Tablet Splitting: Influence of Technique and Tablet Format

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Abstract. *Tablet splitting is a commonly used technique to obtain half of the dose or to facilitate tablet intake. However, there is a risk of not obtaining the correct dose and the efficacy depends on factors such as splitting method and tablet characteristics. Objective: To assess significant differences regarding tablet format or splitting method, regarding loss of mass and splitting accuracy. Methods: Volunteers split ten formulations by hand or using a kitchen knife. Results were treated in order to verify compliance with European Pharmacopeia standards for tablet splitting and recommendations on loss of mass. SPSS was used to assess significant differences between the two methods and tablet format when analysing loss of mass or splitting accuracy. Results: Of the twenty formulation/method combinations, only five complied with all the criteria. There was a significant difference regarding methods and loss of mass, with splitting by hand being the one to achieve the best results. Oblong tablets scored significantly better regarding loss of mass and splitting accuracy. Conclusion: Results seem to indicate that best results can be achieved when splitting tablets if using oblong tablets and splitting them by hand.*

Keywords. Drug compounding/methods, tablets, tablet splitting, tablet characteristics, tablet format

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1 Introduction

Tablet splitting consists in subdividing a tablet in order to facilitate its intake or to provide smaller doses, although its efficacy depends on many factors, such as tablet shape, size, splitting technique/device and patient ability (motor skills and visual accuracy being the most discussed)[1], [2]. This technique is commonly used in households, and is estimated to reach one third of the prescriptions[3]. The main advantages of using this technique are the ease of swallowing a smaller fraction of the tablet, cost reduction and dose flexibility, especially in pediatrics and geriatrics. Whereas the problems associated with this technique are mainly due to the lack of ability to obtain equal parts after breaking the tablet, either due to physical characteristics or the patient´s ability to do so [4], and the loss of mass due to crumbles [5], [6]. It has also been reported that some tablets are difficult to break, especially if they are of smaller size [7]. Altogether, it has been concluded that in some populations the negative experiences with splitting tablets may reach 36% of the prescriptions, leading to poor compliance of the medication regimen[7]. The problem with unequal parts can be overlooked if the splitting occurs to facilitate the intake, but might be a major issue if the main goal is to obtain smaller doses. If the tablets break into several pieces when split, it may be impossible to use the tablet altogether or it may lead to the rejection of the broken pieces, which will increase the costs for the patient [3], [7]. Unequal splitting may increase the variability of the concentration-time profile, which may be important in narrow therapeutics drugs [8], may reduce total exposure with the compound over time because of the loss of substance and has been shown to result in unintended change or failure of drug response in 3% of the patients [3]. Regarding the splitting technique, the most common seem to be breaking tablets by hand, using a knife or a tablet splitter [5]. In order to assess the best method, there have been many studies conducted so far. The results are mixed, but seem to indicate that it may be preferable to split tablets by hand or using a kitchen knife [9]. However, many of these studies have been studying best case scenarios where the person who breaks the tablets is a trained pharmacy professional (normally a pharmacy technician, or a pharmacist) and the formulations are known to be easily breakable [10]. As for tablet characteristics, it has been postulated that oblong tablets split better than round ones, as well as thinner ones [4], [11]. The presence of coating and a score line provides lower variation of the obtained portions, especially if it is a deep one [12], [13]. However, modified or extended-release tablets must not be split even if they present all the characteristics previously mentioned, since splitting will compromise the release of the product, making it available faster than it was intended to [14]. There are some proposed measures in order to improve the tablet splitability. Some are regarding the tablet, recommending that the industry chooses to manufacture tablets that are easily breakable and guarantee less loss of mass and similar halves [15]. Others believe that information should be the first step, which seems to be relevant considering only 12% of patients indicate that they have been given instructions in order to accurately subdivide tablets [5]. In order to regulate the issue, the European Pharmacopeia created a monograph for accuracy of subdivision of tablets. The guidelines advise that in order to assess the accuracy of subdivision one must randomly select 30 tablets, break them and then discard

one half. The other half must be weighted and from the 30 halves only one can be outside the range of 85-115% of the theoretical mass and none can be outside the range 75-125% [16]. It has also been proposed that the loss of mass should not be greater than 3% [16].

The objectives of this study are to assess if there are any significant differences when untrained volunteers split previously selected scored tablets, by analysing the results regarding tablet format, splitting method, loss of mass and the probability of obtaining accurate halves.

2 Methodology

Formulations identified by a team of pharmacy technicians as being often split in hospital practice were gathered. For this study, formulations that were scored, had not expired and had at least 60 tablets available were considered to integrate it. Thirteen formulations were initially listed, however one of them expired before the trial began, one of them was not commercialized in Portugal and the other one had tablets from two different batches. The ten remaining formulations are described in Table 1.

Table 1. Studied formulations

Code	Formulation	Active substance	Format
A	Decadron® 0,5 mg	Dexamethasone	Round
B	Carvedilol GP® 6,25 mg	Carvedilol	Round
C	Lorazepam Cinfa 2,5 mg	Lorazepam	Round
D	Zyloric 100 mg	Allopurinol	Round
E	Tegretol® CR 400mg	Carbamazepine	Round
F	Risperidona Basi 3 mg	Risperidone	Oblong
G	Amlodipina GP® 5 mg	Amlodipine	Oblong
H	Hidantina® 100	Phenytoin	Round
I	ADT 25 mg	Amitriptyline	Round

A total of sixty tablets were randomly chosen from each formulation and were weighted using a Kern Abs 220-4 analytical scale. Half of the tablets (n=30) were then split by hand and the other half was cut using a kitchen knife. The volunteers who split the tablets had no previous experience with splitting and were given no instructions on how to do it. Each half was then weighted individually on the same scale and the results were recorded considering that the half on the right of the operator was half number one (H1) and the other one was half number two (H2). When there were crumbles instead of halves, the authors chose the two biggest portions in order to make the required measurements. The records for each formulation were then inserted in a Microsoft® Excel 2010 spreadsheet, totalling 90 results per formulation/method combination. The software was then used to verify which tablets complied with the specifications from the European Pharmacopeia for splitting tablets and which did not have a loss of mass greater than 3%. As for splitting accuracy, only the results

from H1 were used, since the European Pharmacopeia calls for only one half of each tablet to be weighted. For the loss of mass test, a sum of the weights of both halves was used. In order to assess if there were any significant differences between methods and tablet format, SPSS v22.0 was used in order to perform chi-square tests to assess if there were statistically significant associations between the method and format and the amount of equally subdivided tablets or loss of mass.

3 Results

3.1 Splitting Accuracy

Regarding splitting accuracy, eight of the twenty formulation/method combinations passed the European Pharmacopeia criteria (Table 2). Three of those had been split with a kitchen knife and five had been split by hand.

Table 2. Accuracy of Splitting and Loss of Mass

Code	Method	Outside the 85%-115% range	Loss of mass ≥3%	Passed all tests
A	Knife	12	9	X
	By hand	19	29	X
B	Knife	20	30	X
	By hand	17	0	X
C	Knife	16	24	X
	By hand	10	0	X
D	Knife	1	1	X
	By hand	0	0	✓
E	Knife	0	0	✓
	By hand	0	0	✓
F	Knife	2	1	X
	By hand	0	0	✓
G	Knife	5	18	X
	By hand	0	0	✓
H	Knife	1	2	X
	By hand	1	0	✓
I	Knife	2	1	X
	By hand	2	1	X
J	Knife	12	7	X
	By hand	8	1	X

3.2 Loss of Mass

Twelve of the twenty formulation/method combinations presented at least one tablet with a loss of mass greater than 3%. In one particular case, all of the 30 tablets tested had a loss of mass greater than 30% and another one had 29 tablets with that characteristic (Table 2).

3.3 Approved Formulations

Of the twenty formulation/method combinations, only six complied with all the criteria established (Table 2). Five of them had been split by hand and only one had been split using a kitchen knife. When considering formulations, only one out of the ten (formulation E) complied with all the criteria when using both methods for splitting.

3.4 Chi-Square test

When applying chi-square tests to assess if there was any significant relation between method or tablet format and loss of mass or splitting accuracy, the p-values obtained were as listed on Table 3.

Table 2. Chi-square results

Variables	p-value
Format / Mass uniformity	0.000
Format / Loss of mass	0.000
Method / Mass uniformity	0.163
Method / Loss of mass	0.000

4 Discussion

When a tablet is presented with a scoring line, it is easy to assume that it is prepared to be subdivided, especially because it is of the utmost importance for the patient to achieve the required doses in order for the treatment to be successful. However, the findings of this study indicate that many scored tablets fail to pass the European Pharmacopeia tests and have unacceptable mass losses. These findings are similar to those achieved by other authors. Hill et al. [17] evaluated drug content and weight uniformity for six medications, with warfarin being the one showing the highest number of half tablets falling out of the proxy specification range. Riet-Nales et al. [9] studied the best methods for tablet subdivision. Although studying only one formulation, the experiment showed that tablet splitters and kitchen knife may not accurately subdivide tablets in equal parts. Cook et al. [18] also evaluated one single formulation of cyclobenzaprine, concluding that tablet fractioning could result in unpredictable dosing and therapeutic response. Finally, Carvalho et al. [19] studied three formulations commonly split in a hospital context, with all of them exceeding the Pharmacopeia limits regarding loss of mass. However, these studies tried to evaluate splitting in a context of best-case scenario, which does not accurately describe the day-to-day

experience by untrained users, since usually volunteers are pharmacy practitioners and the pills used are known to split easily [10]. Focusing on studies which tried to describe user experience we can highlight two. One by El-Baseir et al [20] , where untrained users were asked to split five cardiovascular formulations. Results in this study showed a wide weight variability that could be clinically significant when using three different methods (scissors, splitting by hand and a tablet splitter device). The other experiment was by Peek et al. [1] and studied tablet splitting by thirty older men, obtaining results indicating that variation in doses ranged from 9 to 37% from those intended. In the present study, regarding splitting accuracy, only eight formulations achieved the expected results and there seems to be no relation between method and accuracy. However, when considering tablet format, the p-value obtained was 0.000, which means there is an association between format and splitting accuracy, as previously stated by other authors[4], [11], [21]. As for loss of mass, the case seems to be different, as cutting the tablets with a knife seems to produce significantly greater loss of mass when compared with splitting by hand. According to the tests performed, the p-value obtained was 0.000, which means there is a significant relation between method and loss of mass. This is of great importance, because one of the main reasons presented to promote tablet splitting seems to be cost reduction for the patient. However, if the patient fails to produce two halves of the tablets, the cost reduction will be nonexistent and therefore will no longer justify the process. Besides the cost reduction, loss of mass was in some cases so large that it may compromise the treatment efficacy itself. There was also a significant relation between tablet format and loss of mass. These results were to be expected when consulting the literature but should not be verified as they can interfere with treatment and treatment adherence. It is especially serious in the case of tablets which present scored lines, which often lead the patient to think that it is prepared to be split. As these results cannot be extrapolated to similar tablets, these tests should be performed by an independent authority in order to establish which tablets are prepared to be subdivided and provide for the patient to be given those when in need of lower doses. It should also be stated on the brochure if the scored line is optimized for tablet splitting to achieve half of the dose or just to facilitate tablet intake. When counseling patient in the pharmacy, pharmacy professionals should advice the patient in order to improve their experience with the treatment. This includes splitting tablets and the health professional should always verify if the patient is used to the technique and which results they have achieved with it. When the patient is not fully enlightened, the pharmacy professional should explain the available options and advice the patient to split tablets by hand and, only when it is not possible to do so, to split them using any other method, including using a kitchen knife. Regarding tablet format, results indicate that patients who choose oblong tablets will encounter less episodes of significant loss of mass. This study did not evaluate drug content, so it is not possible to assess if the obtained halves could provide the therapeutic levels needed for the treatment to work. It also only evaluated two splitting methods, leaving behind other less popular ones, but which are also applied by patients. Given the many factors which contribute to the accuracy of splitting, it is not possible to extrapolate these findings to similar formulations.

5 Conclusion

Having a scoring line does not assure that it is advisable to split the tablet, since it may lead to unequal halves and/or significant loss of mass. This fact is of great clinical importance if the person splits the tablet in order to obtain half of the tablet dose. The results obtained indicate that choosing an oblong tablet and breaking it by hand are to be considered when in need of tablet splitting. The Pharmacy Technician should take this into account when counselling the patient so that he or she will obtain accurate halves and the loss of mass is not significant.

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