RESEARCH

Evaluation of the Discrepancy between the European Pharmacopoeia Test and an Adopted United States Pharmacopoeia Test Regarding the Weight Uniformity of Scored Tablet Halves: Is Harmonization Required?

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ABSTRACT: The aim of this study was to evaluate whether there exists any discrepancy between the European Pharmacopoeia (Ph. Eur.) and adopted United States Pharmacopeia (USP) tests concerning the weight uniformity measurements of tablet halves after splitting. The USP method does not contain provisions to evaluate split tablets, so here we adopt their whole tablet weight uniformity method. Twenty-nine different commercial scored tablets (local and imported) were divided. The split units were individually weighed and the relative standard deviation (RSD) for each product was calculated and then evaluated according to both the adopted USP and the Ph. Eur. tests of weight uniformity. Twenty out of the 29 products tested failed the USP test, while 14 of them failed the Ph. Eur. test. Nine products passed both the USP and Ph. Eur. tests. Six products passed the Ph. Eur. test but failed the USP test, with all of these products having an RSD greater than 6%. The correlation coefficient between the weight and content of split halves for three randomly selected products—corotenol 100 mg, corotenol 50 mg, and lorazepam 2.5 mg—was found to be 0.986, 0.998, and 0.72, respectively.

A clear difference can be seen between outcomes obtained by the two compendial tablet splitting methods with regard to weight uniformity. Results from the USP test showed that tighter measures are needed to pass the test. Our results argue that the Ph. Eur. should revise the existing weight uniformity test on scored tablets to include the RSD parameter in it. The USP should include this adopted test as a specific test for scored tablet halves, not just whole tablets. Manufacturers in some cases will need to improve the quality of the produced scored tablets in order to pass the USP test, especially those with low therapeutic indices. Finally, harmonization between the pharmacopoeias regarding the weight uniformity testing of split tablets is warranted.

KEYWORDS: Splitting, Weight uniformity, USP, Ph. Eur., Harmonization

LAY ABSTRACT: The aim of this study was to evaluate whether there exists any difference between the European Pharmacopoeia (Ph. Eur.) and adopted United States Pharmacopeia (USP) methods to evaluate weight uniformity when drug tablets are split. The USP method does not contain provisions to evaluate split tablets, so here we adopt their whole tablet weight uniformity method. Twenty-nine different commercial scored tablets were obtained and divided. The split units were individually weighed and the relative standard deviation (RSD) of the split tablets for each product was calculated and then evaluated according to both methods. Twenty out of the 29 products tested failed the USP method, while 14 of them failed the Ph. Eur. method. Six products passed the Ph. Eur. test but failed the USP test because these products had an RSD greater than 6%.

A clear difference can be seen between the pass/fail results of tablet splitting obtained by the two methods. The USP test showed that tighter measures are needed for products to pass the test. We recommend that the Ph. Eur. include the RSD parameter in it to make the method more rigorous. The USP is also recommended to include this adopted test as a specific test for scored tablet halves, not just for whole tablets. In the cases where the tablets failed either test, manufacturers should improve the quality of the produced scored tablets. Finally, using the same weight uniformity method by all pharmacopoeias is recommended.

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1. Introduction

The global market for pharmaceuticals is continuously expanding and, subsequently, the adverse consequences of different regulations and requirements between global regions are becoming more obvious. In this regard, there have been discussions between the regulatory authorities of the European Community, United States, and Japan under the International Conference on Harmonisation (ICH) intended to remove some of these differences. This took the shape of discussions among the corresponding pharmacopoeial authorities in their countries. The ICH brings together the regulatory authorities and pharmaceutical industries of Europe, Japan, and the U.S. to discuss scientific and technical aspects of drug registration. The Pharmacopoeial Discussion Group (PDG), which includes the European Pharmacopoeia (Ph. Eur.), the Japanese Pharmacopoeia (JP), and United States Pharmacopeia (USP), meets in association with the expert working groups of the ICH to harmonize chapters identified by ICH guidelines.

While not part of the ICH, the PDG usually meets in conjunction with ICH and provides the ICH steering committee with reports of its progress (1). Initiatives towards harmonization in pharmacopoeial monographs require an agreement on the purpose and scope of their contents. The choice of analytical methods is affected by their availability, the level of control required, and their transfer reproducibility between different laboratories (2). One of the quality control tests present in all pharmacopoeias is the weight uniformity test for tablets and other dosage forms. This test is necessary to ensure that patients 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, a practice that occurs after manufacture and thus is physically less precise and not directly under the control of the firm making the tablet. In fact, tablet splitting is a known, widely spread, and 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 (3–5).

Many pharmaceutical manufacturers produce tablets with scored lines to facilitate their splitting into two halves or even quarters with roughly equal weights. Unfortunately, the bad performance of score lines may be the principal cause of many problems that may arise when attempting to split tablets (6), such as the loss of powder and small fragments, leading to weight loss as well as possible contamination hazards (7). But the most important problem reported in this regard is the poor weight uniformity of the obtained halves (8, 9), resulting in variable patient dosing. Therefore, despite the presence of many benefits behind the splitting of tablets, the European regulatory authorities discourage the scoring of tablets in order to reduce the practice of administering halves to patients (10).

In 2002, the Ph. Eur. introduced a new test method to assess the accuracy of subdivided scored tablets (11). 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 (12, 13). The USP and the British Pharmacopoeia (BP) contain a quality control test regarding the weight uniformity of dosage units (14). However, they do not have methods to evaluate weight uniformity of the resultant split halves of split tablets or the performance of score lines of tablets in terms of ensuring uniform splitting. The observations of Rosenberg *et al.* (15), among others, call on the USP to include a weight uniformity method for evaluating split halves. Factually speaking, in many countries around the world the performance of tablet score lines remains an optional internal quality control test within a pharmaceutical company. This leads to one of two possibilities: either applying the adopted USP test for whole tablets or ignoring performance of the test completely. So far, there have been no studies to evaluate the inconsistencies between the USP test and the Ph. Eur. test for evaluation of weight uniformity of scored tablet halves. Therefore, we decided to compare the results obtained on some scored tablet products using both the Ph. Eur. and the adopted USP tests on weight uniformity of the resultant split units in order to evaluate whether any discrepancies between pass/fail adjudications result.

2. Materials and Methods

2.1. Selection of Tablets for Splitting

Twenty-nine scored tablet products of different trade names and pharmaceutical active ingredients were selected for this study. The selected tablet products are

TABLE I
Details of the Products Selected for the Study

Trade Name	Active Ingredients	Manufacturer	Dose (mg)
Atacand	Candesartan	Astra Zeneca	16
Atacand plus	Candesartan and	Astra Zeneca	16
	Hydrochlorothiazide		12.5
Coumadin	Warfarin	Taro	5
Salurex	Furosemide	Remedica	40
Anapril	Enalapril	Jerusalem Pharmaceutical Company	20
Anapril	Enalapril	Jerusalem Pharmaceutical Company	10
Angiocare	Enalapril	Pharmacare PLC, licensed by Grunenthal—Spanish Branch	5
Angiopril	Captopril	Birzeit Pharmaceutical Company	15
Angiopril	Captopril	Birzeit Pharmaceutical Company	20
Blocardil	Propranolol	Birzeit Pharmaceutical Company	10
Cardiopril	Captopril	Birzeit Pharmaceutical Company	25
Gastrex	Famotidine	Birzeit Pharmaceutical Company	40
Darone	Amiodarone	Birzeit Pharmaceutical Company	200
Decort	Dexamethasone	Birzeit Pharmaceutical Company	0.5
Lipidex	Atorvastatin	Birzeit Pharmaceutical Company	10
Lipidex	Atorvastatin	Birzeit Pharmaceutical Company	20
Lolip	Atorvastatin	Beit Jala Pharmaceutical Manufacturing Company	40
Lozar	Losartan	Birzeit Pharmaceutical Company	50
Moduril	Amiloride and	Jerusalem Pharmaceutical Company	5
	Hydrochlorothiazide		50
Normin	Atenolol	Birzeit Pharmaceutical Company	100
Peridol	Haloperidol	Belpharm	5
Eltroxin	Thyroxin	GlaxoSmithKline, GmbH & Co.	50
Vascopin	Amlodipine	Jerusalem Pharmaceutical Company	5
Vasopril	Enalapril	Ram Pharmaceuticals	10
Viraserc	Betahistine	Birzeit Pharmaceutical Company	16
Amicore	Amlodipine	Birzeit Pharmaceutical Company	5
Corotenol	Atenolol	Jerusalem Pharmaceutical Company	100
Corotenol	Atenolol	Jerusalem Pharmaceutical Company	50
Lorocare	Lorazepam	Pharmacare PLC	2.5

among commonly split tablets by patients in Palestine. We were provided with the samples for the study by medical representatives and physicians who prescribe those products. Local pharmaceutical companies manufactured some products, while international pharmaceutical companies manufactured others. The details of the products can be seen in Table I. The splitting process was conducted by one individual, a 35-year-old male who works as a lab technician. Tablets were split into two halves and each tablet half was weighed and recorded using a Mettler AM 50 balance (D-63512, Hainburg, Germany). Microsoft Office Excel 2007 was used to perform all related calculations.

2.2. The Splitting Tests

2.2.1. Splitting Test as per the Ph. Eur.: Testing was conducted as per the Ph. Eur. 5.5 in the following manner: Thirty tablets were randomly selected from each batch of the chosen products. The tablets were broken by hand along the break marks; one part of each tablet was taken for the test and the other part

was discarded. Each one of the retained parts was weighed individually and the average mass for each product was calculated. The tablets of a certain product were judged to pass the test if no more than one individual mass was outside the range of 85–115% of the average mass. The tablets were judged to fail the test if more than one individual mass was outside the range of 85–115% of the average mass, or if any individual mass was outside the range of 75–125% of the average mass (11).

2.2.2. The Adopted Splitting Test as per the USP: The USP has no standards for the subdivision characteristics of scored tablets, so the USP test of uniformity of dosage units was adopted as the method to evaluate the weight uniformity of the divided halves in several studies (5), including ours. The USP test calls for selection of 30 tablets from each batch of the selected products to obtain the mean weight of the tablet products. Of these 30 tablets, 10 are selected for analysis. Each tablet is individually weighed, and each must be within the 85–115% range of the target tablet weight. Furthermore, the percent relative standard deviation (RSD), defined as the standard deviation for measured variable divided by the measured variable mean multiplied by 100, must be less than 6%. The remainder of the 30 tablets may be evaluated to allow for a second opportunity to pass this test (14).

In this study, tablet halves were evaluated for their weight uniformity through the following steps:

1. Of the 30 tablets, 10 were individually weighed. Each tablet was split, resulting in 20 fragments. Each half-tablet was weighed.

2. From the resultant 20 tablet halves, the number outside the 85–115% range was recorded. The number of tablet halves outside the 75%–125% range was also counted. The RSD of the half-tablet weights was calculated. If at most one tablet half was outside the 85–115% range (but within the 75–125% range), and if the RSD was 6% or less, the product passed this uniformity test.

3. If two tablet halves of any product were outside the 85–115% range (but within the 75–125% range) or if the RSD was more than 6%, the additional 20 tablets were split. Now, in order to pass this uniformity test, none of the additional 40 tablet halves can be outside the 85–115% range, and the RSD for all the 60 tablet halves should be 6% or less.

4. If three or more of the 20 tablet halves were outside the 85–115% range, the product failed this uniformity test. Also, if any tablet half was outside the 75–125% range, the product failed this uniformity test.

2.2.3. Analysis of the Content of Split Halves: For content evaluation, a high-performance liquid chromatography 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 atenolol (corotenol) and lorazepam (lorocare) in the samples studied. For atenolol tablets, separation was accomplished using a 300 mm × 3.9 mm L1 octadecylsilane C18 column chemically bonded to totally porous silica particles, 5.0 μm in diameter. The atenolol content in the corotenol (100 mg, 50 mg) tablets was evaluated according to the Ph. Eur. 2005 (11). Regarding analysis of the lorazepam 2.5 mg/lorocare tablet, separation was accomplished using a 4.6 mm × 25 cm column that contains 5 μm packing L1 according to the USP 30 (16) method.

3. Results

Table I summarizes the details of tablet products selected for this study. Table II summarizes the results obtained from the splitting test according to both the Ph. Eur. 5.5 and the USP adopted test. Only nine products (31.03%) passed both Ph. Eur. and USP tests after splitting. Fourteen products out of 29 (48.27%) failed the Ph. Eur. 5.5 test for weight uniformity of half-tablets. Twenty products out of 29 (68.96%) failed the USP adopted test. Six products (20.69%) passed the Ph. Eur. test but failed the adopted USP test (Table II). Those which passed the Ph. Eur. but failed the USP tests were Blocardil (propranolol 10 mg), Peridol (haloperidol l5 mg), Salurex (furosemide 40 mg), Lozar (losartan 50 mg), Viraserc (Betahistine 16 mg), and Normin (atenolol 100 mg). Tablet splitting for these six products resulted in halves having weights within the accepted USP range of 85–115% of the average split unit weight. But they failed the test due to the RSD, which was more than 6% for both the 10 tablets tested initially and for the additional 20 tablets tested in the following stage. Blocardil 10 mg had RSD values of 7.42% and 7.43%, Lozar 50 mg 9% and 9%, Normin 100 mg 7.5% and 6.6%, Peridol 15

TABLE II
A Comparison of the Results Obtained upon Conducting the Ph. Eur. Test and the Adopted USP Test on Scored Tablets

Trade Name	Active Ingredients	Splitting Test as per the EUP			The Adopted Splitting Test as per the USP				
		Beyond 85% to 115%	Beyond 75% to 125%	Result	Number of Tablets	Beyond 85% to 115%	Beyond 75% to 125%	RSD%	Result
Amicore	Amlodipine besylate 5 mg	0	0	Pass	10	0	0	3.38	Pass
Anapril	Enalapril maleate 10 mg	7	3	Fail	10	11	3	13.43	Fail
Anapril	Enalapril maleate 20 mg	2	2	Fail	10	1	0	8.93	Fail
					30	5	0	9.64	
Angiocare	Enalapril maleate 5 mg	4	0	Fail	10	6	0	11.33	Fail
Angiopril	Captopril 15 mg	8	6	Fail	10	6	1	13.6	Fail
Angiopril	Captopril 20 mg	10	8	Fail	10	6	2	13.2	Fail
Atacand	Candesartan cilexetil 16 mg	0	0	Pass	10	0	0	4.17	Pass
Atacand plus	Candesartan cilexetil 16 mg & Hydrochlorothiazide 12.5 mg	0	0	Pass	10	0	0	3.73	Pass
Blocardil	Propranolol 10 mg	0	0	Pass	10	0	0	7.42	Fail
					30	3	0	7.43	
Cardiopril	Captopril 25 mg	6	5	Fail	10	6	2	17.2	Fail
Corotenol	Atenolol 50 mg	2	0	Fail	10	2	0	9.8	Fail
					30	3	0	7.3	
Corotenol	Atenolol 100 mg	1	0	Pass	10	1	0	6.6	Pass
					30	1	0	5.2	
Coumadin	Warfarin 5 mg	1	1	Fail	10	4	2	12.99	Fail
Darone	Amiodarone 200 mg	2	1	Fail	10	2	0	9.21	Fail
					30	7	0	8.55	
Decort	Dexamethasone 0.5 mg	1	0	Pass	10	0	0	4.95	Pass
Eltroxin	Thyroxin 50 mcg	6	3	Fail	10	7	3	16.37	Fail
Gastrex	Famotidine 40 mg	0	0	Pass	10	0	0	4.63	Pass
Lipidex	Atorvastatin 20 mg	0	0	Pass	10	0	0	3.41	Pass
Lipidex	Atorvastatin 10 mg	8	0	Fail	10	6	1	12.26	Fail
Lolip	Atorvastatin 40 mg	0	0	Pass	10	0	0	4.48	Pass
Lorocare	Lorazepam 2.5 mg	0	0	Pass	10	0	0	5.3	Pass
Lozar	Losartan 50 mg	1	0	Pass	10	1	0	9.0	Fail
					30	4	0	9.6	
Moduril	Amiloride hydrochloride 5 mg and Hydrochlorothiazide 50 mg	6	1	Fail	10	6	0	8.92	Fail
Normin	Atenolol 100 mg	0	0	Pass	10	0	0	7.5	Fail
					30	0	0	6.6	
Peridol	Haloperidol 5 mg	0	0	Pass	10	0	0	7.51	Fail
					30	1	0	6.9	
Salurex	Furosemide 40 mg	0	0	Pass	10	0	0	8.14	Fail
					30	0	0	7.98	
Vascopin	Amlodipine besylate 5 mg	3	0	Fail	10	9	1	11.84	Fail
Vasopril	Enalapril maleate 10 mg	8	5	Fail	10	6	4	18.29	Fail
Viraserc	Betahistine HCl 16 mg	1	0	Pass	10	4	0	11.33	Fail
Total Failed				14/29					20/29

mg 7.51% and 6.9%, Salurex 40 mg 8.14% and 7.98%, and Viraserc 16 mg recorded the highest RSD value of 11.33%.

The contents of half-tablets for three products (two strengths of atenolol and one of lorazepam) were analyzed, and the correlation between their weights and contents was determined. The correlation coefficient between the weight and content of split halves for atenolol 100 mg was 0.986, for atenolol 50 mg it was 0.998, and for lorazepam 2.5 mg it was 0.72.

4. Discussion

The practice of tablet splitting is frequently pursued in the field of pharmacy, especially when patients need lower doses of certain products but the dosage form is not available commercially or when a reduction of the cost of therapy is required (3–5). For those patients who practice tablet splitting, one would hope that the quality of the provided medication is good, including the desire to achieve an accurate and precise dose in the tablet half that they are taking. In fact, for those patients the resultant half essentially represents their new dosage form. However, the results obtained in this study showed that many products failed to produce acceptable results with regard to weight uniformity of resultant halves after tablet splitting. This may lead to significant irregularities of dosing that can be clinically unacceptable and possibly hazardous for patients who split these products. Considering the strong need to split tablets, in some cases for economic purposes, and taking into account that many split tablets may contain drugs with low therapeutic indices, a clear and consistent method to achieve and ensure uniform halves after splitting is a very important requisite.

The Ph. Eur. 5.5 adopted a specific test method to analyze the uniformity of weights of half-tablets obtained from scored tablets. However, until now, the USP has not introduced any new measures in this regard. Currently, in countries that follow the USP, the situation is quite vague because pharmaceutical manufacturers either do not conduct any testing on their scored tablet products or apply the adopted USP test for whole tablets for testing weight uniformity (15).

As for developing countries, these do not have their own pharmacopoeias, and manufacturers are free to follow either the USP or the Ph. Eur. standards. In Palestine, for example, there is no local official Palestinian pharmacopoeia and, therefore, the Ministry of Health and consequently the local Palestinian pharmaceutical manufacturers and importers can use either the Ph. Eur. or the adopted USP test as the means of quality control on their products. The results obtained in this study showed that 20 products out of 29 failed the USP test, while 14 of the same products failed the Ph. Eur. test, creating regulatory confusion. The two tests gave different pass/fail results for the same products, which means that these two tests cannot be used interchangeably and that there exists a clear discrepancy between them. The adopted USP test seems to have tighter measures for passing the test and, as a result, fewer products could pass this test. This can be explained by the RSD requirement, which is less than 6% for passing products, while this requirement is completely absent in the Ph. Eur. test. These findings are important because performing the adopted USP test is more rigorous in this context and will ensure accurate splitting results and thus greater dosing accuracy and safety for patients who take the administered drugs. The high correlation coefficient observed for some of the analyzed products for content confirms the results observed by other researchers regarding the importance of weight uniformity of the split tablet halves (17–19). In fact, this high correlation is due to the homogeneous distribution of the pharmaceutical active ingredient in the tablet during the manufacturing process.

Thus, in light of our results, we suggest some recommendations in order to reduce the negative patient consequences of having non-uniform splits, which may give rise to overdoses or sub-therapeutic effects, especially with drugs of low therapeutic indices. These recommendations are directed to the pharmaceutical industry sector, pharmacopoeial bodies, and regulatory authorities in countries following either the USP or the Ph. Eur. Pharmaceutical companies should improve the quality of their scored tablet products to make the splitting easier and to produce more uniform halves. This may be achieved by following measures such as: selecting the appropriate shape and size of tablets, deepening the score lines, and manufacturing tablets with appropriate hardness values (20, 21). Otherwise, we suggest reducing the prices of the lower-strength tablet products by pharmaceutical companies to discourage or even eliminate the splitting practice of the higher-dose products, a practice performed by patients driven by economic reasons.

In light of the above findings, we believe that the Ph. Eur. should revise the weight uniformity test of split halves to include an additional requirement, which is the RSD. This will ensure a higher level of accuracy of the results obtained. Additionally, the USP is recommended to adopt a specific test for the weight uniformity of scored tablet halves and require it as a mandatory quality control test on scored tablets. As a result, pharmaceutical manufacturers applying the USP standards will try to improve the quality of their scored tablet products in order to pass this test. Finally, and in the meantime, we strongly advise regulatory authorities (i.e., ministries of health) to advise pharmaceutical manufacturers in their countries to implement the more stringent adopted USP test, as this will maximize the quality and safety profiles of the products manufactured by their companies.

5. Conclusion

Given the clear discrepancy between the USP and the Ph. Eur. methods is seen, we recommend that the USP revise the existing weight uniformity test on whole tablets so that it can be applied to scored tablet halves. We also believe that the Ph. Eur. should include the RSD as an additional requirement for passing tablet products. In the meantime, pharmaceutical manufacturers need to improve the quality of the produced scored tablets in order to pass the adopted USP test for weight uniformity, especially those tablets that contain drugs with low therapeutic indices. In other words, it is very important that pharmaceutical companies ensure high levels of homogeneity of their tablet products in order for the split halves to contain equal content if they have equal weights.

Finally, a harmonization between the pharmacopoeias regarding the weight uniformity test of the resultant halves is warranted.

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Conflict of Interest Declaration

The authors declare that they have no competing interests.

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