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REVIEW ARTICLE

Consequences of tablet splitting in physicochemical characteristics of Simvastatin 40 mg available at the Brazilian Unified Health System at the city of Caxias Do Sul, Rio Grande Do Sul

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Abstract: Simvastatin, a drug of the statin class, acts by lowering the total serum cholesterol and low-density lipoprotein. Patients with dyslipidemia in the city of Caxias do Sul that use simvastatin obtained from the Unified Health System (SUS) are required to split the tablet to adjust the dose. This work aimed to evaluate the effect of cutting simvastatin 40 mg tablets that are available in SUS in Caxias do Sul, and used samples and similar products as references. It evaluated the average weight, content uniformity, and active content of whole and subdivided tablets. All samples studied reached the specifications before being submitted to the splitting process. However, fractionation caused a loss of mass, causing the drug content to vary greatly. Thus, there was no uniformity in the dose halves tested and indicated that the tablet splitting procedure should not be therapeutically indicated.

Keywords: Simvastatin; Tablets splitting; Quality Control; Unified Health System.

INTRODUCTION

Dyslipidemia is a metabolic disease that is characterized by a reduction in high-density (HDL-C) cholesterol and/or an increase in triglycerides (TG) [1]. High-density plasma LDL-C has a direct relationship with the development of coronary artery disease (CAD). In addition, plasma HDL-C levels have been identified as one of the most serious risk factors for atherosclerotic coronary disease [2].

Statins are the most widely used class of drugs for the treatment of hyperlipidemias in primary and secondary prevention to reduce levels of cholesterol-rich plasma lipoproteins, and thus, reduce the risk of CAD. These effects are the result of its inhibitory activity on the enzyme hydroxymethyl glutarylCoA (HMG-CoA) reductase). HMG-CoA reductase blocks the conversion of an HMG-CoA substrate to mevalonic acid, inhibiting the first steps in cholesterol biosynthesis [3].

Patients frequently use solid dosage forms in the pharmacological treatment of dyslipidemia, of which the most common is the tablet. Tablets may vary in size, weight, shape, hardness, thickness, disintegration, dissolution characteristics, and other respects, depending on their purpose of use and method of manufacture (4). Certain tablets are scored, allowing them to be split easily into two or more parts. Tablet splitting is a common practice because of a desire to reduce the cost of the treatment or the need to obtain the required dose in the absence of the required dose presentation [5].

In Brazil, the Ministry of Health (MS), through Ministerial Ordinance No. 1, of January 2, 2015, established the list of medicines and supplies of the National Relation of Essential Medicines (RENAME) within the scope of the Brazilian Public Health Care System (SUS). The drugs listed are incorporated by epidemiological mapping of the most prevalent diseases in each municipality, through REMUME (County Relation of Essential Medicines), which contains the medicines that are part of the national standardization RENAME [6]. REMUME of the county of Caxias do Sul has 138 medicines available free of charge in SUS. Among them, the medicine simvastatin is available only at the dosage of 40 mg. Thus, patients who require a lower dose of the drug need to arrange for dose adjustment or purchase it in pharmacies, which incurs a cost to the patient and results in a limitation of practice.

The aim of this study was to evaluate the effect of tablet splitting on simvastatin available by SUS in Caxias do Sul and on the reference medicine through physicochemical tests of uniformity of unit dose, content, and mean weight in whole and subdivided tablets.

MATERIALS AND METHODS

Samples

Samples analyzed in this work were as follows. The first, the reference medicine, Zocor® 40 mg, was from Merck's laboratory, a pack of 30 oval, dark red, not scored, film-coated tablets purchased from a drugstore in the city. The second sample, also a pack of 30 tablets, is the similar Mevilip® from the Laboris laboratory in the form of round, dark red, scored tablets with a 40 mg concentration dispensed by SUS in Caxias do Sul. The third is the standard sample of simvastatin (Pharmanostra, purity 98.59%) was obtained by a donation from the Federal University of Rio Grande do Sul.

Tablet splitting

For the tablet splitting, a Mezzo & Mezzo tablet cutter was used. Tablets from each laboratory were divided in half.

Assays

Physicochemical quality control tests were performed as described in the Brazilian Pharmacopoeia 5th edition [7] for the test of weight variation. For the determination of active principle content and uniformity of content, a methodology modified from Zepon et al. [8], in a GenesysTM spectrophotometer apparatus was used. All assays were performed with intact and subdivided tablets.

Obtaining the linearity curve of simvastatin

For the linearity, 3 curves of simvastatin, a solution of approximately 1 mg/mL (0.103 g of simvastatin in 100 ml of 0.5% sodium lauryl sulfate) were prepared. After, aliquots of 4.0; 6.0; 8.0; 10.0 and 12.0 μg/mL were prepared using the same solvent, and then read in an ultraviolet (UV) absorption spectrophotometer using 0.5% sodium lauryl sulfate for zero adjustment. The data obtained allowed the elaboration of graphs of solutions concentration *versus* absorbance. From these, the equation of a straight line and the correlation coefficient were determined. The statistical treatment of linearity analysis data of the analytical method involved the determination of the equation of a straight line, the correlation coefficient, and the analysis of variance using Microsoft Office Excel® software, 2007.

Determination of the content

The content of simvastatin was determined by absorption spectrophotometry in the ultraviolet (UV) region according to the methodology of Zepon et al. [8]. For each

sample, 10 tablets were weighed and then transferred and ground to obtain a fine powder. A sample amount equivalent to the average weight of the tablets (obtained from the mean weight analysis) was withdrawn. This quantity was dissolved in a 100 mL volumetric flask, using methanol as the solvent. The mixture was homogenized for 15 minutes. At the end of this step, 5 mL of the solution was filtered and transferred to a 100 mL volumetric flask. The volume was filled with 0.5% sodium phosphate buffer and sodium lauryl sulfate solution. Sample solutions were then analyzed in duplicate in an absorbance spectrophotometer in the UV region at 239 nm using a phosphate buffer solution and 0.5% sodium lauryl sulfate for zero adjustments. The content of the samples was calculated from the calibration curve of the simvastatin standard [8].

Uniformity of content

According to the Brazilian Pharmacopoeia 5th edition [7], to determine the uniformity of unit doses by the method of uniformity of content, it must be separated by at least 30 units and proceed as described for the indicated dosage forms. In the case of solid dosage forms, the Brazilian Pharmacopoeia recommends that 10 units be evaluated individually. So, the tests were performed using 10 tablets of each, selected in random order, following the methodology of Zepon et al. [8]. The content of each tablet was calculated from the calibration curve of the simvastatin standard, and the acceptance value (AV) was calculated according to the equation:

$$AV = |M - X| + ks$$

AV = Acceptance value; M = Reference value according to the mean of the limits specified in the individual monograph for the declared quantity or power, expressed as a percentage.
X = Average of the individual contents (x1, x2, ..., xn), expressed as a percentage of the quantity declared. k = Constant of acceptability. If n = 10 (k = 2.4) and if n = 30 (k = 2.0). s = Standard deviation of the sample.

Statistical analysis

Data were analyzed by GraphPad Prism 5.0 using analysis of variance (ANOVA) and differences among means were determined for significance at $p < 0.05$ using Tukey's test.

RESULTS AND DISCUSSION

The 40 mg intact tablets of the reference product Zocor® presented a mean weight (MW) of 0.410 g ± 0.005 (coefficient of variation (CV) = 1.25%), whereas the similar drug Mevilip® had a MW of 0.407 g ± 0.003 (CV = 0.77%). It showed that all tablets had reached the recommended requirements since none of the units had a variation greater or less than 10% of the average weight value [7]. The analysis of the split drugs showed that the MW of 0.205 g ± 0.011 (CV = 5.39%) for the reference drug Zocor®, and MW of 0.201 g ± 0.010 (CV = 5.18%) of the similar drug Mevilip® (Tables 1 and 2). Only one of the samples of the similar drug Mevilip® presented a variation that was less than 10% of the value of the average weight. An analysis of the specifications of the Brazilian Pharmacopoeia 5th edition (7), which tolerates up to two

units outside the specified limits, it is showed that for this parameter, the broken fragments of both drugs complied with the test.

Tables 1 and 2 show the sum of fragments weight obtained after the tablets splitting. Statistical analysis showed that there was not significant loss of weight comparing the values before and after splitting. However, between the two halves, there is a significant statistical difference ($p < 0.05$) in almost all the unities. The mass loss, in percentage, was calculated from the sum of the masses of the halves in comparison with the mass of the original tablet since, during fragmentation, a weight loss of the tablet was noted, and, in some cases, the tablets were broken in more than two parts. The percentages of mass losses analyzed for the reference drug Zocor® ranged from 0.241% to 1.453%, and only 1 of the 10 tablets analyzed did not lose mass in the process. The mean mass loss was 0.461%, and the high coefficient of variation (approximately 87%) revealed the lack of accuracy in the fragmentation process, even using a tablet cutter. For Mevilip® tablets, the mass loss percentages analyzed ranged from 0.245% to 1.481%, and all fragments showed a mass loss. The mean mass loss was 0.740%, and a coefficient of variation of 54.34% again indicated that there was a lack of precision in the tablet partitioning process. Evaluating the coefficients of variation in the two analyses, it was concluded that neither of them met the requirements of internationally accepted standards, which establish a limit value of 5% [9].

Regardless of the tablet being analyzed, with or without a sulcus, the fragmentation process of simvastatin tablets was not able to produce fragments containing half the weight of the intact tablet, nor did it reproduce the weights of the fragments previously obtained. In addition, a considerable amount of the tablet was reduced to powder, which could not be recovered, resulting in a loss of mass and, consequently, of the drug dose. Also, the differences observed between the two halves show that the pharmacotherapy can suffer a great variation from one day to another of administration, considering that it can not be assured the content of each half. The results obtained here corroborate results previously reported by Hill et al. [10]. In this work, the authors used 12 distinct drugs, in the form of uncoated or coated tablets, which were split using a mechanical cutter (Locking Tablet Cutter, Apothecary Products, Inc.). The results showed relative standard deviations ranging from 0.45% to 8.13%, with mass losses between 0.04% and 1.14%. For the analysis of content and uniformity of unit doses in simvastatin tablets, the simvastatin standard linear curve was constructed. The mean curve, the equation of a straight line, and the value of R^2 were obtained and are shown in Figure 1. Table 3 shows the regression analysis of the linearity curve.

Table 1. Analysis of the mass loss of Zocor® 40 mg tablets after fractionation.

Zocor® Whole Tablet		Fractionated Tablets			Sum of fragments weight (g)
	Biggest fragment (g)		Smallest fragment (g)		
Weight (g)	Weight (g)	(%)	Weight (g)	(%)	
0.415	0.217*	52.28	0.197*	47.47	**0.414**
0.413	0.208*	50.36	0.199*	48.18	**0.407**
0.405	0.206*	50.86	0.198*	48.88	**0.404**
0.415	0.220*	53.01	0.193*	46.51	**0.413**
0.414	0.219*	52.89	0.193*	46.61	**0.412**
0.408	0.225*	55.14	0.180*	44.12	**0.405**
0.414	0.207	50.00	0.206	49.76	**0.413**
0.412	0.215*	52.18	0.195*	47.33	**0.410**
0.400	0.202*	50.50	0.198*	49.50	**0.400**
0.415	0.209*	50.36	0.205*	49.39	**0.414**
Average	**0.213***	**51.76**	**0.196***	**47.77**	**0.409**
Standard deviation (SD)	**0.007**	**1.639**	**0.007**	**1.750**	**0.004**
Coefficient of Variation (CV)	**3.48**	**3.17**	**3.69**	**3.66**	**1.14**

* P < 0.05 indicates a significant difference compared to the other half of the tablet (same line).

Table 2. Mass loss analysis of Mevilip® 40 mg tablets after fractionation.

Mevilip® Whole Tablet		Fractionated Tablets			Sum of fragments weight (g)
	Biggest fragment (g)		Smallest fragment (g)		
Weight (g)	Weight (g)	(%)	Weight (g)	(%)	
0.406	0.206*	50.74	0.198*	48.77	**0.404**
0.405	0.200	49.38	0.199	49.14	**0.399**
0.404	0.214*	52.97	0.187*	46.29	**0.401**
0.407	0.207*	50.86	0.197*	48.40	**0.404**
0.402	0.220*	54.73	0.180*	44.78	**0.400**
0.407	0.207*	50.86	0.195*	47.91	**0.402**
0.408	0.213*	52.21	0.194*	47.55	**0.407**
0.402	0.200	49.75	0.199	49.50	**0.399**
0.406	0.210*	51.72	0.195*	48.03	**0.405**
0.409	0.217*	53.05	0.188*	45.97	**0.405**
Average	**0.209***	**51.62**	**0.193***	**47.63**	**0.403**
SD	**0.007**	**1.644**	**0.006**	**1.514**	**0.003**
CV	**3.201**	**3.18**	**3.235**	**3.18**	**0.66**

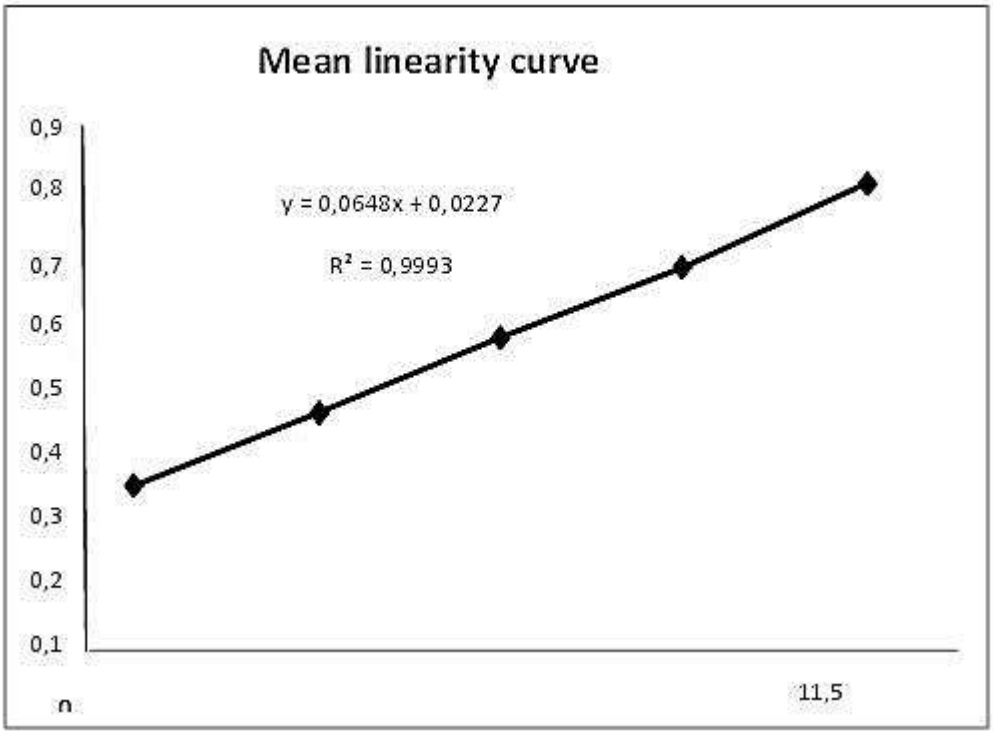
* P < 0.05 indicates a significant difference compared to the other half of the tablet (same line).

Table 3. Results of the regression analysis of the analytical curve of simvastatin by spectrophotometric method for intact and fragmented tablets.

	DF	SS	QM	F	F of significance
Regression	1	0.167962	0.167962	4093.297	8.41E-06
Residue	3	0.000123	4.10E-05		
Total	4	0.168085			

DF = degrees of freedom; SS = sum of squares; QM = quadratic mean.

Figure 1. Mean linearity curve for the simvastatin standard, in the range of 4 to 12 µg/mL.

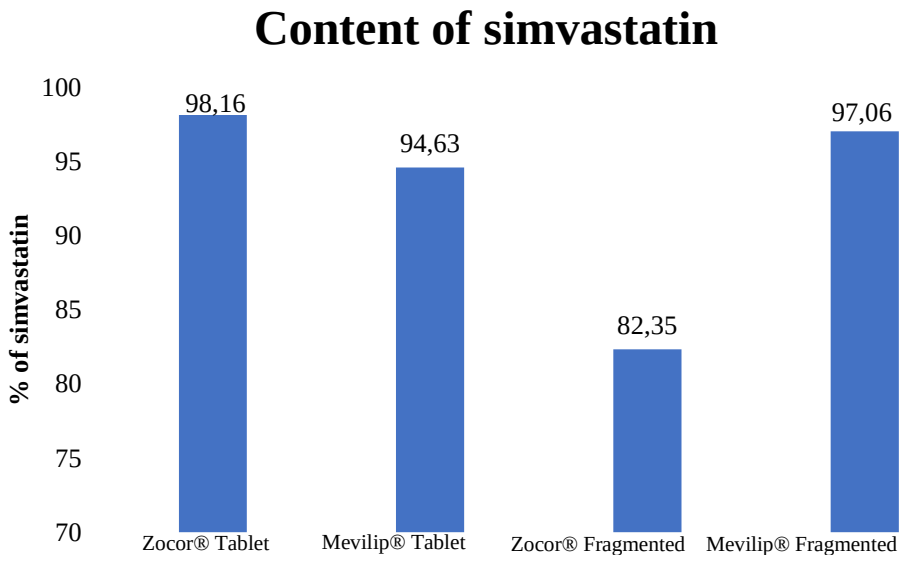


According to RE 899/2003 [11], for a method to be considered valid, it must have a correlation coefficient value (r) equal to or greater than 0.99. Thus, the method of dosing simvastatin by UV (Figure 1) is considered linear, considering that the value obtained for the correlation coefficient (r) was 0.9993. Further, the calculated F value of approximately 4093 is greater than the F of significance and demonstrates both the sensitivity and linearity of the method. It should be emphasized that the method used was previously validated by the authors Zepon et al. (2013).

Figure 2 shows that the values of simvastatin content for intact tablets are within limits specified by the American Pharmacopoeia [12], which establishes from 90% to 110% of active content. When examining the fragmented tablets, it is apparent that the fragments of the drug Zocor® did not reach the smallest limit of content, thus not being in accordance with the specification in the literature. Although the fragments obtained with the Mevilip® tablets reached the content within the specification, the statistical evaluation showed a high coefficient of variation (8.5%), demonstrating the imprecision of the

analysis. These results confirm that tablet fragmentation is not a reliable practice because of the large variance of the active principle found in this analysis [12].

Figure 2. Mean analysis of intact and fragmented tablets for simvastatin content.



Content uniformity tests were also performed to evaluate the dosage of the drug found in the tablet halves, considering that the expected dosage is half the dosage declared in the product presentation. Drugs are considered approved by the Brazilian Pharmacopoeia 5ª ed. [7] in their first stage of the content uniformity test if the drug presents the content of the active principle between 85% and 115% and a standard deviation of less than 6%. Thus, the results obtained in the analyzed tablets of both Zocor® and Mevilip®, which presented mean absorbances of 0.66 ± 0.011 and 0.67 ± 0.019, which consequently resulted in the content of 99.65% ± 1.64 and 99.95% ± 2.89, respectively. Evidence indicated that the two analyses of the intact tablets met the specifications since no tablet exceeded the established limits.

Table 5 shows the results of the uniformity of the content of the fragmented samples of both tablets. Six of the fragments generated for the drug Zocor are outside the content specified by the American Pharmacopoeia [12] (90% to 110%). In comparison, for the drug Mevilip®, three fragments are out of specification. An analysis of the mean contents obtained for the fragments of both samples yielded values of approximately 98% for Zocor® and 104% for Mevilip®, which would result in values within the specifications. However, evaluating the standard deviations and coefficients of variation, high values were observed once again, demonstrating the lack of accuracy of the fragmentation method.

The Brazilian Pharmacopoeia [7] states that each unit of the batch of a drug must contain an amount of the active component close to the quantity declared to ensure that the correct dose is administered. The unit dose uniformity test allows the amount of the active component to be evaluated in individual units of the batch and to verify that this quantity is uniform in the units tested. For solid dosage forms, the dosing must be performed after calculating the AV. The product meets the unit dose uniformity test if the AV calculated for the first 10 units tested is not greater than 15.0 (L1). Table 6 lists the AV values for both samples.

Table 5. Results of the content uniformity test for fragmented simvastatin tablets.

Tablets	Samples	y = abs samples (nm)	x= concentration µg/mL	Content (%)
	1	0.56	8.25	**82.45**
	2	0.75	11.29	**112.85**
	3	0.56	8.25	**82.45**
	4	0.50	7.33	**73.35**
	5	0.73	10.85	**108.53**
Zocor® frationated	6	0.67	10.00	**100.05**
	7	0.83	12.43	**124.27**
	8	0.73	10.93	**109.31**
	9	0.74	10.99	**109.92**
	10	0.56	8.21	**82.15**
	Average	**0.66**	**Average**	**98.53**
	SD	**0.11**	**SD**	**17.11**
	CV	**16.58**	**CV**	**17.36**
	1	0.62	9.14	**91.40**
	2	0.71	10.65	**106.53**
	3	0.63	9.33	**93.26**
	4	0.61	9.13	**91.25**
	5	0.68	10.11	**101.13**
Mevlip® frationated	6	0.75	11.18	**111.77**
	7	0.70	10.50	**104.98**
	8	0.70	10.47	**104.68**
	9	0.74	11.08	**110.85**
	10	0.88	13.20	**131.99**
	Average	**0.70**	**Average**	**104.78**
	SD	**0.08**	**SD**	**12.19**
	CV	**11.27**	**CV**	**11.63**

Table 6. Analysis of Acceptance Values for whole and fragmented tablets of simvastatin.

	Uniformity of Unit Dose
Samples	AV
Zocor® tablet	3.93
Mevilip® tablet	6.93
Zocor® frationated	41.06
Mevilip® frationated	32.54

The results show AVs that meet the specifications only for the intact tablets of the analyzed samples. These results corroborate those obtained in similar work performed with atenolol tablets. In this study, the tablets were fractionated in two different ways: with a homemade knife and with a cutter. The results showed that there was no significant difference between dividing the tablets with the different measures adopted for the doses of 100 mg, 50 mg, and 25 mg. Another finding was that both the use of the homemade knife and the tablet cutter provided fragments with amounts of active principle above the recommended variation limit (7.8%) by the Brazilian Pharmacopoeia [6%]. Thus, this variation did not guarantee the dose received at each administration of the drug, when compared with the contents obtained in intact tablets [13].

The results obtained in this work raise questions about the influence of the type of tablet and the consequences in the process of partitioning it. The scored tablets analyzed tended to produce better results when compared with those that were not scored. The tablet formulation might also have been an important aspect and might have influenced the results. According to RDC No. 140, dated May 29, 2003, the Brazilian Health Regulatory Agency (ANVISA) determined that coated tablets, with controlled release, capsules, and pills cannot be split. A warning must appear on the package leaflet. ANVISA still recommends caution in the partitioning of small tablets, given the difficulty of locating the middle accurately [14].

An analysis of the package leaflets of the medicaments revealed that the Zocor® leaflet warns of the impossibility of partitioning the tablet into two or more parts, or of it being chewed. Mevilip® does not contain any information in its package leaflet about the permission to break the tablet, it only warns about its preservation in the primary packaging, since poor storage may produce small dark spots on the surface of the tablet.

Costa et al. [5] argued that in addition to the size and shape of the tablet, the degree of irregularity after a tablet break might be related to the presence or absence of scores. Some tablets, even with the presence of these scores, may still not break easily into two equally sized pieces. Manufacturers usually consider scored tablets are usually considered by manufacturers as those intended to be split. However, not all tablets with scores can be split. A survey in Germany reported that 70% of patients taking medication considered this a difficult task and that the scores did not guarantee division in equal parts. In this same survey, many people reported that they believed erroneously that the partition was a function of the score. In addition, more than a third of the patients studied thought that all tablets could be broken, and 80% of these patients expected to see information on the product packaging.

The consensus among some healthcare professionals is that the stability and quality of fractionated tablets may not be the same as intact tablets. Once the break exposes the tablet core, the tablet may no longer have the same stability profile determined by the manufacturer's quality control performed on the intact tablet [16, 17]. The fractionation of tablets remains a subject that generates substantial debate. The Institute for Safe Medication Practices advises careful selection of patients before

recommending this practice, considering that some patients who might not understand the proper procedure, and acknowledging that others might be unable to perform the partition, resulting in the partition of contaminated tablets or unequal portions [18, 19, 20].

A seemingly simple procedure like splitting tablets can be associated with economic advantages but requires careful analysis. In addition to varying the dose level and uniformity, there is also the possibility of degradation of the drug, as the drug is removed from its original packaging, and after fractionation, it is maintained under conditions that may be inappropriate.

CONCLUSION

The present study, in order to verify the influence of tablets splitting, evaluated this process in the similar and reference presentations of simvastatin, with the objective of evaluating a common practice in the city of Caxias do Sul. The results demonstrated that the splitting process is inadvisable, since there is a loss of mass of the drug in the process, altering the content and uniformity of the individual doses, which would inevitably lead to the compromise of drug therapy. That being said, and in view of the risks and benefits of the patient, the partitioning of tablets available by SUS is not suggested since the drug is found in the pharmaceutical form and at the commercially recommended dosage. Patients who usually perform the tablet splitting should have perfect understanding of the process, an important task of Pharmaceutical Care, so that the treatment is not impaired. Another alternative would be purchasing the medicine in drugstores with government agreements (popular pharmacy), where it would be possible to use the intact tablet at a small cost to the patient.

AUTHORS' CONTRIBUTIONS:

ATP and MS were responsible by the study conception, acquisition and analysis of data, drafting of manuscript and critical revision of the content; BMB participated in the analysis and interpretation of data and revision of the intellectual content.

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