INFLUENCE OF TABLET SPLITTING ON CONTENT UNIFORMITY OF LISINOPRIL/ HYDROCHLORTHIAZIDE TABLETS

Edina Vranić[1*], Alija Uzunović[2]

[1] Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Sarajevo, Čekaluša 90, 71 000 Sarajevo, Bosnia and Herzegovina

[2] Institute for Quality Control of Medicines, Titova 9, 71 000 Sarajevo, Bosnia and Herzegovina

[*] Corresponding author

Abstract

Dose-related adverse effects of medications are a major problem in modern medical practice. The "correct" dose, based on drug company guidelines in package inserts, may not be correct for many patients. Tablet splitting or dividing has been an accepted practice for many years as a means of obtaining the prescribed dose of medication.

As model tablets for this investigation, two batches of lisinopril- hydrochlorothiazide scored tablets labeled to contain 20/12,5 mg were used. The aim of this study was to establish possible influence of tablet splitting on content uniformity of lisinopril/hydrochlorthiazide tablets.

Determination of the content uniformity of lisinopril and hydrochlorthiazide in our batches, was carried out by HPLC method. The results of content uniformity studies for halves of tablets containing combination of lisinopril-hydrochlorthiazide (supposed to contain 50% of stated 20/12,5 mg in the whole tablet) were: 49,60 ±3,29% and 49,29±0,60 % (lisinopril); 50,33±3,50% and 50,69±1,95% (hydrochlorthiazide) for batch I and II, respectively. We can conclude that the results obtained in this study support an option of tablet splitting, which is very important for obtaining the required dosage when a dosage form of the required strength is unavailable, and for better individualization of the therapy.

KEY WORDS: content uniformity, splitting method, scored tablets, lisinopril, hidrochlorthiazide

Introduction

Dose-related adverse effects of medications are a major problem in modern medical practice. The "correct" dose, based on drug company guidelines in package inserts, may not be correct for many patients. Broad variation in drug response among patients is a common phenomenon in clinical practice. The ability to match doses to patients depends on the availability of multiple dose sizes and adequate dose-response information. These are not always provided, so splitting of the tablets is sometimes necessary (1). Tablet splitting or dividing has been an accepted practice for many years as a means of obtaining the prescribed dose for medication. Patients may be required to split tablets to (2, 3):

- ◊ obtain the required dosage when a dosage form of the required strength is unavailable
- ◊ provide appropriate fractional doses in a flexible dosing regimen or in a gradually increasing or decreasing dosage regimen
- ◊ begin therapy with the lowest possible dose to decrease the incidence of adverse effects or to gauge an individual patient's response

However, the process of splitting tablets cases a number of problems, some of which are patient related while others are related to the tablet or formulation. Uneven splitting of a tablet may result in significant fluctuations in the administered dose. This may be clinically significant for drugs with a narrow therapeutic range. For many drugs, especially those with long half-lives and/or a wide therapeutic range, dose fluctuations are unlikely to be clinically significant. Removing tablets from foil packaging or exposing uncoated tablet surfaces may increase the rate of degradation of the active substance. This has important ramifications as the patient may get lower than intended dose and adverse effects may be increased by degradation products. The tablet dissolution rate and absorption properties may also be affected when tablets are split (4,5,6). Tablets can be split manually into two portions by either breaking with the fingers along a scored line, cutting with a knife or using a specially designed tablet splitter. Uneven division of the tablet or a degree of wasting may occur as some tablets crumble or break into more than two parts. Irregularly shaped tablets may be difficult to load and may not easily be split into equal halves (7,8,9). For our study, lisinopril- hydrochlorothiazide scored tablets labeled to contain 20/12,5 mg were used as a model. Lisinopril and hydrochlorothiazide are combined in an oral formulation for the treatment of hypertension. Hydrochlorothiazide is a commonly used thiazide diuretic. Lisinopril is an angiotensin-converting enzyme inhibitor. The effects of hydrochlorothiazide and lisinopril on blood pressure are additive. Thiazide diuretics lower the blood pressure by increasing the excretion of sodium; whereas ACE inhibitors lower blood pressure by blocking the renin-angiotensin system (10,11,12).

The aim of this study was to:

- ✓ determine possible differences in friability and tablet hardness testing;
- ✓ accept or exclude their influence on mass uniformity according to the friability and tablet hardness results obtained
- ✓ determine *mass uniformity* of the whole and halved tablets split by different methods
- ✓ determine *content uniformity* of the whole and halved tablets split by different methods

Materials and Methods

Reagents

The used reagents were all of analytical grade, unless otherwise stated. Lisinopril dihydrate and hydrochlorthiazide working standards, were provided by Merck (Darmstadt, Germany). Acetonitrile and methanol were HPLC grade and provided by J.T. Baker (Deventer, Holland). Sodium dihydrogen phosphate, disodium hydrogen phosphate were provided by Carl Roth GmbH & Co. (Karlsruhe, Germany).

Tablet ingredients

For the tablet formulations the following ingredients were used and provided by different producers: lisinopril dihydrate and hydrochlorthiazide (Merck Darmstadt, Germany), calcium hydrogen phosphate dihydrate, magnesium stearate and mannitol (Riedel-de Haën, Seelze-Hanover, Germany), croscarmellose sodium (FMC Biopolymer, Philadelphia, USA), pregelatinized maize starch (Anheuser Busch, St. Louis, USA).

Tablet preparation

Lisinopril dihydrate, hydrochlorothiazide, calcium hydrogen phosphate dihydrate, pregelatinized maize starch, croscarmellose sodium and mannitol were mixed and sieved. Mannitol was also separately sieved. This mixture was granulated with purified water. The granulation was dried in fluid bed to the prescribed moisture content and sieved. Sieved magnesium stearate was added. Tabletting was carried out in a rotary tabletting

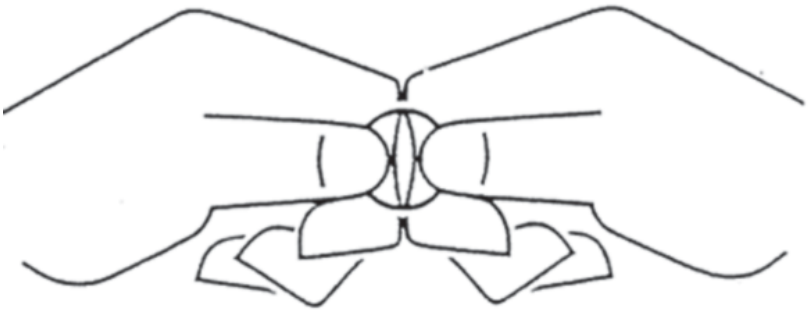

FIGURE 1. Manual method performed for breaking tablets

machine. Both formulation batches ("I" and "II") were prepared under the same technological conditions.

Drug dosage form (tablets) tested

The tablets applied for this study are scored on one side, weighing 210 mg. The tablets are flat and round, with diameter of 8,0 mm and height of 3,5 mm. The score line (break mark) applied has the following characteristics: W (width) = 0,88 mm, D (depth) = 0,42 mm, $\theta = 45^{o}$ and R (engraving cut radius) = 0,05 mm.

Crushing strength testing

The tablet is placed between the jaws, taking into account the shape, the break mark and the inscription. The tablet was oriented in the same way with respect to the direction of application of the force. The measurement was carried out on 10 tablets, taking care that all fragments have been removed before each determination. The results are expressed in the values of the forces measured, all expressed in newtons. The crushing strength was determined using hardness tester (type TBH 28, Erweka, Apparatebau, Germany).

Friability testing

Twenty tablets were placed on a sieve, and any loose dust was removed with the aid of the brush. The tablet sample was accurately weight and placed in the drum. It was rotated 100 times, and the tablets were taken out. Any loose dust from the tablets was removed as before. The friability is expressed as the loss of the mass and it is calculated as a percentage of the initial mass. The friability was determined using Roche friability tester (Erweka, Apparatebau, Germany).

Breakability test methods

✓ *Manual method*

The following manual breakability test was performed; the tablet was held between the thumb and the index finger of each hand on either side of the score line, with the score line facing upwards and without using the nail. Separation into two halves was done by breaking open the tablet at the score line side (legend: score up-break) (Figure 1.).

a) open position

b) tablet placed in "V" shaped holder

c) closing position

FIGURE 2. Tablet splitter

✓ *Tablet-splitter*

For this test tablet splitter "Iris" (Ljubljana, Slovenia) was used. Tablet splitter cover was lifted up (Figure 1a), the tablet was placed into "V" shaped holder (Figure 1b). The cover was firmly brought down and closed to split the tablet (Figure 1c). The tablets were weighed both before and after splitting and the results were compared using statistical methods.

Content uniformity testing

The following experiment examined the content uniformity of the active ingredient in tablets and was carried out by gradient mode high-performance liquid chromatography (HPLC) method. The system consisted of a pump, injection valve, autosampler and variable wavelength detector (Shimadzu, Kyoto, Japan).

The mobile phase consisted of two fractions: A (methanol: phosphate buffer pH 4,5 = 70:30, v/v) and B (methanol: acetonitrile: phosphate buffer pH 4,5 = 70:10:20, v/v). The flow rate was 1,0 ml/min, the injection volume 20 µl, the column temperature 50°C and the detection wavelengths 215 nm (lisinopril) and 240 nm (hydrochlorthiazide). Phenomenex Luna C-18 column (150mm×4,6mm×3µm) was used throughout the experiments.

Results and Discussion

The results of resistance to crushing of tablets and friability testing per batch are presented in Table 1.

	Resistance to crushing of tablets (N):	
	Batch I	Batch II
Sample 1	72,2	67,3
Sample 2	68	66,3
Sample 3	73,2	65,6
Sample 4	69,8	73,9
Sample 5	65,6	71,5
Sample 6	71,8	71,1
Sample 7	69,1	68,7
Sample 8	68,7	77,3
Sample 9	67,3	73,2
Sample 10	67,7	73,2
$\overline{X}$	69,34	70,81
S.D.	2,41394	3,76990
R.S.D	3,48	5,32
min.	67,3	65,6
max.	73,2	77,3
	Friability (%)	
	Batch I	Batch II
	0,15	0,21

TABLE 1. Resistance to crushing of tablets and friability testing per batch

Acceptable values of friability (less than 0,25%, upper limit-loss %≤1) were obtained for both batches of tablets with suitable hardness values, indicating good mechanical properties that are able to withstand handling. The results of mass loss per breakabilty test method and per batch are presented in Table 2, Table 3, Table 4 and Table 5 (expressed as % of tablet weight). No regulatory requirements for the maximum loss of mass upon breaking exist up to now. In view of the results reported for loss of mass on breaking (9) and in line with Ph. Eur. requirements on friability, we consider a loss of 1% acceptable. All samples (whole and halved tablets) meet this requirement. On the other hand, during "tablet splitter" procedure, small dust particles were produced. Loss of mass for manual method for Batch I and II was 0,0003 and 0,0002% respectively. For "tablet splitter" method for Batch I and II loss of mass was 0,0504 and 0,0503% respectively. According to the results obtained, we decided to proceed following tests with the tablets broken by manual method.

Batch I	1/2 tablet mass (g)	2/2 tablet mass (g)	Whole tablet mass (g)	Difference	Loss of mass (%)
Sample 1	0,1023	0,1076	0,2103	-0,0004	0,0002
Sample 2	0,1143	0,0943	0,2098	-0,0012	0,0006
Sample 3	0,0954	0,1137	0,2105	-0,0014	0,0007
Sample 4	0,1046	0,1051	0,2102	-0,0005	0,0002
Sample 5	0,0995	0,1113	0,2112	-0,0004	0,0002
Sample 6	0,1037	0,1058	0,2099	-0,0004	0,0002
Sample 7	0,1007	0,1009	0,2020	-0,0004	0,0002
Sample 8	0,1109	0,0982	0,2091	0,0000	0,0000
Sample 9	0,1167	0,0931	0,2101	-0,0003	0,0001
Sample 10	0,1047	0,1051	0,2104	-0,0006	0,0003
$\overline{X}$	0,11	0,10	0,21	-0,0006	0,0003
S.D.	0,00673	0,00683	0,00264	0,00042	0,00020
R.S.D	6,39	6,60	1,26	-75,39	75,39

TABLE 2. Breakability losses obtained from breaking tablets (Batch I) using manual method

Batch I	1/2 tablet mass (g)	2/2 tablet mass (g)	Whole tablet mass (g)	Difference	Loss of mass (%)
Sample 1	0,1022	0,1038	0,2064	-0,1024	0,0490
Sample 2	0,0972	0,1118	0,2097	-0,0973	0,0466
Sample 3	0,1013	0,1062	0,2077	-0,1008	0,0483
Sample 4	0,1022	0,1086	0,2112	-0,1024	0,0490
Sample 5	0,1056	0,1054	0,2116	-0,1060	0,0507
Sample 6	0,1158	0,0956	0,2116	-0,1158	0,0554
Sample 7	0,1151	0,1021	0,2087	-0,1064	0,0509
Sample 8	0,1056	0,1021	0,2080	-0,1059	0,0507
Sample 9	0,1086	0,0965	0,2092	-0,1126	0,0539
Sample 10	0,1024	0,1066	0,2093	-0,1024	0,0490
$\overline{X}$	0,11	0,10	0,21	-0,1052	0,0504
S.D.	0,00602	0,00505	0,001744	0,00552	0,00264
R.S.D	5,70	4,86	0,832945	-5,24	5,24

TABLE 3. Breakability losses obtained from breaking tablets (Batch I) using "tablet splitter" method

Batch II	1/2 tablet mass (g)	2/2 tablet mass (g)	Whole tablet mass (g)	Difference	Loss of mass (%)
Sample 1	0,1054	0,1047	0,2104	-0,0003	0,0001
Sample 2	0,1045	0,1014	0,2062	-0,0003	0,0001
Sample 3	0,1018	0,1067	0,2088	-0,0003	0,0001
Sample 4	0,1060	0,1043	0,2105	-0,0002	0,0001
Sample 5	0,0997	0,1106	0,2106	-0,0003	0,0001
Sample 6	0,1060	0,1073	0,2135	-0,0002	0,0001
Sample 7	0,1075	0,0982	0,2061	-0,0004	0,0002
Sample 8	0,1110	0,1020	0,2135	-0,0005	0,0002
Sample 9	0,1084	0,1044	0,2129	-0,0001	0,00005
Sample 10	0,1090	0,1014	0,2111	-0,0007	0,0003
$\overline{X}$	0,11	0,10	0,21	-0,0003	0,0002
S.D.	0,00336	0,00355	0,00268	0,00017	$8,0796x10^{-5}$
R.S.D	3,18	3,41	1,27	-51,60	51,60

TABLE 4. Breakability losses obtained from breaking tablets (Batch II) using manual method

Batch II	1/2 tablet mass (g)	2/2 tablet mass (g)	Whole tablet mass (g)	Difference	Loss of mass (%)
Sample 1	0,1185	0,0877	0,2115	-0,1237	0,0587
Sample 2	0,1071	0,1047	0,2121	-0,1073	0,0509
Sample 3	0,0912	0,1189	0,2115	-0,0925	0,0439
Sample 4	0,1127	0,0950	0,2118	-0,1167	0,0554
Sample 5	0,0935	0,1132	0,2082	-0,0949	0,0450
Sample 6	0,1053	0,1041	0,2100	-0,1058	0,0502
Sample 7	0,1038	0,1076	0,2121	-0,1043	0,0495
Sample 8	0,1106	0,1001	0,2136	-0,1133	0,0537
Sample 9	0,1039	0,1064	0,2119	-0,1055	0,0500
Sample 10	0,0941	0,1159	0,2118	-0,0956	0,0453
$\overline{X}$	0,10	0,11	0,21	-0,1059	0,0503
S.D.	0,00890	0,00949	0,00144	0,01000	0,00475
R.S.D	8,55	9,01	0,68	-9,44	9,44

TABLE 5. Breakability losses obtained from breaking tablets (Batch II) using "tablet splitter" method

The results of content uniformity studies for whole tablets containing combination of lisinopril-hydrochlorthiazide (20/12,5) are summarized in Table 5, Table 6, which show the percentage of drug present in each tablet (n=3), standard deviation (S.D.) and relative standard deviation (R.S.D.) as well, for each formulation batch. We have to point out that content uniformity studies for whole tablets were done for our orientation, and for that reason only three tablet samples were used.

Batch I	Lisinopril content (%)	Hidrochlorthiazide content (%)
Sample 1	99,19	101,42
Sample 2	99,56	101,89
Sample 3	99,33	101,62
$\overline{X}$	99,36	101,64
S.D.	0,18566	0,23954
R.S.D	0,19	0,24

TABLE 5. Content uniformity of lisinopril and hydrochlorthiazide expressed as % of declared content in whole tablets present (Batch I)

Batch II	Lisinopril content (%)	Hidrochlorthiazide content (%)
Sample 1	100,75	101,98
Sample 2	101,16	102,30
Sample 3	101,09	102,09
$\overline{X}$	101,00	102,12
S.D.	0,21999	0,16646
R.S.D	0,22	0,16

TABLE 6. Content uniformity of lisinopril and hydrochlorthiazide expressed as % of declared content in whole tablets present (Batch II)

The contents of lisinopril and hidrochlothiazide in each tablet fulfilled pharmacopeial requirements. The results of content uniformity studies for halved tablets containing combination of lisinopril-hydrochlorthiazide (supposed to contain 50% of stated 20/12,5 mg in the whole tablet) are summarized in Table 7 and Table 8 which show the percentage of drug present in each tablet (n=10), standard deviation (S.D.) and relative standard deviation (R.S.D.) as well, for each formulation batch.

Batch I	Lisinopril content (%)	Hidrochlorthiazide content (%)	1/2 tablet mass (g)
Sample 1	49,81	50,83	0,1023
Sample 2	48,76	49,27	0,1143
Sample 3	49,15	50,41	0,0954
Sample 4	48,84	48,32	0,1046
Sample 5	49,49	51,04	0,0995
Sample 6	48,88	49,40	0,1037
Sample 7	49,73	50,45	0,1007
Sample 8	48,75	49,74	0,1109
Sample 9	48,51	49,08	0,1167
Sample 10	54,07	54,71	0,1047
$\overline{X}$	49,60	50,33	0,11
S.D.	1,63278	1,76103	0,00673
R.S.D	3,29	3,50	6,39

TABLE 7. Content uniformity of lisinopril and hydrochlorthiazide expressed as % of the declared content in halved tablets (Batch I) - manual method-

Batch II	Lisinopril content (%)	Hidrochlorthiazide content (%)	1/2 tablet mass(g)
Sample 1	49,28	50,65	0,1054
Sample 2	49,36	52,74	0,1045
Sample 3	49,26	50,58	0,1018
Sample 4	49,16	49,95	0,106
Sample 5	49,28	50,70	0,0997
Sample 6	49,11	50,26	0,106
Sample 7	49,95	51,82	0,1075
Sample 8	48,87	50,17	0,111
Sample 9	49,07	49,17	0,1084
Sample 10	49,58	50,87	0,1090
$\overline{X}$	49,29	50,69	0,11
S.D.	0,29765	0,98949	0,00336
R.S.D	0,60	1,95	3,18

TABLE 8. Content uniformity of lisinopril and hydrochlorthiazide expressed as % of the declared content in halved tablets (Batch II) - manual method-

Determination of the content uniformity of lisinopril and hydrochlorthiazide in our batches, both for whole and halved tablets was carried out by HPLC method. The procedure was performed on three whole tablets and ten halves separately. According to the Ph. Eur. (22), the content uniformity of active substance expressed as % of the declared content should be within the limits of 85-115% and relative standard deviation (R.S.D.) should be equal or smaller than 6%. The results of the content uniformity analysis for the whole tablets were: 99,36 ±0,19% and 101,00 ±0,22% (lisinopril); 101,64 ±0,24% and 102,12 ±0,16% (hydrochlorthiazide) for batch I and II, respectively, which fulfills pharmacopoeial requirements. The results of the content uniformity analysis for the halved tablets were: 49,60 ±3,29% and 49,29±0,60 % (lisinopril); 50,33±3,50% and 50,69±1,95% (hydrochlorthiazide) for batch I and II, respectively. Scored tablets bring added value to solid dosage forms both with respect to their possibility for flexibility of dosing and for cost savings of medication. It may be worthwhile to quantitatively assess these advantages. Although regulations for breaking accuracy have been set recently, regulatory standards are still missing for easiness of breaking and loss of weight. On easiness of breaking an *in vivo* reference test need to be established in a way similar to the test of NEN 1740 on child resistant packages (14). Also a regulatory mechanical test for easiness of breaking is needed. Specifications for breakability by this mechanical method need to be validated against an *in vivo* reference test. The Ph.Eur. test on mass uniformity of subdivided tablets needs to be expanded by an instruction on the breaking of the scored tablets under investigation. It is rational to use the mechanical test on easiness of breaking as the breaking procedure for the test on uniformity of mass of subdivided tablets. Regulatory requirements for a maximum loss of mass are also needed. Limiting the loss of mass to 1% is in line with the Ph. Eur. requirement on friability and studies show that such a requirement is realistic.

Conclusion

- ✓ According to the results obtained, we may conclude that tablets from batch "I" and "II" satisfied pharmacopeial requirements concerning crushing strength and friability
- ✓ Application of two breaking method used, showed differences in loss of mass.
- ✓ The results of content uniformity studies for halved tablets containing combination of lisinopril-hydrochlorthiazide (supposed to contain 50% of stated 20/12,5 mg in the whole tablet) were: 49,60 ±3,29% and 49,29±0,60 % (lisinopril); 50,33±3,50% and 50,69±1,95% (hydrochlorthiazide) for batch I and II, respectively.
- ✓ We can conclude that the results obtained in this study support an option of tablet splitting, which is very important for obtaining the required dosage when a dosage form of the required strength is unavailable, and for better individualization of the therapy.

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