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QUALITY EVALUATION OF PHYSICOCHEMICAL OF INDUSTRIALIZED AND PROCESSED SIBUTRAMINE HYDROCHLORIDE CAPSULES

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ABSTRACT

The growing increase in demand for medicines handled according to the individual needs of each patient has made magazines the best alternative for the acquisition. However, despite the low cost, these drugs do not go through strict quality control, which can put the patient's treatment at risk. The objective of this study was to evaluate the quality of sibutramine hydrochloride capsules handled in two different master pharmacies located in a municipality in the south of Tocantins and the reference drug. For this, the tests of identification, weight variation, unit dose uniformity, and dosing were performed. Capsules obtained in Pharmacy B and the industrialized ones were approved in all the tests, however, the samples of the pharmacy A were reproved in the determination of uniformity of unit doses, presenting results above the limits specified by the Brazilian Pharmacopoeia 5th edition. It is verified the need of Pharmacy A to review the handling procedures, to obtain products with quality, guaranteeing the effectiveness and safety of the treatment.

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INTRODUCTION

Obesity is defined as the accumulation of adipose tissue in the body. It can be diagnosed when the body mass index is more than 30 kg/m^2. In Brazil, there are large percentages of obese individuals and at different rates for men and women. The municipality of Porto Alegre - RS leads the ranking of obese males and females, Campo Grande - MS. In general, doing a study between all capitals and the Federal District, the state of Tocantins stands out to have it is capital Palmas with low obesity rates [1].

It is possible to treat obesity with some changes in eating habits, diets indicated by the appropriate health professional and the practice of supervised exercises. In addition to these alternatives, there are drug treatments, especially Sibutramine Hydrochloride. Universally, Brazil has an important highlight in the use of Sibutramine Hydrochloride, as it consumes the equivalent of 50% of all the substances sold in the world [2]. Sibutramine Hydrochloride is marketed in Brazil in the solid pharmaceutical form of hard capsules, presenting the commercial dosages of 10 and 15 mg. In addition to industrialized presentations, this drug can also be purchased in

formulations manipulated in master pharmacies [3]. Hard gelatinous capsules are the solid pharmaceutical firms with the highest demand in master pharmacies, due to ease and versatility in production and low cost. In addition, capsule medications are easier to administer and accepted by patients [4]. Although it is easy to manipulate, the production of hard capsules represents a major challenge to the pharmacist, related to the technological limitations inherent to the manipulation process and also to quality control [5]. The masterful pharmacy has full responsibility in ensuring the quality of its manipulations and is the pharmacist's responsibility to apply the standards of Good Practices of Drug Manipulation, according to RDC No. 67/2007, determine the validity of the manipulated product and inspect the handling process from the raw material to the finished product. The RDC No. 67/07 determines that for quality control applied to manipulated capsules, at least description, aspect, organoleptic characters and average weight [6] should be performed. To monitor the manipulation process, analyses of content uniformity and asset content at least once every two months should be performed for capsules that have less than 25 mg of the active ingredient [7]. Analyses of active ingredient content and content uniformity are very important to ensure that the amount of active ingredient present in each capsule is appropriate to that specified in the formulation since the incorrect dose is directly related to increased adverse effects, toxicity, and therapeutic inefficacy. In this case, quality control becomes essential to ensure the unit dose of drugs, in addition to ensuring the credibility of the pharmacy of manipulation [8]. Thus, the objective of this work was to perform the chemical-physical quality control of Sibutramine. Hydrochloride capsules, produced and marketed by master pharmacies located in a municipality in southern Tocantins - Brazil and a sample industrialized of the same medicine.

MATERIALS AND METHODS

Samples: The Reference Chemical Substance (SQR) of Monoidratated Sibutramine Hydrochloride was acquired at the National Institute of Control in Quality of Health, Reference Chemical Substances Sector (SSQR), Oswaldo Cruz Foundation. Samples of manipulated capsules of Sibutramine Hydrochloride 15 mg were obtained in two pharmacies located in a municipality in southern Tocantins - Brazil, which were identified as Pharmacy A Sample and Pharmacy B Sample, to preserve the identity of the establishments. For the industrialized sample of Sibutramine Hydrochloride 15 mg, we opted for the reference drug, which was acquired in a local drugstore and was identified as An Industrialized Sample R.
All medications were obtained by presenting special control prescriptions.

Data analysis methodology

Identification test: The identification test was performed for both SQR and for the samples of manipulated and industrialized sibutramine hydrochloride capsules. Samples and QRS were diluted at a concentration of 10 μg/ml using methanol in the first dilution and water in the second dilution and were submitted to spectrophotometry analysis in the ultraviolet region (200-400 nm). The test was performed in triplicate [9].

Determination of weight variation: The determination of weight variation was performed according to that recommended by the Brazilian Pharmacopoeia, through the individual weighing of 20 capsules, followed by the determination of the percentage variation of the capsule content in relation to the mean. Additionally, the standard deviation of the test was calculated, because it is a requirement of Brazilian legislation in relation to pharmacies of manipulation [6, 9].

Uniformity of unit doses: The determination of the uniformity of unit doses was performed by the method of content uniformity. For this test, the content of 10 sibutramine hydrochloride capsules was transferred individually to 10 volumetric balloons (50 ml). Subsequently, 30 ml of methanol were added in each volumetric balloon, followed by mechanical agitation for 30 minutes. The volume of the balloon was completed with the same solvent, and after homogenization, it was filtered and diluted successively with water up to the concentration of 10 μg/ml. For the quantification of the product, a standard curve was constructed in the concentration range from 6 μg/ml to 14 μg/ml using Sibutramine Hydrochloride. The absorbances of the solutions were determined in a spectrophotometer in the absorption range of 223 nm, using water to adjust the zero. The Sibutramine content present in each capsule was calculated, using the straight equation, obtained by the standard curve of Sibutramine Hydrochloride SQR [9, 10]. From the content found, the acceptance value was calculated using the formula:

Where: AV: acceptance value; M: reference value; •: the average of individual contents expressed as a percentage of the declared quantity; k: acceptability constant; s: standard deviation of the sample.

Determination: For the dosing, 20 capsules of Sibutramine Hydrochloride were weighed, homogenized and of this content, the equivalent of 20 mg of sibutramine hydrochloride was transferred to a 50 ml volumetric balloon. The volume of the balloon was completed with the same solvent and, later, the solution was filtered and diluted successively with water up to the concentration of 10 μg/ml. The absorbances of the solutions were determined in a spectrophotometer in the absorption range of 223 nm, using water to adjust the zero and the amount of Sibutramine Hydrochloride was calculated, through the equation of the straight, obtained by the standard curve of hydrochloride by Sibutramine SQR [10].

Data analysis: The individual values of each test performed were tabulated and the standard deviation for each sample was calculated using a spreadsheet. Variance analysis (ANOVA) was applied in the standard curve for certification of linearity and accuracy of results, using assistat software.

RESULTS AND DISCUSSION

Samples A, B, and R, submitted to the identification test, presented the maximum peak absorption at 223 nm, corresponding to that obtained in the SQR (Figure 1). The identification test is an analytical method of a qualitative nature, intended to confirm the identity of the raw material or a given component of a product. The identification of the active ingredient is a basic item to ensure the efficacy and safety of the product [11], and in this case, all analyzed samples presented identification of the active ingredient, according to the reference substance (SQR).

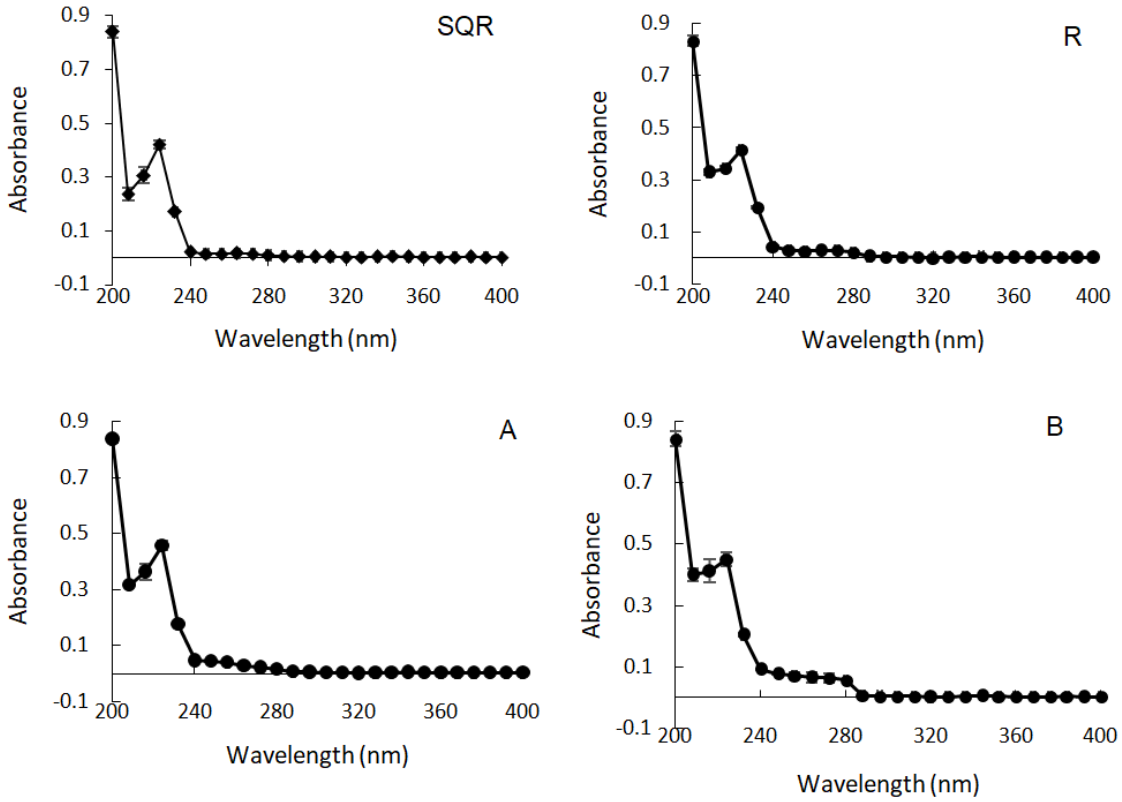

Figure 1. Absorption spectra in ultraviolet sibutramine hydrochloride of the Reference Chemical Substance (SQR), Industrialized Sample (R), Pharmacy Sample A (A) and Pharmacy Sample B (B), prepared at the concentration of 10 µg/mL. The results correspond to the mean ± standard deviation of three determinations

Table 1. Results obtained in the weight variation test of sibutramine hydrochloride capsules 10 mg manipulated and industrialized

Samples	Average ± DP (g)*	Change limit (g)**	Lower weight found (g)	Higher weight found (g)
R	0,229 ± 0,003	0,206 - 0,252	0,226	0,234
A	0,140 ± 0,003	0,126 - 0,154	0,135	0,146
B	0,161 ± 0,003	0,145 - 0,177	0,153	0,165

R (Industrialized sample); A (Pharmacy Sample A); B (Pharmacy Sample B).
* Values for the average weight of 20 capsules.
** Pharmacopoeic variation limit for hard gelatin capsules containing doses less than 300 mg (±10%).

In the weight variation assay, samples A, B and R completed the test, presenting a mean and limit of variation within the pharmacopeia specifications (Table 1). This essay aims to evaluate the weight uniformity of solid pharmaceutical forms, constituting an essential tool for routine quality control of master pharmacies. The execution of this test may indicate the inefficiency in the handling technique used by the pharmacy, and constitutes a criterion of disapproval of the product when it does not comply with the established limits, excluding the need for execution of other tests [12]. According to the Brazilian Pharmacopoeia 5th ed. [2], the variation in the probable weight for hard gelatinous capsules, the content of which is less than 300mg, is ±10%, and two units outside the specified limits and no unit above or below twice the percentages indicated in the varying limits [9]. In this test, the standard deviation is also an important parameter to be analyzed, since they indicate the uniformity of filliness: the higher the standard deviation, the lower the uniformity of fill [13]. In the analyzed samples, the standard deviation was low, demonstrating that all products were bottled evenly. It is noteworthy that industrialized capsules (Sample R) had an average weight higher than the other capsules (approximately 61% in relation to sample A and 70% in relation to sample B).

This suggests that the number of excipients used by manipulations is not standardized [14]. The masterful process should include the biopharmaceutical properties of the asset, and this implies standardizing the excipients used in each product, but there is no obligation to declare on the label the quantities used [2, 6], which can lead pharmacies to adapt their manipulation protocols to more favorable conditions in relation to costs. The determination of average weight alone is not enough to ensure the correct dosage of the drug. To ensure the administration of correct doses, each unit of the product must present an active ingredient quantity close to what is declared on the label. In this case, the drugs should be evaluated for the uniformity of unit doses, which allows us to determine the amount of active ingredient in individual units of the lot and verify that this quantity is uniform in all units tested [9]. This test is essential when it comes to ensuring the efficacy and safety of the medicinal product [15]. To determine the uniformity of unitary doses, a standard curve was first constructed with Sibutramine SQR Hydrochloride at different concentrations (6-14 μg/mL) (Figure 2). The absorbances obtained in each analysis interval were interpolated in the analytical curve, presenting a good correlation with the concentration of SQR sibutramine. The equation of the straight obtained was y = 0.0435x - 0.0498, with a correlation

coefficient of 0.9901. The linearity of the standard curve was confirmed by variance analysis (ANOVA), which demonstrated a significant linear regression ($p<0.05$), proving the validity of the method.

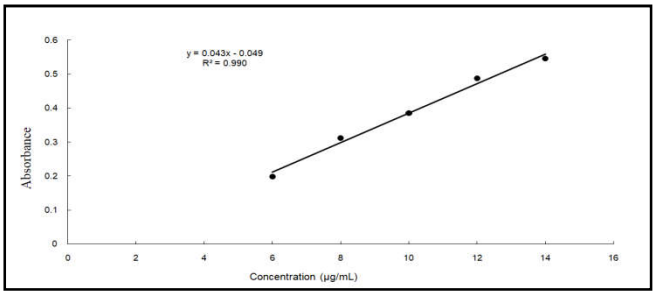

Figure 2. Graphic representation of the standard curve of SQR sibutramine hydrochloride obtained by the spectrophotometric method in the ultraviolet region at 223 nm. Variance Analysis (ANOVA) p<0.05

In the unitary dose determination test, the content uniformity method was used, because the amount of active ingredient is less than 25 mg, being in accordance with what is recommended in the legislation [6]. According to the criteria established by the Brazilian Pharmacopoeia 5th ed. [2], only the capsules of Pharmacy B and the industrialized sample (R) were approved in the uniformity test of unit doses, because the Acceptance Value (AV) calculated for 10 capsules (N= 10) was 14.95 in the sample of pharmacy B and 13.56 in the industrialized sample R, being below the maximum permitted acceptance value, L1=15 (Table 2). However, the sample of pharmacy A did not comply with the test, since it presented VA of 34.44, above the maximum acceptance limit (L1=15).

Table 2. Individual and mean values, as a percentage, obtained in the evaluation of content uniformity of manipulated and industrialized capsules analyzed by spectrophotometry in the ultraviolet region at 223nm

Capsule	R (%)*	A (%)*	B (%)*
1	108,80	98,10	90,85
2	113,86	124,22	89,24
3	105,57	120,99	90,39
4	105,12	105,46	89,70
5	108,11	104,08	91,77
6	110,18	122,49	90,85
7	107,42	121,91	92,00
8	105,12	118,12	93,61
9	106,50	108,45	92,69
10	111,10	115,01	89,24
Average (%)	108,17	113,88	91,77
±DP	2,87	9,19	2,16
VA	13,56	34,44	14,95
Situation	Approved	Disapproved	Approved

SD= standard deviation; *VA*= acceptance value; A (Pharmacy Sample A)
* Valores referentes a média de três determinações.

Similar results were observed by [14], which failed two batches of Sibutramine Hydrochloride capsules because the uniformity of content of unit doses presented acceptance values above L1=15. According to the authors, these results indicate non-compliance with Good Handling Practices and consequent impairment of the quality of Sibutramine capsules. Meneghini and Adams (2007) [16], also disapproved of the manipulated diazepam capsules due to the uniformity of unit doses if they presented themselves outside the specified limits. Similarly, Scandolara et al. (2008) [17], when evaluating Piroxicam capsules, found that such variation in the uniformity of unit doses can be attributed to the lack of standardization of the procedures, involving since the homogenization of excipients and active principle until encapsulation. In addition to the uniformity of unit doses, it is also recommended by legislation that the drug be submitted to dosing tests, which aim to quantify the active substance content in the formulation to be administered, being considered a test of extreme relevance in the evaluation of the quality of drugs [3], since an incorrect dose may cause the adverse effects, toxicity and therapeutic inefficacy of the drug [18]. For this method, the sibutramine concentration was calculated from the same standard curve used in the determination of unit doses. The results described in table 4 showed that the capsules manipulated by pharmacies A and B and the industrialized sample (R) met the value recommended by the Brazilian Pharmacopoeia, where the average content of these capsules remained in 106.21% for sample R, 103.27% for the sample of pharmacy A and 103.30% for the sample of pharmacy B. As there is no official monograph for the dosing of Sibutramine Hydrochloride, the minimum limit of 90% and maximum of 110% of the declared quantity of the drug was used, which is the limit of variation commonly accepted action for most drugs analyzed by spectrophotometry [3].

Table 4. Dosing results of manipulated and industrialized sibutramine hydrochloride capsules analyzed by the spectrophotometric method in the ultraviolet region at 223nm

Sample	Absorbances	Content (%)	Medium Content (%)	±DP (%)
R	1,064	106,69	106,21	1,73
	1,039	104,29		
	1,074	107,64		
A	1,045	104,87	103,27	1,46
	1,025	102,95		
	1,015	101,99		
B	1,027	103,14	103,30	0,73
	1,037	104,10		
	1,022	103,60		

* R (Industrialized sample); A (Pharmacy Sample A); B (Pharmacy Sample B).

Differently, the results obtained in this study, [14] disapproved of two manipulation pharmacies in dosing tests. These disapprovals occurred precisely in the same samples failed in the uniformity test of unit doses. However, the authors used another limit of variation for dosing, of 98-102% of the declared amount of the drug, as proposed by Diefenbach (2007) [10]. But due to the non-official monograph for this product in Brazil, the use of the variation limit, as provided for in this study, is in accordance with what the Brazilian Pharmacopoeia recommends for other products analyzed by this same method. Thus, the samples were considered approved in this test because they were within the range limit of 90 to 110%.

Conclusion: It is possible to conclude with the results that the capsules manipulated by pharmacy B and the R capsules were approved in all tests performed and therefore approved. However, samples from pharmacy A were disapproved in the uniformity test of unit doses. With this it is possible to affirm that there is a need to review the manipulation procedures, which involve raw material analysis, weighing process, mixing of powders, encapsulation process, and storage of master formulations, to obtain product quality, ensuring the effectiveness and safety of the treatment.

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