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INFLUENCE OF SUBDIVISION (BREAKABILITY) TEST ON PHYSICOCHEMICAL PARAMETERS OF DEXKETOPROFEN TROMETAMOL TABLETS

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Abstract: Presence of score mark in a pharmaceutical tablet implies that the dosage form may be subdivided into half doses. A score or breakline is a debossed line running across the planar surface of the tablet. This characteristic is useful because the score can be used to facilitate the breaking of the tablets into fractions when less than a full tablet is required for a dose. The purpose of this study was to demonstrate a practical approach to evaluate the breakability robustness as a part of tabletting validation of scored tablet. In the present study Dexketoprofen Trometamol tablets were evaluated for breakability test according to pharmacopeial standards. Tablets were splitted by splitter (mechanically) and by hand (non-mechanically). Splitting of uncoated as well as coated tablets was performed to evaluate the breakability before and after the coating of tablets. Changes in physicochemical parameters of the splitted tablets were evaluated such as weight of the tablet, friability, content uniformity, and dissolution. All these parameters were evaluated for both innovator as well as test formulation. Tablets splitted manually as well as mechanically were evaluated for content uniformity and results were within specification.

Keywords: Dexketoprofen Tablets, Scored Tablets, Breakability Test, Content Uniformity, Tablet Splitters.

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INTRODUCTION

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for systemic effects. In addition oral medication is the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations mainly because of patient acceptance, convenience in administration and cost effective manufacturing process. For many drug substances, conventional immediate release formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamic profiles with an acceptable level of safety to the patient[1]. Tablets with single or multiple score lines allow the administration of a portion of the tablet, which can then be considered as the unit dosage of the drug[2]. Consistent scoring assures that the patient is able to adjust the dose, by breaking the tablet in the same manner as reference listed drug. This enables the patient to switch between manufacturers of the same product without encountering problem related to the dose. For many years OGD has recognized the importance of having the scoring configuration of generic tablets be the same as that of the reference listed drug[3].

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:

1. Obtain the required dosage when a dosage form of the required strength is unavailable.

2. Provide appropriate fractional doses in a flexible dosing regimen or in a gradually increasing or decreasing dosage regimen.

3. Begin therapy with the lowest possible dose to decrease the incidence of adverse effects or to gauge an individual patient's response[4].

Main advantages of tablet scoring are dose flexibility in geriatrics and paediatrics, dose flexibility, ease of swallowing and cost reduction[5]. Uniformity of mass of subdivided scored tablets is an important quality attribute of the tablet score lines[6].

Basic aim of the present study was to determine the mass uniformity and friability of whole and halved tablets splits by different methods, to determine the content uniformity, assay and dissolution of whole and halved tablets.

MATERIALS AND METHODS:

Materials:

Dexketoprofen Trometamol was obtained from Emcure Pharmaceuticals, Mannitol was received from Rouquette Pharma, Sodium Starch Glycolate from DFE Pharma, Maize Starch form Universal & LHPC LH-11 form Shin-Etsu, Magnesium Stearate from Ferro and Opadry white from Colorcon.

Methods:

Preparation of Dexketoprofen Trometamol tablets

Dexketoprofen Trometamol, Mannitol, Sodium Starch Glycolate, Maize Starch & LHPC was sifted through 40 # and mixed in blender for about 10 min at 12±1 rpm. Prelubrication was done by sifting, Sodium Starch Glycolate, Mannitol, & LHPC through 40# sieve and was mixed with above material in blender for about 10 minutes. Magnesium stearate was passed through 60# sieve and above mixer was lubricated with magnesium stearate for about 3 minutes. The lubricated granules were then compressed in to tablets.

Tablet description with Score:

Tablets of Dexketoprofen tablets were used to study the subdivision of tablets. Tablets were white to off-white round; film coated debossed with "1" and "2" separated by a break line on one side and plain on other side. Deep notch breakline was given similarly as in case of innovator**.**

Figure: 1. Dexketoprofen Trometamol Tablets with deep notch break line.

Breakability test methods

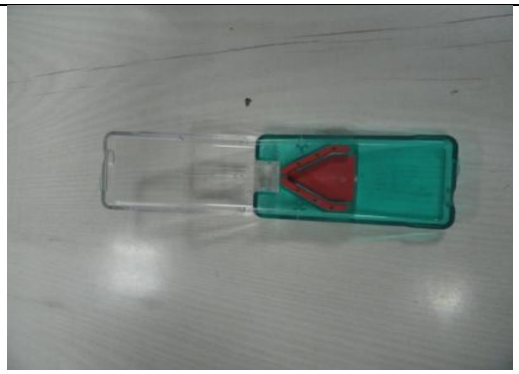
1. **Manual method**

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.

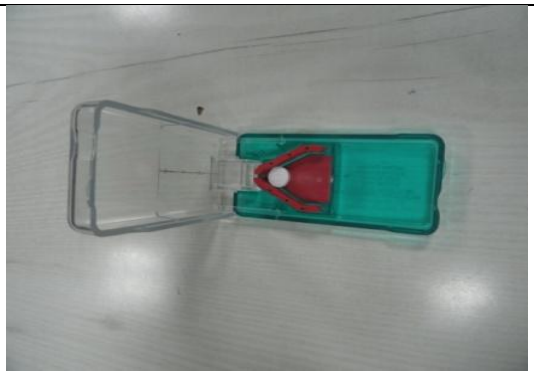

Figure: 2 Tablet splitting by hand (Manually)

2. Tablet-splitter

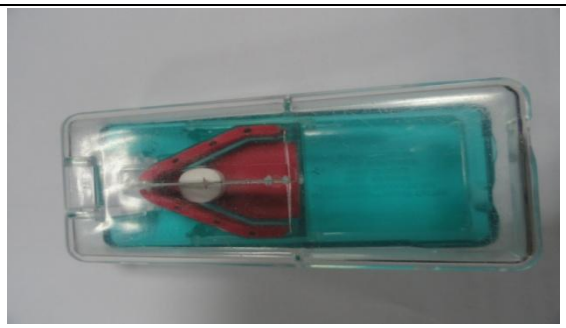
For this test tablet splitter was used. Tablet splitter cover was lifted up and the tablet was placed into "V" shaped holder. The cover was firmly brought down and force was applied to close the splitter to split the tablet. The tablets were weighed both before and after splitting and the results were compared using statistical methods.



1.Open Position



2.Tablet Placed In Splitter



3.Splitter In Close Position

4.Tablets Splitted In Two Halves

Figure: 3. Different steps of splitting tablets by tablet splitter.

European Pharmacopoeia test for uniformity of mass:

The Ph. Eur. states: ''Take 30 tablets at random and break them by hand, 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''[7].

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''[7].

Tablet Scoring according to USFDA:

Testing 15 tablets to ensure a loss of mass of less than 3.0 percent between the individual segments (30 for bisected tablets, 45 for trisected tablets, etc.) when compared to the whole tablet. The resulting data for each tablet should be provided to the Agency for evaluation[8].

RESULT AND DISCUSSION:

Tablet splitting is often used to adjust the administered doses. It is also used as a method to reduce medication costs. Dexketoprofen Trometamol tablets were used to study the effect of breakability test. It implies a break line over it which makes it easy to divide in two equal halves. Deep notch breakline was used for Dexketoprofen tablets as it makes it easier to split the tablets in equal parts in comparison to simple breakline. Splitting by hand was done by using thumb and index figure without using nails to break it in equal parts. The purpose of this investigation was to study the influence of breakability methodology on mass uniformity and content uniformity of the tablets. Splitting of uncoated and coated tablets was done. Two methods for breaking the tablets were used, non-mechanically by hand and mechanically by tablet splitter. Both the method used for splitting the tablets and it shows no significant difference in loss of mass. Content uniformity of splitted tablets of both innovator as well as test product was evaluated according to the pharmacopeial guidelines and ICH guidelines.

Content uniformity of both tablets splitted by non-mechanical method as well as mechanical method was evaluated and results were well within limits. Dissolution study was also conducted on splitted tablets of both innovator as well as test product and results were within specifications.

CONCLUSION:

From the above study it can be concluded that tablet splitting may not have adverse effects and can reduce the cost for both patient as well as manufacturers. On the basis of results obtained it can be concluded that both uncoated and coated tablets splitted manually or mechanically satisfied pharmacopeial requirements concerning loss of mass and content uniformity. There was very slight difference in loss of mass by applying two different methods for splitting the tablets. So, the study supports an option of tablet splitting particularly when a required dose is unavailable. It also provides an option to choose generic drugs with score line as in reference drug for reduced cost.

Table: 1. Breakability losses obtained from breaking uncoated tablets using manual method:

No. of units	Total wt of tablets in mg	Wt of 1/2 tablets in mg (left)	Wt of 1/2 tablets in mg(right)	wt of tablet after breakability in mg
1	277	134	135	269
2	278	142	133	275
3	282	135	146	281
4	274	138	133	271
5	276	143	132	275
6	277	126	149	275
7	275	144	128	272
8	276	143	131	274
9	277	144	131	275
10	278	141	135	276
11	279	142	134	276
12	277	144	132	276
13	278	139	139	278
14	280	145	132	277

15	277	141	132	273
16	278	143	134	277
17	279	140	136	276
18	277	129	148	277
19	279	139	137	276
20	276	139	134	273
21	276	138	139	277
22	277	135	132	267
23	279	138	140	278
24	278	138	137	275
25	276	139	137	276
26	276	129	144	273
27	277	130	142	272
28	277	132	145	277
29	277	129	146	275
30	279	123	134	257
AVG	**277.40**	**137.40**	**136.90**	**274.30**
MIN	**274**	**123**	**128**	**257**
MAX	**282**	**145**	**149**	**281**
STDV	**1.59**	**5.95**	**5.68**	**4.30**
% RSD	**0.57**	**4.33**	**4.15**	**1.57**
As per Ph.EUR				
Average		**LIMIT:**	**85% (116.8mg)**	**115% (158.0mg)**
		LIMIT:	**75% (103.1mg)**	**125 % (171.8 mg)**
		One side	123	145
		Second side	128	149

Table: 2. Breakability losses obtained from breaking coated tablets using manual method:

No. of units	Total wt of tablets in mg	Wt of 1/2 tablets in mg (left)	Wt of 1/2 tablets in mg(right)	wt of tablet after breakability in mg
1	284	145	136	281
2	284	144	139	283
3	281	140	139	279
4	282	144	135	279
5	286	140	143	283
6	285	135	146	281
7	285	140	143	283
8	282	142	140	282
9	282	143	139	282
10	281	141	140	281
11	284	143	138	281
12	285	148	136	284
13	280	143	134	277
14	282	141	140	281
15	280	140	135	275
16	285	152	131	283
17	283	129	153	282
18	286	137	149	286
19	287	139	148	287
20	290	151	137	288
21	292	154	137	291
22	279	137	141	278
23	284	135	142	277
24	279	137	140	277

25	283	148	134	282
26	287	150	137	287
27	280	143	136	279
28	284	143	140	283
29	284	145	136	281
30	285	158	127	285
AVG	**283.70**	**142.90**	**139.03**	**281.93**
MIN	**279**	**129**	**127**	**275**
MAX	**292**	**158**	**153**	**291**
STDV	**2.96**	**6.14**	**5.30**	**3.59**
% RSD	**1.04**	**4.30**	**3.81**	**1.27**
Initial wt	**8.511gm**		**After breakability**	**8.458 gm**
			FRIABILITY	**0.63%**
As per Ph.EUR				
Avg		**LIMIT:**	**85% (122.0 mg)**	**115% (164.3 mg)**
		LIMIT:	**75% (107.0 mg)**	**125% (178.6mg)**
		One side (Left)	129	158
		second side(Right)	127	153

Table: 3. Breakability Test for Dexketoprofen coated tablet 25 mg by mechanical

No. of units	Total wt of tablets in mg	Wt of 1/2 tablets in mg (left)	Wt of 1/2 tablets in mg(right)	Wt of tablet after breakability in mg	Loss after breakability in mg	% loss	Diff between left & right
1	287	150	136	286	1	0.35	-14
2	286	152	134	286	0	0.00	-18
3	284	127	157	284	0	0.35	30

4	285	158	126	284	1	0.35	-32
5	281	145	135	280	1	0.35	-10
6	280	143	136	279	1	0.00	-7
7	287	150	137	287	0	0.00	-13
8	284	160	123	283	1	0.35	-37
9	282	138	142	280	2	0.70	2
10	281	154	126	280	1	0.35	-28
11	280	146	134	280	0	0.00	-12
12	280	142	138	280	0	0.00	-4
13	285	143	140	283	2	0.70	-3
14	284	141	143	284	0	0.00	2
15	283	149	134	283	0	0.00	-15
AVG	**283.27**	**146.87**	**136.20**	**283.07**	0.20	0.07	-10.67
MIN	**280**	**127**	**123**	**280**			
MAX	**287**	**160**	**157**	**287**			
STDV	**2.49**	**8.18**	**8.15**	**2.52**			
% RSD	**0.88**	**5.57**	**5.99**	**0.89**			

Table: 4. Breakability Test for Dexketoprofen coated tablet 25 mg by manual

No. of units	Total wt of tablets in mg	Wt of 1/2 tablets in mg (left)	Wt of 1/2 tablets in mg(right)	wt of tablet after breakability in mg	loss after breakability in mg	% loss	Diff between left & right
1	280	149	130	279	1	0.35	-19
2	284	141	143	284	0	0.00	2
3	287	160	124	284	3	1.05	-36
4	285	152	131	283	2	0.70	-21

5	280	137	142	279	1	0.35	5
6	284	152	130	282	2	0.70	-22
7	285	118	166	284	1	0.35	48
8	282	150	131	281	1	0.35	-19
9	283	138	145	283	0	0.00	7
10	283	137	146	283	0	0.00	9
11	286	156	129	285	1	0.35	-27
12	285	123	161	284	1	0.35	38
13	283	147	134	281	2	0.70	-13
14	282	135	146	281	1	0.35	11
15	286	149	136	285	1	0.35	-13
AVG	**283.67**	**142.93**	**139.60**	**282.53**	1.13	0.40	-3.33
MIN	**280**	**118**	**124**	**279**			
MAX	**287**	**160**	**166**	**285**			
STDV	**2.09**	**11.79**	**12.00**	**1.96**			
% RSD	**0.74**	**8.25**	**8.60**	**0.69**			

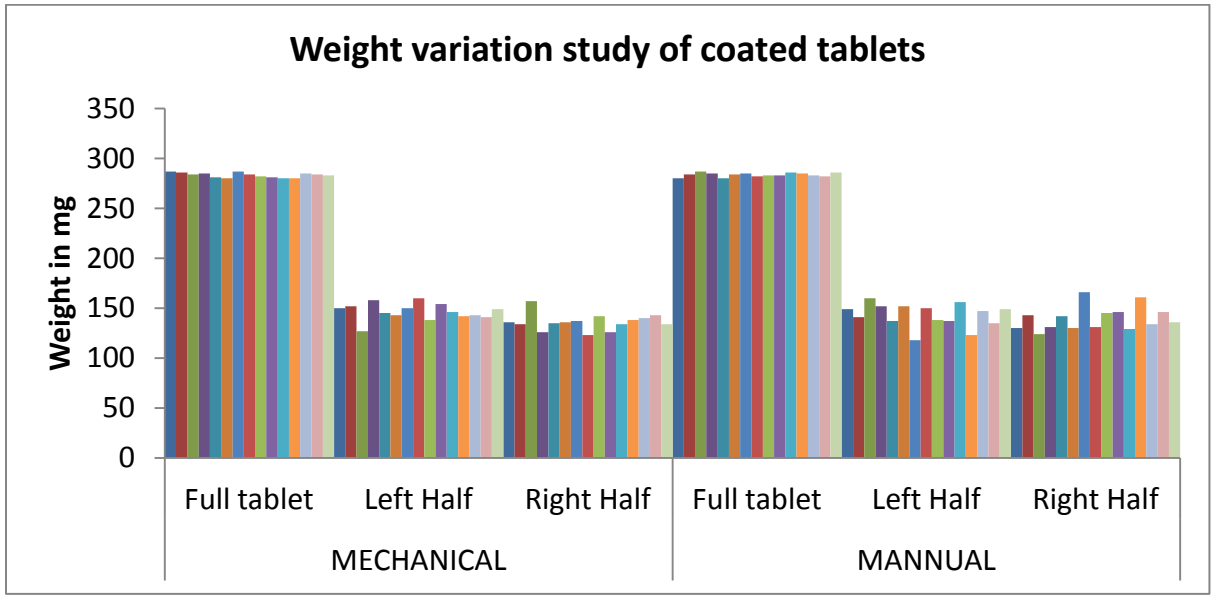


Figure: 4. Weight variation study of coated tablets splitted by manually and mechanically.

Table: 5. Content uniformity of innovator and Dexketoprofen Trometmol tablets splitted non-mechanically

Unit	Innovator	Dexketoprofen Trometmol
1	101.80	103.18
2	97.45	104.70
3	107.01	104.93
4	100.26	102.80
5	100.96	108.85
6	106.40	101.86
7	98.41	103.37
8	101.83	106.57
9	106.88	104.71
10	98.46	101.73
AVG	**101.95**	**104.27**
% RSD	**3.56**	**2.11**
MIN	**97.45**	**101.73**
MAX	**107.01**	**108.85**

Table: 6. Content uniformity of innovator and Dexketoprofen Trometmol tablets splitted mechanically

Unit	Innovator	Dexketoprofen Trometmol
1	97.70	96.41
2	97.81	97.47
3	102.48	104.36
4	96.59	105.98
5	104.72	92.74
6	100.23	105.52
7	102.05	106.63

8	98.62	99.82
9	98.03	103.78
10	103.14	98.47
AVG	100.14	102.12
% RSD	2.79	6.57
MIN	96.59	92.74
MAX	104.72	106.63

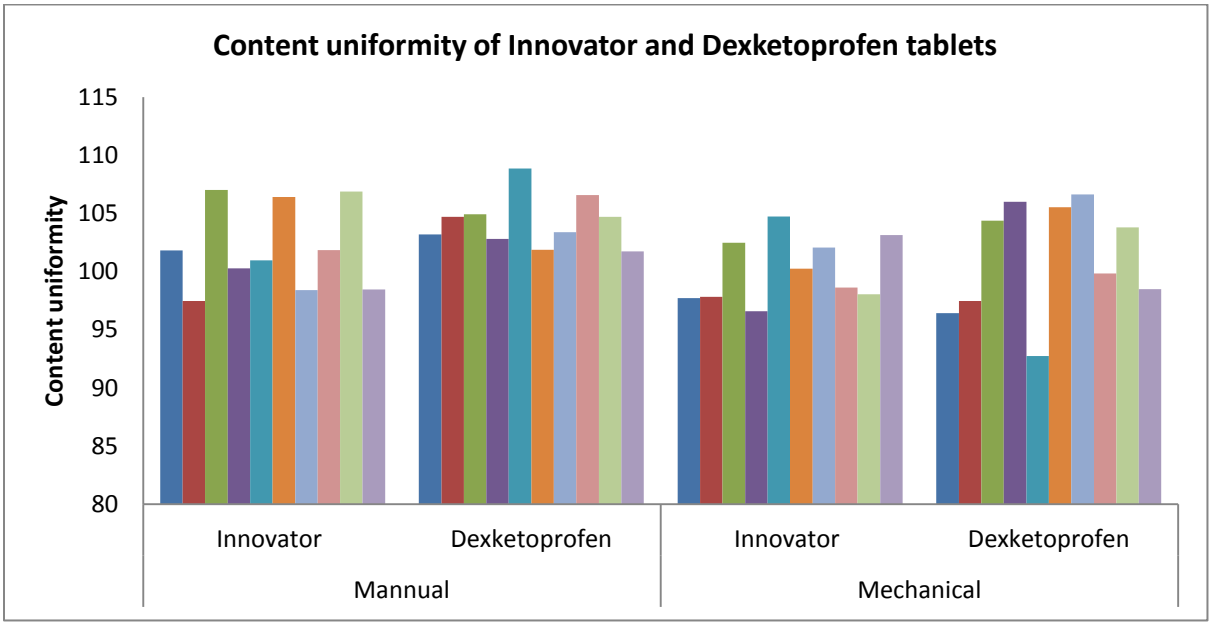


Figure: 5. Content uniformity of innovator and Dexketoprofen tablets splitted manually and mechanically

Table: 7. % Drug release of innovator and Dexketoprofen Trometmol tablets splitted mechanically

Units	% Drug release	
	Innovator	Dexketoprofen Trometamol
1	100.1	97.3
2	100.4	101.7
3	99.7	105.4

4	99.8	102.6
5	101.9	94.7
6	104.5	105.9
AVG	**101.1**	**102.9**
MIN	**99.7**	**94.7**
MAX	**104.5**	**11.7**
% RSD	**1.84**	**6.01**

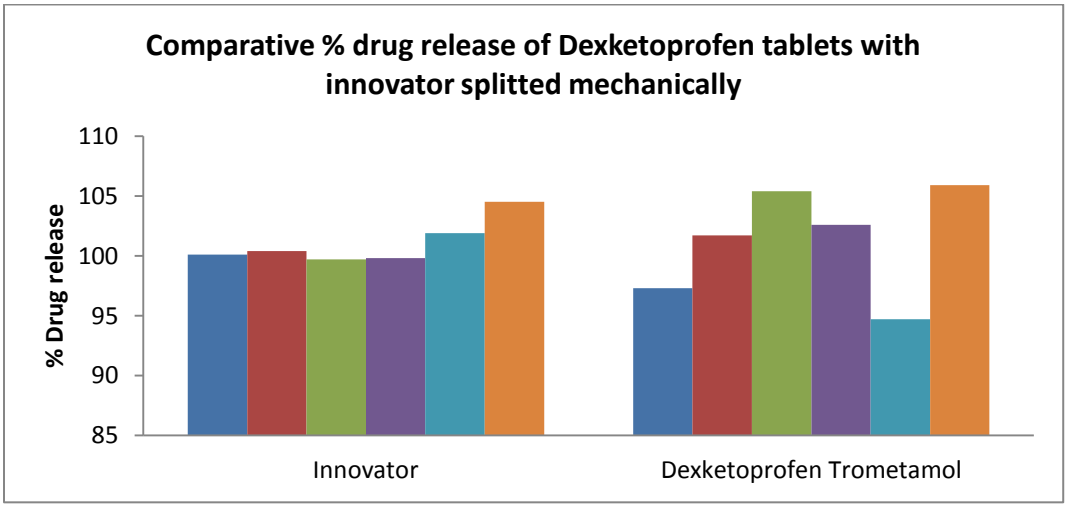


Figure: 6. % Drug release of innovator and Dexketoprofen Trometamol tablets splitted mechanically

REFERENCES:

1. Kotta Kranthi Kumar, K.Sampath Kumar, G.Satheesh Formulation and Evaluation of Clopidogrel Bisulfate Immediate Release Tablets USP 75mgInternational Journal of Pharmacy & TechnologyJuly-2013; Vol. 5; Issue No.2; 5481-5504.

2. Bart De Spiegeleer, Lieven Van Vooren, Thomas Thonissen, Philippe Joye, Bart Cornelissen, Geert Lammens and Guido Slegers, Mass Uniformity: Influence of Operational Compression Conditions on Breakability of Scored Tablets as Part of Manufacturing Robustness Evaluation, Journal of Food and Drug Analysis, Vol. 13, No. 1, 2005, Pages 22-29.

3. Scoring Configuration of Generic Drug Products; Center for Drug Evaluation and Research; Director Office of Generic Drugs 11/1/95, recertified 09/05/2012. 1-4.

4. Edina Vranic; Alija Uzunovic, Influence Of Tablet Splitting on Content Uniformity Of Lisinopril/ Hydrochlorothiazide Tablets, Bosnian Journal of Basic Medical Sciences 2007; 7 (4): 328-334.

5. E. van Santena, D.M. Barendsa,*, H.W. Frijlinkb, Breaking of scored tablets: a review, European Journal of Pharmaceutics and Biopharmaceutics 53 (2002) 139–145.

6. Koos C. van der Steen, Henderik W. Frijlink, C. Maarten A. Schipper, and Dirk M. Barends1, Prediction of the Ease of Subdivision of Scored Tablets from Their Physical Parameters, AAPS PharmSciTech, Vol. 11, No. 1, March 2010.

7. European Pharmacopoeia, 2011, 7th edition Vol. 1, Council of Europe Strasbourg pp. 736.

8. Guidance for Industry Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) March 2013 CMC.