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ORIGINAL ARTICLE

Weight and content uniformity of lorazepam half-tablets: A study of correlation of a low drug content product

Abdel Naser Zaid [a,*], Rowa' J. Al-Ramahi [a], Abeer Abu Ghoush [a], Aiman Qaddumi [b], Yara Abu Zaaror [b]

[a] *Department of Pharmacy, An-Najah National University, P.O. Box 7, Nablus, Palestine*
[b] *Pharmacare Ltd., Beitunia, P.O. Box 677, Ramallah, Palestine*

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Abstract The aim of this study was to investigate the degree of correlation between the weight and the content of spilt-halves of lorazepam 2.5 mg tablets. Weight variation and drug content of lorazepam half-tablets were evaluated according to the European Pharmacopoeia tests. Only one individual mass of the 30 half tablets was outside the limits of 85–115% of the average mass, but since it was within 75–125% of the average mass, the product passed the test. Each individual content was between 85% and 115% of the average content (99.8% expressed as a percent to label claim) and within the limits of 75–125%, so the product passed the uniformity of content test. The correlation coefficient (r) between the weight and the content of split halves was found to be 0.994. The weights of split tablet halves appear to be directly correlated with their drug content even for a medication with a low drug content, thus it is recommended that pharmacists who split tablets into two halves, assure the weight uniformity of the resultant halves. Manufacturers should develop formulation and manufacturing procedures that ensure high degree of correlation between weight and content not only among the whole tablet but also among the obtained tablet halves.

1. Introduction

To ensure the consistency of dosage units, each unit in a given batch should contain the active drug within a narrow range around the label claim. The uniformity of dosage units can be evaluated either by measuring the content uniformity or the weight of the tested units (Green et al., 2009; The United States Pharmacopeial Convention, 2011). The test for weight variation is applicable for hard capsules, uncoated tablets and film-coated tablets containing 25 mg or more of a drug substance comprising 25% or more, by weight, of the dosage unit or, in the case of hard capsules, the capsule contents, except that uniformity of other drug substances present in lesser proportions is demonstrated by meeting the requirements for content uniformity. Unless the 25 mg/25% threshold limit is met, the use of the mass/weight variation test as an alternative test for content uniformity is not considered interchangeable in all International Conference on Harmonization (ICH) regions (The United States Pharmacopeial Convention, 2011; International Conference on Harmonization, 2008). The test for content uniformity is required for all dosage forms not meeting the above conditions for the weight. These tests are necessary to ensure that patients

* Corresponding author. Tel.: +970 92345113; fax: +970 92345982.
E-mail address: anzaid@najah.edu (A.N. Zaid).

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take a precise pharmaceutical dose. This issue is of high importance not only for whole tablets but also for the obtained halves in cases of tablet splitting since the resultant splits are essentially the new dosage form for the patient. In fact, tablet splitting is a known, widely spread, and an accepted practice in the field of pharmacy. The reasons behind this practice include providing the patient with the desired dose if the product is not available in the required strength, starting therapy with the lowest possible doses to reduce the incidence of side effects of certain drugs, reducing medication costs, and making the swallowing of large tablets easier (Green et al., 2009; Duncan et al., 2002; Fawell et al., 1999) Nevertheless, some problems may arise due to this practice, the most important problem reported in this regard is the poor weight and content uniformity of the obtained halves (Kristensen et al., 1995; Zaid et al., 2010; Zaid and Ghosh, 2011; Cook et al., 2004; Teng et al., 2003; Polli et al., 2003). Uneven splitting of a tablet product may result in significant fluctuations of the administered dose. This may be clinically significant especially for drugs with a narrow therapeutic range (Vranic and Uzunovic, 2007).

In 2002, the European Pharmacopoeia (Ph. Eur.) introduced a new test on the accuracy of subdivision of scored tablets (European Pharmacopoeia, 2002). Consequently, this test has become a mandatory test in many European countries in order to achieve uniform halves after tablet splitting and manufacturers following the Ph. Eur. standards must consider badly performing tablets as defective products (Van Santen et al., 2002; Rodenhuis et al., 2003). The United States Pharmacopeia (USP) and the British Pharmacopoeia (BP) contain a quality control test regarding the weight uniformity of dosage units. However, they do not have tests regarding the weight uniformity of the resultant split halves or the performance of score lines of tablets. Several authors have advised to add Pharmacopoeial standards for the subdivision characteristics of scored tablets (Green et al., 2009; Rosenberg et al., 2002; Zaid et al., 2012).

The aim of this study was to investigate degree of correlation between the weight and the content of spilt-halves of lorazepam 2.5 mg tablets. Lorazepam 2.5 mg tablets were chosen because lorazepam is a potent drug and the tablets will therefore contain a small amount of drug, and because Benzodiazepines are among the most commonly used classes of medications in the field of medicine. Their therapeutic actions as anxiolytics, sedative hypnotics, anticonvulsants, and muscle relaxants have led to their use as first-line treatments. High-potency benzodiazepines (e.g., alprazolam, clonazepam, and lorazepam) have replaced low and medium potency benzodiazepines in all benzodiazepine clinical indications due to their greater therapeutic effects and rapid onset of action. Usually a maximum dose of 2 mg/day of any of the high-potency benzodiazepines when given for more than 1 week is recommended. Although benzodiazepines act rapidly and are well tolerated medication in general, still their long term use presents some clinical issues such as dependence, rebound anxiety, memory impairment, and discontinuation syndrome (Chouinard, 2004).

2. Materials and methods

Lorazepam tablets (2.5 mg) were prepared by Pharmacare PLC. The physical parameters of the obtained tablets were evaluated. Weight variation and drug content of lorazepam half-tablets were evaluated according to the European Pharmacopeia (Ph. Eur.). The target drug content and weight of a half-tablet were defined as equal to one-half of the mean drug content and weight for whole tablets.

2.1. The European Pharmacopoeia test for uniformity of mass

The Ph. Eur. states: ''Take 30 tablets at random and, from all the parts obtained from 1 tablet, take 1 part for the test and reject the other part(s). Weigh each of the 30 parts individually and calculate the average mass. The tablets comply with the test if not more than 1 individual mass is outside the limits of 85–115% of the average mass. The tablets fail to comply with the test if more than 1 individual mass is outside these limits, or if 1 individual mass is outside the limits of 75–125% of the average mass'' (European Pharmacopoeia, 2008).

2.2. The European Pharmacopoeia test for uniformity of content

The Ph. Eur. states: ''Subdivide 10 tablets and randomly select 10 parts from 10 subdivided tablets and, using a suitable analytical method, determine the content of active substance(s) in each individual part. The preparation complies with the test if each individual content is between 85% and 115% of the average content. The preparation fails to comply with the test if more than one individual content is outside these limits or if one individual content is outside the limits of 75–125% of the average content. If one individual content is outside the limits of 85–115% but within the limits of 75–125%, determine the individual contents of another 20 units (subdivided tablet parts) taken at random. The preparation complies with the test if not more than one of the individual contents of the 30 units is outside 85–115% of the average content and none is outside the limits of 75–125% of the average content'' (European Pharmacopoeia, 2002).

2.3. Assay of lorazepam in tablet halves

For content evaluation, an HPLC system from Merck Hitachi, (Interface module D-7000, Autosampler L-7200, Pump L-7100, Detector L-7450) was used for the analysis and quantification of lorazepam in the samples studied. Separation was accomplished using a 4.6-mm∗25-cm column that contains 5-μm packing L1 according to the USP 30 method (United States Pharmacopeial Convention, 2007) (Table 1).

Microsoft Office Excel 2007 was used to perform all related calculations.

3. Results

Tablets were evaluated for physical parameters such as hardness, friability, shape and diameter. These parameters were within the accepted criteria for uncoated tablets with an average hardness of 4.9 KN, friability of 0.96%, average diameter of 7.0 ± 0.3 mm.

The average mass of the 30 halves was 64.4 mg, only one individual mass of the 30 half tablets was outside the limits of 85–115% of the average mass (54.1 mg), but since it was within 75–125% of the average mass, the product passed the Ph. Eur. Test (Table 2).

Table 1 Summary of HPLC parameters for lorazepam assay.

Parameter	Specification
Column	A 4.6-mm∗25-cm column that contains 5-μm packing L1(C_{18})
Flow rate	1 mL/minute
Injection volume	20 μm
Wavelength	230 nm
Mobile phase	Filtered and degassed mixture of water, acetonitrile, and glacial acetic acid (60:40:0.4)

In content uniformity testing for half tablets, each individual content was between 85% and 115% of the average content (99.8% expressed as a percent to label claim) and within the limits of 75–125%, so the product passed the uniformity of content test (Table 3).

The correlation coefficient (r) between the weight and the content of split halves of lorazepam 2.5 mg was found to be 0.994.

Table 3 Results of uniformity of content test for lorazepam 2.5 mg, 10 halves.

Sample Number	Content of lorazepam in each unit of half tablet expressed as a percent to label claim (%)	85–115% of the average content
1	97.7	Yes
2	96.4	Yes
3	97.1	Yes
4	99.7	Yes
5	90.9	Yes
6	113.0	Yes
7	99.9	Yes
8	103.3	No
9	98.4	Yes
10	101.9	Yes
Average:	99.8	Yes
Result		Pass

4. Discussion

The main objective of any pharmacopeia is to provide the manufacturers of drugs and pharmaceutical dosage forms with a series of quality control tests (QC) that ensures high quality of the final obtained dosage forms. Most of these tests require sophisticated instruments that cannot be found in community pharmacies. Accordingly, pharmacists are unable to judge on the quality of these dosage forms except for the visual QC or weight uniformity of certain solid dosage forms such as tablets and capsules. In fact, the content uniformity testing of a dosage unit is one of the Pharmacopoeial tests that are carried out only in the QC departments of the industry or in laboratories of the regulatory body as Ministry of Health (MOH). Therefore, tablet products with high quality should be designed and manufactured to have a high degree of correlation between the weight and content uniformity of the produced tablets. This is done with the purpose of ensuring that patients will take an accurate and precise dose of the medication. This last objective is not necessarily realized if the tablet is split in two halves to administer half of the labeled dose, especially if the splitting process is not performed successfully to give two equal halves or if the drug was distributed unevenly throughout the tablet during its manufacture.

Several studies have been conducted to investigate the weight uniformity of the obtained tablet halves (Kristensen et al., 1995; Zaid et al., 2010; Zaid and Ghosh, 2011; Cook et al., 2004). These studies have focused on weight uniformity because this parameter should be correlated to the uniformity of content which cannot be investigated using tools available in a pharmacy setting. Weight uniformity of tablet halves cannot be relied upon to achieve equal doses of drug in the resultant splits when the tablets contain low amount of potent active ingredient (PAI) such as the case of potent drugs. In fact, the USP modified its weight uniformity test of tablets

Table 2 Results of uniformity of mass tests for lorazepam 2.5 mg.

Sample number	Weight of half tablet (g)	85–115% of the average mass	75–125% of the average mass	Sample number	Weight of half tablet (g)	85–115% of the average mass	75–125% of the average mass
1	0.06510	Yes	Yes	16	0.05930	Yes	Yes
2	0.05810	Yes	Yes	17	0.05560	Yes	Yes
3	0.06871	Yes	Yes	18	0.06660	Yes	Yes
4	0.06740	Yes	Yes	19	0.06320	Yes	Yes
5	0.06780	Yes	Yes	20	0.05810	Yes	Yes
6	0.06400	Yes	Yes	21	0.05410	No	Yes
7	0.06410	Yes	Yes	22	0.05800	Yes	Yes
8	0.06862	Yes	Yes	23	0.07100	Yes	Yes
9	0.07012	Yes	Yes	24	0.06500	Yes	Yes
10	0.06920	Yes	Yes	25	0.05820	Yes	Yes
11	0.06510	Yes	Yes	26	0.07000	Yes	Yes
12	0.06310	Yes	Yes	27	0.06810	Yes	Yes
13	0.06600	Yes	Yes	28	0.07100	Yes	Yes
14	0.06420	Yes	Yes	29	0.06800	Yes	Yes
15	0.06320	Yes	Yes	30	0.06100	Yes	Yes
Average	0.0644						
Result	Pass						

to include a test of content uniformity for tablets containing less than 25% of the PAI. Unfortunately, the USP does not have any test regarding the weight uniformity or the content uniformity of the obtained tablet halves (Green et al., 2009). The Ph. Eur. requires testing weight uniformity of tablet halves but does not require any test with regard to their content uniformity. Accordingly, it is important to investigate the degree of correlation between weight split halves of tablets and its content uniformity as this would provide assurance to the community pharmacist who performs the splitting process for the patient. This is especially in cases of scored tablets that contain very potent drugs such as lorazepam 2.5 mg/tablet. This very low dose may easily result in the uneven distribution of lorazepam throughout the tablets which later on leads to fluctuations of plasma drug levels even if the patient is taking tablet halves with equal weights. Therefore, manufacturers should develop high quality formulations and adopt manufacturing procedures that guarantee uniform distribution of the active ingredient throughout the tablet product.

The results obtained in this study have shown that lorazepam 2.5 mg/tablet could pass both the weight uniformity and the content uniformity of split halves. Additionally, a high degree of correlation between the weights of the split tablet halves and their lorazepam content has been seen. This is despite the low weight, small size and low content of the tablets. This study suggests that it is possible for manufacturers to modify their formulation and manufacturing parameters in order to improve this aspect of pharmacy practice.

For patients who practice tablet splitting, it is expected that the quality of the medication is maintained after the tablet has been split, including accurate medication dosage and desired therapeutic effect. Drug content variation in half-tablets appears to be highly correlated to their weight variation. The correlation coefficient between the weight and the content of split halves was 0.994. This result is similar to the findings of other studies which have shown that drug content variation in half-tablets appeared to be attributable primarily to weight variation occurring during the splitting process (Vranić and Uzunović, 2007; Hill et al., 2009). Studies have shown that half tablets are more likely to pass mass uniformity test if they have a suitable hardness, shape, and friability (Zaid and Ghosh, 2011; Polli et al., 2003). Tablet manufacturers should be able to determine the most appropriate size shape, friability and hardness of tablets to facilitate proper splitting.

5. Conclusion

The weight of split tablet halves appears to be directly correlated with their drug content, thus it is recommended that pharmacists who split tablets into two halves, assure the weight uniformity of the resultant halves since this may be associated with content uniformity for these tablet halves. Manufacturers should investigate the physical factors such as tablet, size, shape, friability and hardness that may play an important role in achieving both weight and content uniformity.

Furthermore, manufacturers should develop formulation and manufacturing procedures that ensure high degree of correlation between weight and content not only among the whole tablet but also among the obtained tablet halves.

6. Conflict of interest

None.

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