



Quality assessment of samples of generic and similar aspirin tablets (500 mg) marketed in Brazil

Avaliação da qualidade de amostras de comprimidos de ácido acetilsalicílico (500 mg) genéricos e similares comercializados no Brasil

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ABSTRACT

The interchangeability between a generic and the respective reference drug is based on the concept of therapeutic equivalence between them, usually provided by evidence of pharmaceutical equivalence, bioequivalence, Good Manufacturing Practices (GMP), and quality control. This study aimed to evaluate the pharmaceutical equivalence between four brands of 500 mg aspirin tablets (two generic, G, and two similar, S) in relation to the reference drug (Aspirin® Bayer, R). The following tests were performed: uniformity of mass; friability; disintegration time; hardness; limit of free salicylic acid; assay; uniformity of dosage units; dissolution; identification; and dissolution profile. The similar drug 2 (S2) is out of specifications in the tests of limit of free salicylic acid, friability and assay. The drug S1 was not approved in the limit test. Moreover, the results from the dissolution profile (graphic and f2 factor) showed that the six test drugs were not pharmaceutically equivalent to the R.

Keywords: pharmaceutical equivalence, generic, similar, reference, interchangeability

RESUMO

A intercambialidade entre o medicamento genérico e seu o seu respectivo medicamento de referência baseia-se no conceito de equivalência terapêutica entre os mesmos, geralmente assegurado pela comprovação da equivalência farmacêutica, da bioequivalência, boas práticas de fabricação e controle de qualidade. A equivalência farmacêutica entre dois medicamentos relaciona-se à comprovação *in vitro* de ambos conterem o mesmo fármaco, mesma dosagem e a mesma forma farmacêutica, podendo ou não conter excipientes idênticos. O objetivo desse trabalho foi avaliar a equivalência farmacêutica entre quatro marcas de comprimidos de ácido acetilsalicílico 500mg (dois genéricos, G1 e G2; dois similares, S1 e S2) em relação ao medicamento de referência (Aspirina® Bayer 500 mg). Foram realizados ensaios de: peso médio; friabilidade; desintegração; dureza; identificação; limite de ácido salicílico livre; doseamento; uniformidade de doses; e perfil de dissolução. Em relação a pureza, friabilidade e doseamento o lote S2 foi reprovado em todos os ensaios; já o S1 apenas no ensaio de pureza. Entretanto, os resultados encontrados no perfil de dissolução mostraram que os medicamentos-testes não são equivalentes farmacêuticos ao medicamento de referência (R).

Palavras-chave: equivalência farmacêutica, genérico, similar, referência, intercambialidade

INTRODUÇÃO

In recent years, issues related to drugs and pharmaceutical services are gaining space in the government agenda and society. In recent decades, increasingly safe and effective drugs for almost all diseases have been developed. This quality not only is a commercial attribute, but also legal and moral, since the

non-compliance of quality specifications considered essential can have serious implications, such as lack of effectiveness in the treatment due to therapeutic sub-doses, toxic effects caused by therapeutic over-doses and, consequently, lack of patient adherence to treatment (Köhler *et al.*, 2009).

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The process to ensure quality, safety, and efficacy of drugs is based on compliance with health regulations, nationally coordinated by Brazilian Health Surveillance Agency (ANVISA), which publishes a series of standards to guide the entire implementation process of the national drug policy (Gil *et al.*, 2007). Generic drugs were introduced in Brazil by the Law No. 9787 of February 10, 1999. Its emergence helped raise the population's access to effective drugs, with guaranteed therapeutic, and lower cost. For a generic drug to be interchangeable with its reference product, it needs to be a therapeutic equivalent, which helps to ensure that both have the same efficiency. The interchangeability between drugs is based on this concept, which is ensured by the proof of pharmaceutical equivalence, bioequivalence, good manufacturing practices, and quality control (Storpirtis *et al.*, 2004).

A study on pharmaceutical equivalence between two drugs (a test drug – similar or generic – and its reference product) relates to the *in vitro* evidence that both contain the same drug in the same quantity and dosage form and containing or not identical excipients (Shargel *et al.*, 1999). Both must meet the updated specifications of the Brazilian Pharmacopoeia or other authorized codes, or even with other applicable quality standards (Brasil, 2003). The test drug, meeting these specifications, is safe for use in the population (Ansel *et al.*, 2000). The pharmaceutical equivalence is guaranteed by means of chemical and physical tests described in the respective monographs published in the official compendia recognized by law (Brasil, 2010a), and is one of the studies, along with the relative bioavailability, which must be performed to ensure the interchangeability of a generic product with its reference product (Brasil, 2003)

The resolution #31/2010 (Brasil, 2010a) exempts certain types of medication from the relative bioavailability study. Among these are drugs containing aspirin, acetaminophen, metamizole or ibuprofen, even as tablets. In these cases, the pharmaceutical equivalence study, and in particular the study on dissolution profile, is the essential step to determining the bioequivalence between two medications (Brasil, 2010a). Other drugs in this situation are those presented in the form of modified release adhesives for topical use, creams, ointments, gels, pastes, and suspensions, whose pharmaceutical equivalence is verified by studying the dissolution profile (Storpirtis, 1999).

The evaluation of pharmaceutical equivalence for drugs in tablets form is very important since these are forms in which most problems can occur affecting the dissolution and undertaking bioequivalence (Prista *et al.*, 1995). Thus, during drugs production, certain factors must be controlled to ensure the therapeutic efficacy (Ansel *et al.*, 2000), thus guaranteeing the safety, efficacy, and quality of the product throughout the expiration date (Peixoto, Santos JR & Santos, 2005).

Aspirin (ASA, 2-acetoxibenzoic, Figure 1) is an important drug and has analgesic, antipyretic and anti-inflammatory activity, it would also be effective in treating various heart and circulatory disorders (Goodman & Gilman, 2006; Silva, 2010). Most drugs prepared with aspirin are marketed as over-the-counter, and are exempt from the study of relative bioavailability, according to the resolution #31/2010 (Brasil, 2010a). Considering the

medicinal importance of this drugs and the importance of pharmaceutical equivalence for its quality assessment, this study aimed to evaluate the overall quality and pharmaceutical equivalence between four test drugs (two generic and two similar) and its corresponding reference product of Aspirin 500 mg tablets.

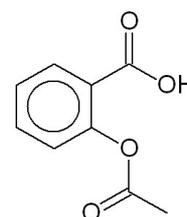


Figure 1. Structural formula of aspirin

MATERIAL AND METHODS

Samples and assays

Samples of five different brands of Aspirin 500 mg tablets were used. All were acquired in commercial drugstores located in Cascavel-PR. One of the brands corresponds to the reference product (R), Aspirin[®] Bayer 500 mg (Batch: 827481). The others correspond to four different lots produced by four different laboratories, two generic drugs (G1 and G2) and two similar (S1 and S2). Tests were performed following the method described in General Methods (Brasil, 2010b) and in monograph (Brasil, 2010c) of the Brazilian Pharmacopoeia 5th Edition - F. Bras. V, except for the chemical identification test of the active principle, which was carried out as described in the monograph of the USP-NF 28 (US Pharmacopeial Convention, 2005). The dissolution profile was performed following the advice of the Guide for Study Performing and Development of Pharmaceutical Equivalence and Dissolution Profile Report (Brasil, 2010a). Volumetric (VS), reagents (SR), and indicator (SI) solutions were prepared following the specifications of F. Bras. V (2010b).

Uniformity of mass

Twenty tablets from each sample were individually weighed on an analytical balance (0.1 mg sensitivity), and the average-weight was determined (Brasil, 2010b).

Disintegration

The immersion liquid for this test was water at $37 \pm 1^\circ\text{C}$. For each product, 18 tablets were used (Brasil, 2010b). With the help of the inbuilt chronometer, the time needed for total disintegration of the tablets was recorded (in minutes).

Hardness

The test consisted of compressing a tablet across its diameter until it broke. This parameter was evaluated with a digital tablet hardness tester. For each product, 10 tablets were used (Brasil, 2010b).

Friability

Twenty tablets from each sample were individually weighed on an analytical balance and then placed in the drum of a friability test. After 5 minutes of testing (100 rotations), the drum was stopped; the powder generated by

the tablets was collected, and the tablets were again weighed (Brasil, 2010b).

Identification

A quantity of powder equivalent to 0.5 g Aspirin from 20 tablets grinding was transferred to an Erlenmeyer flask with 20 mL of water, and then the mixture was heated to boiling. In the end, three drops of ferric chloride III SR were added (US Pharmacopeial Convention, 2005).

Limit test of free salicylic acid

A quantity of powder equivalent to 0.2 g Aspirin from 20 tablets grinding, being transferred into a 100 mL volumetric flask. Subsequently, 4 mL of ethanol were added, and the volume was completed to 100 mL with chilled water, making sure that the temperature was always below 10 °C. The mixture obtained was filtered and 50 mL of filtrate were immediately transferred to a Nessler tube. In a second tube, 3 mL of 0.01% salicylic acid (w/v) were transferred, and the volume was completed to 50 mL using water. In each tube 1 mL of nitric ammonium ferric sulphate SR was added (Brasil, 2010c).

Assay

20 tablets of aspirin were weighed and pulverized and an amount equivalent to 0.5 g of Aspirin was transferred to a 250 mL Erlenmeyer flask, in which was added 30 mL of 0.5 M sodium hydroxide VS. The mixture obtained was gently boiled for 10 minutes. The base excess was titrated with 0.5 M hydrochloric acid VS, using phenol red SI as indicator. The same procedure was performed to the blank test. Each mL of 0.5 M sodium hydroxide VS is equivalent to 45.040 mg of Aspirin (Brasil, 2010c).

Dose uniformity

This test was performed by the mass variation method. Thus, the content of each tablet was determined based on test results of quantitative analysis. 10 tablets were individually weighed. The Aspirin contents were calculated assuming a homogeneous distribution of this component (Brasil, 2010b).

Dissolution test

The dissolution was carried out using 0.05 M acetate buffer medium (pH 4.5), with a volume of 500 mL. Paddles (apparatus II) were used at 50 rpm. A 10 mL aliquot of sample was collected after 30 minutes, filtered, and the absorbance in the region of ultraviolet were determined at 265 nm. The dissolution medium was used for zero adjustment. The amount of Aspirin dissolved in the medium was determined by comparing the readings obtained with that of a 0.008% solution (w/v) of Aspirin SQR F. Bras. prepared just before use (Brasil, 2010c). This test was performed in triplicate.

Dissolution profile

The dissolution profile was performed using the same methodology described for the dissolution test, but this test was performed for 35 minutes with aliquots collection at the times 5, 10, 15, 20, 30, and 35 minutes. In each sample, a 10 mL aliquot of dissolution medium was removed, this volume being immediately replaced. Each

analytical run was performed in triplicate. The similarity (f_2) factor (BRASIL, 2010) was calculated according to Equation 1.

$$f_2 = 50 \times \log \left\{ \left[1 + \frac{\sum_{t=1}^n (R_t - T_t)}{n} \right]^{-0.5} \right\} \times 100$$

Eq. 1

where: n is the number of collection times; R_t is the amount of reference product dissolved in the medium at t collection time, T_t is the amount of test drug dissolved in the medium at the t test collection time (Brasil, 2010a).

RESULTS AND DISCUSSION

The uniformity of mass test allows checking whether there is homogeneity among units from the same batch. Those showing different weights may have different active levels as well (Ansel *et al.*, 2000). Whereas the four brands had mean weight close to 0.600 mg, the maximum acceptable weight variation is $\pm 5.0\%$ with up to two units out of bounds, and none with more than twice the variation (Brasil, 2010b). Thus, according to the figures presented in Table 1, all samples complied with these limits and were approved in this test.

Table 1. Results for uniformity of mass test

Drug*	R	G1	G2	SI	S2
Uniformity of mass (g)	0.599	0.612	0.617	0.612	0.578
CV (%)	3.5	1.44	1.30	2.10	0.7
Result	Approved	Approved	Approved	Approved	Approved

*n = 20 tables from each brand

The methods of abrasion resistance, specifically the friability test, evaluate what happens to a tablet due to its handling. If a tablet is very friable, it means that it tends to show mechanical erosion. Thus, an important property of a tablet is its ability to resist friction, ensuring that the correct drug amount is administered, and the tablet appearance will not change due to handling (Aulton, 2006). Tablets with losses of less than 1.5% of their weight are considered acceptable (Brasil, 2010b). As shown in Table 2, the sample S2 showed friability much higher than this limit, being the most susceptible to deterioration and weight loss; therefore, it has failed.

Table 2. Results for friability test

Drug	Mass Loss (%)
R	0.094
G1	0.460
G2	0.414
SI	1.243
S2	4.035

Hardness is related mainly to the strength of a tablet during processes of packaging, storage and transportation. However, very resistant drugs may have prolonged dissolution time (Ansel *et al.*, 2000). The minimum hardness recommended is 30 N to the system where the force is exerted by a coil spring (Brasil, 2010b). According to Table 3, all lots may be approved under this criterion, except for lot S2, exactly that one which had failed in the friability test, which also has the lowest hardness. This result and that obtained in this friability test show that this drug does not have adequate mechanical resistance to be normally handled.

Table 3. Results for hardness test

Drug	R	G1	G2	S1	S2
Hardness	81.8	105.65	142.9	70.0	35.2
(N)					
CV(%)	4.8	17.5	7.5	4.2	1.6
Result	Approved	Approved	Approved	Approved	Failed

The disintegration process of a solid dosage form is a major step towards its bioavailability (Serra, 1998). The testing time used was 30 minutes, and after this time the tablets should be completely dissolved. Following the specifications described in general methods of F. Bras. V (Brasil, 2010b), all samples had disintegrated within a time of 30 minutes. Table 4 shows the disintegration times for each drug, showing that the results are consistent with that specified.

Table 4. Results for disintegration time test

Drug	Disintegration Time (minutes)
R	0.46
G1	2.16
G2	0.38
S1	5.50
S2	0.95

The chemical identification test aimed to confirm that the active principle under study was actually used for the production of each drug. All test drugs were approved in this test, since all solutions presented formation of violet color as expected. The purity test, however, aims to determine if the salicylic acid content, the major Aspirin degradation product, is within the acceptable limit. This test is an indicator of the drug stability, since it originates in the occurrence of the active ingredient hydrolysis. Moreover, salicylic acid had more potent toxic effects than ASA (Bricks, 1998). Samples S1 and S2 showed a more intense violet color than the standard solution for comparison, and thus have a higher quantity of free salicylic acid than the tolerated amount (0.3%) (US Pharmacopeial Convention, 2005).

The assay shows a mean concentration of active principle in the drug. The F. Bras. V (Brasil, 2010c) states

that Aspirin tablets are required to provide an average content between 95% and 105% on the declared value of the drug. The content assessment should also be performed via doses uniformity test, since variations between units in a lot may occur. The method for determination of content uniformity can be applied in all cases and is required for all types of tablets, coated or not, transdermal systems, suspensions in containers in a single dose or in soft capsules. Limits for these variations are specified by the pharmacopoeias (Aulton, 2006). According to F. Bras. V (2010b), Aspirin tablets must present 85% to 115% of active content in each unit dose and a coefficient of variation (CV%) less than or equal to 6%. Considering the limits, three test drugs were approved in the assay and dose uniformity test, while sample S2 has failed in both (Table 5).

Table 5. Results of dose uniformity tests

Drug	Dose	CV(%)	Result	Dose	CV(%)	Result
Uniformity						
R	98%	0.51	Approved	97% - 99%	1.40	Approved
G1	102%	0.98	Approved	96% - 99%	2.10	Approved
G2	97%	1.06	Approved	99% - 104%	3.50	Approved
S1	105%	0.95	Approved	102% - 108%	4.00	Approved
S2	109%	0.91	Failed	106% - 109%	2.00	Approved

The dissolution test aims to determine the time a drug takes for being released and dissolved in liquids from the absorption site (Ansel *et al.*, 2000). This quality parameter is extremely important for solid dosage forms, since the drug has to be dissolved in biological fluids for being absorbed (Aulton, 2006). The solid pharmaceutical forms for oral use are manufactured using various adjuvant pharmaceuticals and may be produced through processes that involve multiple steps. These factors may affect the dissolution time, affecting the absorption and, consequently, the expected therapeutic effect (Storpiertis *et al.*, 2004). According to F. Bras. V (Brasil, 2010c), at least 80% of Aspirin should be dissolved after 30 minutes. As it can be observed in Table 6, the drugs R, G1, and G2 were approved in the spot test of dissolution, but the same did not occur with drugs S1 and S2.

Table 6. Results for dissolution test

Drugs	Dissolved content (%)	CV(%)	Result
R	99	1.39	Approved
G1	88	1.96	Approved
G2	86	2.24	Approved
S1	31	2.0	Failed
S2	54	0.64	Failed

Results presented in Tables 2 to 6 shows that in a process of routine quality control, the drugs R, G1, and G2 would pass all criteria, while S1 and S2 would not be approved. However, for a drug to be considered a pharmaceutical equivalent, Brazilian law determines that the study on the dissolution profile compared to its reference product must

be evaluated (Brasil, 2010a). This approach can also assist in the development and optimization of formulations, allow the monitoring of manufacturing processes, minimize the risk of lack of bioequivalence between lots, evaluate the influence of critical variables in the production process, establish the mechanism and releasing kinetics, allow correlations in vitro/in vivo and the comparison of different formulations (Anderson *et al.*, 1998). For this, it is evaluated the curve obtained between the dissolution time and the contents in each collection time (Brasil, 2010a). Figure 2 shows the dissolution curves obtained for each test drug and R. A simple observation of the five curves already indicates that the behavior of test drugs as to their time of dissolution is fairly different from the reference product's behavior.

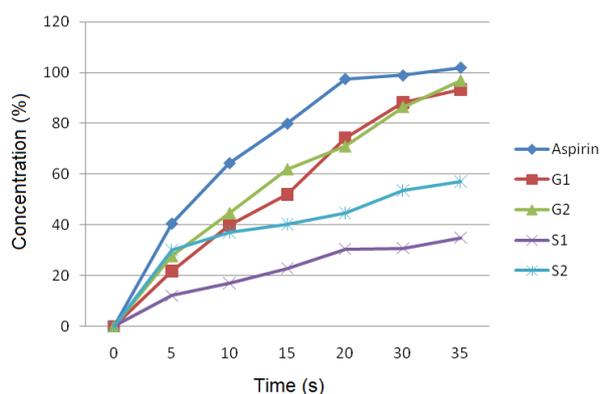


Figure 2. Dissolution profile of the analyzed drugs

However, when the dissolution has value equal to or higher than 85% of dissolved drug within 15 minutes (Brasil, 2010a), the simple curves inspection is not sufficient to determine if the profiles are equivalent or not, since there may be errors in a visual reading of the chart (Marcolongo, 2003). Thus, test drugs can be compared to the reference product using two calculated factors based on the results for each collection point, the similarity factor (f_2 , Equation 2). The f_2 factor corresponds to a similarity measure between percentages of both profiles (Marcolongo, 2003).

Results of f_2 factor are shown in Table 7. Since two dissolution profiles are considered equivalent, values of 50 to 100 must be obtained (Brasil, 2010a). Thus, it is possible to confirm that dissolution profiles of test drugs are significantly different from the reference product, and thus cannot be considered pharmaceutically equivalent.

Table 7. Results of f_2 factor between the test drugs and R

Groups	f_2
R x G1	35
R x G2	39
R x S1	12
R x S2	20

Results show that the four different brands of Aspirin 500 mg did not present the necessary quality to be used as therapeutic agents, in addition to not being considered a pharmaceutical equivalent to R. A previous result obtained by our group showed that the quality problems related to drugs containing aspirin may be considered a significant problem. Bunhak, de Melo and Stoef (2010) conducted an equivalent study to that presented in this work with pediatric Aspirin tablets (100 mg). In that paper, eight lots produced by two different laboratories (both as similar drugs) were analyzed, and all six lots from one of the laboratories had f_1 and f_2 values outside the specified limits. Moreover, despite the two lots belonging to the second laboratory having been approved on the dissolution profile, they were not approved concerning the free salicylic acid contents.

Deviations from the recommended quality of a drug may lead to serious consequences for patients or even an entire public health system. Unfortunately, the results of this study cannot be considered an isolated case. In a recent article by this group (Giordani & de Melo, 2012), deviations of quality were also observed in a group of drugs based on metamizole. Two generic and two similar drugs (corresponding to 66.7% of the samples) were not approved. Köhler *et al.* (2009), in another study with metamizole, had a worse result: all samples were not approved. For their part, Brum *et al.* (2012) observed that two generic drugs based on acetaminophen proved to be not equivalent to its reference drug, which corresponded to 25% of the analyzed sample (n=8). The results presented here add up to these and other works (Castro *et al.*, 2005; Rodrigues *et al.*, 2006; Rodrigues *et al.*, 2008; Scandolaria *et al.*, 2008) showing that an increasing demand for a tougher legislation and a more active supervision on the quality of similar drugs and generic drugs are necessary.

CONCLUSION

Results lead to the conclusion that all analyzed drugs cannot be considered equivalent to its reference pharmaceutical drug. Although generic drugs (G1 and G2) are in conformity with the pharmacopoeial tests performed, both these and similar drugs (S1 and S2) have dissolution profiles different from that of the reference product. This indicates that it is imperative to assess the quality parameters of generic and the similar drugs not only after production but also when these are already being marketed.

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