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RESEARCH ARTICLE

Influence of physical factors on tablet splitting, weight and content uniformity of atenolol tablets

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Abstract Tablet splitting is widely practiced worldwide. Several studies have considered weight variation of split tablets as a mean of estimating drug content uniformity but the analysis of their drug content and physical factors that may affect splitting are limited. The aim of this study is to evaluate the impact of manufacturing parameters and splitting on content and weight uniformity of atenolol tablets. Atenolol tablets (100 and 50 mg) were prepared under the same manufacturing conditions and using the same excipients. The obtained tablets were checked for hardness, weight, and disintegration. The weight and the content of the two strength atenolol tablets after splitting into two halves were evaluated. Atenolol tablets (100 mg) showed higher values of hardness, disintegration time and diameter than atenolol tablets (50 mg). Atenolol tablets (100 mg) passed both weight and content uniformity while atenolol tablets (50 mg) failed these tests. Half tablet weight appears to be directly correlated with its drug content. Manufacturers should investigate physical factors such as tablet hardness, diameter, and disintegration time that may play an important role in achieving both weight and content uniformity in the resultant tablet halves.

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Introduction

Tablet splitting is a widely spread and accepted practice in the field of pharmacy. Patients usually split tablets for various reasons such as providing the patient with the desired dose when 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 (Duncan et al. 2002; Fawell et al. 1999; Green et al. 2009). Nevertheless, some problems may arise due to this practice, some of which may be patient related while others may be attributed to the tablet or formulation. The most important problem reported in this regard is the poor weight uniformity of the obtained halves (Kristensen et al. 1995; Zaid et al. 2010; Zaid and Ghosh 2011; Cook et al. 2004). Uneven splitting of a tablet may result in significant fluctuations of the administered dose. This may be clinically significant especially for drugs with a narrow therapeutic range (Vranić and Uzunović 2007). The drug content of each unit should be within the acceptable limits around the label strength. For this purpose, two tests are available in pharmacopoeias; the content uniformity test and an alternative simplified test, the weight uniformity test (Hill et al. 2009; Katori et al. 2001). Several studies have considered weight variation of split tablets as a mean of estimating drug content uniformity (Kristensen et al. 1995; Zaid et al. 2010; Zaid and Ghosh 2011; Cook et al. 2004; Teng et al. 2002; Polli et al. 2003). Although studies of weight differences among split tablets have been performed, the more important role of drug

content analysis is yet to be established. A study performed by Hill et al. (2009) on six commonly split tablets showed that drug content variation in half-tablets appeared to be attributable primarily to weight variation occurring when tablets powder or fragment during the splitting process.

In cardiology, beta blockers are an important class for the treatment of high blood pressure, arrhythmias, angina pectoris, and for prevention of myocardial infarction. With chronic treatment, they reduce mortality and prolong survival in hypertensive patients and those with coronary heart disease. In neuropsychiatry, beta blockers have been used for the treatment of acute stress reactions and generalized anxiety, essential tremor and prophylaxis of migraine (Emilien and Maloteaux 1998). Atenolol is one of the most widely used beta blockers in medicine, and in this study our aim was to study two strengths of atenolol in order to determine the mass and content uniformity of the split tablet halves and to investigate possible physical factors that may influence the obtained results.

Materials and methods

Materials

Atenolol was purchased from IPCA Laboratories (India); Colloidal Silicon Dioxide was obtained from Aerosil; (Evonik, Germany), Croscarmellose Sodium (FMC-Ireland), Magnesium Stearate, (Magnesia, Germany), Microcrystalline Cellulose (Avicel pH 101; FMC Corp, Ireland), Polyethylene Glycol was obtained from BASF (Germany), sodium lauryl sulphate was achieved from Cognis, (Germany), Talc was purchased from Beechamores, (India). Sodium hydroxide (Merck, KgaA, and Darmstadt, Germany) monobasic potassium phosphate (Merck, KgaA, Darmstadt, Germany). The remaining other chemicals used were of analytical grade and obtained from commercial sources.

Instruments

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 atenolol in the samples studied. Separation was accomplished using a 300 mm × 3.9 mm L1Octadecylsilane C18 column chemically bonded to totally porous silica particles, 5.0 µm in diameter (Waters Spherisorb ODS1). An electronic balance (Precisa 205 ASCS) was used for weight measurements. Vernier caliper was used for thickness and diameter determination, and a TA-100 Erweka friabilator was used for friability determination, and for hardness testing a hardness tester from (Pharma test PTB311E) was utilized.

Method

Atenolol tablets (100 and 50 mg) were prepared by Jerusalem Pharmaceutical Company under the same manufacturing conditions and using the same excipients. The wet granulation method was applied for the manufacture of Atenolol Tablets. Atenolol, Microcrystalline Cellulose, half quantity of Croscarmellose Sodium and Sodium Lauryl Sulphate were mixed by using Ribbon mixer. The powder mixture was granulated with the binder solution of Polyethylene Glycol in purified water. The wet mass was passed through sieve mesh No. 10, and dried at 45 degrees until water content becomes about 3 %. The dried granules were passed through sieve mesh No. 20, and blended with the remaining half quantities of Croscarmellose Sodium and Sodium Lauryl Sulphate. Magnasium Stearate was added to the resulting powder mixture and mixed for 3 minutes. Tablets were formed by using rotary tablet press. The obtained tablets were checked for hardness, disintegration time and diameter. Weight variation and drug content of atenolol tablets were evaluated according to the European Pharmacopeia (Ph. Eur.). All tablets were split manually by the same person. The weight and the content of the two strength atenolol tablets after splitting into two halves were evaluated. 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.

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).

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

Table 1 Summary of HPLC parameters for atenolol assay

Parameter	Specification
Column	300 mm × 3.9 mm, 5.0 μm RP-C18
Flow rate	0.6 ml/min
Injection volume	10 μL
Wavelength	226 nm
Mobile phase	pH 3.0 ± 0.1 phosphate buffer:methanol (7:3).

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).

Assay of atenolol in tablet halves

The amount of atenolol in the halves was determined according to the United States Pharmacopeia (USP) (2005) assay method. The HPLC system, Merck Hitachi, (Interface module D-7000, Autosampler L-7200, Pump L-7100, Detector L-7450) was used for the analysis and quantification of DFS in the studied samples. Separation was accomplished using a 300 mm × 3.9 mm, 5.0 μm RP-C18 column (Table 1).

Testing procedures for hardness, friability, and disintegration

The testing procedures for hardness, friability, and disintegration were according to the USP (2011) assay method as follows:

Hardness Test: "Place the tablet between the jaws of hardness tester, for each measurement orient the tablet in the same way with respect to the direction of application of the force. Operate the tester and record the value when the tablet crushes. Carry out the measurement on 10 tablets, taking care that all fragments of tablets have been removed before each determination. Calculate the hardness as the average value of measurements".

Friability test: "Take a sample of whole tablets corresponding as near as possible to 6.5 g. The tablets are carefully dedusted prior to testing. Accurately weigh the tablet sample, and place the tablets in the drum of friability tester. Rotate the drum 100 times, and remove the tablets. Remove any loose dust from the tablets as before, and accurately weigh. Calculate the friability as the percentage loss of mass".

Disintegration test: "Place one tablet in each of the six tubes of basket of the disintegration tester. Operate the apparatus, using deionized water maintained at 37 °C ± 2 °C, as the immersion fluid. Record the time required for the all the tablets to be disintegrated completely".

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

Results

All Atenolol 100 mg and 50 mg whole tablets passed the weight and content uniformity tests. For atenolol 100 mg half tablets, the average mass of the 30 halves was 168.3 mg, only one individual mass of the 30 half tablets was outside the limits of 85–115 % of the average mass (139.7 mg), but since it was within 75–125 % of the average mass, the product passed the Ph. Eur. test. As for atenolol 50 mg, the average mass of the 30 halves was 81.9 mg, two half tablets were outside the limits of 85–115 % of the average mass (66.4 and 65.9 mg), and the product failed the Ph. Eur. test (Table 2).

In content uniformity testing for atenolol 100 mg half tablets, only one individual content (82.1 %) was outside the limits of 85–115 % of the average content (98.9 % expressed as a percent to label claim) but was within the limits of 75–125 %, and thus the individual contents of an additional 20 halves were taken at random. The contents of all the 20 halves were within 85–115 % of the average content, so the product passed the uniformity of content test (Table 3).

For atenolol 50 mg half tablets, the preparation failed to comply with the Ph. Eur. test of content since more than one individual content (77.55 and 78.0 %) of the first 10 halves were outside the limits of 85–115 % of the average content expressed as a percent of label claim (Table 4).

Atenolol tablets (100 mg) showed higher values of hardness (8.9 vs 3.7 KN), longer disintegration time (10.6 vs 6.75 min) and diameter (10.02 vs 8.3 mm) than atenolol tablets (50 mg) (Table 5).

Table 2 Results of uniformity of mass testing for atenolol tablet halves

Sample number	Atenolol 100 mg				Atenolol 50 mg			
	Weight of whole tablet (mg)	Weight of half tablet (mg)	85–115 % of the average mass	75–125 % of the average mass	Weight of whole tablet (mg)	Weight of half tablet (mg)	85–115 % of the average mass	75–125 % of the average mass
1	338.7	175.8	Yes	Yes	159.2	93.1	Yes	Yes
2	328.2	160.1	Yes	Yes	171.2	81.7	Yes	Yes
3	334.5	170.2	Yes	Yes	165.9	92.7	Yes	Yes
4	340.8	165.4	Yes	Yes	168.2	93.9	Yes	Yes
5	339.7	167.8	Yes	Yes	168.2	82.3	Yes	Yes
6	362.7	180.2	Yes	Yes	160.6	78.9	Yes	Yes
7	371.0	185.5	Yes	Yes	162.2	81.8	Yes	Yes
8	336.2	168.3	Yes	Yes	157.7	90.5	Yes	Yes
9	328.9	139.7	No	Yes	171.4	84.0	Yes	Yes
10	327.6	169.8	Yes	Yes	158.2	79.6	Yes	Yes
11	335.8	167.4	Yes	Yes	163.3	84.1	Yes	Yes
12	332.3	167.6	Yes	Yes	167.6	79.5	Yes	Yes
13	329.7	171.2	Yes	Yes	163.6	79.9	Yes	Yes
14	339.1	163.9	Yes	Yes	165.0	88.4	Yes	Yes
15	333.9	162.6	Yes	Yes	159.3	79.4	Yes	Yes
16	334.3	161.9	Yes	Yes	162.7	65.9	No	Yes
17	333.4	166.8	Yes	Yes	159.8	89.0	Yes	Yes
18	337.9	163.6	Yes	Yes	160.0	72.9	Yes	Yes
19	340.4	174.8	Yes	Yes	161.7	73.7	Yes	Yes
20	334.8	171.6	Yes	Yes	159.7	85.8	Yes	Yes
21	333.7	181.1	Yes	Yes	173.4	81.4	Yes	Yes
22	339.2	184.1	Yes	Yes	169.8	80.5	Yes	Yes
23	327.9	164.9	Yes	Yes	162.3	66.4	No	Yes
24	334.9	187.1	Yes	Yes	169.5	87.3	Yes	Yes
25	329.3	156.5	Yes	Yes	161.9	78.5	Yes	Yes
26	342.2	166.8	Yes	Yes	163.4	78.8	Yes	Yes
27	350.4	162.3	Yes	Yes	163.2	87.7	Yes	Yes
28	327.6	157.5	Yes	Yes	161.1	82.8	Yes	Yes
29	332.2	165.3	Yes	Yes	159.9	76.2	Yes	Yes
30	340.4	170.3	Yes	Yes	159.4	79.2	Yes	Yes
Average	337.3	168.3			163.7	81.9		
Result		Pass				Fail		

The correlation coefficient between the weight and the content of split halves of atenolol 100 mg was 0.986 and for atenolol 50 mg it was 0.998.

Discussion

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. The European Pharmacopoeia 2002 devised two tests for mass and content uniformity of scored tablets after splitting (Green et al. 2009; European Pharmacopoeia 2008). Consequently, the test of mass uniformity has become a mandatory test in many European countries; manufacturers following Ph. Eur. standards must consider badly performing tablets as defective (Green et al. 2009; Van Santen et al. 2002). Many studies have been conducted to explore the weight uniformity of the obtained halves since this is expected to reflect content uniformity of the medication (Kristensen et al. 1995; Zaid et al. 2010; Zaid and Ghosh 2011; Cook et al. 2004; Teng et al. 2002; Polli et al. 2003). However, the content uniformity of the obtained halves was rarely investigated. In fact, a well

Table 3 Results of uniformity of content test for atenolol 100 mg, 30 halves

Sample #	Content of atenolol in each unit of whole tablet expressed as a percent of label claim (%)	Content of atenolol in each unit of tablet half expressed as a percent to label claim (%)	85–115 % of the average content
1	98.0	103.4	Yes
2	98.3	94.1	Yes
3	99.3	100.1	Yes
4	100.1	97.2	Yes
5	98.4	98.7	Yes
6	98.1	105.1	Yes
7	99.7	109.1	Yes
8	96.4	98.1	Yes
9	98.5	82.1	No
10	96.8	99.8	Yes
11	100.6	95.2	Yes
12	103.0	98.1	Yes
13	96.3	96.2	Yes
14	97.7	102.7	Yes
15	100.2	100.9	Yes
16	107.0	106.4	Yes
17	99.5	108.2	Yes
18	103.8	96.9	Yes
19	103.0	110.0	Yes
20	100.2	92.0	Yes
21	98.4	98.4	Yes
22	104.7	98.5	Yes
23	99.9	100.6	Yes
24	101.0	96.4	Yes
25	99.4	95.6	Yes
26	99.4	98.1	Yes
27	106.8	95.4	Yes
28	94.5	92.6	Yes
29	99.0	97.1	Yes
30	103.8	100.1	Yes
Average	100.1	98.9	
Result			Pass

formulated tablet should assure the homogeneity of all components in all parts of the compressed tablets. This study was conducted to assure that weight uniformity of the obtained halves correlates to their content uniformity and to investigate possible physical factors that may influence the obtained results. The results of this study showed that atenolol 100 mg half-tablets passed the Ph. Eur. test of weight and content uniformity after splitting while atenolol 50 mg half-tablets failed both weight and content uniformity tests of the obtained halves. Drug content variation in half-tablets appears to be highly correlated to their weight

Table 4 Results of uniformity of content test for atenolol 50 mg, 10 tablet halves

Sample #	Content of atenolol in each unit of whole tablet expressed as a percent of label claim (%)	Content of atenolol in each unit of half tablet expressed as a percent to label claim (%)	85–115 % of the average content
1	95.6	77.5	No
2	93.9	104.6	Yes
3	94.1	85.7	Yes
4	95.0	86.6	Yes
5	93.9	100.8	Yes
6	101.9	95.7	Yes
7	99.8	94.6	Yes
8	95.4	78.0	No
9	99.6	102.6	Yes
10	95.2	92.3	Yes
Average	96.4	91.8	Yes
Result			Fail

Table 5 Physical characteristics of whole atenolol tablets (100 and 50 mg)

Parameter	Number of tablets	Atenolol tablet (100 mg)	Atenolol tablet (50 mg)
Hardness (KN)	10	8.9	3.7
Disintegration time (min)	6	10.6	6.75
Diameter (mm)	10	10.02	8.3
Shape	10	Oblong	Oblong

variation. The correlation coefficient between the weight and the content of split halves was 0.986 for atenolol 100 mg and 0.998 for atenolol 50 mg. These results are similar to the findings of a study by Hill et al. (2009) which has shown that drug content variation in half-tablets appeared to be attributable primarily to weight variation occurring when tablets powder or fragment during the splitting process.

The manufacturing process parameters and the types of excipients that have been used are not likely to have any influence on the splitting results since both tablets contained the same excipients and were manufactured under the same conditions. However, these variables usually play an important role in achieving a homogenous distribution of the pharmaceutical active ingredients in the obtained compressed tablets. This issue can be observed here in this study since the tablets that failed the splitting test of weight uniformity also failed the content uniformity test.

In fact, there are some differences in the physical characteristics between the two strength tablets since atenolol tablets (100 mg) showed higher values of

hardness, disintegration time and diameter than atenolol tablets (50 mg). It is possible that these parameters may facilitate the splitting process. Other studies have shown that half tablets are more likely to pass mass uniformity test if they have a suitable hardness (Zaid and Ghosh 2011; Polli et al. 2003). Extreme hardness requires greater force which may cause the tablet to uncontrollably rock during splitting (Polli et al. 2003). In a study by Zaid and Ghosh (2011) among 14 medications, one formulation of atorvastatin passes the Ph. Eur. test of mass uniformity, this product had the highest hardness (10.02 Kp) compared to the other products. The shape of the two strengths was oblong but the diameter of the product that passed the test was larger, it seems that the manufacturers need to find the suitable size and shape of tablets to facilitate proper splitting.

Limitations

This study includes two strengths of atenolol only. There is little financial value in splitting this particular drug today but the idea can apply to other expensive drugs. Future studies might include more medications with different values of hardness, shapes and diameters to confirm the results and find the suitable values for good tablet splitting, The clinical significance in dose variability in half tablets was not investigated, for medications with high therapeutic indices; several studies have shown no effect of tablet splitting on therapeutic outcomes (Duncan et al. 2002; Gee et al. 2002; Rindone 2000). Dose variability is expected to be of greater potential importance for drugs with a narrow therapeutic index.

Conclusion

From the obtained results, it can be seen that atenolol 50 mg tablets failed both weight and content uniformity requirements of the Ph. Eur. Half tablet weight appears to be directly correlated with 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. Consequently, if these halves are consumed by patients, fluctuations in the drug- plasma concentration may happen and this can be dangerous especially for drugs having low therapeutic indices. Manufacturers should investigate the physical factors such as tablet strength, diameter, and hardness that may play an important role in achieving both weight and content uniformity.

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