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Practice report

Comparison of tablet splitting techniques for dosing accuracy of nebivolol tablets: Hand splitting versus tablet cutter and knife

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ABSTRACT

Tablet splitting is a common practice in clinical settings to lower doses, facilitate swallowing or save costs. Splitting devices can be used when hand splitting is difficult or painful. However, data on the accuracy of tablet splitting are limited and it presents a number of patient or formulation-related problems. Thirty nebivolol IR tablets on the Turkish market were split by hand, a tablet cutter (Rabır®) or a knife, and tested for weight variation, loss of mass, disintegration, and friability. The accuracy of split tablets was in the range of 75.4–121, 82.4–115, and 86.9–115% when split by hand, the cutter, and knife, respectively. No significant difference in accuracy was determined between the left and right sides split by the cutter ($p = 0.222$). The differences were significant for hand and knife splittings ($p < 0.005$). The precision was 9.02, 7.87, and 6.11% (CV%) for hand, tablet cutter, and knife, respectively. Only hand splitting failed to comply with the subdivision test of European Pharmacopoeia. The split portions met USP standards for friability (<1%). Splitting decreased the disintegration time (4.5 vs. 2.2 min). Overall, the accuracy of the tablet cutter was more favorable than hand splitting and knife. The study demonstrated that the splitting technique may result in inaccurate dosing and significant drug fluctuations for nebivolol tablets.

1. Introduction

Today, oral dosage forms, especially tablets, have an important place in the treatment. Tablet splitting is the most commonly used technique in cases where lower doses are required for the treatment and there are no suitable dose strengths on the market (Nolly et al., 2005; Elliott et al., 2014). It is also an important approach for cost savings or changing and optimizing drug doses, especially for special patient populations such as the elderly, children, newborns, and patients with swallowing difficulties, and patients receiving long-term treatment for chronic diseases (Duman et al., 2000; Quinzler et al., 2006; Abu-Geras et al., 2017).

There is no consensus on which technique is the best for dividing tablets (Teixeira et al., 2017). However, the most commonly used methods are those performed by hand splitting, knife, or tablet splitting devices (Somogyi et al., 2017). The size, shape, hardness, structure, depth of the scoreline, and components of the tablet, and splitting technique/device can affect the accuracy of tablet splitting (Peek et al., 2002; Tahaineh and Gharaibeh, 2012; Elliott et al., 2014). For example, when harder tablets are divided, it is possible that they break up into powder and there is a loss of medicine, and round or small tablets may also cause larger deviations (McDevitt et al. 1998; Polli et al. 2003). Various studies have shown that the accuracy of tablet splitting varies significantly, because the patient's state of health may affect the ability to properly split tablets (Rosenberg et al. 2002; Teng et al. 2002; Polli et al. 2003; Verrue et al. 2011; Helmy, 2015). Particularly, it is stated that it would be difficult to split tablets in patients with arthritis and rheumatism, movement disorders, poor cognitive function, or poor vision (Van Riet-Nales et al., 2014).

Changes in the mass and content of drugs with tablet division may affect the performance of the product, resulting in a decrease in the effectiveness of the treatment, or the emergence of side and toxic effects (Shah et al., 2010; Seong et al., 2019). Split portions must comply with content or mass uniformity requirements (Chaudhri et al., 2019). Drugs that are planned to be split are desired to have wide therapeutic windows, a relatively long half-life, and low toxicity (Nolly et al., 2005). Splitting is not recommended for modified-release and controlled-release products,

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and orodispersible tablets (Gharaibeh and Tahaineh, 2020). For this reason, extended-release and time-release products such as oral contraceptive pills should not be split.

Although tablet subdivision is a common practice, there is currently limited literature investigating the evidence on splitting a tablet and obtaining the correct dose (Chaudhri et al., 2019). The FDA (Food and Drug Administration) has recently published an official guide for healthcare professionals and patients (FDA, 2017). Evaluation of the accuracy of the tablet splitting process is outlined in the international guidelines such as the US Food and Drug Administration (FDA) and European Pharmacopeias (EP) (European Pharmacopoeia, 2008; Elliott et al., 2014; Ashames et al., 2018). However, there are many questions about the application since this issue is complex. Therefore, there is a need for a standard and international harmonized protocol for the subdivision of tablets.

In cardiology, β-blockers constitute an important group in the treatment of arrhythmia, angina pectoris, heart attack, and high blood pressure. With chronic treatment, death is reduced and life expectancy is prolonged in patients with coronary heart disease and hypertension (Zaid et al., 2012). However, full doses of β-blockers used cannot be tolerated, thus requiring a dose titration and an initial treatment with a small starting dose (Bachynsky et al., 2002). Nebivolol is a selective β1-blocker with vasodilatory properties used in the treatment of hypertension and heart failure (McNeely and Goa, 1999; Moen and Wagstaff, 2006). It has less bioavailability (12%) due to its low water solubility (0.091 g/100 mL) and dissolution rate (Nikam and Patil, 2020). Nebivolol was chosen as the model antihypertensive drug, as it frequently needs dose titration in the range of 1.25–10 mg. However, only 5 and 10 mg nebivolol tablets are commercially available in the Turkish drug market. This study aimed to compare the accuracy and precision of the three splitting techniques (hand, knife, and tablet cutter (Fig. 1)) for 5 mg-scored nebivolol tablets.

2. Material and methods

2.1. Material

Nebivolol immediate release (IR) tablets (5 mg, scored, oval, film-coated) were used to compare the splitting techniques. The commercial IR tablets of 5 mg nebivolol (20G518) were purchased from the local drug market in Turkey. The studies were conducted using the same batch of products.

2.2. Study design

Three techniques for tablet splitting were investigated: hand splitting, a tablet cutter, and a knife. The splitting procedure was performed by two researchers (female, 27-years old and 32-years old, Faculty of Pharmacy, Gazi University) (Fig. 2). 30 tablets for the product were split by hand, knife, and a commercially available tablet cutter (Rabır pill cutter, Orjinalmedikal Medical Equipment Company, Turkey). The weights of each bisected tablet were determined by Ohaus TP200S analytical balance (Florham Park, NJ, USA). It was recorded whether a tablet part resulted from the right or left side of the tablet cutter, knife, or the operator's hands. Split tablets were tested for weight variation and loss of mass. The subdivision test was performed according to European Pharmacopoeia. Uniformity of content was not tested, because the content of the active substance was greater than 2 mg.

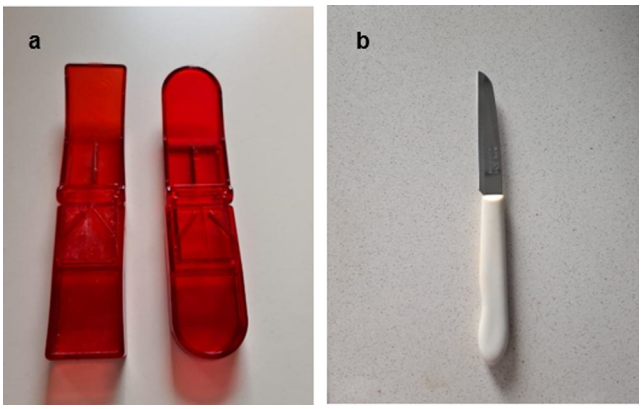

Fig. 1. a) Tablet cutter and b) knife used for tablet subdivision in the study.

2.2.1. Disintegration time

Nebivolol product was also tested for disintegration to explore whether the split tablet portions meet the same characteristics as for the intact product. Disintegration tests were performed using DIST-3 Triple Basket Tablet Disintegration Tester (PharmaTest, Germany). Split tablet portions and intact products of nebivolol were placed in 1000 mL of pH 1.2 disintegration medium at 37 ± 0.5 °C. Experiments were carried out in triplicate.

2.2.2. Friability

The measurement of friability was made by using the PharmaTest friabilator (PTF 10E, Germany). 20 tablets were dedusted and weighed before the test. The drum was rotated at 25 rpm for 4 min. At the end of the test, the powder of the tablets was dedusted and re-weighed. If the value of friability (loss %) is less than or equal to 1%, weight loss is acceptable.

2.2.3. Hardness

The hardness test was performed with 10 randomly selected tablets using the CGS HighSpeed Hardness Tester HDT, 1V-3 (Germany). The mean crushing strength was calculated and expressed as (N ± SD).

2.2.4. Diameter – Thickness

The diameter and thickness of tablets were measured with a caliper for each of the cases.

2.3. Data analysis

The accuracy and precision of splitting techniques were calculated for the drug product. Accuracy was calculated as the percentage of the weight of the split tablet versus the theoretical weight of the split tablet portion. Precision was calculated as the relative standard deviations of the weight measurements. A comparison of accuracy between left and right sides was made. The data are presented as mean ± standard deviation (SD). The independent *t*-test was used to assess differences between the two groups. Differences were considered statistically significant at $p < 0.05$.

The compliance to regulatory requirements (European Pharmacopoeia and FDA) was investigated. Test for weight variation was adapted to the test on the subdivision of tablets in European Pharmacopoeia. Briefly, 30 tablets for the product were split by hand, knife, and a commercially available tablet cutter (Rabır pill cutter, Orjinalmedikal Medical Equipment Company, Turkey). All the parts obtained from one tablet were taken. The 60 parts were weighed individually. The tablets comply with the test if not more than one individual mass is outside the limits of 85 percent to 115 percent of the theoretical weight of the split tablet portion. The tablets fail to comply with the test if more than one individual mass is outside these limits, or if one individual mass is outside the limits of 75 percent to 125 percent of the average mass. 30 tablets were also tested for a loss of mass less than 3.0 percent between 60 individ-

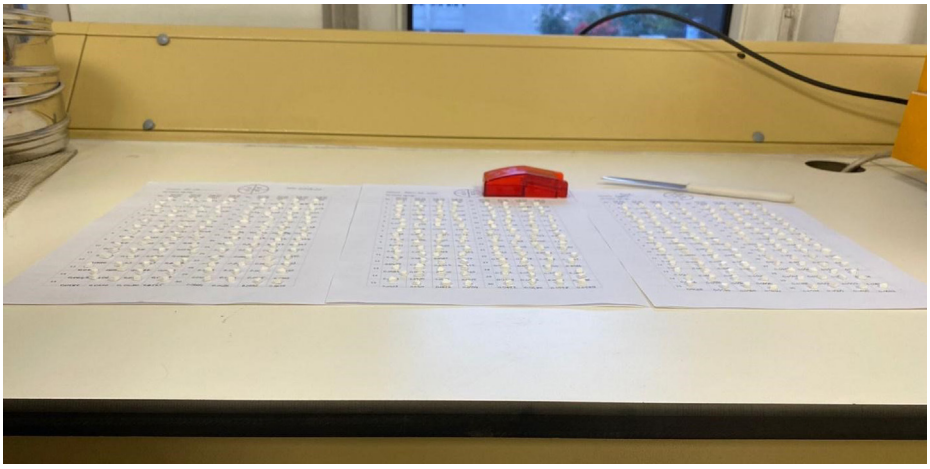

Fig. 2. Three techniques for tablet splitting were investigated: hand splitting, a tablet cutter and knife. Nebivolol immediate release (IR) tablets (5 mg, scored, oval, film coated) were used to compare the splitting techniques. 30 tablets for the product were split by hand, knife and a commercially available tablet cutter (Rabır pill cutter, Orjinalmedikal Medical Equipment Company, Turkey).

ual split tablet portions when compared to the whole tablet according to FDA guidance.

3. Results

3.1. Accuracy and precision

The diameter and thickness of the tablet were 9.10 ± 0.01 and 3.13 ± 0.02 mm, respectively. The hardness value was 47 ± 6 N.

The accuracy of split tablets was in the range of 75.4–121, 82.4–115, and 86.9–115% when split by hand, the cutter, and knife, respectively (Table 1). No significant difference in accuracy was determined between the left and right sides split by the cutter ($p = 0.222$). The differences were significant for hand and knife splittings ($p < 0.005$).

Of the nonmechanically and mechanically (using cutter) split tablet portions, 22 and 25% deviated by more than 10% from the ideal weight, respectively. However, 6.7% deviated by more than 10% from the ideal weight for the other mechanically (using a knife) split tablet portions.

The precision was 9.02, 7.87, and 6.11% (CV%) for the hand, the cutter, and knife, respectively.

3.2. Regulatory requirements

Compliance with regulatory requirements when nebivolol tablets were split by hand, knife, and the tablet cutter are presented in Table 2, 3, and 4, respectively.

Only hand splitting failed to comply with the subdivision test of European Pharmacopoeia. However, none of the techniques complied with the FDA requirement for loss of mass (>3.0%). Most of the split tablets displayed a loss of mass greater than 3%.

The split portions of all tablets met USP standards for friability (<1%). Splitting decreased the disintegration time. Disintegration times of intact and half tablets were 4.5 and 2.2 min, respectively.

4. Discussion

The accuracy and precision of three techniques for the subdivision of nebivolol IR tablets were investigated: hand splitting, knife, and tablet cutter. Nebivolol was selected as the model antihypertensive drug because it is frequently used by a wide variety of patients in Turkey for the treatment of hypertension and heart failure. Dose titration is required in the dose range of 1.25–10 mg (Rachamin et al., 2021). Therefore the purpose was to determine whether it is correct to split nebivolol tablets or not from a pharmaceutical point of view and evaluate the current standards for tablet splitting.

For data analysis, both parts of the split tablets were taken into account, since the accuracy and precision depend on the selection of the tablet parts. Additionally, the left and right sides were compared statistically. Actually, in practice, both parts from the same tablet are used by the same patient if there is no stability problem regarding splitting. The accuracy and precision were calculated on basis of the theoretical weight of an intact tablet in this study. It was calculated as the average weight of the tablets tested. This approach was considered acceptable since the variability in the weight of 30 intact tablets of nebivolol was found to be low (1.0–1.3%).

The results indicated differences between the mechanically and non mechanically techniques. Accuracy of tablet cutter was more favorable than hand splitting and knife since no significant difference in accuracy was determined between left and right sides for the cutter. However, none of the products met the US regulatory requirements (FDA, 2013). For tablet splitting, splitters and knives are commonly used when hand splitting is difficult or painful due to the physical properties of tablet or special patient's limitations (Notenboom et al., 2016; Van Riet–Nales et al., 2020). It was demonstrated that the tablet splitter used in this study may accurately and precisely subdivide tablets into equal parts for nebivolol tablets. However, it must be kept in mind that the splitting procedure was performed by professional researchers. Therefore the impact of the operator was not evaluated in the present study. Moreover, tablet splitting may be problematic for the special patient groups with Alzheimer's or Parkinson's diseases (Ganzetti et al., 2021).

The tablet cutter was selected based on its availability on the Turkish market and potential usage by the patients. The study showed that the dosing accuracy, and precision of a specific type of tablet splitter should be tested. Authorities should take appropriate actions to ensure the accuracy, precision and sustainability of tablet splitters to enter the market. Moreover, tablet splitters should be considered as medical devices. Since one model/make of tablet cutter tested in this study did not work properly resulting in improper splitting, and large crushing, and loss of mass (data not

Table 1
Accuracy of tablet splitting for nebivolol IR tablet product.

Tablet No	Accuracy (%)					
	Hand Splitting		Tablet Cutter		Knife	
	Right Side	Left Side	Right Side	Left Side	Right Side	Left Side
1	95.8	101	100	99.6	97.7	102
2	93.8	107	91.3	107	90.4	109
3	94.5	103	92.8	105	103	98.5
4	96.8	107	111	89.3	100	103
5	99.0	105	115	82.4	96.1	102
6	90.8	112	109	93.6	95.3	106
7	106	91.5	94.7	95.6	104	93.7
8	87.8	110	100	101	104	95.7
9	94.2	106	113	85.9	96.7	99.1
10	101	98.1	99.0	98.7	99.6	100
11	93.0	108	96.7	98.6	101	96.4
12	96.9	101	106	94.6	98.6	102
13	90.2	110	87.1	112	97.0	102
14	95.1	108	86.4	115	107	94.2
15	90.8	104	107	88.4	104	93.7
16	95.6	103	108	95.0	102	99.8
17	116	87.5	94.2	105	95.7	103
18	96.7	108	99.6	98.4	93.0	105
19	89.9	111	102	99.2	105	98.1
20	90.6	110	88.5	106	97.2	100
21	75.4	120	103	96.5	110	90.2
22	98.7	103	93.6	105	109	90.2
23	86.8	114	99.9	95.9	106	91.2
24	93.9	103	91.6	107	92.9	102
25	83.3	117	113	87.7	115	87.0
26	93.8	105	105	89.0	110	90.3
27	91.8	106	98.6	106	109	87.8
28	105	93.0	104	97.6	103	95.9
29	91.7	109	108	94.8	107	93.0
30	106	97.3	101	96.2	98.9	99.6
	$p < 0.005$		$p = 0.222$		$p < 0.005$	
mean	94.7	105	101	98.1	102	97.7
SD	7.4	7	8	7.7	6	5.6
CV%	7.8	6.8	7.8	7.8	5.9	5.7

Table 2
Compliance to regulatory requirements of nebivolol tablets split by hand.

European Pharmacopoeia / Weight Variation					US FDA / Loss of mass	
Split tablet portions in the specified range (n)				Complies	>3.0% (n)	Complies
< 75%	75–85%	85–115%	>125%			
0	2	55	0	No	51	No

Table 3
Compliance to regulatory requirements of nebivolol tablets split by a knife.

European Pharmacopoeia / Weight Variation					US FDA / Loss of mass	
Split tablet portions in the specified range (n)				Complies	>3.0% (n)	Complies
< 75%	75–85%	85–115%	>125%			
0	0	60	0	Yes	40	No

Table 4
Compliance to regulatory requirements of nebivolol tablets split by the tablet cutter.

European Pharmacopoeia / Weight Variation					US FDA / Loss of mass	
Split tablet portions in the specified range (n)				Complies	>3.0% (n)	Complies
< 75%	75–85%	85–115%	>125%			
0	1	59	0	Yes	45	No

shown). Specific break mark tablets should also be tested for dosing accuracy before being marketed if they are intended to be subdivided by a splitting device or hand. The ease, accuracy, and precision of the process should be evaluated. It should be a standard protocol. There is a lack of standardized and international harmonized methodologies for tablet splitting.

In addition, other dosage forms such as oral solution, suspension, syrup, sprinkles, dispersible tablets, and mini tablets allowing flexible dosing and easy swallowing may be considered as an alternative treatment when splitting are not properly performed due to any reasons (Ranmal et al., 2018). It should be realized that tablet splitting may result in dosing inaccuracies, which may have a serious effect on clinical outcomes. It should also be remembered that splitting may produce dust and the drug exposures may cause harmful health effects depending on the type of active substances (Tahaineh and Gharaibeh, 2012; Elliott et al., 2014).

For the subdivision of tablets, tablet geometry and size are of great importance. Since the parameters such as diameter, width, depth of the scoreline, shape (oblong, round, flat, or biconvex), and hardness are critical for the tablets (Van Santen et al., 2002). Another pitfall of the study was only one trade product was tested. Breaking the film coating increases the surface area, may affect the stability of drugs. It is known that nebivolol tablets on the Turkish drug market maintain their stability under 25 °C for 2 years (RxMediaPharma, 2021). However, there is no information on the stability of split tablets and it should also be evaluated. The disintegration of both intact and half tablets occurred in 5 min. Therefore, splitting seems not to affect the bioavailability of nebivolol tablets due to the disintegration and dissolution.

5. Conclusion

Overall, the accuracy of the tablet cutter was more favorable than hand splitting and knife for nebivolol tablets. The study demonstrated that the splitting technique may result in inaccurate dosing and significant drug fluctuations for nebivolol tablets. Therefore, the dosing accuracy and precision of a specific type of tablet splitter should be tested. Specific medicine should also be tested for dosing accuracy before being marketed if it is intended to be subdivided by a splitting device or hand.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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