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Evaluation of the nimesulide content in splitting tablets

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Abstract. Nimesulide is a non-steroidal anti-inflammatory drug (NSAID) that inhibits the action of the enzyme cyclooxygenase-2 and is widely used in many countries for the treatment of pain and inflammation. It is often given on a dosage adjustment basis mainly in the elderly and children. In the present work the nimesulide tablet splitting process from three different suppliers was studied using a tablet cutter in order to verify the influence of the breakdown of the same on the content of each obtained fragment. The tests of average weight, hardness, friability, disintegration, dosage and uniformity of unit doses were performed following the official methodology established by the Brazilian Pharmacopoeia. The samples studied met the official specifications before being submitted to the partition procedure; however, after dividing the tablets, the drug content in the halves presented excessive variation, showing that this procedure should not be performed for the drug Nimesulide. In cases of need for varying administration doses of Nimesulide, it is recommended that the drug be manipulated or that another pharmaceutical form is used in order to ensure dosage in each unit of the dosage form.
Key words: Nimesulide, splitting tablets, quality control.

Introduction

Tablets are the most commercially available pharmaceutical form in the world due to ease of administration and low cost (BANKER, 1986), but in many cases the splitting tablets habit is mainly performed with the objective of adjusting therapeutic dosage, facilitate the ingestion of the drug or reduce the cost of treatment (CONTI, 2007; BERG et al, 2010; VERRUE et al, 2010). Thus, tablet splitting has become a common practice, especially in the treatment of children and the elderly (FAELELBOM, 2016).

One of the problems in tablet splitting is that they can cause changes in weight and content due to fragmentation and disintegration, which can compromise the patient's treatment and even endanger their health due to low or overconcentration of the active substance (HILL et al., 2009; HABIB et al., 2014).

Tablet splitting is still a well-discussed subject, which has both advantages and disadvantages. The greatest advantage reported is in the reduction of annual costs in patients who make continuous use of medicines, while the number of disadvantages is greater, for example: contamination at the time of the partition and its packaging, difficulty in division, loss of mass, the dosage is not guaranteed, among others (FERREIRA et al., 2011; VAN SANTEN et al., 2001).

In quality control, tablet splitting may cause changes in tablet weight, may interfere with disintegration and dissolution of tablets, compromising patient management and even leading to unexpected risk (HILL et al, 2009; HABIB et al, 2014).

Among the various pharmaceutical classes, anti-inflammatory drugs are widely used drugs, especially Nimesulide that is marketed in several countries. It is indicated for the treatment of pain and inflammation, besides being one of the most used in self-medication (MORAIS, 2007). They act by selectively inhibiting cyclooxygenase-2 (COX-2) and the oral dose is 100 mg twice daily (BRUNTON et al., 2012; KATZUNG et al., 2017).

Thus, the objective of this study was to evaluate the individual contents of the active substance Nimesulide in tablet samples (reference, generic and similar) available in the Brazilian market of medicines after their splitting.

Methods

Samples

Samples from three laboratories producing nimesulide tablets at the 100 mg strength were studied. The drugs were purchased commercially from the municipality of Sinop-MT, being designated as: R (reference), G (generic) and S (similar). The tablets from each laboratory belonged to the same manufacturing batch. For ethical reasons, the names of the drug manufacturers were not informed.

Reference Chemical Substance (RCS)

The chemical reference substance (RCS) of pharmaceutical grade, nimesulide, has been assigned by Arte Farma.

Reagents

All reagents used were analytical grade: distilled water, sodium hydroxide (Synth®), methanol (Synth® and Neon®).

Equipment

The equipment used was: analytical balance (Shimadzu-AUY220), ultrasound (Cristófoli), disintegrator (Logen model LS-DT-3), durometer (Logen-medelo LSD-DI and New Ethics - model 298 ATTS), spectrophotometer (FIMR) (Affinity - 1 - Shimadzu), dissolutor (Quims - Q850), friabilometer (New Ethics - model 300-1), Fourier Transform Infrared Spectrophotometer (Shimatzu).

For the analysis of the studied drugs, the tests recommended in the Brazilian Pharmacopoeia (BRAZIL, 2010) were applied, which were described as follows:

*Identification***:** For the identification test, the Fourier Transform Infrared (FTIR) absorption spectrophotometry method was used using the Affinity-1 Fourier Transform infrared spectrophotometer. Spectra were obtained using potassium bromide pellets containing about 1-2% nimesulide, which were recorded at room temperature in the range of 2000-500 cm^{-1}. For each sample, 20 scans were recorded with a resolution of 4 cm^{-1}. The test was considered positive if the samples had absorption maxima only at the same wavelengths and with the same relative intensities as those observed in the nimesulide spectrum (RCS), prepared in an identical manner.

Mean weight determination**:** 20 tablets of each pharmaceutical were individually weighed as well as the tablets broken into analytical balance, and the average weights, standard deviation and coefficient of variation were calculated. According to the Brazilian Pharmacopoeia, of the twenty units tested, no more than two units outside the specified limits can be tolerated (variation limit of 7.5%); however, no sample should contain unit weight above or below twice the percentages indicated. For the split tablets the same procedure was adopted since there is no methodology in the pharmacopoeias for the same ones. Thus the partition was performed using tablet cutter.

*Friability***:** Twenty tablets of each pharmaceutical were weighed and introduced into a friabilometer. After 100 revolutions performed for 4 minutes (25 rpm), the tablets were removed from the apparatus and all residue or dust were removed and reweighed. The friability was calculated by the difference between the initial weight and the final weight of the tablets. Tablets with loss less than 1.5% of their weight were considered acceptable. Tablets that have been chipped or separated into two layers will not be considered for calculating the percentage of friability.

Disintegration time: Six tablets of each brand were subjected to transparent tubes of the equipment contained in a basket. Then the acrylic disks were added over the tablets. The basket containing the tubes with the respective samples was transferred to the apparatus support. The basket was then subjected to vertical movements in a liquid medium (water) at 37 ºC ± 2 ºC until the tablets completely disintegrated. The time limit set as the general acceptance criterion is 30 minutes.

Hardness: Ten units were submitted to the test, using the durometer, aiming to verify the resistance of the same to a force applied diametrically. According to the Brazilian Pharmacopoeias, the minimum acceptable is 30 N (approximately 3 kgf).

*Dosing***:** 20 whole tablets were weighed and sprayed. After grinding, the amount of powder equivalent to 0.1g of Nimesulide was transferred to a 100mL volumetric flask, added with 60 mL of 0.1 M sodium hydroxide and stirred for 40 minutes. The volume was then filled with the same solvent and then filtered. The filtrate was diluted to a concentration of 0.002 % (w / v) using 0.1 M sodium hydroxide. A standard solution was prepared in the same concentration, using the same solvent. The absorbances of the solutions were determined at 392 nm using 0.1 M sodium hydroxide to adjust for zero and the amount of $C_{13}H_{12}N_2O_5S$ in the calculated tablets.

Uniformity of unit dose: The same dosing procedure was used and the assay was performed individually with 10 whole tablets and 10 divided tablets.

Results and discussion

The identification test performed by FTIR showed that all products contain nimesulide (Figure

1), as they presented the same absorption bands as nimesulide RCS.

In Table 1 and 2 are the results of the mean weight of the whole and split Nimesulide R, G and S tablets where a greater variation was observed in the similar tablets. In whole tablets, R and G had the same coefficient of variation (CV %) of 0.920% while similar tablets had a variation of 2.75%. It was observed that all the tablets were presented according to the limits recommended by the Brazilian Pharmacopoeia (BRASIL, 2010), whose limit of variation is +/- 7.5 %. Split tablets, however, showed a high coefficient of variation, which reproves all tablets in the determination of average weight.

Similar studies performed by Van Santen et al (2002) and Quinzler et al (2006) showed that split tablets present greater variations than intact tablets.

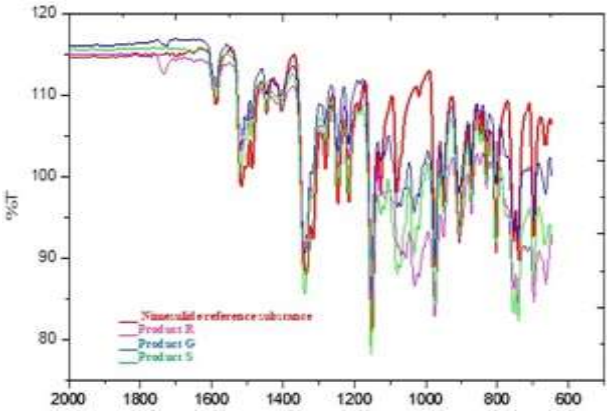

Figure 1. Infrared region spectra of nimesulide RCS and samples of nimesulide tablets R, G and S.

Table 1. Mean weight, standard deviation and coefficient of variation (CV %) of samples of intact Nimesulide

Tablets	Individual Weight (mg) R	Individual Weight (mg) G	Individual Weight (mg) S
Average weight	403.8	403.8	402.4
Standard deviation	3.733	3.709	11.09
CV (%)	0.920	0.920	2.75

Table 2. Mean weight, standard deviation and coefficient of variation (CV %) of samples of Nimesulide R. G and S split tablets.

Tablets	Individual Weight (mg) R	Individual Weight (mg) G	Individual Weight (mg) S
Average weight	200.3	202.9	204.1
Standard deviation	17.69	25.70	20.20
CV (%)	8.83	12.7	9.90

In the hardness test (Table 3), which evaluates tablet strength at crushing, it was shown that S tablets had a greater variation (1.21) indicating a lower crushing resistance than tablets R and G. The same occurred with the friability test (Table 4) in which the S-tablets presented greater variation although they were within the limit allowed for these tests. This variation is often due to the excipients and their moisture content, as they lead to compromise of the physical stability of the tablets and may interfere with the therapeutic efficacy of the drug, which may lead to discontinuation of treatment due to the poor appearance caused by breaks and cracks of the pharmaceutical form.

Table 3. Hardness test of samples of Nimesulide tablets R, G and S.

	Hardness (kfg)		
Tablets	R	G	S
Average	4.44	4.82	7.45
Standard deviation	0.254	0.132	1.214

Table 4. Friability of samples of Nimesulide tablets R, G and S.

Tablets	Weight loss (%)
R	0.352
G	0.256
S	0.480

The disintegration assay verifies that tablets disintegrate within the specified time all tablets have disintegrated less than 30 minutes (Table 5) and are in accordance with Brazilian legislation. The shortest test time of drug S suggests to be related to the excipients used and to the friability test where greater loss of material was observed.

Table 5. Disintegration of samples of Nimesulide tablets R, G and S.

Product	Disintegration Time
R	2 minutes and 2 seconds
G	1 minutes 33 seconds
S	51.9 seconds

The results of the determination of Nimesulide in tablets R, G and S are in Table 6 and all tablets (R, G and S) presented values within the established by the Brazilian Pharmacopoeia (BRASIL, 2010), which is 95.0% and 105.0%. It was also possible to observe that even the tablets being of different origins had the same content of Nimesulide, and did not differ significantly between them ($p > 0.05$).

Table 6. Determination of Nimesulide content in R, G and S tablets.

	Standard	R	G	S
Content (%)	99.0	96.3	96.4	96.2

Standard deviation	0.0707	0.203	1.07	0.590

For the unit dose uniformity test of tablets, the Brazilian Pharmacopoeia establishes that the test can be performed by two methods: weight variation and content uniformity. For uncoated tablets containing more than 25 mg of drug and that drug represents a proportion greater than 25 % of the dosage form, the content uniformity test is performed by weight variation, but when they are less than 25 mg or less than 25 % of the weight of the pharmaceutical form, these should be tested for content uniformity (BRASIL, 2010). According to the average weights of the analyzed products, the values obtained were greater than 25 % of the weight of the pharmaceutical form. For this reason, unit dose uniformity tests were performed by weight variation and for approval in the test, the Brazilian Pharmacopoeia establishes that the samples must present an acceptance value (AV) of less than 15 (BRASIL, 2010). For the whole tested tablets (Table 7), all are approved for uniformity of unit doses, since they have VA less than 15, which guarantees the dosage and consequently the effectiveness of the treatment.

Table 7. Nimesulide R, G and S content uniformity assay of whole tablets.

Tablets	Content (%)R	Content (%)G	Content (%)S
1	101.3	101.5	104.5
2	100.7	99.10	102.7
3	98.8	100.5	99.6
4	102.4	102.2	104.8
5	101.6	101.3	93.4
6	102.6	102.9	105.3
7	102.3	101.0	106.3
8	104.3	100.6	106.2
9	105.0	99.2	97.5
10	96.1	101.9	104.6
Average	101.5	101.0	102.49
Standard deviation	2.586	1.223	4.294
AV	6.21	2.93	10.3

In the same test, using splitting tablets (Table 8), it was observed that none of the tablets (R, G and S) had an acceptance value of less than 15, as established in the Brazilian Pharmacopoeia (2010), showing that the partition compromised the amount of active substance in each part of the tablet, i.e. even meticulously performing the partition with the aid of a tablet cutter, the accuracy of the partitions is unsatisfactory to reach the target dose. These results agree with Pinheiro et al (2006), where it was verified that almost never one part of the tablet will be identical to another. It was found that the non-homogeneity occurs by a non-perfect cut of the tablets and in all cases, neither of the parts presented the same mass of the other part, consequently one of the parts was always larger than the other.

In this way, none of the tablets passed the unit dose uniformity test, the G tablets being the most varied. The dose content variation can be attributed to the loss of powders and fragmentation, occurring during the break, to the excipients used, hardness and to the groove of the tablet.

These data showed that Nimesulide tablets do not indicate splitting, since changes in the concentration of the substance in one of the parts may compromise therapeutic efficacy. Another aspect to be taken into account is the time and place where one of the split tablet halves are stored, since humidity, light, and temperature may interfere with the stability of the pharmaceutical form.

Table 8. Content uniformity assay of Nimesulide split tablets R, G and S.

Tablets	Content (%) R	Content (%) G	Content (%) S
1	107.9	110.0	118.2
2	96.36	98.63	101.6
3	119.5	118.6	112.7
4	90.22	87.5	93.18
5	104.1	110.5	110.0
6	92.72	86.36	90.68
7	102.3	120.2	112.7
8	99.31	82.04	95.45
9	94.25	95.68	108.2
10	92.72	100.7	95.45
Average	98.94	101.0	103.8
Standard deviation	9.870	13.50	9.730
AV	23.7	32.4	23.4

For division of a tablet to occur it is necessary to follow criteria of pharmaceutical technology and quality control to guarantee safety for the patient. Teixeira et al. (2016) points out that US legislation already provides the minimum criteria for marketed tablets that can be broken, representing a significant step forward in making the practice of splitting safer.

Some drugs, such as Clonazepam, Citalopram, Paroxetine, Nefazodone, Sertraline, Olanzapine, Atorvastatin, Pravastatin, Doxazosin and Sildenafila have been tested and can be broken because they meet the therapeutic safety criteria (STAFFORD AND RADLEY, 2002). In the case of Nimesulide, an alternative for dose variation would be the manipulation of the drug, with the predetermined dosage, guaranteeing the quality, safety and efficacy of the drug.

Conclusion

The results of this work indicated that the Nimesulide tablet splitting procedure is inadvisable, since the unit dose uniformity tests presented irregularity, which would lead to compromising plasma levels and, consequently, drug therapy. It is suggested that when differentiated doses are required, the drug is replaced by another pharmaceutical form or otherwise manipulated so that the user may be making use of the required dose.

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