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Blend uniformity validation in low dose formulation of levocetirizine hydrochloride tablet

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ABSTRACT

One of the most challenging problems conformations oral solid dosage form manufacturers today is the difficulty in applying scientifically valid methods to blend uniformity validation. Validation of final blending process, as one of a series of unit operations, is important to ensure satisfactory active ingredient content in a tablet, in particular, in low dose formulations. Routine final blend evaluation for active ingredient homogeneity is unwarranted, although it may be appropriate in certain circumstances. However, the final product (e.g. tablets, capsules) is required to be tested for the uniformity of dosage units to meet the Pharmacopoeia requirements. In this work, the blend uniformity is validated in a low dose tablet formulation to the predetermined protocols as part of concurrent process validation. The selected product is Levocetirizine Hcl (Each tablet contains Levocetirizine Hcl 5 mg).The test for content uniformity is applicable to this product as per requirement of BP / USP / IP, hence the study is conducted to assure the compliance to official requirements of content uniformity in the product by demonstrating adequate blend uniformity during the mixing operation.

Keywords: Levocetirizine hydrochloride, Validation, Determination, Blend uniformity, UV spectrophotometer.

INTRODUCTION

Levocetirizine is a third-generation non-sedative antihistamine, developed from the second-generation antihistamine cetirizine. Chemically, levocetirizine is the active enantiomer of cetirizine. It is the R-enantiomer of the cetirizine. Levocetirizine is an inverse agonist that decreases activity at histamine H1 receptors. This in turn prevents the release of other allergy chemicals and increased blood supply to the area it and provides relief from the typical symptoms of hay fever. It does not prevent the actual release of histamine from mast cells.

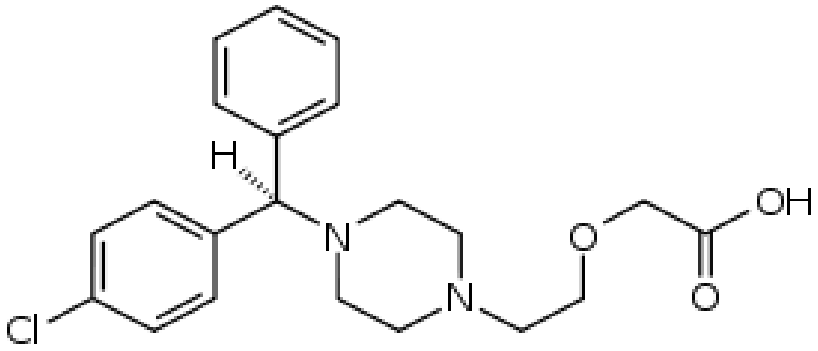


Fig.1: Levocetirizine hydrochloride

MATERIALS AND METHODS

List of the chemicals

Levocetirizine Hcl (RL Chemicals, Ltd, Chennai), Ammonium Acetate (S.D. fine- chem. Ltd;) Glacial Acetic Acid (Ranbaxy, Fine Chemicals Ltd;), Isopropyl Alcohol (Ranbaxy, Fine Chemicals Ltd;), Distilled Water (Merck Ltd.,)

List of the equipment's

Thief apparatus (Chitra equipment's pvt ltd Mumbai), UV Spectro photo meter (Shimadhz UV-1800), Mechanical stirrer (lab chemicals Mumbai), Mettle weighing balance, Essay Mass mixer (Balaji pharma, Chennai)

Plan of work

To evaluate the results of blend uniformity studies in relevance to the acceptance criteria for content uniformity testing as per IP, BP and USP.

Blend uniformity study

In this study we Select 3 batch of blend location. From the blend, sample at least 10 locations, with at least 3 replicates from each #Assay 1 per location. During filling or compression, sample from at least 20 locations, taken at least 7 dosage units each. Assay at least 3 dosage unit per each location, Blend uniformity assay and validation.

Experimental

From blend we Selected three batches of salbutamol tablets .Ten samples of different location were taken from each batch .Samples were taken from thief apparatus (sampling rod).Quantity of sample was 1 to 3 x (150 mg) taken .From the 10 samples, 3 samples taken for content uniformity test .Assay method done by **UV** method. Assay values meet criteria. RSD less than or equal to **5.0%** and all individual are within the mean +\ - 10 of the mean value.

From dosage unit

20 samples collected periodically in every three batches. Tablets are collected in every 30 minutes. SO that every 30 minutes collected 7 tablets. Assay done by 3 tablets from the 7 tablets .Assay method done by UV method .Assay values meet criteria. RSD of all individuals less than or equal to 6.0 %. Each location mean is within 90.0 % to 110.0 % of target potency and all individuals are within 75.0 % and 125% of target potency.

Blend uniformity assay

***Name of the product*:** L-CET 5mg TABLETS (to Levocetirizine HCl 5MG)
***Label claim*:** Each uncoated tablet contains. Levocetirizine HCl (Equivalent to Levocetirizine HCl 5MG)

Content of levocetirizine hcl I.P (by UV)

Preparation of Analytical Standard Solution

In a 100-mL volumetric flask, about 30 mg of Levocetirizine Dihydrochloride standard was taken and the standard was dissolved by adding 30 mL of 0.1 M Hydrochloric acid and was added to sonication for 2 to 3 minutes. After sample temperature came to room temperature, volume the sample up to mark with 0.1 M Hydrochloric acid. Then,5 mL of this solution was taken in a 100- mL volumetric flask and was diluted to 100 mL with 0.1 M Hydrochloric acid.

Preparation of Sample Solution

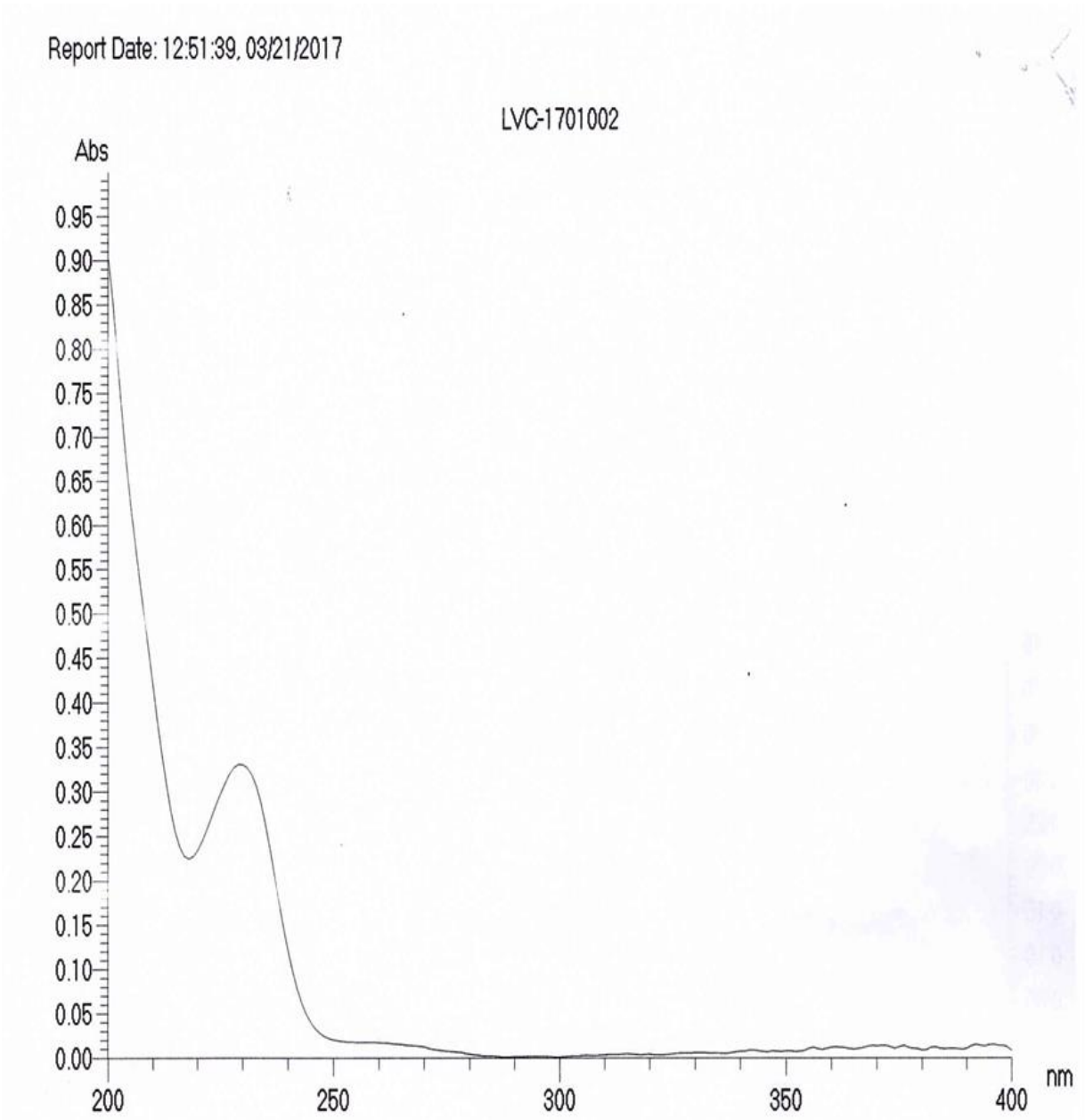
In a 100-mL volumetric flask, about 30 mg of test sample was taken and the sample was dissolved

by adding 30 mL of 0.1 M Hydrochloric acid and was added to sonication for 2 to 3 minutes. After sample temperature came to room temperature, volume the sample up to mark with 0.1 M Hydrochloric acid. Then,5 mL of this solution was taken in a 100-mL volumetric flask and was diluted to 100 mL with 0.1 M Hydrochloric acid.

Table No.: 1.1 Results of Blend Samples Batch (1)

S.No	Sample Area	Content in mg	Sample Weight	Content in %
01	172	5.24	118.2	4.90
02	170	5.22	120.1	4.85
03	177.3	5.31	118.9	4.95
04	149.6	4.95	109.6	4.78
05	164.1	5.14	116.2	4.84
06	161.3	5.10	114.9	4.83
07	157.6	5.06	114.3	4.80
08	163	5.13	112.6	4.89
09	156.8	5.05	112.3	4.82
10	163.9	5.14	105.3	5.03

Mean	48.69
SD	0.075136
RSD	4.02



Sample: LVC-1701002
File name: DEFLT5389.UDS
Run Date: 12:50:42, 03/21/2017
Operator: Administrator
Comment: LEVOCETIRI INE

Peak Integration
Method: Rectangular
Sensitivity: 1
Threshold: 0.0100

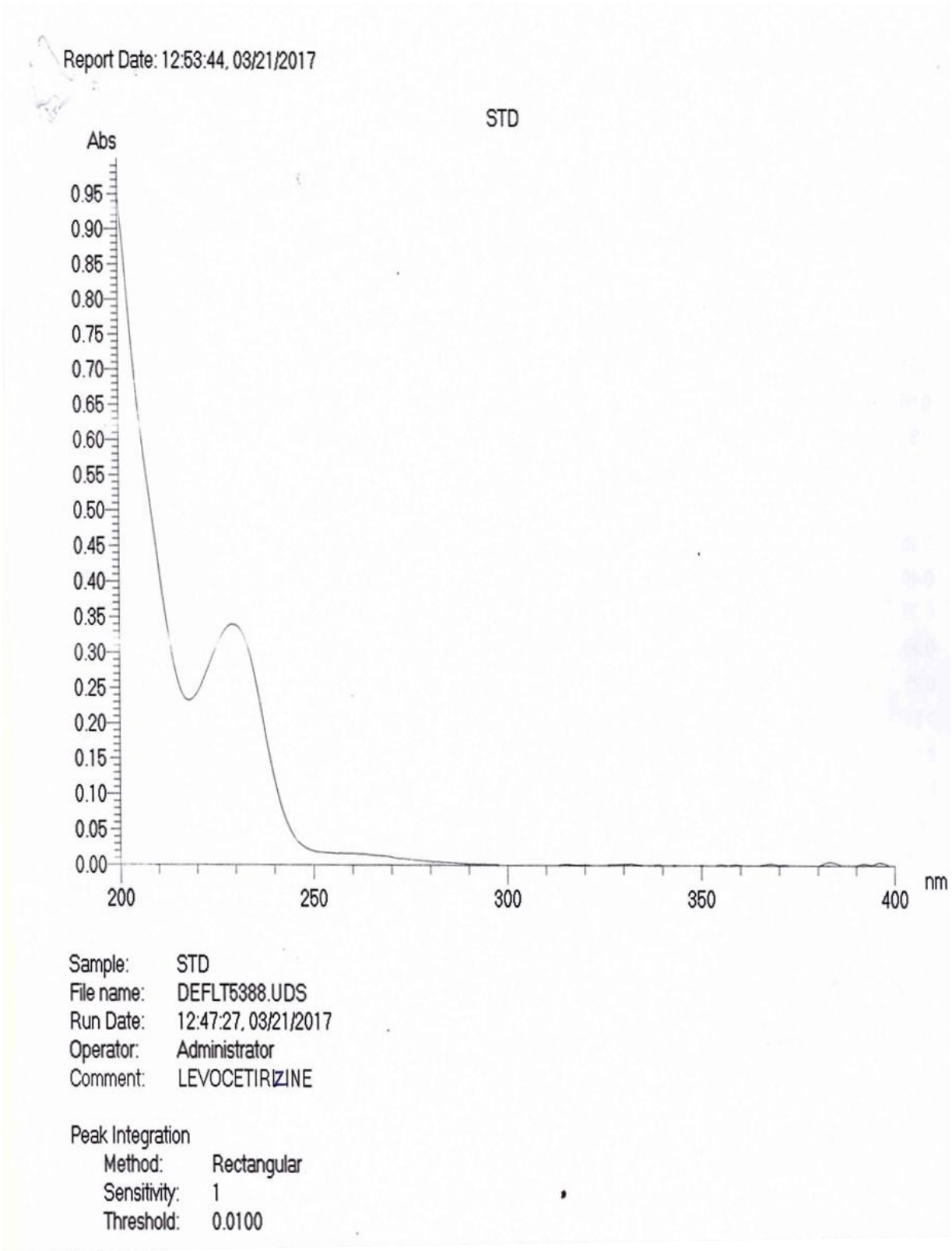


Table No: 1.2 Results of Blend Samples Batch (1I)

S.No	Sample Area	Content in mg	Sample Weight	Content in %
01	149.3	5.06	118.8	4.73
02	156.5	5.16	120.2	4.79

03	131.4	4.81	102.6	4.76
04	150	5.07	116.5	4.77
05	146.5	5.02	116.9	4.73
06	155.9	5.15	117.3	4.83
07	145	5.00	112.6	4.77
08	153.2	5.11	118.4	4.78
09	150.6	5.08	104.9	4.98
10	145.9	5.01	109.6	4.83

Mean	47.99
SD	0.07214
RSD	4.00

Table No: 1.3: Results of Blend Samples Batch (III)

S.No	Sample Area	Content in mg	Sample Weight	Content in %
01	112.8	5.10	115.8	4.812
02	115.9	5.16	119.1	4.810
03	112.6	5.09	117.7	4.779
04	133	5.47	123.1	5.010
05	112.9	5.10	119.6	4.756
06	122.6	5.28	117.6	4.939
07	112.6	5.09	118.6	4.766
08	110.9	2.06	115	4.794
09	102.6	4.91	108	4.767
10	101.1	4.88	102.6	1.833

Mean	48.27
SD	0.083151
RSD	4.55

Table No: 1.4 Results of Dosage Unit Batch (I)

S. No	Sample area	Content (in mg)	sample weight	Percentage	Mean
1	148.8	4.94	102.3	4.898	
2	141.2	4.84	103.2	4.785	
3	143.7	4.88	102.4	4.831	4.838
4	148.6	4.94	102.3	4.896	
5	139.3	4.82	104.1	4.746	
6	140.8	4.76	99.3	4.772	4.805
7	147.9	4.86	104.2	4.785	
8	150.7	4.97	102.9	4.911	
9	150.9	4.97	104.1	4.892	4.863
10	149.8	4.95	103.7	4.885	
11	149.6	4.95	102.8	4.899	
12	139.3	4.82	104.2	4.744	4.843
13	161.3	5.10	103.6	5.032	
14	142.6	4.86	102.8	4.810	
15	165.3	5.16	104.6	5.062	4.968
16	149.6	4.95	103.2	4.892	

17	151.9	4.98	104.6	4.895	
18	142.8	4.86	102.3	4.822	4.869
19	143.6	4.87	102.9	4.821	
20	177.4	5.31	103.8	5.230	
21	143.6	4.87	104.6	4.791	4.948
22	181.6	5.37	106.2	5.231	
23	142.4	4.86	100.1	4.856	
24	155.6	5.03	102.3	4.985	5.024
25	142.5	4.86	102.3	4.818	
26	142.6	4.86	101.2	4.839	
27	169.3	5.21	108.3	5.040	4.899

Contd.. Table 1.4

30	151.4	4.98	101.8	4.941	4.861
31	142.1	4.85	102	4.818	
32	145.1	4.89	103.3	4.833	
33	143.5	4.87	101.7	4.841	4.830728
34	156.3	5.04	105.8	4.928	
35	150.11	4.96	101.6	4.928	
36	139.97	4.83	103.4	4.766	4.874
37	139.47	4.82	105.6	4.723	
38	151.02	4.97	104.2	4.891	
39	149.6	4.95	101.7	4.920	4.845
40	143.54	4.87	102.1	4.835	
41	141.97	4.85	103.4	4.792	
42	151.54	4.98	102	4.939	4.855
43	141.15	4.84	105.7	4.743	
44	146	4.91	102.4	4.861	
45	148.05	4.93	101.7	4.900	4.834
46	140.86	4.84	101.1	4.818	
47	142.51	4.86	101	4.841	
48	148.7	4.94	101	4.921	4.860
49	142.88	4.86	101.3	4.841	
50	146.69	4.91	103.3	4.853	
51	161.3	5.10	105.2	5.001	4.898
52	149.9	4.96	102.8	4.903	
53	147.51	4.92	102.3	4.882	
54	147.9	4.93	104.2	4.852	4.879
55	142	4.85	101.8	4.820	
56	142	4.85	103.2	4.796	
57	142.6	4.86	103.8	4.793	4.803
58	148.7	4.94	101.8	4.906	
59	142.9	4.86	102.8	4.814	
60	140.8	4.73	101.2	4.705	4.808

Mean	49.414
SD	5.319994
RSD	0.099644

Table No: 1.5 Results of Dosage Unit Batch (I1)

S.No.	Sample Area	Content (in mg)	Sample weight (in mg)	Percentage (%)	Mean
1	138.9	4.91	102.3	4.871	
2	139.1	4.82	102.3	4.774	
3	140.3	4.83	103.8	4.764	4.803
4	143.6	4.87	102.3	4.832	
5	143.6	4.87	102.7	4.825	
6	144.3	4.88	102.5	4.837	4.831
7	146.3	4.91	102.3	4.866	
8	140.9	4.84	104.3	4.763	
9	147.6	4.93	103.6	4.859	4.829
10	136.9	4.79	104.3	4.713	
11	140.7	4.84	104	4.765	
12	159.6	5.08	106.6	4.954	4.811
13	144.3	4.88	105.2	4.790	
14	181.3	5.37	104.6	5.262	
15	180.2	5.35	105.8	5.223	5.091
16	161.3	5.10	105.1	5.003	
17	180.2	5.27	103.9	5.185	
18	152.3	4.99	104.2	4.907	5.032
19	155.3	5.03	104.2	4.945	
20	155.9	5.03	104.6	4.945	
21	174.3s	5.27	105.4	5.158	5.016
22	145.3	4.90	103.2	4.837	
23	147.6	4.93	102.3	4.883	
24	140.3	4.83	102.3	4.790	4.837
25	148.3	4.94	102.1	4.895	
26	142.1	4.85	102.4	4.811	
27	179.3	5.34	103.9	5.252	4.986
28	140.9	4.84	100.9	4.822	
29	140.3	4.83	101.1	4.811	
30	182.2	5.38	101.3	5.347	4.993
31	159.6	5.08	101	5.062	
32	135.5	4.77	99.6	4.775	
33	169.3	5.21	102.7	5.151	4.996
34	135.6	4.77	101.6	4.742	

Contd.. Table 1.5

35	120.6	4.57	102.2	4.540	
36	181.3	5.37	101.1	5.340	4.874
37	137.9	4.80	101.3	4.776	
38	131.7	4.72	101.1	4.700	
39	186.3	5.43	101.7	5.390	4.956
40	144.6	4.89	102.1	4.848	
41	152.3	4.99	101.9	4.950	
42	137.4	4.79	101.9	4.760	4.853

43	143.6	4.87	102.1	4.835	
44	139.6	4.82	100.1	4.820	
45	171.3	5.24	102.1	5.189	4.948
46	140.5	4.83	101.8	4.801	
47	140.2	4.83	102.1	4.792	
48	161.3	5.10	100.9	5.086	4.893
49	146.1	4.91	101.1	4.886	
50	134.6	4.76	101.4	4.732	
51	142.9	4.86	101.1	4.844	4.901
52	156.3	5.04	102.5	4.990	
53	139.6	4.82	102.3	4.781	
54	137.8	4.80	104.2	4.726	4.832
55	145.8	4.90	101.8	4.869	
56	139.9	4.83	103.2	4.769	
57	145.8	4.90	102.3	4.860	4.833
58	141.8	4.85	101.8	4.818	
59	141.3	4.84	102.5	4.799	
60	140	4.83	100.3	4.821	4.813

Mean	49.023
SD	0.088339
RSD	4.633912

Table No: 1.6 Results of Dosage Unit Batch (II1)

S.No	Sample Area	Content	Sample wt (in mg)	Percentage	Mean
1	122.3	5.27	105.3	5.160	
2	101.1	4.88	102.6	4.833	
3	102.4	4.90	103.7	4.837	4.943
4	93.8	4.74	102.3	4.705	
5	100	4.86	101.9	4.825	
6	101	4.88	99.9	4.880	4.804
7	101.3	4.88	103.8	4.815	
8	95.7	4.78	102.1	4.743	
9	101.3	4.88	101.8	4.851	4.803
10	99.6	4.85	99.1	4.869	
11	102	4.90	103.5	4.833	
12	94.5	4.76	102.1	4.722	4.808
13	99.9	4.86	103.5	4.795	
14	101.2	4.88	100.8	4.867	
15	95.8	4.78	100.4	4.775	4.851
16	100.8	4.87	100.2	4.871	
17	99.1	4.84	100.6	4.832	
18	118.8	5.21	104.2	4.121	4.941
19	97.9	4.82	101.2	4.799	
20	102	4.90	102.2	4.856	
21	96.5	4.79	102.3	4.755	4.803

22	99.2	4.85	103.3	4.786	
23	102.2	4.90	100.8	4.886	
24	121.8	5.27	106.8	5.121	4.931
25	97.7	4.82	102.3	4.776	
26	95.7	4.78	100.3	4.775	
27	103.6	4.93	103.2	4.867	4.806
28	97.6	4.82	100.2	4.812	
29	101.1	4.88	101.3	4.856	
30	99.1	4.84	102.1	4.805	4.824
31	101.3	4.88	103.6	4.819	
32	99.5	4.85	102.3	4.809	

Contd. Table 1.6

33	102.3	4.90	102.3	4.860	4.829
34	96.6	4.80	101.7	4.767	
35	98.2	4.83	100.1	4.825	
36	115.5	5.15	108.4	4.982	4.858
37	96.7	4.80	100.6	4.788	
38	100.2	4.86	102.5	4.818	
39	97.9	4.82	100.5	4.812	4.806
40	97.9	4.82	103.5	4.759	
41	105.3	4.96	101.1	4.937	
42	97.7	4.82	101.7	4.787	4.828
43	102.2	4.90	100.8	4.886	
44	112.8	5.10	102.4	5.049	
45	100.3	4.87	99.1	4.883	4.939
46	98.9	4.84	100.8	4.825	
46	98.9	4.84	100.8	4.825	
47	99.2	4.85	102.6	4.798	
48	99.9	4.86	100.8	4.843	4.822
49	97.9	4.82	103.7	4.756	
50	100.3	4.87	101.1	4.845	
51	115.5	5.15	102.1	5.104	4.902
52	99.4	4.85	101.9	4.814	
53	96.5	4.79	100.9	4.779	
54	101	4.88	101.4	4.853	4.815
55	99.5	4.85	101.8	4.818	
56	101.2	4.88	100.9	4.866	
57	101.6	4.89	101.4	4.864	4.849
58	101.8	4.89	100.3	4.888	
59	105	4.95	101.3	4.928	
60	95.7	4.78	101.9	4.747	4.854

Mean	47.530
SD	0.095295
RSD	5.13

RESULTS AND DISCUSSION

The blend samples

B.No.	Parameters	Results	Acceptance criteria
1	RSD	4.02%	Less than or equal to 5.0%
	Variation of individual values to the mean	- 4.76 %to 8.61%	+/- 10% of mean
2	RSD	4.00%	Less than or equal to 5.0%
	Variation of individual values to the mean	- 3.86 %to 10%	+/- 10% of mean
3	RSD	4.55%	Less than or equal to 5.0%
	Variation of individual values to the mean	- 4.2 %to 10%	+/- 10% of mean

Tablet samples

B.No.	Parameters	Results	Acceptance criteria
1	RSD	5.31%	Less than or equal to 6.0%
	Variation of each location mean to target potency	4.9%	+/- 10% of target potency
	Variation of individual values to the target potency	-7.6% to 23.2%	+/- 25% of target potency
2	RSD	4.6%	Less than or equal to 6.0%
	Variation of each location mean to target potency	4.9%	+/- 10% of target potency
	Variation of individual values to the target potency	-9.7% to 24.86%	+/- 25% of target potency
3	RSD	5.51%	Less than or equal to 6.0%
	Variation of each location mean to target potency	4.9%	+/- 10% of target Potency
	Variation of individual values to the target potency	-5.89% to22.7%	+/- 25% of target potency

RESULTS

The uniformity of dosage units needs to be established for all the tablet formulations. The uniformity of dosage units is established either by uniformity of weight or content uniformity in the formulations. Pharmacopoeia describes criteria for performing content uniformity on the basis of the drug content / proportion in the formulation. The blend uniformity in granules following mixing operation is crucial in determining the compliance of final product to the official requirements.

- Blend uniformity in the granules to the predetermined acceptance criteria
- Blend uniformity on the basis of the content uniformity from compressed tablets
- Mixing operation is good enough to provide content uniformity in the final product

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