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Physical-chemical Quality Control of Acetaminophen, Dipyrone, Nifedipine, Prednisone and Spironolactone tablets sold in the city of São Luís de Montes Belos, Goiás, Brazil.

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ABSTRACT

Physical-chemical quality control analyses of acetaminophen, dipyrone, nifedipine, prednisone and spironolactone tablets were performed in the three commercialized pharmaceutical specialties (reference, generic or similar) in the city of São Luís de Montes Belos, Goiás, Brazil. Using the monograph of each product from the Brazilian Pharmacopoeia 5th were evaluated organoleptic properties, average weight, hardness, friability, dissolution, disintegration, uniformity of dosage units and identification test. One- or two-way ANOVA grouped analysis was used, followed by Bonferroni post-tests, with *P* values <0.05. Medicines showed results within the standards pharmacopoeias for organoleptic properties, average weight, hardness, friability, disintegration, uniformity of dosage units and identification test. In the dissolution assay, similar nifedipine did not meet the established requirements. Furthermore, the similar sample of acetaminophen had a standard deviation in which some samples were below the established 80%. Results obtained allow to conclude that practically all samples - less similar nifedipine and some similar acetaminophen - were in accordance with the specifications indicated in the Brazilian Pharmacopoeia 5th.

Keywords: quality control, acetaminophen, dipyrone, nifedipine, prednisone, spironolactone.

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INTRODUCTION

The Guidance for Industry Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practices Regulations (CGMP) establishes that every pharmaceutical product must ensure consistent finished product quality through a variety of tests to safeguard the required levels of safety and effectiveness [1]. Likewise, the Brazilian Health Regulatory Agency (ANVISA) determines that quality control is essential at all stages of a medicine production. The proper analysis of raw material, intermediate and finished products, associated with the proper control of production processes, play a fundamental role in the final quality [2].

Medicines in Brazil are commercially classified as reference, generic or similar. Examples of products widely used in the Brazilian territory are acetaminophen, dipyrone, nifedipine, prednisone and spironolactone. Acetaminophen [N-(4-hydroxyphenyl)acetamides], also known as Paracetamol, is an analgesic and antipyretic medicine described as a white crystalline powder, odorless, with a slight bitter taste. It is slightly soluble in water, soluble in boiling water, easily soluble in ethanol, soluble in sodium hydroxide, practically insoluble in chloroform and ethyl ether. Dipyrone [(1,5-Dimethyl-3-oxo-2-phenylpyrazol-4-yl)methylamino]methanesulfonic acid, also known as Metamizole, is an analgesic, anti-inflammatory and antipyretic which is described as a crystalline powder, off-white and odorless medicine. Dipyrone is soluble in water and methanol, slightly soluble in ethanol, practically insoluble in ethyl ether, acetone, benzene and chloroform [2].

In like manner, nifedipine [3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-, bis(2-(methyl(phenylmethyl)amino)ethyl) ester] is a calcium-channel blocker medicine, physically described as yellow crystals, odorless and tasteless. Nifedipine is practically insoluble in water, soluble in ethyl acetate, slightly soluble in ethanol, very slightly soluble in chloroform and acetone. Prednisone [17,21-Dihydroxypregna-1,4-diene-3,11,20-trione 21-pivalate] is a corticosteroid medicine. It is described as a white or off-white crystalline powder, odorless. It has polymorphism and is very slightly soluble in water, slightly soluble in ethanol, chloroform, dioxane and methanol. Last, spironolactone [4-Pregnen-21-oic acid-17α-ol-3-one-7α-thiol γ-lactone 7-acetate, 7α-(Acetylthio)-17α-hydroxy-3-oxopregn-4-ene-21-carboxylic acid γ-lactone] is a potassium-sparing diuretic medicine physically described as crystalline powder, light beige to tan. Spironolactone is practically insoluble in water, easily soluble in benzene and chloroform, soluble in ethyl acetate and in absolute ethanol, and slightly soluble in methanol (Figure 1) [2].

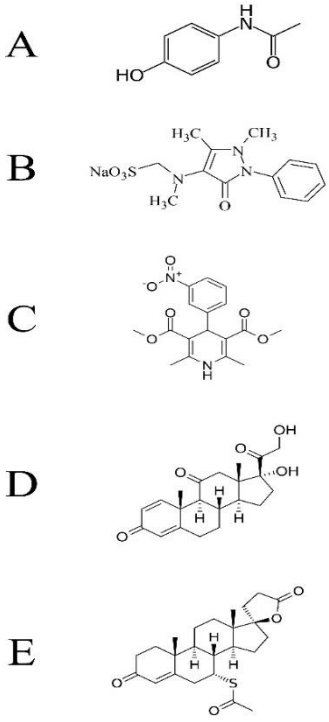

Figure 1. Chemical Structures of (A) acetaminophen, (B) dipyrone, (C) nifedipine, (D) prednisone and (E) spironolactone.[2]

The diversity of products offered on the market makes quality control essential to ensure that a medicine will not harm population's health, as it is known that the same drug produced in the same concentration and in the same pharmaceutical form may present discrepancies in physical-chemical characteristics when compared to different brands, due to several factors such as the quality of raw materials and production methods [3]. From such facts, this work aimed to perform physical-chemical quality control analyses of acetaminophen, dipyrone, nifedipine, prednisone and spironolactone tablets in the three commercialized pharmaceutical specialties (reference, generic or similar) in the city of São Luís de Montes Belos, Goiás, Brazil, using the monograph of each product from the Brazilian Pharmacopoeia 5th.

MATERIAL AND METHODS

Acetaminophen 750 mg, Dipyrone 500 mg, Nifedipine 20 mg, Prednisone 5 mg and Spironolactone 50 mg tablets were obtained from a drugstore (Latitude: 16.51987°S; Longitude: 50.36970°W) in the city of São Luís de Montes Belos, Goiás, Brazil. From each laboratory, 150 tablets of a same manufacturing batch were acquired, and samples were identified as A (reference), B (generic) and C (similar) [for laboratories protection] [2]. Experiments were performed in the laboratories of pharmacotechnical development and pharmaceutical technology at the University Center Brasília de Goiás. All analyses and drugs reference standards were accomplished from the United States Pharmacopoeia (USP 29) and Brazilian Pharmacopoeia 5th [2, 4].

Experimental Section

Organoleptic properties

Samples were evaluated for the presence of deformations, color uniformity, size and shape, missing, broken or cracked tablets, legibility on the package and any other apparent alteration.

Identification test

The identification test applied corresponds to the dosing test assay, which analyzes UV-Vis absorbances in the range of 200 nm to 500 nm (Instrutherm, UV-2000A). And as a complement, specific colorimetric identification tests were carried out for each active agent:

Acetaminophen

To 10 mL of a 1% (w/v) solution of acetaminophen, was added one drop of SR ferric chloride (Cromato Produtos Químicos LTDA, SP, BR). A violet-blue color was developed.

Dipyrone

10 tablets of dipyrone were weighed and pulverized. To 0.5 g of the powder were added a few drops of concentrated hydrogen peroxide (Start Química, MG, BR). A blue color was developed, which quickly faded to intense red (strong exothermic reaction).

Nifedipine

50 mg of nifedipine were dissolved in 1 mL of dimethylsulfoxide (Labsynth, SP, BR). A yellow color was developed, with maximum absorption at 330 nm. This color turned red with the addition of 5 drops of SR sodium hydroxide (Dinâmica Química Contemporânea, SP, BR), absorbing at 451 nm.

Prednisone

To 6 mg of weighed and pulverized prednisone, 2 mL of sulfuric acid were added (Dinâmica Química Contemporânea, SP, BR). The solution was left to rest for 5 minutes. An orange color was

developed. The solution was poured, dropwise and with stirring, into 10 mL of water. The orange color changed first to yellow and then gradually to blue-green.

Spironolactone

100 mg of spironolactone were dissolved in a mixture of 10 mL of water and 2 mL of SR sodium hydroxide. The mixture was boiled for 3 minutes, cooled, 1 mL glacial acetic acid (Dinâmica Química Contemporânea, SP, BR) and 1 mL SR lead acetate (Vetec Química Fina, RJ, BR) were added. Brown to black lead sulfide precipitate was formed.

Average weight determination

For average weight determination, 20 tablets of each sample were individually weighed on an analytical balance (Shimadzu, AUW-D) and the average, the limits of variation and standard deviation were calculated.

Hardness test

For hardness test, 10 tablets from each sample were individually submitted to the action of a durometer (Ethik Technology, DUR 2980100) that measured the force – in Newton (N) – applied diametrically, necessary to crush them.

Tablets Friability

For friability, tablets from each sample were submitted to 25 rotations per minute (rpm), for four minutes (100 rotations) in a friabilometer (Nova Ética, 300-1), and the weight loss percentage of 20 units of dipyrone 500 mg, nifedipine 20 mg, prednisone 5 mg and spironolactone 50 mg; and 10 units of acetaminophen 750 mg was calculated, based on the difference between the initial and final weight values.

Uniformity of dosage units

For this assay, 10 tablets from each sample were individually weighted. Each tablet was transferred to a 100 mL volumetric flask, 5 mL of 1% (v/v) hydrochloric acid (Dinâmica Química Contemporânea, SP, BR) were added, and shaken until complete disintegration. Then 70 mL of methanol (Dinâmica Química Contemporânea, SP, BR) were added and left to stand for 10 minutes. The volume of the volumetric flask was completed with methanol, the content was homogenized and filtered on filter paper, discarding the first milliliters. Dilution of the filtrate was carried out until 0.004% (w/v) and absorbances were measured at 275 nm for acetaminophen, at 258 nm for dipyrone, at 350 nm for nifedipine, at 239 nm for prednisone and at 238 nm for spironolactone, using methanol for zero adjustment. The same was done with the Chemical Reference Substances (CRS).

Dissolution test

For dissolution test, a 1% hydrochloric acid solution was used as the dissolving medium. 6 tablets from each sample were submitted to 100 rpm for 30 minutes in a dissolution apparatus (Nova Ética, 299). After the test, aliquots of the dissolution medium were taken and absorbances were measured at 275 nm for acetaminophen, at 258 nm for dipyrone, at 350 nm for nifedipine, at 239 nm for prednisone and at 238 nm for spironolactone, using 1% hydrochloric acid (v/v) as zero. To compare the obtained reading, the same was done with the Chemical Reference Substances (CRS).

Disintegration test

For disintegration test, 6 tablets from each sample were individually added to the disintegrator's baskets (Nova Ética, 301-AC) with water at 37°C for 30 minutes. This device uses a system with baskets and tubes, suitable container for immersion liquid, thermostat system for the heating maintenance and a vertical movement mechanism for baskets and tubes with specific frequency and paths.

Statistical analysis

Results were expressed as mean ± standard deviation. Windows version of the GraphPad Prism 5.01 software was used to perform statistical tests. And, one- or two-way ANOVA grouped analysis was used, followed by Bonferroni post-tests, with *P* values <0.05.

RESULTS AND DISCUSSION

According to the World Health Organization (WHO), the pharmacovigilance in ensuring the quality of drug products aims to reduce health-related problems caused by errors in medicines production, with the main characteristics of detecting, evaluating, preventing and understanding potential causes of quality deviations and reactions that may be caused by the drug [3]. The pharmaceutical form "tablet" exhibits a series of advantages in the administration of medicines with systemic effects and, therefore, has greater acceptance by the population [5]. Tablets' production costs lower when compared to other oral pharmaceutical forms, allow the administration of an exact single drug dose and present greater stability [6]. Depending on the manufacturing method, composition and the purpose of their administration, tablets may vary among themselves, including from batch to batch, in relation to thickness, diameter, size, weight, shape, hardness, disintegration characteristics, among other aspects [7]. Therefore, during production, these factors must be controlled by the quality control sector, in order to ensure – in addition to the appearance of products – their therapeutic efficacy [8].

Commercial presentations of medicines in Brazil are classified as reference, generic and similar. According to ANVISA, the reference medicine is an innovative product, registered to the responsible federal agency, whose efficacy, safety and quality have been scientifically proven; the generic medicine is an exact copy of the reference medicine, produced after the patent period, presenting efficacy and safety equivalent and, with it, being interchangeable. Interchangeability is ensured by therapeutic equivalence tests. Generic medicines are identified by their active ingredient and on the packaging, there is a yellow stripe that reads "Generic Medicine". Lastly, the similar medicine is that one that contains the same active ingredient, has the same concentration, pharmaceutical form, route of administration, dosage and therapeutic indication of the reference medicine. However, it may differ in characteristics related to the size and shape of the product, expiration date, packaging, labeling, excipients and vehicle, and must always be identified by a trade name or brand [9].

Quality control is essential at all stages of the medicine production. A product in solid form can undergo changes due to the action of various factors such as humidity, temperature, light and oxygen in the environment and by the characteristics of the solid state of the active ingredient and excipients used in the formulation [10]. Accordingly, it is important to observe if there are organoleptic alterations on tablets such as color, odor, presence of deformations, size, shape, cracks, presence of foreign material, legibility on the package, etc. In the products evaluated in this study, all samples were compliant, primary and secondary packaging were in perfect condition, no tablets missing from blisters, no deformities, cracks, foreign material, and sizes and coloring were uniform.

Identification tests are qualitative analytical methods, that is, they aim to confirm the identity of the active ingredient present in the medicine [11]. In this study, the applied identification test corresponded to the dosing test assay, via UV-Vis absorbances in the range of 200 nm to 500 nm, and also specific colorimetric identification. Table 1 compares the results obtained in the test with the data specified in the monograph of each active ingredient.

According to the results shown in Table 1, the absorbances obtained were close to the absorbances specified in the monographs of each medicine [2]. The largest discrepancies were seen in similar acetaminophen and nifedipine. Colorimetric identification tests – also performed for each active ingredient – confirmed the specificity of each sample. Thus, all samples fulfilled the corresponding identification.

Brazilian Pharmacopoeia 5th establishes that the acceptable weight variation for tablets with an average weight less than 80 mg is 10%, between 80 mg to 250 mg, 7.5%; for tablets weighing more than 250 mg, ± 5%; and no more than two units can be outside these limits. Table 2 presents the average weight and hardness results for each sample analyzed. Regarding the average weight, all samples met the established requirements, demonstrating that the manufacturing process was adequate. It suggests there was correct filling of the matrix and adjustment of the upper and lower punches [12]. The hardness test is mainly applied to uncoated tablets, allowing the determination of the tablet's resistance to crushing or rupture under radial pressure using a durometer. Results demonstrate that reference acetaminophen

tablets presented an average resistance value of 213.25 N; generic acetaminophen tablets, 218.32 N; and similar samples of acetaminophen, 168.83 N. Reference dipyrone tablets presented an average resistance value of 102.75 N; generic dipyrone tablets, 88.83 N; and similar dipyrone tablets, 122.01 N. Reference nifedipine tablets showed an average resistance value of 56.93 N; generic nifedipine tablets, 59.77 N; and similar nifedipine tablets, 43.95 N. In the same aspect, reference prednisone tablets presented an average resistance value of 76.75 N; generic prednisone tablets, 104.04 N; and similar samples of prednisone, 63.11 N. Ultimately, reference spironolactone tablets had an average resistance value of 105.48 N; generic spironolactone tablets, 79.07 N; and similar spironolactone tablets, 85.33 N. These results are acceptable, due to in the Brazilian Pharmacopoeia 5th the assay is only informative and has no specification.

The friability test is carried out in the friabilometer, a device that consists of a rotating cylinder, which spins around its axis at a speed of 25 rotations per minute. The test determines the resistance of tablets to abrasion when subjected to mechanical action and applies only to uncoated tablets. It consists of accurately weighing a determined number of pills, submitting them to the action of the device and removing them after 100 rotations. For tablets with an average weight equal to or less than 0.65g, 20 tablets should be used. For tablets with an average weight greater than 0.65g, 10 tablets should be used [4, 13]. Brazilian Pharmacopoeia 5th determines that no tablet may be broken, chipped or cracked at the end of the assay. Tablets with a loss equal to or less than 1.5% are considered acceptable. All samples passed the friability parameter, as shown in Table 3. Resembling results of friability were found when performing physical-chemical quality control analysis of acetaminophen, dipyrone and spironolactone tablets dispensed in Brazil [14-16].

The uniformity of dosage units assay was performed using the "uniformity of content" procedure, recommended by the monograph of acetaminophen, dipyrone, nifedipine, prednisone and spironolactone tablets [2]. The active ingredient content in tablets can vary from 90.00% to 110.00%. To calculate the content, acetaminophen, dipyrone, nifedipine, prednisone and spironolactone CRS solutions were used, which obtained the respective absorbances 0.892 nm, 0.831 nm, 0.079 nm, 0.242 nm and 0.511 nm [4]. Results in Table 3 show that all analyzed samples complied with the requirement for this test. Note the importance of this assay, due to it is possible to verify if pharmaceutical forms have the same concentration of active ingredients indicated by the manufacturer. The administration of a drug with a concentration of active ingredient higher than the declared can cause intoxication to the patient. However, the drug with an active ingredient content below the declared amount will result in therapeutic failure, affecting the patient clinical condition [17, 18].

The dissolution test determines the percentage of medicine that is released into the dissolution medium under defined conditions [2]. Dissolution is related to the medicine bioavailability in the body. Therefore, it is essential that it is dissolved, releasing a percentage of the active ingredient into the dissolution medium, so it can exert its pharmacological action [18]. Table 4 shows the results obtained in the dissolution test for all samples. Brazilian Pharmacopoeia 5th recommends that the minimum percentage of active principle released from each tablet is 80% for 30 minutes. As shown in Table 4, the only sample that did not meet the established requirements was the similar nifedipine. Furthermore, the similar sample of acetaminophen had a standard deviation in which some samples were below the established 80%. Formulation characteristics or the pharmaceutical form itself can influence the speed and extent of medicine dissolution, such as particle size, quantities and characteristics of aggregating agents, lubricants, mixing time, uniformity and humidity of powders and granules [19, 20]. Comparable results were found by Bueno et al [21] and Messa et al [22].

In determining the disintegration test as shown in Table 4, all tablets completely disintegrated before 30 minutes, which is the maximum time recommended [2]. Through these results, it is suggested that medicines in question – after being administered – disintegrate into smaller particles, consequently they will present rapid dissolution and absorption, becoming available to exert their pharmacological actions. These results agree with studies that evaluated the quality of spironolactone, propranolol and acetylsalicylic acid [23-25].

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Table 1. Identification test via UV-Vis absorbances at 275 nm for acetaminophen, at 258 nm for dipyrone, at 350 nm for nifedipine, at 239 nm for prednisone and at 238 nm for spironolactone.

Samples		Absorbances (monograph)	Absorbances (samples)
Acetaminophen	A	0.73	0.687
	B	0.73	0.661
	C	0.73	0.589#
Dipyrone	A	0.75	0.743
	B	0.75	0.733
	C	0.75	0.701
Nifedipine	A	0.69	0.705
	B	0.69	0.633
	C	0.69	0.448#
Prednisone	A	0.43	0.427
	B	0.43	0.407
	C	0.43	0.405
Spironolactone	A	0.22	0.201
	B	0.22	0.193
	C	0.22	0.195

A (reference), B (generic) and C (similar). # $P<0.05$

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Table 2. Values obtained in average weight determination and hardness assay from acetaminophen, dipyrone, nifedipine, prednisone and spironolactone tablets.

Samples		Average weight (mg)	Hardness (N)
Acetaminophen	A	827.07 (820.11 - 836.21)* (4.73)**	213.25 (6.46)**
	B	835.99 (829.11 - 841.41)* (3.87)**	218.32 (2.94)**
	C	835.31 (822.01 - 846.91)* (7.83)**	168.83 (3.62)**
Dipyrone	A	524.57 (518.51 - 538.89)* (5.01)**	102.75 (1.81)**
	B	604.47 (585.01 - 624.51)* (10.19)**	88.83 (6.88)**
	C	604.41 (593.79 - 611.89)* (4.81)**	122.01 (6.09)**
Nifedipine	A	108.99 (107.21 - 110.77)* (2.51)**	56.93 (6.09)**
	B	115.49 (112.59 - 118.31)* (1.84)**	59.77 (4.31)**
	C	167.52 (159.91 - 172.29)* (2.91)**	43.95 (8.16)**
Prednisone	A	201.45 (196.92 - 205.49)* (2.47)**	76.75 (10.92)**
	B	197.89 (190.83 - 205.11)* (3.81)**	104.04 (13.67)**
	C	198.59 (195.68 - 205.31)* (2.21)**	63.11 (0.94)**
Spironolactone	A	403.19 (390.92 - 412.21)* (5.98)**	105.48 (7.29)**
	B	330.12 (323.22 - 343.12)* (5.11)**	79.07 (2.69)**
	C	329.97 (321.51 - 338.01)* (3.94)**	85.33 (6.87)**

A (reference), B (generic) and C (similar); limits of variation*; standard deviation**

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Table 3. Friability determination and uniformity of dosage units assay from acetaminophen, dipyrone, nifedipine, prednisone and spironolactone tablets.

Samples		Weight loss percentage (%)	Content (%)
Acetaminophen	A	1.23	103.46 (2.88)*
	B	1.36	98.77 (1.16)*
	C	1.38	97.04 (2.44)*
Dipyrone	A	0.26	102.13 (2.01)*
	B	0.89	99.84 (1.17)*
	C	0.95	96.99 (2.18)*
Nifedipine	A	0.22	100.35 (1.88)*
	B	0.33	96.51 (1.94)*
	C	0.31	96.46 (3.33)*
Prednisone	A	0.42	103.31 (2.18)*
	B	0.58	99.54 (4.11)*
	C	0.72	97.02 (2.82)*
Spironolactone	A	0.33	100.77 (1.67)*
	B	0.32	98.12 (3.14)*
	C	0.37	98.46 (4.82)*

A (reference), B (generic) and C (similar); standard deviation*

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Table 4. Values obtained in the dissolution and disintegration tests from acetaminophen, dipyrone, nifedipine, prednisone and spironolactone tablets.

Samples		Content dissolved in the medium (%)	Disintegration (min)
Acetaminophen	A	86.57 (1.22)*	2.51
	B	87.04 (2.16)*	2.56
	C	83.18 (5.54)*#	2.22
Dipyrone	A	95.95 (2.78)*	4.55
	B	92.22 (4.31)*	5.42
	C	84.78 (4.13)*	4.21
Nifedipine	A	102.33 (4.82)*	8.22
	B	90.91 (7.14)	7.14
	C	50.52 (4.98)*#	2.31
Prednisone	A	99.97 (4.96)*	4.24
	B	98.08 (7.16)*	4.13
	C	102.64 (7.12)*	5.23
Spironolactone	A	101.33 (5.69)*	7.14
	B	109.01 (9.55)*	7.02
	C	88.73 (6.06)*	6.16

A (reference), B (generic) and C (similar); standard deviation*; # $P<0.05$; Minutes (min)

CONCLUSION

From obtained results, it could be concluded that practically all evaluated samples meet the specifications indicated in the Brazilian Pharmacopoeia 5th, presenting properties that qualify them as products suitable for consumption. Discrepancies were observed in similar acetaminophen and nifedipine related to identification test and dissolution assay.

Conflict Of Interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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