

Original Research

Prevalence of tablet splitting in a Brazilian tertiary care hospital

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Abstract

Background: Although a highly common practice in hospital care, tablet splitting can cause dose variation and reduce drug stability, both of which impair drug therapy.

Objective: To determine the overall prevalence of tablet splitting in hospital care as evidence supporting the rational prescription of split tablets in hospitals.

Methods: Data collected from inpatients' prescriptions were analyzed using descriptive statistics and used to calculate the overall prevalence of tablet splitting and the percentage of split tablets that had at least one lower-strength tablet available on the market. The associations between the overall prevalence and gender, age, and hospital unit of patients were also assessed. The results of laboratory tests, performed with a commercial splitter, allowed the calculation of the mass loss, mass variation, and friability of the split tablets.

Results: The overall prevalence of tablet splitting was 4.5%, and 78.5% of tablets prescribed to be split had at least one lower-strength tablet on the market. The prevalence of tablet splitting was significantly associated with the patient's age and hospital unit. Laboratory tests revealed mean values of mass loss and variation of 8.7% (SD 1.8) and 11.7% (SD 2.3), respectively, both of which were significantly affected by the presence of coating and scoreline. Data from laboratory tests indicated that the quality of 12 of the 14 tablets deviated in at least one parameter examined.

Conclusions: The high percentage of unnecessary tablet splitting suggests that more regular, rational updates of the hospital's list of standard medicines are needed. Also, inappropriate splitting behavior suggests the need to develop tablets with functional scores.

Keywords

Drug Stability; Tablets; Drug Prescriptions; Inpatients; Prevalence; Medication Errors; Reproducibility of Results; Drug Industry; Cross-Sectional Studies; Brazil

INTRODUCTION

The oral intake of tablets is the most common method of drug administration.¹ Individualized oral drug therapy may require tablet splitting, or tablet subdivision because appropriate doses are not always available on the market.² For that reason, as well as to lower costs and facilitate swallowing, tablet splitting is a widespread practice, especially in hospitals.³⁻⁵ However, splitting tablets can cause dose variation and reduce drug stability.⁶⁻⁸ The negative effects of tablet splitting in drug therapy are more pronounced for tablets containing drugs with low therapeutic indexes.⁷ Nevertheless, published studies on

tablet splitting in hospital care have been few.^{4,9}

Unnecessary splitting should be avoided in order to minimize eventual adverse impacts on drug therapy. Tablet division performed when at least one pharmaceutical alternative (i.e., a tablet containing the same active pharmaceutical ingredient at the required or lower strength) is commercially available can be considered unnecessary. In identifying unnecessary tablet splitting in hospital environments, it is important to consider that, for logistical reasons, hospitals keep a limited number of drug products in stock. Therefore, if any pharmaceutical alternative available on the market is not included in the hospital's list of standard medicines, then it is not an option.

The quality of the halves needs to be guaranteed to minimize the adverse impacts of tablet splitting on drug therapy, especially the inaccuracy of desired doses. The quality of split tablets can be expressed by several parameters, including mass loss, mass variation, friability, hardness, drug stability, tablet disintegration, and drug dissolution. The quality depends upon several factors, including tablet properties, splitting technique, and the manipulator's ability.¹⁰⁻¹³ In particular, the presence and depth of the tablet's scoreline and the tablet's size, shape, production method, and composition can significantly affect the quality of split tablets.^{9,14}

Although criteria for decisions to split tablets remain undefined, knowledge about their composition, manufacture, and drug release mechanism is essential to

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assist such decisions.³ In that context, though pharmacists play a fundamental role in multi-professional health teams as capable guides in tablet subdivision, they also face challenges with identifying theoretical grounds to perform the practice appropriately.

In the study presented here, a survey on the overall prevalence of tablet splitting in a tertiary care hospital in Brazil was performed to shed light on trends in tablet subdivision in hospitals. Laboratory tests were performed with a view of evaluating the potential impacts of tablet splitting on drug therapy.

METHODS

A cross-sectional descriptive study was conducted that involved the analysis of prescriptions for inpatients in a public tertiary care hospital, specifically Hospital das Clínicas, a 258-bed teaching institution in Goiânia, Goiás, in central Brazil. Based on the findings, drug products that were frequently split were submitted to a laboratory study in order to evaluate the impact of splitting on the physical and mechanical characteristics of subdivided tablets.

The study met the ethics requirements established in Brazilian legislation and was approved by the Ethics Committee of the Clinical Hospital of the Federal University of Goiás (approval number 1.822.184).¹⁵

Data collection and evaluation of prescriptions

All legible prescriptions containing drug products and sent to the hospital's pharmacy were collected every 7 days for 3 months in 2016. Prescriptions containing medication not supplied by the pharmacy were also included, although repeat prescriptions were not. Data collected from the prescriptions included age (until 11 years old; 12 to 18 years old; 19 to 59 years old; equal or greater than 60 years old), gender (female; male), inpatient unit (surgical clinic; medical clinic; obstetric clinic; orthopedic clinic; pediatric clinic; emergency adult; emergency pediatric; tropical medicine; surgical ICU; medical ICU; neonatal ICU), drug name, number of tablets fragments (two; four; others), tablet splitting decision (prescriber; pharmacist).

Data from the prescriptions were used to calculate (1) the overall prevalence of tablet splitting, defined as the number of tablets prescribed to be split, divided by the total number of tablets in the sample and multiplied by 100; (2) the prevalence of tablet splitting of a given product, defined as the number of tablets of a given

product prescribed to be split, divided by the total number of tablets of this product in the sample and multiplied by 100; and (3) the percentage of unnecessary tablet splitting, defined as the number of tablets prescribed to be split that had at least one pharmaceutical alternative, divided by the total number of tablets in the sample and multiplied by 100. Pharmaceutical alternatives are defined as tablets available in the Brazilian market that have the same active pharmaceutical ingredient at the required or lower strength. The search for pharmaceutical alternatives was performed concerning an official list published by the Brazilian Health Agency.¹⁶

All collected data were analyzed using descriptive statistics and the SPSS version 20.0 (IBM, Armonk, USA). The associations between the overall prevalence of tablet splitting and the gender, age, and hospital unit of patients were assessed using the nonparametric Mann-Whitney test.

Laboratory tests of tablet splitting

The 14 most frequently prescribed split tablets (Table 1) were submitted to mechanical and physical assays in order to determine the appropriateness of splitting in each specific case. Three lots of each innovator drug product were purchased from a drugstore, whereas propranolol tablets, currently unavailable on the market, were substituted with a generic drug product for laboratory tests.¹⁷

A commercial tablet splitter (Inconterm, São Paulo, Brazil) was used to split the tablets, which were assessed for mass loss, mass variation, and friability. In particular, 10 tablets from each batch were individually weighed using an analytical balance (Bel Engineering, model S203, São Paulo, Brazil) before and after splitting. The results are expressed as a mean of 3 batches (n=30). Mass loss (ML) and Mass variation (Mv) were calculated according to Equations (1) and (2).

$$M_L = \frac{2M_h}{M_w} \times 100 \quad \text{Equation (1)}$$

$$M_V = 1 - \left(\frac{M_h}{\frac{1}{2}M_w}\right) \times 100 \quad \text{Equation (2)}$$

Where, M_w is the whole tablet mass, and M_h is the mass of one halve.

Table 1. Drug products submitted to laboratory tests

Drug	Dose	Brand	Manufacturer	Score	Coat	Batch number
Amiodarone	100 mg	Atlansil®	Sanofi-Aventis	Yes	No	713934; 515709; 539029
Carbamazepine	200 mg	Tegretol®	Novartis Biociências	Yes	No	1646087; 1719841; 1720167
Clonazepam	0.5 mg	Rivotril®	Roche	Yes	No	RJ1052; RJ1048; RJ1051
Furosemide	40 mg	Lasix®	Sanofi-Aventis	Yes	No	6E9360; 721584; 717735
Hydralazine	25 mg	Apresolina®	Novartis Biociências	No	Yes	1706811; 1706808; 1711869
Hydrochlorothiazide	25 mg	Clorana®	Sanofi-Aventis	Yes	No	636404; 524009; 717869
Lamotrigine	25 mg	Lamictal®	GlaxoSmithKline	No	No	1613900051; 1613900052; 1627900064
Losartan	50 mg	Cozaar®	Merck Sharp & Dohme	Yes	Yes	N004622; N016050; N007232
Methyldopa	250 mg	Aldomet®	Aspen Pharma	No	Yes	A862697; A860288; A863491
Prednisone	5 mg	Meticorten®	Merck Sharp & Dohme	No	No	N013489; N009888; M003377
Propranolol	40 mg	Generic Teuto	Laboratório Teuto	Yes	No	1057586; 1057565; 1057585
Quetiapine	25 mg	Seroquel®	AstraZeneca	No	Yes	45200; 43969; 43878
Sodium warfarin	5 mg	Marevan®	Farmoquímica S/A	Yes	No	161744; 161743; 162104
Ursodeoxycholic acid	50 mg	Ursacol®	Zambon	Yes	No	1052493; 1041362; 1050363

Table 2. Splitting data of the fourteen most prescribed split tablets

Drug	Frequency of splitting in the entire sample (%)	Prevalence of splitting (%)	Alternatives in the hospital	Alternatives ^c In the Brazilian market
Clonazepam	25.2	38.5	No	Yes
Sodium warfarin	11.3	44.3	No	Yes
Propranolol	7.1	25.4	No	Yes ^b
Amiodarone	5.8	15.9	No	Yes
Hydralazine	4.6	47.8	No	Yes
Prednisone	3.3	4.2	Yes ^a	Yes
Carbamazepine	2.9	15.6	No	No
Methyldopa	2.9	13.6	No	Yes
Quetiapine	2.9	25.9	No	Yes
Losartan	2.1	3.0	No	Yes
Furosemide	2.1	4.0	No	No
Ursodeoxycholic acid	2.1	55.6	No	Yes
Lamotrigine	2.1	83.3	No	Yes
Hydrochlorothiazide	1.6	3.2	No	No

^aTwo prescriptions for prednisone 5 mg have been identified. There is no pharmaceutical alternative for this strength.
^bTwo prescriptions for propranolol 10 mg have been identified. There is no pharmaceutical alternative for this strength.
^cTablets available in the Brazilian market that have the same active pharmaceutical ingredient at the required or lower strength

Last, friability was calculated as the percentage of mass loss of 10 whole tablets, or 20 halves of each drug product tumbled at 25 rpm for 4 min (Nova Ética friabilometer, model 300, São Paulo, Brazil). Following international specifications, values of mass loss and friability above 3% and 1%, respectively, were considered to be inadequate.^{18,19} Mass variation exceeding 10% was also considered to be inappropriate, because tablet splitting by pharmacy personnel is a form of extemporaneous compounding and, therefore, the specification is stricter than that of United States Pharmacopeia for intact dosage units.²⁰

Statistical analysis was performed using GraphPad Prism (version 7.0). Possible differences in mass variation, mass loss, and friability among the groups (i.e., scored vs. unscored tablets and coated vs. uncoated tablets) were investigated by performing the Welch unequal variance t-test or the Mann-Whitney U test.

RESULTS

A total of 2,942 prescriptions for 2,674 inpatients were collected and analyzed. The prescriptions included 5,303 tablets, 238 of which were prescribed to be split, for an overall splitting prevalence of 4.5%. The entire sample of split tablets comprised 44 drugs, and the splitting prevalence was calculated for the 14 most prescribed drug products (Table 2), which corresponded to nearly 80% of all split tablets in the sample. As shown in Table 2, 78.5% of the split tablets had at least one pharmaceutical alternative available on the Brazilian market when the study was conducted. Tablets containing clonazepam, sodium warfarin, and propranolol were the most frequently split and showed a high splitting prevalence as well (Table 2).

Another aspect investigated relates to decisions to split tablets, which are informally delegated to the prescriber, represented by the physician in most cases. At the hospital examined, the decision to perform the subdivision of

Table 3. Statistical evaluation of the overall prevalence of splitting and age, sex and inpatient unit

Variables	Total	Patients with split tablets prescribed (%)	p-value ^a	
Sex ^b	Female	1433	8.3	0.426
	Male	1144	7.5	
Age group ^c	up to 11 years	229	5.6	0.001
	12 to 18 years	132	7.5	
	19 to 59 years	1164	8.4	
	>60 years	658	12.9	
Inpatients units	Surgical clinic	686	6.2	0.004
	Medical clinic	625	15.2	
	Obstetric clinic	291	6.1	
	Orthopedic clinic	256	0.3	
	Pediatric clinic	90	16.6	
	Emergency adult	260	4.2	
	Emergency pediatric	87	3.4	
	Tropical medicine	107	6.5	
	Surgical ICU	99	3.0	
	Medical ICU	70	12.8	
	Neonatal ICU	103	0.9	
TOTAL	2674	7.7		

^a Mann-Whitney test for valid data.
^b 91 missing cases
^c 491 missing cases

Drug name	Mass loss % (SD)	Mass variation % (SD)	Friability (%)	
			whole tablet	split tablet
Ursodeoxycholic acid	4.7 (1.4)	6.4 (0.8)	1.3	11.4
Amiodarone	24.5 (6.1)	15.2 (4.7)	0.1	6.4
Carbamazepine	5.2 (1.8)	17.3 (4.0)	0.0	0.1
Clonazepam	13.9 (1.7)	9.6 (2.0)	0.6	2.9
Furosemide	14.6 (2.3)	12.5 (1.0)	0.4	6.2
Hydralazine	6.6 (3.0)	13.3 (4.9)	0.0	0.6
Hydrochlorothiazide	10.1 (0.7)	10.9 (1.7)	0.1	8.6
Lamotrigine	16.8 (1.9)	12.9 (2.5)	0.2	4.8
Losartan	4.8 (1.6)	10.7 (1.4)	0.0	0.0
Methyldopa	4.9 (0.8)	13.4 (1.2)	0.0	6.0
Prednisone	0.9 (0.4)	5.0 (1.3)	0.1	0.0
Propranolol	2.5 (1.5)	6.9 (1.5)	0.4	0.3
Quetiapine	1.8 (0.3)	20.5 (3.8)	0.1	2.3
Sodium warfarin	11.5 (1.5)	9.5 (1.6)	0.9	1.3
Mean	8.7 (1.8)	11.7 (2.3)	0.3	3.6

The results out of specification are in bold. SD = Standard deviation

tablets was most often made by the physician (77.8%). In only 22.2% of cases the pharmacist made that decision.

Table 3 presents the associations of the overall prevalence of splitting with the gender, age group, and hospital unit of patients, among which the associations with age group and hospital unit were significant ($p < 0.05$). It was also observed that most of the tablets were split in half (95.8%), whereas few (4.2%) came with prescriptions recommending tablet splitting in quarters.

The 14 most frequently split tablets were submitted to laboratory tests in order to determine the quality of the halves. The mean mass loss was 8.7% (SD 1.8) (Table 4), whereas the mean mass variation was 11.7% (SD 2.3). To clarify the influence of a tablet's properties on the quality of the halves, a statistical analysis of those parameters was performed, the results of which appear in Figure 1. As shown in Figure 1a, coated tablets exhibited less mass loss (4.5%; SD 1.7) than uncoated ones ($p = 0.01$). By contrast, as shown in Fig. 1b, mass variation was significantly higher for coated tablets ($p = 0.03$). Figure 1c and 1d reveal that the presence of a scoreline increased mass loss after splitting;

however, no significant differences in splitting accuracy (i.e., mass variation) emerged between scored and unscored tablets.

Last, the friability of the halves increased compared to that of the whole tablets (Table 4). Nine of the 14 tablets did not meet the United States Pharmacopeia requirements for the friability of split tablets ($< 1\%$).^{18,21}

DISCUSSION

In the few studies on the frequency of tablet splitting in hospitals, Arnet *et al.* and Quinzler *et al.* have observed higher splitting frequency (10.1% and 8.5%, respectively) than the one observed in the study reported here (4.5%).^{9,22} The differences may stem from the varying characteristics of the hospitals, including the number of beds, medical specialties available, and patient profile. Regardless of the inter-hospital variation, the prevalence of tablet splitting is clearly high, which underscores the need to understand its causes and propose alternatives to mitigate its potential adverse effects.

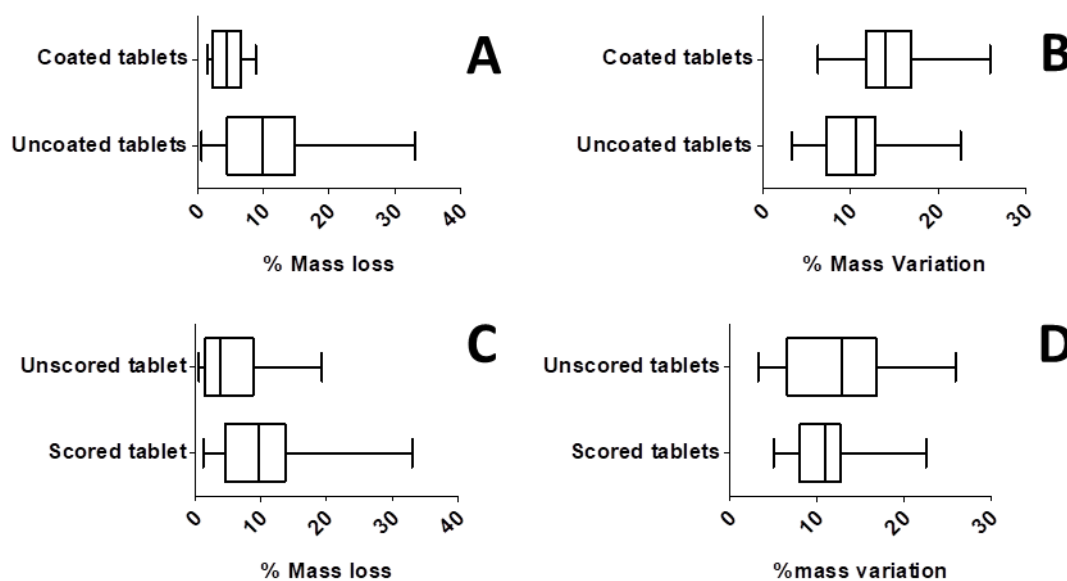


Figure 1. Mass loss and mass variation as functions of the presence of tablet coating and scoreline

In a Swiss hospital, Arnet *et al.* examined the frequency of inappropriate tablet splitting, which they defined as occurring when at least one pharmaceutical alternative was available on the Swiss market, when scored tablets were available, and when manufacturers had expressly prohibited splitting.⁹ Applying those criteria to their data, the authors detected a frequency of inappropriate tablet splitting of 2.8%. Although somewhat similar, the percentage of unnecessary tablet splitting in our study was 3.53%. The higher percentage suggests that more regular, rational updates of the hospital's list of standard medicines may dramatically decrease of overall prevalence of tablet splitting and the percentage of unnecessary tablet splitting.

The effectiveness of health systems and the safety of all individuals require the careful selection of medicines by drug and therapeutics committees in hospitals.²³ Such committees should select drug products based on evidence of efficacy, safety, and cost-effectiveness for a particular disease or clinical situation, as well as compare them to therapeutic alternatives available, in order to obtain an appropriate list for rational use.²⁴⁻²⁶ Our findings also suggest the need to take into account tablet divisibility as an important factor in choosing standard drug products for use in hospitals.

Clonazepam, sodium warfarin, and propranolol tablets were the three most frequently split tablets in the hospital examined. Although clonazepam and propranolol have a broad therapeutic window that ensures their safety and effectiveness against potential dose fluctuations, clonazepam adverse effects, like drowsiness, dizziness, and confusion, are related to its plasma concentration and dose.²⁷ In its turn, the splitting of sodium warfarin tablets is especially risky. Because sodium warfarin has a narrow therapeutic range, and dose variation can cause severe bleeding, a hospital's standardization of lower-strength warfarin tablets is crucial for the rational management of therapy with the drug.²⁸⁻³⁰ Differences in the pharmacological properties of propranolol, clonazepam, and warfarin also highlighted the need for the evaluation of each drug product in order to assess better the risks involved in splitting them.

Prescriptions for splitting controlled drug release tablets based on polymeric coating (nifedipine retard, n=1, and quetiapine XR, n=3) appeared in the study sample. Such systems are designed to release drugs gradually in the body, and their splitting, especially when against the manufacturer's instructions, can significantly impair the effectiveness of treatment, as well as increase the risk of adverse effects.³¹ The prescriptions for splitting controlled drug delivery tablets likely stem from the lack of technical training among physicians; after all, the safest evaluation of tablet splitting involves an analysis of the pharmacological and toxicological aspects of the drug, together with knowledge of the drug product composition and drug release mechanisms. For those reasons, pharmacists are the most qualified healthcare professionals for the task.^{3,32}

The statistical analysis of the overall prevalence of tablet splitting revealed a significant relationship between the age group of patients and tablet splitting. That association was expected because tablet splitting is exceptionally common in geriatric and pediatric populations, which are also known

to be the most susceptible to the adverse clinical consequences of tablet splitting.^{3,33,34} Splitting-related toxicity is more severe among elderly patients due to altered pharmacokinetics that increases the occurrence of adverse effects.³⁴

Another relevant aspect of the prescription of split tablets is the number of tablet fragments to be generated. In our study, about 95% of tablets were split in half, whereas researchers in Switzerland observed a two-part tablet division in 87.6% of cases.³⁵ The subdivision of a tablet into more than two parts considerably increases mass loss and mass variation, which makes tablet splitting even riskier.³⁶ Moreover, the functional score of most tablets is generally intended for mid-fractionation, and any other technique would not have the support of the pharmaceutical laboratory and, in turn, not be recommended.

Laboratory tests revealed that the mean mass loss was 8.7% (SD 1.8) (Table 4), which is far superior to that reported by Teixeira *et al.* (<2%), who studied the tablet subdivision of drug products available on the Brazilian market.³ Other researchers have also reported lower values of mean mass loss (0.2–3.8%).^{3,5,37,38} By contrast, the mean mass variation was 11.7% (SD 2.3), which is within the range of previously reported data (9.9–25%).^{3,5,11,38}

A multitude of factors can affect the practice of tablet splitting and tablet behavior as a result, as well as explain the differences mentioned above. Tablet size, shape, and presence of a scoreline can determine the accuracy of tablet subdivision. Tablet composition, method of manufacture, and splitting procedure can also determine a tablet's behavior during subdivision.^{30,39,40} In general, the subdivision of oblong, coated, and scored tablets results in halves of quality higher than that of round, uncoated, and uncoated ones.³ Also, denser and more uniform structures have exhibited better subdivision behavior.^{40,41}

Statistical analysis was also performed to identify any significant differences between coated and uncoated as well as scored and unscored split tablets. Coated tablets showed lower percentages of mass loss, possibly because harder tablets have often been produced to accommodate coating, which has resulted in tablets with higher mechanical resistance and, in turn, less mass loss after splitting. However, those stronger tablets can also cause more irregular subdivision, which increases mass variation.³

Surprisingly, the presence of a scoreline did not result in better splitting accuracy. In addition to the multiple variables that simultaneously affect the performance of tablet splitting, many of the tablets evaluated probably had aesthetic scores only. In those cases, the depth and shape of the aesthetic scores might not contribute to a more regular subdivision, unlike functional scores, which have previously been evaluated by manufacturers as being adequate guides for splitting.^{14,18}

Friability tests showed that nine of the 14 tablets did not meet the FDA requirements for split tablets.¹⁸ Not coincidentally, eight of these nine tablets also showed mass loss greater than 3%, presumably because of tests for both mass loss and friability related to the mechanical strength of the tablets. In practice, such a result impedes the subsequent use of the other half of each divided tablet, the

physical integrity of which cannot be guaranteed in handling required for storage, even for a brief period. In our sample, for instance, amiodarone tablets failed in all laboratory tests and exhibited a remarkable mass loss of 24.5% (Table 4). In that case, the need to resort to the pharmaceutical alternative is clear. Similarly, sodium warfarin tablets, which had a high prevalence of splitting (Table 2) and present a recognized pharmacological threat of dose variation, resoundingly failed the mass loss test (Table 4) and demonstrated exceptionally high mass variation. Contrary to current clinical practice, the mentioned tablets should not be subjected to splitting in any case.

Because 12 out of 14 split tablets failed in at least one parameter of quality, the need to improve drug standardization in the examined hospital is clear, particularly as a means to avoid or minimize the occurrence of adverse effects caused by tablet splitting. Moreover, those data suggest that manufacturers should re-evaluate most of the drug products studied in order to improve their capacity to be split.

CONCLUSIONS

A high prevalence of the tablet splitting was observed in the public tertiary care hospital examined, and based on

the data collected, more regular, more rational updates of the list of standard medicines in the hospital could dramatically reduce it, especially with the acquisition of lower-strength tablets available on the market. Data from the laboratory tests revealed that 12 out of the 14 studied tablets presented deviation at one of the selected parameters of quality (i.e., mass loss, mass variation, and friability), which indicates the need to increase the commercial availability of drug products designed to be split.

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CONFLICT OF INTEREST

No conflicts of interest have been declared.

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