as well as to know the favorable conditions for the storage of these products, in order to guarantee the maintenance of their initial characteristics, since the improper storage of the medicine can generate countless dangers.

5. Conclusion

According to the results found, it can be concluded that not all samples are safe in terms of their physical and chemical quality due to the variation in volume and content of active ingredient outside the parameters specified by the Brazilian Pharmacopoeia. In the pH analysis, both the BHU samples and those from the commercial pharmacy were considered approved according to the Pharmacopeial descriptions. In relation to storage, at the time of collection, the conditions were favorable to preserve the quality of the medication. Thus, regardless of the dispensing location, it is of paramount importance to maintain the quality of the medicine recommended by the Good Manufacturing Practices, which will ensure reliability and safety to patients in guaranteeing the use for the purposes for which they are intended.

Limitations of the Study

The study has limitations in terms of sample size, different batches for analysis, a limited study of collection sites and basic methodological tools. With this, we suggest more detailed studies on the quality of ferrous sulfate drug.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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