Research Article

Prospective Validation of Paracetamol Tablet Dosage Form

Nidhi Aswal*, Pallavi Joshi, Alka N Choudhary and Preeti Kothiyal

Department of Quality Assurance, Shri Guru Ram Rai Institute of Technology and Science, Dehradun, Uttarakhand, India.

ABSTRACT

Validation is an integral part of cGMP. It is one of the most important part of quality assurance. The in-process quality control parameters ensure that consistently product are produced of high quality and Process Validation is a very important method to assure these parameters are met with the standard. Here, three batch of Paracetamol tablets are formulated and evaluated. The process like mixing, granulation, drying, lubrication, compression and different evaluation test like weigh variation, hardness, thickness, friability, disintegration are validated in order that finished product meet all the specifications under the acceptance criteria.

Keywords: Paracetamol tablet, Validation, Process Validation.

INTRODUCTION

Validation is documented act of proving that any procedure, process, equipment, material, activity or system actually leads to the expected results. Validation act of proving, in accordance of GMPs that any process actually leads to expected results." Documented evidence that the process, operated with in established parameters, can perform effectively reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes[1] whereas process validation is establishing documented evidence which provides high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics.[2]

The prime objective of any pharmaceutical plant is to manufacture products of requisite attribute and quality consistently, at the lowest possible cost.[3] Although validation studies have been conducted in the pharmaceutical industry for a long time, there is an ever-increasing interest in validation owing to their industry's greater emphasis in recent years on quality assurance and productivity improvement.[4] Validation is a necessary part of a quality assurance program and is fundamental to an efficient production operation. Process validation establishes the flexibility and constraints in the manufacturing process controls in the attainment of desirable attributes in the drug product while preventing undesirable properties.[5] This is an important concept, since it serves to support the underlying definition of validation, which is a systematic approach to identifying, measuring, evaluating, documenting, and re-evaluating a series of critical steps in the manufacturing process that require control to ensure a reproducible final product.[6-13]

Experimental

Validation procedure

a) Three batches of 100 tablets batch size to be manufactured as described in the batch manufacturing record.
b) Current version of standard operating procedures to be followed.
c) Record the observations at every stage in the below specified data sheets.
d) Record the results after every process of the manufacturing and validate as per ICH guidelines Q2R1
e) After the compression evaluation parameters are to be validated. The process control variables are shown in table 1

MATERIALS

Paracetamol was used as an active pharmaceutical ingredient. Starch used as a disintegrant. Lactose used as a diluents to increase the bulk. Magnesium stearate used as a lubricating agent and the wet granulation soluble starch was added. The details of raw materials are shown in table 2.

Equipments

For the validation mortar and pestle was used for mixing and wet granulation. Weighing machine was used to weight the ingredients and for weight variation. Single punch machine was used for the compression method. For hardness testing Monsanto apparatus was used. Roche friability apparatus was used for friability testing. Dissolution and disintegration apparatus was taken. For the assay method

Double Beam Ultraviolet Spectroscopy was used. The equipments to be used during process validation are shown in table 3

Process of Tablet Manufacturing
The critical process considered during the process validation of Paracetamol 100 mg tablets were-

1. Dry Mixing
2. Drying
3. Wet granulation
4. Compression

Dry mixing
The dry-mixing step involved mixing of active ingredients with other additives using the Mortar and Pestal. The content of Paracetamol in the dry mix was tested, to validate dry mixing process. In dry mixing stage 3 batches Batch A , Batch B ,Batch C are considered for validation. Each sides sampled from (location 1), (location 2), (location 3) layer taken for analysis of assay and RSD% was calculated.

Drying
Drying of the wet granules was done at 55^{o}C-65^{o}C for 2-3 hours. The loss on drying was checked at regular interval to establish the correlation with outlet temperature. In dry stage of different time interval of each batch was considered for validation and the RSD % was calculated.

Wet granulation
Binding solution was added and mixed through Mortar and Pestal.

Binder solution preparation:
Soluble starch taken and distilled water in vessel and mixed properly and slurry made and added to Mortar and Pestal and paste prepared. In wet granulation stage 3 batches Batch 1 , Batch 2 ,Batch 3 are considered for validation. Each sides sampled from (location 1), (location 2), (location 3) layer taken for analysis of assay and RSD% was calculated.

Compression
Compression of the mixer was done and 100 mg Paracetamol tablets were manufacture 100 tablet in each batch by using single punching machine and the evaluation parameters were validated by taking UV spectrophotometer as standard. Assay of the Paracetamol tablet of the three batches A,B,C from location 1,2,3 done and RSD % value was calculated.

Evaluation parameters of tablet for process validation

1. Content uniformity
2. Weight variation
3. Thickness
4. Hardness
5. Friability
6. Assay

Content uniformity
After the compression method the content uniformity of tablets was tested. The assay method was followed to check the content uniformity.

Weight variation
Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated.

Hardness
The crushing strength Kg/cm^2 of prepared tablets was determined for 10 tablets of each batch by using Monsanto tablet hardness tester. The average hardness and standard deviation was determined.

Thickness
Twenty tablets were randomly selected from each batch and thickness was measured by using Digital Vernier Caliper.

Friability
Twenty tablets were weighed and placed in the Roche friability testing apparatus and apparatus was rotated at 100 rpm. After revolutions the tablets were deducted and weighed again Table 8 The percentage friability was measured using the formula,

$$\% F = \{1-(Wt/W)\} \times 100$$

Where, % F = friability in percentage
W = Initial weight of tablet
Wt = weight of tablets after revolution Paracetamol

Dissolution Test
Dissolution test were carried out to determine the amount of drug released during a specific period of time using USP apparatus-I. 5ml of sample was withdrawn after specified time interval, and was replaced by an equal volume of fresh dissolution medium to maintain the sink condition. Collected samples were analyzed spectrophotometrically at measured wavelength of 257nm

Disintegartion Test
Six tablets from each batch were utilized for disintegration studies in distilled water at 37°C

using an Educational Sciences Disintegration Apparatus USP std. The disintegration time was taken to be the time no granule of any tablet was left on the mesh of the apparatus.

Assay of Paracetamol

20 tablets weighed accurately a quantity of powder equivalent to 0.15gms of paracetamol and 50ml of 0.1M NaoH, diluted with 100ml of water, shacked for 15minutes and sufficient water added to produce 200ml then mixed and filtered and diluted 10mlof filtrate to 100ml with water. To 10ml of resulting solution add 10ml of 0.1 M NaOH diluted to 100ml with water and measure the absorbance of the resulting solution at about 257nm.

RESULTS AND DISCUSSIONS

Process of tablet manufacturing

The paracetamol tablets were formulated and the results of the validation at every step of different process were recorded. The results of process validation of paracetamol of each batch in every stage are as follow:

Dry mixing process

The dry-mixing step involves mixing of active ingredients with other additives using mortar pestle. In dry mixing stage 3 batches like Batch A, Batch B, Batch C were considered for validation. Each side sampled from Location 1 (A1, A2, A3), Location 2 (B1, B2, B3), Location 3 (C1, C2, C3) layer of mortar pestle were taken in self sealing bags for QC analysis of assay. The results of dry mixing are shown in table 4.

All the % assay were under the acceptable criteria of standards. So the content uniformity was acceptable for manufacturing of tablets.

Wet granulation process

In wet granulation stage 3 batches Batch 1 , Batch 2 ,Batch 3 are considered for validation. Each sides sampled from (location 1), (location 2), (location 3) layer taken for analysis of assay and RSD% was calculated. The results of validation of wet granulation process are shown in table 5.

Drying

The loss on drying was checked at regular interval to establish the correlation with outlet temperature. In dry stage assay as done and RSD% calculated at different time interval of all the three batches are shown in table 6.

Compression process

The sample was filled in the dies of single punch machine where the powder mixer were compressed into tablets. Compression carried out as per batch manufacturing recorded. Results of compression are shown in table 7.

Evaluation parameters

The formulated tablets were evaluated as according to parameters. Weight variation, thickness, hardness, friability, dissolution and disintegration were validated and the obtained data was recorded.

Weight variation

The manufactured tablets were evaluated on the weight variation test. The results are shown in table 8& fig no1.

Thickness

The tablets were evaluated on the basis of their thickness. The results of the thickness test are shown in the table 9 & fig no2.

Hardness

Hardness of the 10 tablets of each batch is checked. And the results are shown in the table 10& fig no 3.

Friability

The friability test carried out for the three batches. The friability results are shown in table 11.

Dissolution Test

Dissolution test were carried out to determine the amount of drug released during a specific period of time using USP apparatus-I. Collected samples were analyzed spectrophotometrically at measured wavelength of 257nm. The dissolution results are shown in table 12& fig no 4.

Disintegartion Test

The disintegration test carried out for the three batches. The disintegration results are shown in table 13. All the parameters are under the acceptance criteria shown in table 14& fig no5.

CONCLUSION

In this research first the formulation and manufacturing process of the Paracetamol tablet were validated as per validation protocol. Then the evaluation of formulated tablets had been done. The manufactured tablets of each batch passed the acceptable criteria of evaluation parameters (i.e. content uniformity, weight variation, thickness, friability, hardness, dissolution and disintegration). And there were negligible variations between the process validation results of each batch which were under acceptable criteria.

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Table 1: Process Control Variables

Seiving	Sieve size
Mixing	Mixing time
Granulation	Sieve size
Drying	Dryer,drying time
Lubrication	Lubricant amount,
Compression	Uniformity of weight, thickness, friability, disintegration, dissolution

Table 2: Details of raw materials

S.No	Ingredients	Pharmacopoeial standards	Theoritical quantity	Actual quantity	Quantity per batch
Paracetamol	50mg	USP	50mg	50mg	5gm
Lactose	25mg	USP	25mg	25mg	2.5gm
Binder	7mg	USP	7mg	7mg	0.7gm
Soluble starch	15mg	USP	15mg	15mg	1.5gm
Talc	1.5mg	USP	1.5mg	1.5mg	0.15gm
Magnesium stearate	1.5mg	USP	1.5mg	1.5mg	0.15gm

Table 3: Equipments to be used during Process Validation

Processing stage	Processing equipments
Weigh verification	weighing balance
Sifting	Sieve size
Drying	Tray dryer
Hardness	Monsanto hardness tester
Thickness	Vernier caliper
Friability	Roche friability tester
Disintegration	USP std.
Dissolution	USP std.
Compression	Compression machine
Assay testing	Double beam U.V spectrophotometer

Table 4: Assay of Paracetamol after dry mixing

Content of Paracetamol									
	Batch A			Batch B			Batch C		
	A1	A2	A3	B1	B2	B3	C1	C2	C3
Location 1	99.6	99.4	100.6	99.9	99.6	101.9	100.1	99.3	99.8
Location 2	101	101.1	99.6	101.3	102	100.9	99.0	101.2	101.4
Location 3	101.2	100.8	101.4	102	101.6	99.9	101	100.7	100.9
Average	100.6	100.4	100.5	101.06	101.06	100.9	100.03	100.4	100.7
Standard deviation	0.87	0.90	0.90	1.06	1.2	1	1.18	0.98	0.81
Percentage of RSD	0.86	0.89	0.89	1.04	1.1	0.9	1.17	0.97	0.80

Table 5: Assay result after wet granulation

	Batch A			Batch B			Batch C		
	A1	A2	A3	B1	B2	B3	C1	C2	C3
Location 1	99.6	99.9	100.2	99.4	100.2	99.8	100.1	99.6	100.8
Location 2	101	100.8	99.8	102.3	101.3	101	99.0	100.2	101
Location 3	102.1	101	101	101	99.9	101.4	101	100.9	99.2
Average	100.9	100.5	100.3	100.9	100.4	100.7	100.03	100.2	100.3
S.deviation	0.72	0.58	0.61	1.45	0.73	0.83	1.15	0.65	0.98
RSD%	0.71	0.57	0.61	1.43	0.70	0.82	1.14	0.64	0.97

Table 6: Assay after drying

		Content of Paracetamol		
		Batch no 1	**Batch no 2**	**Batch no 3**
After 15 min	Location 1	100.8	99.7	100.1
	Location 2	99.6	102.3	99.0
	Location 3	100.9	102	101
	Average	100.4	101.3	100.03
	Standard deviation	0.32	1.42	1.001
	Percentage of RSD	0.31	1.4	1.00
After 30 min	Location 1	99.9	100.5	99.9
	Location 2	99.8	100.2	99.4
	Location 3	100.2	99.7	98.9
	Average	99.96	100.13	99.4
	Standard deviation	1.24	0.404	0.5
	Percentage of RSD	1.24	0.403	0.503
After 45min	Location 1	98.9	98.6	99.8
	Location 2	99	99.2	99.6
	Location 3	100.6	99.9	98.9
	Average	99.5	99.2	99.43
	Standard deviation	0.95	0.65	0.47
	Percentage of RSD	0.954	0.655	0.47

Table 7: Assay after compression

	Batch A			**Batch B**			**Batch C**		
	A1	**A2**	**A3**	**B1**	**B2**	**B3**	**C1**	**C2**	**C3**
Location 1	99.6	99.9	100.2	99.4	100.2	99.8	100.1	99.6	100.8
Location 2	101	100.8	99.8	102.3	101.3	101	99.0	100.2	101
Location 3	102.1	101	101	101	99.9	101.4	101	100.9	99.2
Average	100.9	100.5	100.3	100.9	100.4	100.7	100.03	100.2	100.3
Standard deviation	0.72	0.58	0.61	1.45	0.56	0.83	1.15	0.65	0.98
Percentage of RSD	0.71	0.57	0.60	1.43	0.55	0.82	1.14	0.64	0.97

Table 8: Weight variation result of the formulated tablets

Sample no.	**Batch 1 (mg)**	**Batch 2**	**Batch 3**
1	99.9	100	100.3
2	99.8	100	100
3	99.6	99	99
4	100.1	100.2	100
5	100.1	99	99.4
6	100	99	100
7	100	99	99
8	100	100	99.9

9	100.3	100.1	99
10	99.7	100	99.8
11	99.9	100	100
12	100	100	100.1
13	99.3	99.7	100
14	99.1	99.8	100.6
15	99.3	99.3	100
16	100.1	99.9	99.9
17	100	99	99
18	100	99.6	99.1
19	100.4	100	100.5
20	100	100	100.3
Maximum	100.4	100.2	100.6
Average	99.88	99.68	99.79
Minimum	99.1	99	99

Table 9: Thickness test result of the formulated tablets

Sample no	Batch 1	Batch 2	Batch 3
1	3.04	3.01	2.81
2	2.81	3.02	2.80
3	2.91	2.91	2.92
4	3.13	3.11	2.83
5	2.84	2.90	2.81
6	2.81	3.10	2.90
7	2.91	2.91	3.20
8	2.80	3.12	3.015
9	2.92	2.90	3.12
10	3.10	2.91	3.22
11	3.01	2.90	3.14
12	3.09	2.90	3.02
13	3.08	3.12	3.115
14	3.06	3.12	3.11
15	3.05	3.04	3.05
16	2.93	3.05	3.20
18	2.81	3.10	3.02
19	2.91	3.12	2.91
20	2.90	2.90	2.90
Average	2.95	3.007	3.004
Maximum	3.13	3.12	3.2
Minimum	2.90	2.90	2.80

Table 10: Hardness test result of the formulated tablets

Sample no.	Batch1	Batch2	Batch3
1	3.2	4.4	3.6
2	4.1	3.6	3.3
3	3.4	3.5	3.2
4	3.6	3.6	3.7
5	3.6	3.6	4.1
6	3.3	2.8	4.1
7	3.2	3.9	3.3
8	3.7	3.6	4.1
9	4.1	3.3	3.5
10	4.2	3.3	3.6
Maximum	4.2	4.4	4.1
Average	3.64	3.56	3.65
Minimum	3.2	3.3	3.2

Table 11: Friability test result of the formulated tablets

Batch no	Initial weight of 20 tab	Final wt of 20 tab	Friability % loss
1	1.99	1.98	0.5%
2	1.86	1.85	0.53%
3	1.92	1.91	0.52%

Table 12: Dissolution test result of the formulated tablets

Batch no.	Drug release after 10min	Drug release after 20min	Drug release after 30min
1	48	88	102
2	52	92	98
3	40	88	99

Table 13: Disintegration test result of the formulated tablets

Tablet	Batch no 1	Batch no 2	Batch no 3
1	2.4	2.6	2.4
2	2.5	2.5	2.6
3	2.4	2.4	2.4
4	2.5	2.1	2.3
5	2.4	2.5	2.2
6	2.5	2.2	2.3

Table 14: he acceptance criteria for the Process Validation of manufacturing of the Paracetamol 100mg tablet dosage form

PARAMETER STANDARD	STANDARD
Appearance	White to off white colored circular tablets with plain surfaces on both sides
Group weight variation(g)	2.1 g ± 2% (2.038 g-2.162 g)
Individual weight variation(mg)	100 mg ± 4% (94.8 mg -111.2 mg)
Thickness(mm)	3mm±0.2mm(2.80mm-3.20mm)
Hardness(Kg/cm$^{2)}$ (kg/cm2)	NLT 2.5 Kg/cm^2
Friability(%w/w)	NMT 0.8 % w/w
Disintegration time(min)	NMT 12min
Content Uniformity	100 ± 10%
RSD %	NMT 2.0 %
Dissolution	NLT 70 % in 45 min

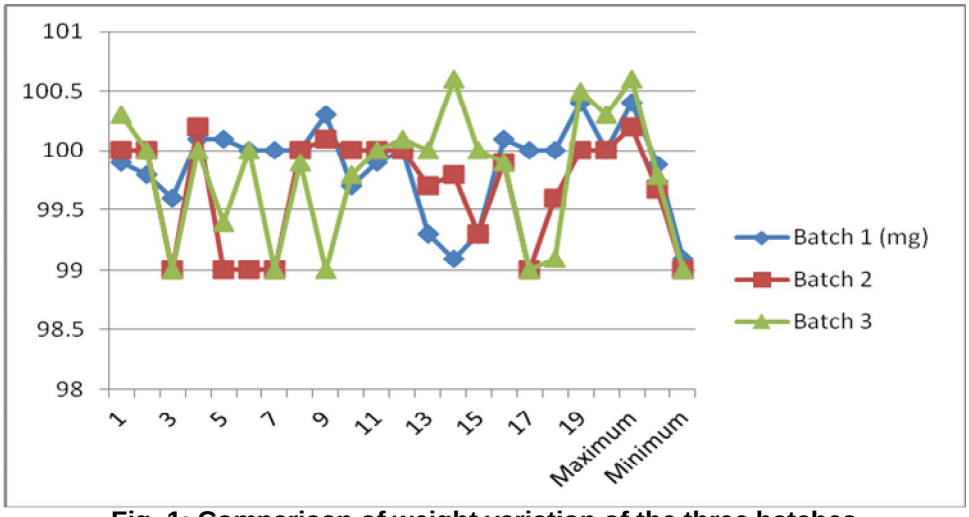

Fig. 1: Comparison of weight variation of the three batches

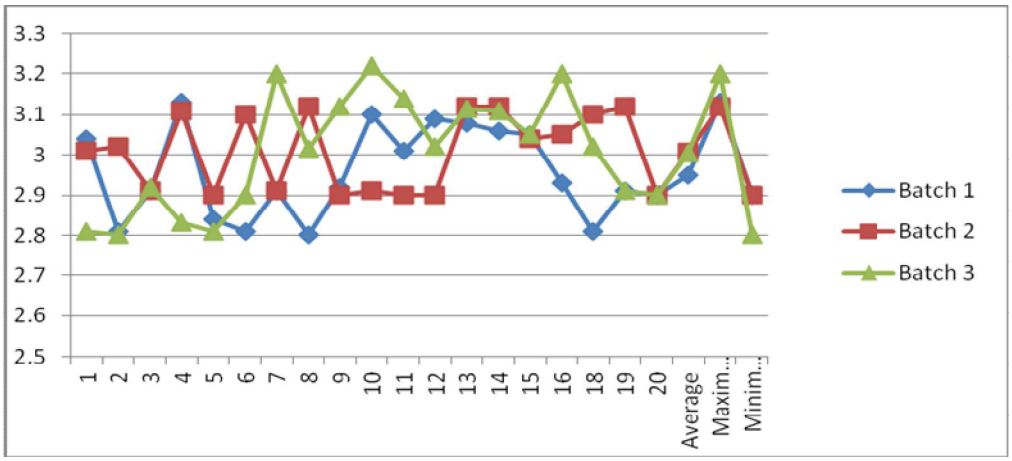

Fig. 2: Comparison of thickness of the three batches

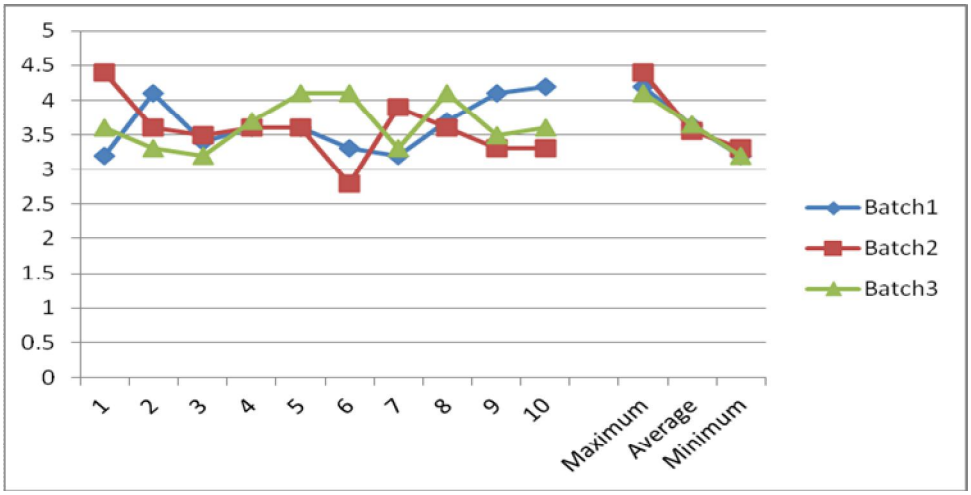

Fig. 3: Comparison of the hardness of the three batches

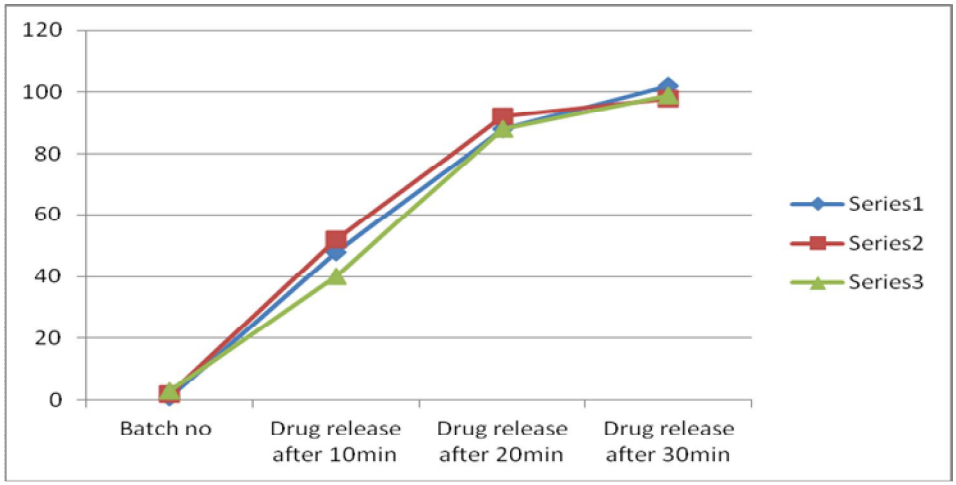

Fig. 4: Dissolution test comparison of the three batches

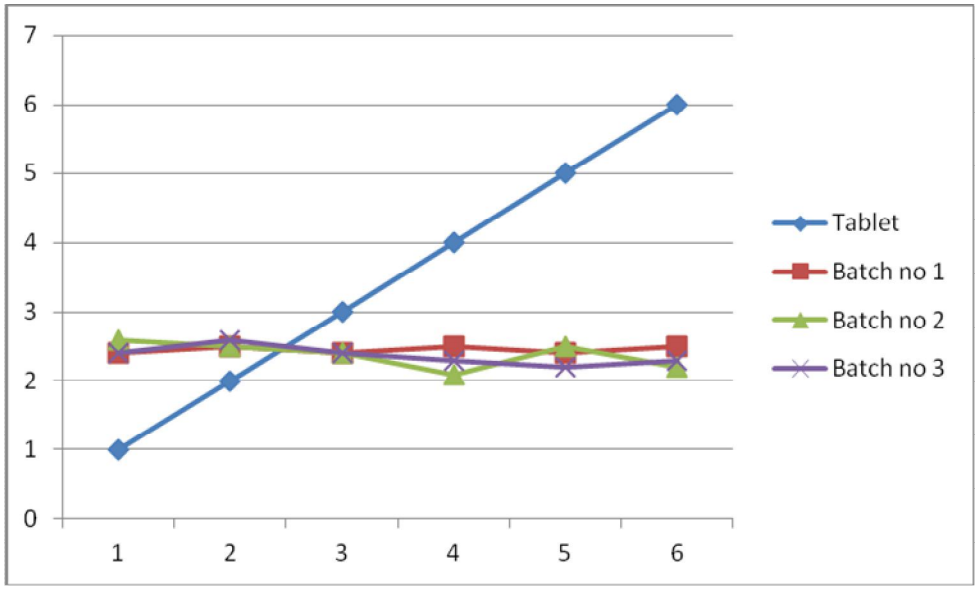

Fig. 5: Disintegration test comparison of the three batches

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