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Tablet Splitting and Weight Uniformity of Half-Tablets of 4 Medications in Pharmacy Practice

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Abstract

Background: Tablet splitting is a common practice for multiple reasons including cost savings; however, it does not necessarily result in weight-uniform half-tablets. *Objectives:* To determine weight uniformity of half-tablets resulting from splitting 4 products available in the Jordanian market and investigate the effect of tablet characteristics on weight uniformity of half-tablets. *Methods:* Ten random tablets each of warfarin 5 mg, digoxin 0.25 mg, phenobarbital 30 mg, and prednisolone 5 mg were weighed and split by 6 PharmD students using a knife. The resulting half-tablets were weighed and evaluated for weight uniformity. Other relevant physical characteristics of the 4 products were measured. *Results:* The average tablet hardness of the sampled tablets ranged from 40.3 N to 68.9 N. Digoxin, phenobarbital, and prednisolone half-tablets failed the weight uniformity test; however, warfarin half-tablets passed. Digoxin, warfarin, and phenobarbital tablets had a score line and warfarin tablets had the deepest score line of 0.81 mm. *Conclusion:* Splitting warfarin tablets produces weight-uniform half-tablets that may possibly be attributed to the hardness and the presence of a deep score line. Digoxin, phenobarbital, and prednisolone tablet splitting produces highly weight variable half-tablets. This can be of clinical significance in the case of the narrow therapeutic index medication digoxin.

Keywords

tablet splitting, weight uniformity, pharmacy practice

Introduction

Tablet splitting is a common practice in clinical settings.[1,2] In the primary care setting in Germany, a cross-sectional survey assessing 882 patients found that among the 3158 drugs used in the analysis, 24.1% (762 drugs) were split. Of the split tablets, 8.7% (66 drugs) lacked a score line and 3.8% (29 drugs) were not recommended to be split, even with a splitter, according to information from the marketing authorization holder.[1]

Tablet splitting has a number of advantages including cost-saving potential and providing proper dosage in cases where slow dose titration and dose tapering are necessary.[3,4] A study conducted in outpatient setting evaluated 2019 patients who participated in a hydroxymethylglutaryl-CoA reductase inhibitor tablet splitting program in the period between April and September 2000. The results showed that the total cost avoidance after 1 year of utilizing tablet splitting program for atorvastatin, lovastatin, and simvastatin was $138 108, and the average cost avoided per patient per year was $68.40.[3]

On the other hand, tablet splitting may result in the administration of a wrong dose due to uneven splitting, which can be of significant risk if the split medication is a narrow therapeutic index medication, although no evidence of negative clinical outcomes could be found in the medical literature. A retrospective analysis investigated changes in efficacy and safety after implementing a tablet-splitting program on patients receiving simvastatin. A 3787 patients were evaluated and the results showed no significant difference in average change from baseline in low-density lipoprotein cholesterol levels, nor incidence of transaminase increase.[5] Rindone investigated the efficacy of splitting lisinopril tablets in patients with hypertension in a randomized crossover clinical trial. A total of 29 patients were randomized to taking whole tablet or a split tablet for 2 weeks and then switched in a crossover fashion. By the end of the study, no statistically significant differences in systolic/diastolic blood pressures were found between patients taking whole tablets versus split tablets.[6] Weissman et al investigated the effect of splitting risperidone tablets on clinical outcomes for schizophrenic patients. The results showed an increase in the rate of unscheduled mental health appointments and medication possession ratio (MPR) in the split-tablet group. The authors related the increase in

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MPR not to an increase in patients' adherence rather to patients losing tablets, misunderstanding splitting instructions, or ingesting whole tablets instead of half-tablets.[7]

Several studies evaluated weight uniformity of split medications, Hill et al evaluated 6 commonly split medications: warfarin sodium, simvastatin, metoprolol succinate, metoprolol tartrate, citalopram, and lisinopril.[8] Weight uniformity of split half-tablets was assessed by comparing the actual weight of the half-tablets with the calculated one-half average weight for the whole tablets included in the analysis. The percentages of weight difference between half-tablets and sample mean values were compared with proxy US Pharmacopeia (USP) specifications. The results showed that the proportion of half-tablets that fell outside the proxy USP specifications for weight were 33.3% for warfarin, 20% for metoprolol succinate, and 23.3% for lisinopril, while simvastatin, metoprolol tartrate, and citalopram fell within the proxy USP specifications. The study also found that 11.1% of half-tablets of scored medications and 14.4% half-tablets of nonscored medications fell outside the proxy USP specifications for weight.[8] Polli et al evaluated 12 split medications, finding that 8 medications passed the weight uniformity test (atorvastatin, citalopram, furosemide, glipizide, metoprolol, paroxetine, sertraline, and warfarin) while 4 medications failed (lisinopril, lovastatin, rofecoxib, and simvastatin). The criteria used in the study were adapted from the USP "Uniformity of Dosage Units" test for whole tablets.[9]

Another disadvantage of tablet splitting is drug waste; the tablet characteristics or the technique used can result in traces or small fragments which lead to inaccurate dosage. Confusion and nonadherence are other disadvantages for tablet splitting.[10] In some instances, a score on a tablet can be misleading; patients or health care providers can be under the impression that scored tablets are always suitable for splitting which is not necessarily the case.[11]

Not all tablets are suitable for splitting, splitting enteric coated, sustained and controlled release formulations can increase the risk of side effects and compromise effectiveness.[12] Narrow therapeutic index medications available as nonscored tablets may not be suitable for splitting. Patients' state of health can affect their ability to properly split their tablets. For example, patients with manual, eyesight, or cognitive problems may face difficulties in tablet splitting.[13] Navarro pointed that tablet splitting is an accepted practice in managed care pharmacy for suitable drugs and if performed by patients without physical disabilities under the pharmacists' guidance.[14]

Different splitting techniques can result in large dose deviations or weight losses; Verrue et al studied the mean deviation from theoretical weight and mean weight loss after tablet-splitting with 3 different techniques; splitting device, scissors, or kitchen knife. The results showed lower mean deviation from theoretical weight and less weight loss with the splitting device compared to the 2 other methods.[15]

To our knowledge, there are no studies describing the frequency of tablet splitting or the most common tablet splitting techniques used in Jordan; however, it is well known to the authors that tablet splitting is a common practice and tablet splitters are not commonly used and not even available in all pharmacies in Jordan. The objective of this study is to evaluate the weight uniformity of half-tablets of 4 products sold in the Jordanian market. In the absence of data regarding the most commonly split medications in Jordan, we chose 4 products that are commonly split from our professional experience and used for long-term therapy. We included narrow therapeutic index medications and medications that require tapering. We also aim to determine factors that affect accuracy of the splitting including tablet hardness (crushing strength), presence of score line, and depth of the score line.

Methods

Four commonly split drugs available in Jordanian market were studied: warfarin sodium 5 mg (Orfarin 5 mg, Lot #1269546, expiry date 09-2011; Orion Corporation, Espoo, Finland), digoxin 0.25 mg (Lanoxin, Lot #B0998G, expiry date 07-2013; GlaxoWellcome GmbH & Co., Bad Oldesloe, Germany), phenobarbital 30 mg (Phenotal 30, Lot #036, expiry date 06-2013; darou Pakhsh, Tehran, Islamic Republic of Iran), and prednisolone 5 mg (Corotrope 5, Lot #39733, expiry date 04-2012; Remedica Ltd, Limassol, Cyprus). Tablets of these products were removed from unopened original packs. Six supervised PharmD students performed tablet splitting using the same knife. All volunteers were right handed with no physical disability affecting the ability to split tablets.

Each volunteer was instructed to split 5 randomly selected tablets of each medication. The weights of the whole and half-tablets were measured. All weight measurements were performed using a sensitive balance (Mettler Toledo, AT261 delta range, Switzerland).

The criteria for assessing weight uniformity were adapted from Polli et al.[9] Polli et al[9] adapted their methodology from USP chapter <905>[16] and reference #.[17] The criteria are as follows: 30 random tablets from each product were weighed and the average weight per tablet was calculated. The tablets were weighed individually and split using the knife and the resulting halves were also weighed individually. To comply with the adapted criteria, the results of 10 random tablets were used for weight uniformity analysis. The relative standard deviation (RSD) of the halves was calculated and the number of halves outside the ranges 85% to 115% and 75% to 125% were counted.

- The perfect split tablets are half-tablets within the 85% to 115% range by weight.
- The tablets pass the weight uniformity test if one half or less was outside the 85% to 115% range and within the 75% to 125% range and if the RSD was less or equal 10.0%.
- If 2 half-tablets were within the 75% to 125% range but outside the 85% to 115% range or if RSD is more than 10% then another 20 tablets should be split. To pass the uniformity tests, all 40 half-tablets should be within the 85% to 115% range and the RSD for the 60 half-tablets should be less or equal 10%.

Table 1. Tablet Characteristics of the 4 Products

Product	Average weight (mg) N = 30	Diameter (mm) N = 5	Thickness (mm) N = 5	Score depth (mm) n = 5	Flat-faced tablet	Average tablet hardness (Newton) N = 5
Digoxin	112.5 ± 2.2	7.04 ± 0.00	2.68 ± 0.03	0.18 ± 0.06	No	40.3 ± 8.4
Phenobarbital	66.1 ± 3.9	5.58 ± 0.03	2.67 ± 0.10	No score	No	41.2 ± 5.7
Prednisolone	111.7 ± 1.4	6.52 ± 0.01	2.50 ± 0.02	0.20 ± 0.01	Yes	54.3 ± 2.8
Warfarin sodium	138.4 ± 1.0	7.02 ± 0.02	2.86 ± 0.01	0.81 ± 0.02	Yes	68.9 ± 3.4

Table 2. Weight Variation Analysis for Half-Tablets of Each Product

Product	Average weight for split 10 tablets (mg; n = 20)	Number of halves outside 85%-115%	Number of halves outside 85%-115% and within 75%-125%	Number of halves outside 75%-125%	Relative standard deviation %	Result
Digoxin	52.9	6	5	1	13.2	Reject
Phenobarbital	32.5	12	5	7	25.9	Reject
Prednisolone	55.6	8	6	2	16.0	Reject
Warfarin sodium	69.1	0	0	0	7.0	Accept

- The half-tablets fail the weight uniformity test if more than 2 of the 20 half-tablets were outside the 85% to 115% range, or if any half-tablet was outside the 75% to 125% range.

Tablet characteristics including diameter, thickness, and score depth were measured using a micrometer. Tablet hardness was measured using hardness tester (Copley, Switzerland) with a platen speed of 1.5 mm/s.

All tablets were split using a knife with a stainless steel blade. The dimensions of the blade were measured at the midpoint using a micrometer: the length and height of the blade were 7.40 cm and 1.60 cm, respectively, and the width of the blade at the nonsharpened end was 0.11 cm. The length of the edge of the sharpened end was 0.10 cm. The wooden handle has the following dimensions at the midpoint: 11.70 × 2.13 × 1.36 cm. Tablets were split on a glassine weighing paper placed on a flat surface (bench top). Volunteers were instructed to hold the knife in their right hand, place the sharp end along the score of the tablet, and apply incremental force on the nonsharpened end of the knife using the left hand until tablet split.

Results

The basic characteristics (average weight, diameter, thickness, score depth, tablet structure, and hardness) of the 4 products studied are listed in Table 1. Among the 4 products, 3 had a score line along one face of the tablet. Warfarin sodium tablets had the highest hardness and weight (a high hardness value indicates a stronger compact which requires larger force to break). In addition, the score depth of warfarin sodium tablets was 0.81 ± 0.02 mm, which represents 28% of the total thickness. However, digoxin and prednisolone tablets have a score depth of 0.18 ± 0.06 and 0.20 ± 0.01 mm, respectively, representing 8% of the thickness of both digoxin and prednisolone tablets.

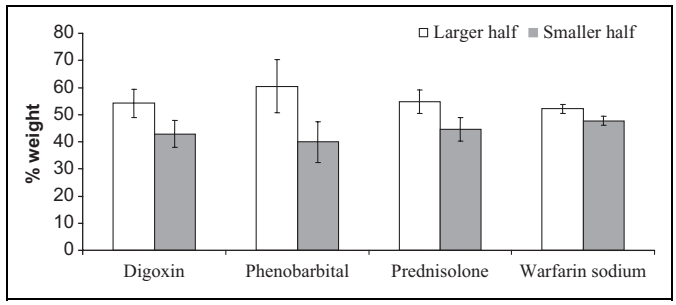

Figure 1. Average percentages of half-tablets' weight to whole tablets' weight for each product.

The results of the weight uniformity test performed on half-tablets of the 4 products are found in Table 2. Warfarin sodium tablets passed the weight uniformity test, with no half-tablets outside the 85% to 115% range and an RSD less than 10%. However, digoxin, phenobarbital, and prednisolone half-tablets failed; all 3 products had an RSD more than 10% and half-tablets outside the 75% to 125% range.

Average percentages of half-tablets' weight to the weight of whole tablets for each product are shown in Figure 1. The figure also lists corresponding standard deviations. The closer the average percentages of weights of the smaller and larger half-tablets to 50% indicate a close to perfect split (high accuracy). In addition, a large standard deviation on the column indicates a high variability (low uniformity) in half-tablet weights. Warfarin sodium half-tablets were closer to 50%, with a small standard deviation; this is in agreement with the weight uniformity test results. However, half-tablets of other products have average percentages for the weights of the smaller and the larger

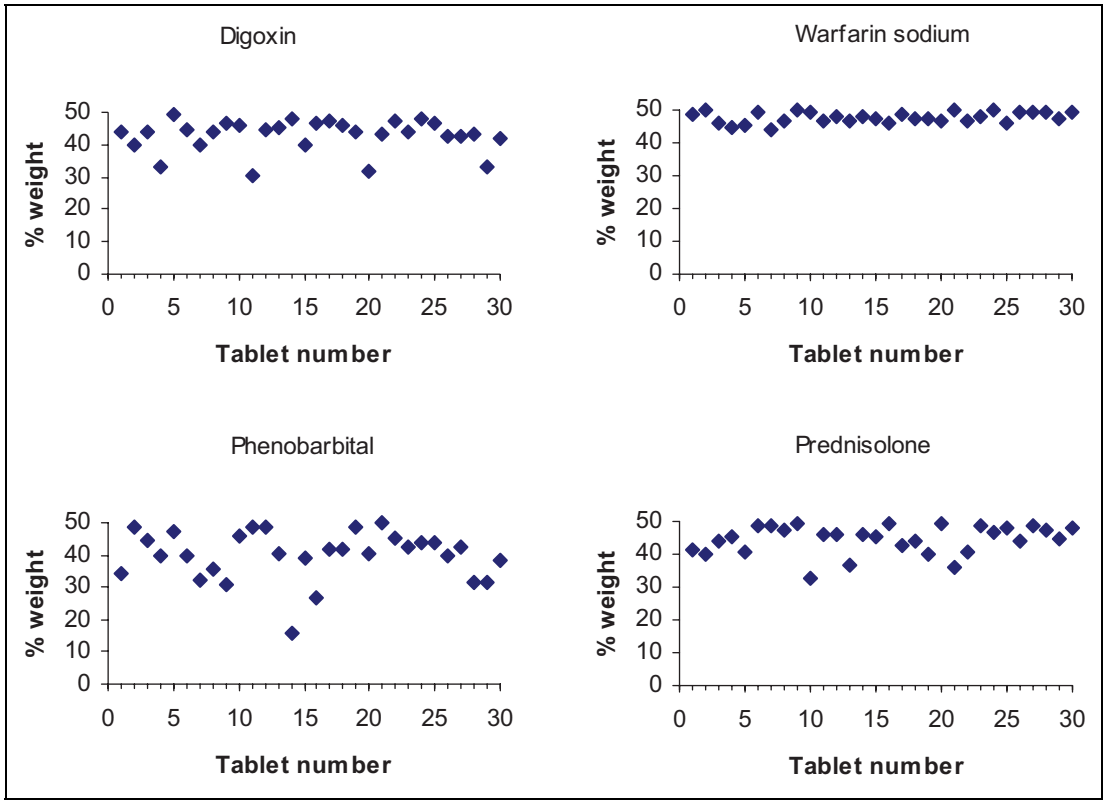

Figure 2. Percentage weight of the smaller half to tablet weight of digoxin, warfarin, phenobarbital, and prednisolone tablets.

half-tablets that are far from 50% along with large standard deviations.

Plots of percentage weights of the smaller half-tablets to tablet weights for each of the 4 drugs are shown in Figure 2. These plots provide further insight into the scatter (variability) of half-tablets from the perfect split (50%). Figure 2 shows the smaller half-tablets of warfarin sodium gather close to the 50% with minimal scatter. However, the smaller half-tablets of the rest of the products show high scatter from 50%. Moreover, Figure 2 shows that phenobarbital half-tablets have the highest scatter. This finding is coherent with the result of phenobarbital half-tablets having the highest RSD among the group.

Discussion

While tablet splitting is a common practice. Recent articles that question tablet-splitting safety illustrate why studies that determine tablet characteristics of tablets that split accurately are important.[18,19]

Warfarin sodium tablets are the heaviest, have the largest thickness, highest crushing strength, and deepest score line with a flat face. This combination of characteristics seems to provide an ideal tablet for accurate and uniform splitting. On the other hand, phenobarbital tablets have the smallest weight, the smallest diameter, beveled face, along with no score line. This combination of characteristics seems to provide tablets with poor splitting accuracy and uniformity. Other studies found an association between tablet characteristics and splitting behavior. The effect of presence of a score line on weight uniformity of split tablets was investigated. In a study with a similar design to our study, Polli et al found that of the 12 products investigated all scored tablets passed the uniformity test while most nonscored tablets failed (4 of 6 products).[9] Hill et al found that 11.1% of half-tablets of scored medications failed the weight uniformity test compared to 14.4% of half-tablets of nonscored medications. In their study, they chose the more stringent USP specifications for weight uniformity; 95% to 105% for warfarin sodium and 90% to 110% for citalopram, lisinopril, metoprolol succinate, metoprolol tartarate, and simvastatin compared to the 85% to 115% used in our study. In addition, Hill et al study used tablet cutter instead of a knife.[8] The half-tablets of digoxin and prednisolone tablets failed the weight uniformity test (Table 2) and had a large magnitude of weight scatter (Figures 1 and 2); although the presence of score lines can help improve the accuracy of the split, nevertheless it can be misleading.[11] Patients or health care providers might be under the impression that such tablets produce even splits. This can be of greater concern especially for potent drugs such as digoxin. Another study investigating the effect of resistance to crushing (crushing strength) on predicting the ease of subdivision of scored tablets. The results suggested that crushing strength is the most important contributor followed by diameter, score mark (1- or 2-sided), and finally the shape (flat or biconvex). Accordingly, a large crushing strength is expected to improve the accuracy and uniformity of tablet split.[20] On the other hand, other researchers found opposite

predictions on the effect of crushing strength on tablet splitting behavior.[9] Thus, achieving a high degree of accuracy and uniformity in tablet splitting requires a contribution of a number of tablet characteristics, and it cannot be concluded by a single character.

Such results can be of clinical significance in the case of narrow therapeutic index medications such as warfarin and digoxin, small dose changes can result in sub- or supratherapeutic doses.[21,22] Warfarin is available in 2 strengths in the Jordanian market (3 mg and 5 mg tablets),[23] which mandates tablet splitting in many patients' cases; digoxin is available in 3 strengths in the Jordanian market (0.0625 mg, 0.125 mg, and 0.25 mg),[23] it is also commonly split during the dosing taper process either for unavailability or for cost-saving reasons.

To the best of our knowledge, no available guidelines regulate the tablet splitting practice in Jordan. We recommend initiating a data base that can be accessed electronically and specify what tablets can be divided and what tablets cannot be, depending on the presence of score lines, depth of the score lines, tablets hardness, and other relevant characteristics. Many medications available in Jordan are imported from the United States and Europe; tablet-splitting information can be quoted and applied to such products, in addition US Food and Drug Administration issued a draft guidance for industry regarding tablet scoring, which we recommend to be applied by Jordanian drug manufacturers.[24] A prospective intervention study conducted in Germany implemented an electronic prescription system that provided the information on the divisibility for solid oral dosage forms. By the end of the study, there was a significant reduction in inappropriate splitting.[25] Other ways to regulate this practice is to educate pharmacists and pharmacy students about tablets splitting, what tablets can be split, and which patients can split them.

Limitations

The criteria used to evaluate weight uniformity are derived from the criteria set for whole tablets and were applied for half-tablets. The study investigated weight uniformity without looking at the drug content, a further study investigation drug content can give more comprehensive view. Another limitation is that the volunteers who split tablets were PharmD students who understood the importance of accurate splitting, and they were healthy with no physical disabilities affecting their splitting accuracy; however patients may have different health problems that can affect accuracy of tablet splitting. A future study evaluating clinical significance and effects on patients' outcomes will give more comprehensive view.

Conclusion

From a weight uniformity perspective, warfarin sodium tablets can be split with small degree of weight variability that can be attributed to the increased hardness and presence of a deep score line. However, digoxin, phenobarbital, and prednisolone tablet splitting can lead to half-tablets with high weight variability, which may lead to toxicity or inefficacy in case of the narrow therapeutic index medication digoxin. In addition, the presence of score lines on digoxin and prednisolone tablets is misleading.

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