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DETERMINATION OF 50MG SODIUM DICLOFENAC CONTENT IN GENERIC AND SIMILAR REFERENCE MEDICINAL PRODUCT BY ULTRAVIOLET-VISIBLE SPECTROPHOTOMETRY

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ABSTRACT

Diclofenac classified pharmacologically as an anti-inflammatory non-steroidal (NSAID), is used to treat pain and inflammation, especially. It is found on the market in the pharmaceutical forms of suppository, ointment, gel and tablet. Quality control of this substance plays a large role in manufacturing, as it is of great value to identify and analyze the raw materials to be used as well as all inputs relevant to the drug development process. One of the tests that are used to determine the content of Diclofenac Sodium in tablets is the ultraviolet spectrophotometry technique. This study aimed to verify the content of the drug Diclofenac sodium in a reference drug, generic and similar, and to analyze the application of the visible ultraviolet spectrophotometric method described in the Brazilian Pharmacopoeia V. After the spectrophotometric analysis, the following results were obtained: the samples reference drugs had masses of R1 = 72.205 mg; R2 = 54.926 mg; R3 = 70.857 and the average concentration content 131.99%. Generic drugs had mass values equal to G1 = 69.509 mg; G2 = 70.980 mg; G3 = 70.367 mg and the average concentration content is 140.56%. Similar drugs had masses of S1 = 89.362 mg; S2 = 61.666 mg; S3 = 71.593 mg and the average concentration content 148.41%. Only the analyzed sample (R2) met the requirement for this test, being considered approved according to the content informed by Pharmacopoeia (90-110), indicating a possible failure in Good Manufacturing Practices and Quality Control.

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INTRODUCTION

Potassium diclofenac has the molecular formula C14H10Cℓ2KNO2, and is, in the chemical environment, known as the 2 - [(2,6-dichlorophenyl) amino] benzenoacetic acid potassium salt. It has the molecular weight 334.24 g mol/1 (Fernandes, 2017; Suzuki, 2012). Pharmacologically classified as a non-steroidal anti-inflammatory drug (NSAID), being used for acute treatment of post-traumatic inflammatory pain threshold, non-articular rheumatism, in painful, postoperative conditions, painful spinal syndromes, inflammatory conditions in gynecology and as pharmacotherapy for severe infections that lead to pain and inflammation in the upper areas: ear, nose or throat (Fernandes, 2017; Mckenzie 2014; Pershing 2015). The drug appears as a white crystalline powder, with affinity for absorption of air humidity, considerable solubilization in water, soluble in methanol and soluble in ethanol. It has some routes of administration, such as: oral, intramuscular, rectal or topical. Suppository, ointment, gel and tablet dosage forms are found on the market (Cesar *et al*., 2017). According to Silva *et*

al. (2017).Quality control plays a large role in the manufacture of a drug. It is very useful to identify and analyze the raw materials to be used as well as all inputs linked to manufacturing. This careful manufacturing, coupled with proper control of all production processes and the like, are invaluable in providing the final product with the desired safety and efficacy (Silva; Matheus; Monteiro,2017; Harrison, 2013). In the current scenario, there is a range of products supplied in the Brazilian market, so that the same active ingredient manufactured in the same concentration and in the same pharmaceutical form, may vary on physical and chemical characteristics when in analogy with different brands (Cesar *et al*., 2017). The same author points out that the use of products of doubtful origin, improper processes, temperature, storage and transportation, are some of the factors that compromise this quality control. This corroborates the studies by Alves (2018), in which he points out quality control as essential during all processing phases, encompassing several methods that favor the maintenance of an ideal result and avoid these deviations in the manufacturing standard. In Brazil, the National Health Surveillance Agency (ANVISA) is the agency that controls the application of quality control in the pharmaceutical industries. In turn, in laboratories, the regulations come from the Brazilian Pharmacopoeia, being the official code in the country (Alves, 2018). In order to guarantee the proper quality standard in the manufacture of Diclofenac Sodium 50mg, it goes through several tests that allow to show the principles of efficacy, quality and safety. One of the tests that are employed to determine the content of Diclofenac Sodium in tablets is the ultraviolet spectrophotometry technique, according to the methodology informed by the Brazilian Pharmacopoeia (Souza *et al*., 2018; Sequira, 2013; Puavilai, 2012).

Spectrophotometry is based on the absorption of light by molecules that are dispersed in a solution. Electromagnetic radiation, which makes up light, with a wavelength (λ) between 380 and 750 nm is visible to the human eye, constituting a small portion of the electromagnetic spectrum. The zone of the spectrum where the radiation has a wavelength below 380 nm is called ultraviolet (UV), while those with a wavelength above 750 nm correspond to the infrared zone. (Oliveira, 2017; Souza, 2016). Also according to Oliveira (2017), the spectrophotometer is a compact and easy to operate instrument. It can be applied in transmittance measurement, absorbance and direct reading of transparent material concentration. They are widely used in the field of hygiene and medicine, clinical examinations, biochemistry, chemical fuel engineering, environmental monitoring and inspection, quality control for qualitative and quantitative analysis of samples (Caron, 2016). The tablets that were analyzed from Diclofenac Sodium could have a margin ranging from 90.00% to 110.00% (Brazil, 2010, Cesar *et al*., 2017). The ultraviolet absorption spectrum exhibits maximums at 218 and 275 nm, identical to those observed in the standard solution spectrum (Brazilian Pharmacopoeia, 2010). Some studies show that a survey that was made on the site of products that are not regular at ANVISA, evidence between the period 2010-2016, nine specific resolutions imposing the withdrawal of different batches of medicines containing diclofenac sodium in the market. This leads to the need and paramount importance of performing good manufacturing practices (Brasil, 2010b), allowing the drug not to be released for commercialization before its proven efficacy and safety, in accordance with ANVISA and Brazilian Pharmacopoeia regulations (BRAZIL, 2010a; Cesar *et al*., 2017; Alves, 2018). Therefore, the quality control certification is of great contribution to the population that makes use of the medicines from the pharmaceutical laboratories, since these products are easily accessible in pharmacies, drugstores, hospital environments, Basic Health Units, among others (Cesar *et al*., 2017; Jackson 2019; Olsen, 2012). The administration of drugs with a lower or higher content than stated on the label, therefore, can cause problems to the user due to therapeutic failure, compromising the patient's clinical condition (Gondim *et al*., 2017). In this sense, evaluating the presentation forms of Diclofenac (reference, similar and generic) allowed to prove the safety and quality of the product to be marketed in the country, where it is expected that they (in full) agree with existing specifications, giving the same bioequivalence and bioavailability certified by ANVISA (Alves, 2018). Generic and similar drugs need to pass bioavailability and bioequivalence tests to ensure that they are effective from their use. Thus, bioavailability is a term that expresses the rate or concentration of an active ingredient that reaches the systemic circulation starting from its site of administration and exerts therapeutic action (Low, 2013; Testa, 2012). According to Anderson (2012) and Hamaguchi (2014) this parameter expresses the extent and speed of the biopharmaceutical and pharmacokinetic phases of the active substance. Two products can be compared by bioequivalence through four different studies: comparative clinical, pharmacokinetic, in vitro and pharmacodynamic. (Anvisa, 2006; Parfitt, 2012) Bioequivalence evaluates only the microbiological and physicochemical conditions provided in pharmacopoeias. (Narkar, 2015) And often the tests that are performed come down to determination of viscosity, density, appearance, identification, content, pH and average weight, so that neither the release of the drug from the formulation nor the Skin permeability of the drug are evaluated at the time of registration (Lippold *et al*., 2012; FDA, 2008). Thus, this study aimed to verify the content of the drug Diclofenac sodium in reference, generic and similar drug and to analyze the application of the visible ultraviolet spectrophotometric method described in Brazilian Pharmacopoeia V, verifying complies with the values recommended by the regulatory agency.

RESEARCH METHODOLOGY

Place of Study: The drugs used for the study came from a pharmacy in the municipality of Planalto, located in the state of Bahia.

Type of Study: The methodology of the study is of the experimental type in which it used to determine the Diclofenac Sodium content, the method proposed by the Brazilian Pharmacopoeia that uses the spectrophotometric analysis in the ultraviolet (UV) region in alkaline medium. The ultraviolet absorption spectrum exhibits maximums at 218 and 275 nm, identical to those observed in the standard solution spectrum. It is intended to contain at least 90,0% and at most 110,0% of the declared quantity of diclofenac (Brazilian Pharmacopea, 2010).

Materials: The materials used for analysis were: 1000 mL volumetric flask, 100 mL volumetric flask, 50 mL beaker, pistil grade, glass rod, pasteur pipette, spatula, micropipette, analytical balance, spectrophotometer, 50mL burette, Diclofenac standard, sodium hydroxide (0.1 mol \ L NaOH), and distilled water.

Sample: Diclofenac Sodium 50 mg tablets were purchased from a pharmacy in the municipality of Planalto, Bahia, from known laboratories with the reference (R), generic (G) and similar (S) presentations. The analyzes were performed in the chemistry laboratory of the Independent Faculty of the Northeast- FAINOR.

METHODS

Stockstock: The Solution was prepared by weighing 0.1000 g of the diclofenac standard in a beaker dissolving with 60 mL of 0.1 mol / L NaOH and transferred to a 100mL volumetric flask with distilled water, obtaining a solution of 1000 mg / L (stock solution) (Brazilian Pharmacopea, 2010).

Diclofenac Content: The tablets were weighed and sprayed. He transferred 50 mg of Diclofenac equivalent powder to a 100 ml volumetric flask, adding 70 ml 0.1 M sodium hydroxide. He sonicated for 15 minutes and made up to volume with the same solvent filtered. After The filtrate was transferred 5 ml into a 50 ml volumetric flask, made up to volume with the same solvent and homogenized to obtain a 50 µg / ml solution. The standard solution was prepared under the same conditions. He measured the absorbances of the solutions at 276 nm using 0.1 M sodium hydroxide for zero adjustment. The amount of Diclofenac in the tablets was calculated from the readings obtained (Brazilian Pharmacopea, 2010). The calibration curve was constructed using the standards with the following concentrations: 1, 2, 4, 8, 10, 16, 20, 30, 40, 50 mg/L. In the preparation of the standards 0.1 ml (1 mg / l), 0.2 ml (2 mg / l), 0.4 ml (4 mg/l), 0.8 ml (8 mg/l), 1.0 mL (10 mg/L), 1.6 mL (16mg / L), 2.0 mL (20mg / L), 3.0 mL (30mg/ L), 4 mL (40mg/L) and 5 0.0mL (50mg/L) using a volumetric pipette and taking care to complete the volume of the 100.00 mL volumetric flask with 60 mL of 0.1 mol/L NaOH and the remainder with distilled water using Pasteur pipette, checking the meniscus.

***Procedure*:** Diclofenac Sodium analyzes were performed in the different presentations, one reference drug, one generic drug and one similar drug. Of these, the analyzes were made in triplicate.

RESULTS

To interpret the research results, qualitative and quantitative analysis were performed through a spreadsheet using the Microsoft Excel® 2013 program using statistical measures, expressed as graphs and tables.

RESULTS AND DISCUSSION

Diclofenac sodium calibration curve presents a good linearity range, reproducing values of linear regression coefficient R^2 = 0.994, which is in accordance with the value recommended by Resolution No. 899/2003, of correlation coefficient equal to 0.99 sample was used with triplicate analyzes of the reference drug (R1, R2, R3), generic (G1, G2, G3) and similar (S1, S2, S3). After spectrophotometric analysis, the following results were obtained: the reference drug samples presented masses of R1=72.205mg; R2 = 54.926 mg; R3=70.857 and the average concentration content 131.99%. Generic drugs had mass values equal to G1=69.509 mg; G2=70.980 mg; G3=70.367 mg and the average concentration content is 140.56%. Similar drugs had masses of S1=89.362 mg; S2=61.666 mg; S3= 71.593 mg and the average concentration content 148.41%. According to the Brazilian Pharmacopoeia (2010), the ideal amount of Diclofenac Sodium concentration to be found in a tablet should be within a range of 90.0% to 110.0% average concentration content. Samples of the generic and similar medicinal products do not fit the recommended concentration of active ingredient, but only one sample of the reference medicinal product within the concentration range acceptance range, as shown in Table 01. The assay is intended to quantify the content of active ingredient contained in us. Tablets analyzed and may have a range of 90.00% to 110.00% in the case of diclofenac (Brazil, 2010a). Analyzing the data in Table 1, it is observed that only the analyzed sample (R2) met the requirement for this test. To avoid these results related to low or high concentration of active ingredients, it is the Pharmaceuticals Laboratories and Industries should be concerned with Quality Control Management regarding compliance and compliance with the laws governing the principles of Good Manufacturing Practice (GMP) tailoring the most rigorous and strict quality control to the results, while

Figure 1. Diclofenac calibration curve One

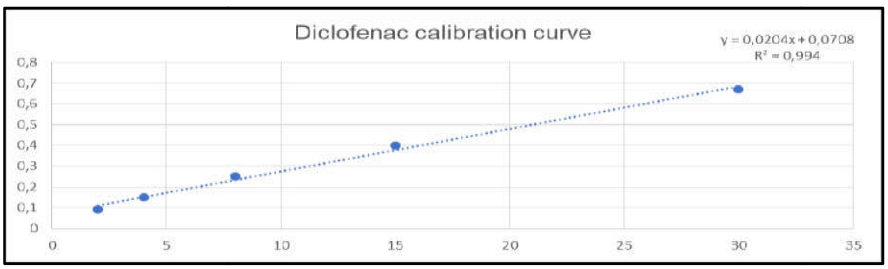

Table 1. Result of Diclofenac Sample Analysis

Sample	*Diclofenac Mass (mg)*	*Concentration Content (%)*	*Acceptance Content (%)*	*Result*
R1	72.205	144.41	90-110	Disapproved
R2	54.926	109.853	90-110	Approved
R3	70.857	141.716	90-110	Disapproved
G1	69.509	139.02	90- 110	Disapproved
G2	70,980	141,961	90-110	Disapproved
G3	70,367	140,735	90-110	Disapproved
S1	89,362	178,725	90-110	Disapproved
S2	61,666	123,333	90-110	Disapproved
S3	71,593	143,186	90-110	Disapproved

this process is intertwined with public health and directly linked to the user of this drug that needs therapeutic success (Silva *et al.,* 2015). The pharmaceutical industry should have as a basis for the execution of all manufacturing processes the Manual of Good Manufacturing Practices of Medicines, because it brings subsidy and necessary measures that help in the reduction of cross-contamination, particle contamination, exchange or mixture of ingredients, risks that are intrinsically related to the production processes of a pharmaceutical industry (Barreto, 2017). Lots of potassium diclofenac containing medicines are commonly collected by ANVISA because they are not in compliance. A survey conducted on ANVISA's website for irregular products showed that nine specific Resolutions were published in the period 2010-2016, requiring market recall of different batches of diclofenac-containing medicines. This shows the need and importance of following good manufacturing practices (Brasil, 2010b), so that the requirements established by the Brazilian Pharmacopoeia (Brasil, 2010a) are met.

Final Considerations

With the accomplishment of this work, it can be verified with the samples used in the research, containing the substance Diclofenac sodium 50mg, that only one sample (R2) of the reference drug was within the ideal active ingredient content and recommended by the current legislation. , accusing a possible failure in Good Manufacturing Practices and Quality Control. This information infers the importance of quality control in the pharmaceutical industries to ensure that the drug, in its final state, is fully viable for the marketing and consumption of patients. Thus, Good Drug Manufacturing Practices need to be rigorously standardized and made so that there is adequate concentration without interference with drug therapy.

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