



Whole vs. Half-Tablets – a Case of Diazepam

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ABSTRACT

Background: Tablet splitting is commonly used in clinical practice as a way to attain a desired drug dose and/or reduce its side effects, particularly among paediatricians and psychiatrists. However, uneven tablet scoring can lead to significant fluctuations of the administered doses, where subpotency or superpotency of drugs might harm the patients. The aim of this study was to evaluate the influence of tablet splitting on dose uniformity of diazepam by the utilisation of Ph. Eur. 9.0 and FDA recommendations.

Methods: Mass variation of whole and half-tablets in parallel with the determination of their content uniformity were performed according to the pharmacopoeial methods. The weight loss after tablet splitting was assessed by employing FDA guidelines. It was also investigated if tablet splitting influenced the *in vitro* dissolution properties of diazepam tablets.

Results: Diazepam whole tablets fulfilled the pharmacopoeial requirements in regard to all the investigated properties. The weight uniformity of scored diazepam tablets ranged from 63.80% to 122.55% label claim. The losses of mass after splitting diazepam tablets were 5.71%. Despite the average content of diazepam in half-tablets was found to be 104.24% label claim, the requirements of Ph. Eur. were not fulfilled. Diazepam content in half-tablets ranged from 0.76 mg to 1.21 mg, thus, patients might receive doses that vary by as much as 45%. However, after weight adjustment, diazepam content in each of the tested half-tablets was in the range of 85-115% of the average drug content meeting the Ph. Eur. criteria. Dissolution profiles of whole and half-tablets were found to be similar, following the Hixson-Crowell kinetic model.

Conclusion: According to the results, splitting of diazepam tablets greatly influenced the drug content in the obtained parts, ie the dose accuracy was fully dependent of the ability to score the tablet into exactly equal halves.

Key words: tablet splitting, diazepam, tablet scoring, half-tablets, dose adjustment.

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INTRODUCTION

Since patients show a large variability in body surface area and weight, there is a broad variation in drug response among the patients. In order to accomplish proper drug treatment, a large variation of tablet strengths is required, but this is not always provided. Besides, adverse effects of drugs, which are considered as one of the major problems in modern pharmaceutical practice,

are dose dependent. Despite the manipulation of medicines renders their use unlicensed, tablet splitting is commonly used in clinical practice as an approach to attain a desired drug dose and/or reducing its side effects, particularly among paediatricians and psychiatrists.¹⁻⁴ Healthcare professionals often prescribe half-tablets either to achieve lower drug doses than the lowest com-

mercially available strength or to reduce treatment costs because different dose strengths of the same drug frequently have similar prices¹ or higher-strength tablets are payable by insurance companies, unlike lower drug doses.⁵ Another reason for tablet scoring is a facilitated drug administration due to ease of swallowing.^{6,7}

On the other side, there are many potential concerns associated with tablet splitting. The most important problems are variation in weight and drug content in half-tablets, as well as drug stability of halves obtained by splitting whole tablets. As a result of uneven tablet scoring, administered dose can significantly fluctuate, especially in case of drugs with narrow therapeutic index, where subpotency or superpotency of drugs might harm the patients.^{1-3, 8, 9}

Tablets can be either hand-split along a scored line or the scoring can be obtained by using a knife or specially designed tablet splitter (Figure 1). Because some tablets can break into more than two parts, the occurrence of tablet wasting is possible. Several studies have reported weight differences among split medications. However, some of these studies have evaluated uniformity of drug content solely by means of variation in weight of half-tablets,^{5,7} while a few studies have evaluated the drug content in the halves.^{1, 4, 8}

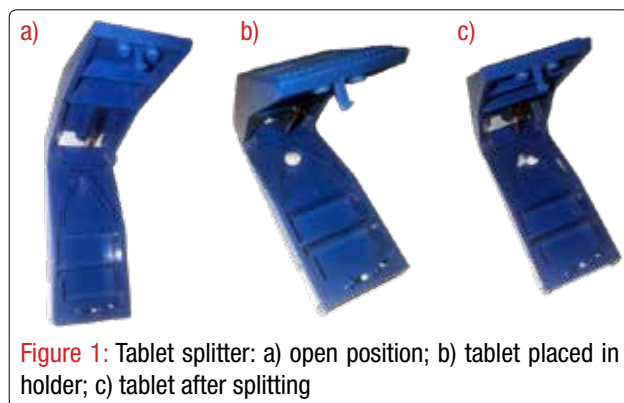


Figure 1: Tablet splitter: a) open position; b) tablet placed in holder; c) tablet after splitting

To address these issues, the European Pharmacopoeia 4.0 (Ph. Eur.)¹⁰ introduced guidelines for measuring the dosing accuracy of subdivided scored tablets. Hence, this assessment became mandatory in many European countries in order to provide accuracy in dosing of split tablets. However, a score line on tablets can be misleading, as not all scored tablets are suitable for splitting.⁸ According to the rules of Ph. Eur. and Guideline on Summary of Product Characteristics (SmPC) adopted by the European Commission, one of the following phrases should

be used in the SmPC for tablet designed with a score line:⁶

- "The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses"
- "The tablet can be divided into equal halves"
- "The tablet must not be divided at all"

This information is significant to both healthcare professionals and patients as well, because it is believed among patients that the score line on a tablet represents a sign that the tablet can be split.⁶

It is also important to note that until now guidelines for the assessment of the drug content of split tablets have not been established in any official pharmacopeia. However, as a response to problems concerning tablet splitting, the US Food and Drug Administration (FDA) developed Guidance for Industry on tablet scoring,¹¹ providing the criteria for scored tablets, as a part of the FDA drug reviewing process. According to the Guidance,¹¹ the split tablets should fulfil the same requirements as the whole tablets having equal strength

Diazepam (Figure 2) is one of the most prescribed benzodiazepines¹² with sedative, anxiolytic, anticonvulsant, muscle relaxant and amnestic action, which is mediated by enhancement of the activity of gamma-amino

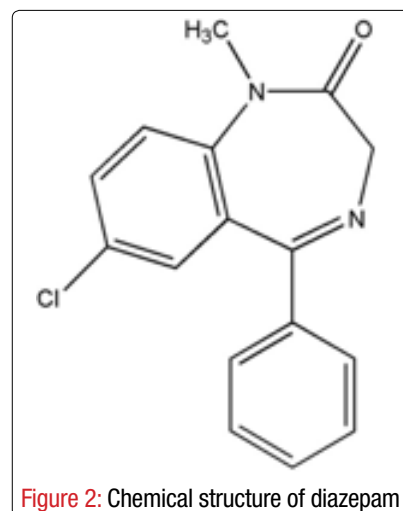


Figure 2: Chemical structure of diazepam

inobutyric acid (GABA), a major inhibitory neurotransmitter in the brain.¹³ In clinical practice, it is used in the short-term treatment of severe anxiety disorders, insomnia and for premedication and sedation. Diazepam is also indicated in the treatment of status epilepticus and febrile convulsions, as well as in the control of muscle spasm. The use of diazepam is associated with the risk of dependence, which is very much affected by the given dose and treatment duration. Therefore, doses of diazepam should be the lowest that can control symptoms and courses of treatment

should not be longer than 4 weeks, with the drug being withdrawn gradually. Dosage reduction may also be required in elderly and debilitated patients, as well as patients with hepatic or renal impairment. Also, low doses of diazepam may be given to children (ie in children 1–12 months diazepam is given initially 250 microgram/kg twice daily for the treatment of muscle spasm in cerebral spasticity or in postoperative skeletal muscle spasm; 1 to 5 mg at bedtime have been used in children and adolescents aged from 12 to 18 years to treat night terrors and sleepwalking).¹³⁻¹⁵

The aim of this study was to evaluate the effect of tablet splitting on dose uniformity of diazepam by the utilisation of Ph. Eur. 9.0¹⁶ and FDA recommendations.¹¹ For this purpose, determined mass variation of whole and half-tablets was determined in parallel with the determination of their content uniformity. The weight loss after tablet splitting was also evaluated. Finally, the authors were interested to investigate if tablet splitting influenced dissolution properties of diazepam tablets.

METHODS

Reagents

All chemicals used in this study were of analytical grade. Sulphuric acid, methanol and hydrochloric acid (35%) were purchased from Lach-Ner (Neratovice, the Czech Republic).

Tablets

Diazepam tablets (2 mg) were obtained from the local market. Tablets were round, convex, without score lines, with average diameter and thickness of 8.07 ± 0.02 and 4.30 ± 0.04 mm, respectively. Inactive ingredients were: lactose monohydrate, corn starch, povidone and magnesium stearate.

Tablet splitter

In this work tablet splitter (Romed - Holland) was used. Tablet splitter was opened (Figure 1a) and the investigated tablet was positioned and scored by closing the splitter (Figure 1b). The weight of tablets was measured before and after scoring (Analytical balance, TE214S, Sartorius, Goettingen, Germany).

Uniformity of mass of whole tablets

Mass uniformity of whole tablets was determined according to Ph. Eur. 9.0. monograph

"Uniformity of mass of single dose preparations".¹⁶ Twenty randomly taken tablets were weighted and the average mass was calculated. In order to pass the test, not more than two of the individual masses should differ from the average mass by more than 7.5% and none more than 15%.

Subdivision of tablets

According to the European Pharmacopoeia "Test for subdivided scored tablets",¹⁶ thirty tablets of the chosen product were selected at random. These thirty tablets were split and assessed to have passed the test if no more than one individual mass was not within 85-115% of the average mass and if no individual mass was outside the limits of 75-125% of the average mass. Additionally, the limit for relative standard deviation (RSD) from the United States Pharmacopoeia¹⁷ (USP) was applied, stating that the product passed the test if the RSD is less or equal to 6%. However, the USP has a somewhat different method for making a decision which halves to weigh. Namely, all of the weighed tablet parts must be within the 85-115% range of the target tablet weight. Thus, in this study the Ph. Eur. criteria¹⁶ were used with the addition of the RSD limit from the USP.¹⁷

Loss of mass after scoring the tablets

In accordance with the requirements of the FDA tablet scoring guidance for industry,¹¹ splitability of diazepam tablets was checked by calculating a loss of mass obtained by scoring fifteen tablets. The difference in mass of split tablet portions when compared to the whole tablets-should be less than 3%.

Content uniformity of whole and scored diazepam tablets (Ph. Eur. 9.0)¹⁶

The individual content of diazepam of ten randomly taken tablets was determined. The tablets comply with the test if individual content is range of 85% and 115% of the average content. The tablets fail to comply with the test in the case of more than one individual content being outside the above-mentioned limits. Any of individual contents also must not be out of the boundaries of 75-125% of the average content. In the cases when one individual content falls outside the range of 85-115% but within the limits of 75-125%, another twenty tablets randomly selected should be analysed on drug content. In order to pass the test, not more than one of the individual contents of thirty units is out of the range of 85-115% and none being outside the limits of 75-125% of the average drug content.

In this study, ten randomly selected diazepam tablets were tested. Because FDA Guidance¹¹ recommends that the scored tablets should fulfil the same criteria as the whole tablets, five tablets taken at random were split and the content of the drug was also measured in ten obtained half-tablets.

Drug assay

Content of diazepam in tablets and half-tablets was determined according to the British Pharmacopoeia¹⁸ as follows. Firstly, 1 ml of water was added to one tablet. The tablet was then allowed to disintegrate for 15 minutes. Afterwards, 80 ml of a 0.5% w/v solution of sulphuric acid in methanol was added and then shaken for 15 minutes. Sufficient volume of the methanolic sulphuric acid was added to produce 100 ml and filtered. The absorbance of the filtrate was measured at 284 nm and diazepam content was calculated according to the value of A (1%, 1 cm) at 284 nm (UV-1800 spectrophotometer, Shimadzu, Japan), which is 450.

Microsoft Office Excel was employed for all calculations.

Dissolution test

The dissolution test of whole and half-tablets was carried out according to the USP42-NF37¹⁷, by using apparatus 1 (Erweka 726) at a stirring speed of 100 rpm. Temperature was maintained at 37°C during the entire experiment. The test was performed in 900 ml of 0.1 M hydrochloric acid. Dissolution samples in the amount of 5 ml were taken at the following intervals (after 10, 20 and 30 min). Withdrawn samples were supplemented with the same volume of freshly prepared dissolution medium to maintain sink conditions. The acquired samples were filtered using 0.22 µm membrane filters (Chromafil® X-tra PTFE-20/25, Macherey-Nagel, Düren, Germany). Diazepam concentration was determined by using UV-VIS spectroscopy, at 242 nm (UV-1800 spectrophotometer, Shimadzu, Japan). If necessary, the samples were diluted with dissolution medium prior to drug quantification.

As oral bioavailability of diazepam is fully dependent on dissolution of a dosage form, the evaluation of dissolution properties and the comparison of dissolution profiles for whole and scored tablets are very important. The obtained dissolution profiles were compared by utilising a model-independent approach, which includes the determination of a difference factor (f_1) and a similarity factor (f_2),¹⁹ according to the equa-

tions (1) and (2) as follows:

$$f_1 = \frac{\sum_{t=1}^n |R_t - T_t|}{\sum_{t=1}^n R_t} \times 100 \quad (1)$$

$$f_2 = 50 \times \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \quad (2)$$

where n is the time points number, R_t is the dissolution value of the reference product (whole tablets) at time t , and T_t is the dissolution value of the test product (half-tablets) at time t . The assessment of similarity of dissolution profiles was based on f_1 and f_2 values, which should be in a range of 0-15 and 50-100, respectively.²⁰ In addition, drug release data were fitted to different kinetic models (Table 1) and the linear regression was evaluated by using R^2 (squared correlation coefficient) as the main criterion concerning the selection of the model best describing diazepam dissolution from the investigated whole and half-tablets.

Table 1: Mathematical models applied to dissolution profiles of diazepam whole and half tablets¹⁸

Model	Equation
Zero order	$Q_t = Q_0 + K_0 t$
First order	$\log Q_t = \log Q_0 - K_1 t / 2.303$
Higuchi	$Q_t = Q_0 + K_H t^{1/2}$
Korsmeyer-Peppas	$Q_t = K_{KP} t^n$
Hixson-Crowell	$Q_0^{1/3} - Q_t^{1/3} = K_{HC} t$

Q_t : amount of drug released in time t ; Q_0 : initial amount of drug in dissolution media; K_0 , K_1 , K_H , K_{KP} , K_{HC} : release rate constants.

Data analysis

Dissolution tests results obtained with six replicates were presented as the average amount of diazepam dissolved (%) ± SD. The statistical analysis was carried out by using Student's t-test. p values lower than 0.05 were considered as statistically significant. Microsoft Excel software package was employed for all analyses.

RESULTS

Uniformity of mass of whole tablets

Table 2 shows mass of twenty whole tablets (g) and whether the weight of each investigated sample fitted in the range of 85-115% of the average tablet weight. Average mass of twenty diazepam tablets was found to be 201.87 mg.

Table 2: Results of mass uniformity for whole diazepam tablets.

Sample number	Weight of whole tablet (g)	85-115% of the average mass
1	0.2077	Yes
2	0.1980	Yes
3	0.2038	Yes
4	0.2027	Yes
5	0.2053	Yes
6	0.2022	Yes
7	0.2032	Yes
8	0.2014	Yes
9	0.2039	Yes
10	0.2020	Yes
11	0.1969	Yes
12	0.1959	Yes
13	0.2012	Yes
14	0.1987	Yes
15	0.2047	Yes
16	0.2104	Yes
17	0.2010	Yes
18	0.1939	Yes
19	0.2040	Yes
20	0.2004	Yes
Average	0.2019	
SD	0.0039	
RSD	1.95	
Meet Ph. Eur. ac-ceptance criteria	Yes	

Uniformity of mass of half tablets

Masses of thirty half-tablets (g) were determined (Table 3) and it was evaluated if they were in a range of 85-115% and 75-125% label claim. Average mass of thirty half-tablets was 93.7 mg, which represents 92.83% of the predicted mass of half-tablet. The weight uniformity of scored diazepam tablets ranged from 64.4 mg to 123.7 mg, which is equivalent to 63.80% to 122.55% label claim. Also, the weight of twelve samples of scored tablets was not beyond the limits of 85-115% of the average mass, with four of them outside 75-125% of the average (Table 3).

Loss of mass after scoring the tablets

The mass loss (g) produced by scoring the tablets was expressed as % of the whole tablet weight. As can be seen from Table 4, on average

Table 3: Results of mass uniformity for diazepam half tablets.

Sample number	Weight of whole tablet (g)	85-115% of the average mass	75-125% of the average mass	Sample number	Weight of whole tablet (g)	85-115% of the average mass	75-125% of the average mass
1	0.1183	No	No	16	0.1237	No	No
2	0.0806	Yes	Yes	17	0.0943	Yes	Yes
3	0.1112	No	Yes	18	0.0958	Yes	Yes
4	0.0976	Yes	Yes	19	0.1063	Yes	Yes
5	0.1012	Yes	Yes	20	0.1072	Yes	Yes
6	0.0881	Yes	Yes	21	0.0767	No	Yes
7	0.1149	No	Yes	22	0.0784	No	Yes
8	0.0817	Yes	Yes	23	0.1032	Yes	Yes
9	0.1011	Yes	Yes	24	0.0908	Yes	Yes
10	0.0719	No	Yes	25	0.0964	Yes	Yes
11	0.1145	No	Yes	26	0.0764	No	Yes
12	0.0692	No	No	27	0.0916	Yes	Yes
13	0.1020	Yes	Yes	28	0.0644	No	No
14	0.0997	Yes	Yes	29	0.0892	Yes	Yes
15	0.0895	Yes	Yes	30	0.0738	No	Yes
Average	0.0937						
SD	0.0154						
RSD	16.49						
Pass	No						

5.71% of tablet mass was lost during the scoring procedure.

Content uniformity of whole and scored diazepam tablets

In this part of the study, uniformity of diazepam content in whole and half-tablets was determined and the obtained results were presented in Table 5. The average content of diazepam in ten randomly taken whole tablets was 105.98%

Table 4: Mass losses obtained by scoring diazepam tablets using tablet splitter

Sample number	whole tablet mass (g)	1/2 tablet mass (g)	2/2 tablet mass (g)	Loss of mass (%)
1	0.2037	0.0945	0.0850	11.88
2	0.2041	0.1054	0.0930	2.79
3	0.2047	0.1121	0.0918	0.39
4	0.1999	0.0926	0.0897	8.80
5	0.2026	0.0968	0.0955	5.08
6	0.2027	0.0969	0.0951	5.28
7	0.2000	0.1000	0.0905	4.75
8	0.2041	0.0868	0.1016	7.69
9	0.1993	0.1010	0.0888	4.77
10	0.2029	0.1030	0.0967	1.58
11	0.2078	0.1219	0.0846	0.63
12	0.2003	0.0976	0.0883	7.19
13	0.2047	0.0843	0.1060	7.03
14	0.2043	0.0976	0.0981	4.21
15	0.2027	0.0852	0.0901	13.52
Average loss (%)	5.71			
SD	3.79			
RSD	66.38			
Pass	No			

label claim, whereas half-tablets contained on average 104.24% label claim of the drug.

In addition, adjustment of drug content for weight of half-tablets was made and it was revealed that diazepam content in weight-adjusted half-tablets was less variable and similar to the drug content in whole tablets (105.05%).

Dissolution test

In vitro dissolution test revealed that drug dissolved (%) from whole and half-tablets in 30 minutes was 96.48 ± 1.35 and 96.16 ± 4.88 , respectively (Figure 3). In addition, dissolution profiles of whole and half-tablets were found to be similar as depicted in Figure 3. This is also

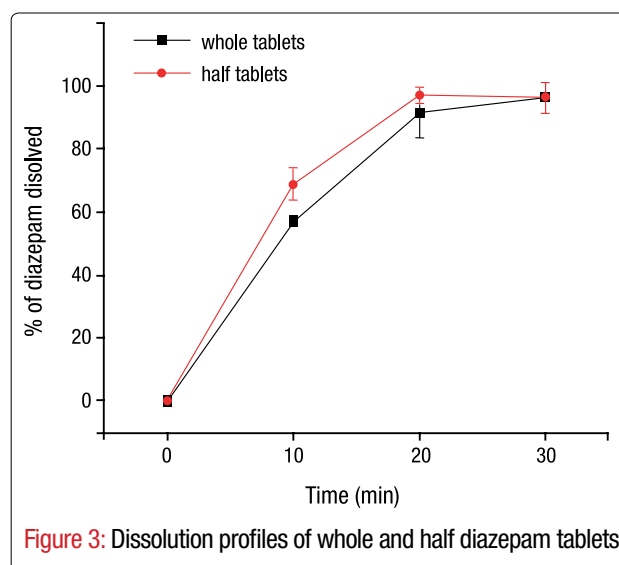


Figure 3: Dissolution profiles of whole and half diazepam tablets

Table 5: Results of content uniformity for whole and half diazepam tablets

Sample number	whole tablets		half tablets			weight-adjusted half tablets	
	Content of diazepam (% of label claim)	85 -115% of the average content	Content of diazepam (% of label claim)	85 -115% of the average content	75-125% of the average content	Content of diazepam (% of label claim)	85 -115% of the average content
1	107.78	Yes	115.78	Yes	Yes	103.16	Yes
2	99.78	Yes	120.22	No	Yes	95.27	Yes
3	106.11	Yes	104.89	Yes	Yes	103.32	Yes
4	110.33	Yes	94.67	Yes	Yes	101.66	Yes
5	112.67	Yes	110.67	Yes	Yes	96.89	Yes
6	105.00	Yes	120.89	No	Yes	103.18	Yes
7	105.89	Yes	94.22	Yes	Yes	117.47	Yes
8	108.44	Yes	75.56	No	No	112.45	Yes
9	103.11	Yes	97.78	Yes	Yes	105.36	Yes
10	100.67	Yes	107.78	Yes	Yes	111.71	Yes
Average	105.98		104.24			105.05	
SD	4.07		14.05			6.97	
RSD	3.84		13.64			6.64	
Pass	Yes		No			Yes	

confirmed with the values of f_1 and f_2 which were 7.25 and 55.96, respectively.

The values of correlation coefficients (R^2) obtained by fitting the drug release data are presented in Table 6. As can be noticed the drug release from whole and half-tablets followed the same kinetics, ie the Hixson-Crowell kinetic model.

Table 6: The values of correlation coefficients (R^2) obtained by fitting the drug release data

Sample	Model				
	Zero order	First order	Higuchi	Korsmeyer -Peppas	Hixson -Crowell
whole tablets	0.84	0.98	0.98	0.97	0.99
half tablets	0.72	0.97	0.95	0.98	0.99

DISCUSSION

Uniformity of mass of whole tablets

Taking into account that not one individual mass was outside the limits of 92.5-107.5% of the average mass, diazepam tablets fulfilled the Ph. Eur. requirements as expected.

Uniformity of mass of half tablets

According to the results obtained in this part of the study, the requirements for mass uniformity of split tablets were not fulfilled. Moreover, according to the calculated RSD, which was found to be 16.49, diazepam tablets did not pass the test for uniformity of mass. These results can be attributable to the small size and round shape of tablet, which is in line with earlier findings,^{8, 21}

where tablets having diameter smaller than 8 mm showed poor splitting behaviour. Besides, a lack of a score line on the tablets, generally, makes the tablets difficult to split evenly.^{8, 21}

Loss of mass after scoring the tablets

In agreement with mass variation of half-tablets, manipulation of whole tablets led to an increased friability of the investigated solid dosage form of diazepam. As expected, the losses of mass after splitting diazepam tablets exceeded 3%. Thus, the FDA requirements were not fulfilled. In addition, it should be noted that there was high variability among the tested samples, with up to 13.52% of the tablet mass lost during the scoring procedure. Taking into account these results coupled with weight uniformity of the half-tablets, high variations in drug content of scored tablets can be expected.

Content uniformity of whole and scored diazepam tablets

As presented in the Results section, content of the drug for whole tablets ranged from 99.78% to 112.67% label claim, indicating that the whole tablets fulfilled the Ph. Eur. acceptance criteria regarding drug uniformity.

On the other hand, despite the average content of diazepam in half-tablets was found to be close to the label claim, the requirements of Ph. Eur. were not fulfilled.¹⁶ Actually, four samples contained diazepam outside the limits of 85-115% label claim. However, the drug content of all ten samples of half-tablets was in range of 75-125% label claim. In addition, three samples were not beyond the boundaries of 85-115% of the average drug content in half-tablets, while one of them also did not fit to the range of 75-125% of the average drug content. Because diazepam content in half-tablets ranged from 0.76 mg to 1.21 mg, patients might receive doses that varied by as much as 45%. This finding correlates well with the results of weight uniformity. However, in order to deeper investigate the cause for these results, the drug content was adjusted for weight of half-tablets, since it is supposed that the drug in tablets is dispersed uniformly. Thus, it is presumed that the drug content in half-tablet with known weight is proportional to the ratio of the half tablet's weight to the whole tablet's weight:

$$\text{weight-adjusted target drug content} = \frac{\text{measured half tablet weight} \times \text{target drug content for whole tablets}}{\text{measured whole tablet weight}}$$

Then the difference (%) between weight-adjusted drug content and the label diazepam content of half-tablet was calculated. Accordingly, after weight adjustment, a large reduction in drug content variation was found. Moreover, one half-tablet fell outside the limits of 85-115% label claim, but still inside the range of 75-125%. In addition, diazepam content in each of the tested half-tablets was in the range of 85-115% of the average drug content meeting the Ph. Eur. criteria.¹⁶ Taking into account these results, it could be concluded that the weight of half-tablets directly correlated with the content of diazepam and it is the main reason for diazepam content variation. Therefore, the administration of required dose of diazepam is determined by the patient's ability to split tablets perfectly in equal parts.

Dissolution test

The obtained results revealed that the whole tablets as well as half-tablets met USP42-NF37 requirements¹⁷ (not less than 85% of the label amount of diazepam is dissolved in 30 minutes). As the major quantity of diazepam was dissolved within the first 20 minutes, the drug product is expected to exhibit fast action.

Furthermore, Hixson-Crowell kinetic model best describing drug release from whole as well as from half-tablets indicated that the change in tablets' surface area and diameter occurred during the release process. Hence, this model assumes that drug release rate is not limited by diffusion, but rather by drug particles dissolution rate.²² In the case of diazepam whole and half-tablets, the obtained f_1 and f_2 factors, similar amounts of the drug dissolved in each time point of the experiment as well as similar dissolution mechanisms suggested that the dissolution properties of whole tablets would not be altered by their manipulations, such as scoring and dividing. Therefore, if tablet splitting could be performed without significant mass losses, the tablet scoring could be suggested as a mean of a swallowing facilitation.

CONCLUSION

According to the results, splitting of diazepam tablets greatly influenced the drug content in the obtained parts, ie the dose accuracy was fully dependent on the ability to score the tab-

let into exactly equal halves, which was somehow expected. On the other hand, dissolution profiles of scored tablets were similar to the *in vitro* release kinetic of whole diazepam tablets, indicating that the investigated tablets can be split in order to facilitate swallowing of the tablets. Also, if tablets are scored perfectly into two equal parts, dissolution properties of a half-tablet would be the same as in the case of taking the whole tablet and thus similar bioavailability could be presumed.

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CONFLICT OF INTEREST

None.