THE PROCESS VALIDATION OF TABLET CONTAINING IRBESARTAN 300MG AND HYDROCHLOROTHIAZIDE 12.5mg

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ABSTRACT

The objective of this study was to understand about the process validation and process qualification of tablet containing Irbesartan 300mg and Hydrochlorothiazide 12.5mg. The quality of product depends upon the consistency in the quality parameters of the process. In this study three batches of tablet containing Irbesartan 300mg and Hydrochlorothiazide 12.5mg having batch No. A1, A2 and A3, with batch size of 500.00 tablets each were validated at the facility of PharmEvo (Pvt.) Ltd. All three batches were evaluated at the granulation stage for sieving, mixing time, final blending and content uniformity. The physical parameters like thickness, hardness, weight variation, friability and disintegration time and chemical parameters like assay and dissolution were evaluated at compression and coating stage. All the physical and the chemical parameters of the tablet were observed within the specification set by company during the development of formulations.

Keywords: *Process Validation, Tablet, Irbesartan, Hydrochlorothiazide*

INTRODUCTION

The origins of validation in the world healthcare industry started when they observed the failure in the terminal sterilization of parenteral products in 1970s. These problems were observed in the large volume parenteral (LVP) sterilization problems of Abbott and Baxter, while in the U.K. cite the Davenport incident. All these incident occurs because the end products were not sterilized properly. As result these non-sterilized products were release into market and when administered to the patients the death occurs and eventually the regulatory investigation started. After the completion of investigation finally it was decided that validation is must for all products and hence the concept of validation started **(**Nash & Wachter, 2003). The food and drug administration in 2011 has given an idea of "lifecycle" methodology for the validation that includes scientifically sound Process design, Process qualification and continued process verification.

LITERATURE REVIEW

Validation as the collection and data evaluation from process design stage over commercial production which establishes scientific evidence that the process is capable of consistently delivering quality product. Process validation consist of three steps as per FDA 2011 like stage 1, 2 and 3. In Stage 1, process design, the process of commercial product manufacturing is defined based on knowledge gained through development and

scale-up activities. In Stage 2, process qualification, the process design is evaluated to determine that the process is capable of reproducing commercial manufacturing. In Stage 3, continued process verification, which is assured by the routine production that the process remains in a state of control (FDA, 2011). Process validation is now considered as a part of current good Manufacturing Practices (cGMP) and it is an important that the manufacturer must qualify his product much rigorously than earlier time (Aruchuri, Trivedi & Pavuluri, 2012).

Various regulatory bodies and the authorities recommend the validation programme. Furthermore the concept of cGMP is of no important without the process validation (Kumar & Bharat, 2013). Process validation not only improve the quality of products but also reduce the manufacturing cost as there are minimum chances of failure of product which are qualified (Patell, Rathwal & Patel, 2011). Pharmaceutical industries use extensive facilities, highly qualified personnel, expensive materials and equipment's. Effective use of all these resources is important for the continued success and necessary even for survival of the Pharmaceutical industries. As a result, the number of Product failures- rejects, reworks, recalls and complaints are gets reduced (Sharma, Rana, Bala & Seth, 2013).

MATERIAL AND METHOD

Materials

All the material used for the manufacturing of Tablet containing Irbesartan 300mg & Hydrochlorothiazide 12.5mg were provided by the PharmEvo (Pvt.) Ltd and work done at their own manufacturing facility. Irbesartan was procured from Zhuhai Sanxin fine chemical Co Ltd China & hydrochlorothiazide from the Pol Pharma, Poland. All other ingredients used in the formulation were pharmaceutical grades. Equipment's such as Sieves having mesh # 10, 16, 30, 60 & 200, Gral Mixer (Faisal Engineering), Tray dryer (Thermotex), Rotary Tablet Press (Liverpool England, ZPW23), weighing balance (AND, GF 300), digital Vernier caliper (Mitutoya), the Friability apparatus (Galvano Scientific), Hardness taster (Galvano Scientific, MH-1) and HPLC (Shimadzu, LC-20) were used.

Validation Protocol

Three batches having batch No. A1, A2 and A3, with batch size of 500.00 tablets manufactured at the facility of PharmEvo (Pvt.) Ltd. All the procedure for the operation of equipment's were followed as current standard operating procedure (SOP) of the company. All the parameters were recorded in the validation protocol. All the physical and the chemical parameters were evaluated at the granulation, compression and coating stage.

Tablet Manufacturing Procedure

Granulation

All ingredients used in formulation given in table No 1. Irbesartan, Lactose Monohydrate, Microcrystalline Cellulose (MC) # PH -102, Starch Pregelatinized, Croscarmellose Sodium were checked and sieved through mesh no.30 & transferred into Gral mixer and mixed for 01 minute. Hydrochlorothiazide (micronized) was passed through mesh no. 60 and added into Gral Mixer. A solution of Poloxamer 188 was prepared by adding slowly in water through continuous mixing. A homogenous solution was obtained by adding Isopropyl Alcohol. This solution was added into the pre mixture in the Gral Mixer and mixed for 02 minutes at low speed (40.00 RPM) and for 01 minute at high speed (100 RPM). The wet mass was passed through sieve no.10, then evenly spread the granules over the Stainless steel trays of dryer **(**Alam, 2012). Initially the wet mass was dried at room temperature for 3-4 hours to evaporate organic solvent. Then the wet mass was dried at temperature 45˚C until the desired LOD was achieved (Limit, 1.50 - 2.5 %). The granules were cooled down and then passed through sieve no.16 & transfer into Gral mixer again. Finally MC # PH -102, Croscarmellose Sodium, Talcum Powder, Colloidal Silicon Dioxide (Aerosil 200) & Magnesium Stearate passed through mesh no.60 & mix into Gral mixer & finally blended for 02 minutes.

Table 1: Composition of Core Tablets

Ingredients	Quantities (mg/tab)	Quantity/batch (g)	Functions
Irbesartan	300.000	150.00	API
Hydrochlorothiazide (micronized)	12.500	6.25	API
Lactose Monohydrate	117.440	26.96	Filler
M.C. Cellulose # PH -102	53.910	24.00	Filler
Starch Pregelatinized	48.000	4.50	Disintegrant
Cross Carmellose Sodium	9.000	0.08	Disintegrant
Lake of Quinoline Green	0.150	9.00	Color
Poloxamer 188	18.000	45.00	Dissolution Enhancer
Isopropyl Alcohol (IPA)	90.000	5.00	Wetting Agent
Purified water	10.000	15.00	Wetting Agent
M.C. Cellulose # PH -102	30.000	3.00	Filler
Cross Carmellose Sodium	9.000	1.50	Disintegrant
Talcum Powder	6.000	1.50	Lubricant
Colloidal Silicon Dioxide (Aerosil 200)	3.000	150.00	Glidant
Magnesium Stearate	3.000	6.25	Lubricant

Table 2: Coating Materials composition

Raw Material	Quantities (mg/tab)	Quantity/batch (g) *	Function
Opadry White ii 85G68918	12.00	36.00	Coating agent
Lake of Quinoline Green 19140	0.150	0.08	Color
Purified Water	68.850	34.43	solvent

* All Coating material quantities contains 500% excess to compensate loss during coating.

Compression

All the three batches A1, A2 and A3, were compressed into tablet using ZPW 23 Rotary compression machine. It was operated at 6 RPM with an average production speed of 132 tablets/minute. The tablet samples were collected at the begging, middle and end of three batches and then evaluated for their physical and chemical characteristics **(**Thaduvai, Rao & Jeybaskaran, 2012).

Coating procedure

The purified water was taken in in S.S. Manufacturing Vessel. Slowly Opadry White ii 85G68918 was added with continuous stirring to form uniform solution. Finally Lake of Quinoline Green was added done continuous stirring to completely disperse. The solution was mixed for 45 minutes thorough Silverson to completely disperse.

Characterization of Tablets

All three batches were evaluated before and after coating for their physical properties and chemical characteristics.

Weight Variation

100 tablets were sampled randomly from the three batches separately and each tablet was weight individually and recorded in the protocol.

Hardness

The hardness test was conducted on 40 tablets using hardness tester (YD-2) separately for all the batches and the crushing strength determined in $Kg/cm^{2.}$ The minimum, Maximum and the average hardness of the tablet calculated and recorded in the protocol.

Thickness

For thickness test sample of 100 tablet were collected separately from each three batches and the thickness were measured using calibrated analog Vernier caliper.

Friability

20 tablets from each three batches were taken, and weighted accurately. The initial

weight W1 was recorded and then the tablets were put into the friabilator and operated at the speed of 25RPM for 04 minutes. After the defined period of time the tablets were collected from the friabilator carefully and checked physically for any type of cracking or capping. Then again weighted and noted these tablets accurately, W2.

The friability test calculated using the following equation

$$F= (W1-W2)/W1 \times 100 \quad \text{……Equation 01}$$

Disintegration Time

Six tablets were collected from each batch and transferred into the tubes of disintegration apparatus (BJ-2) using discs containing water in a beaker. The apparatus was operated until no solid mass left on the mesh of the tubes and the disintegration time was noted.

Assay of Core and Coated Tablet

Assay of core & Coated tablet was performed according to the method give in the USP 35-NF30 (USP35–NF30).

Dissolution Test of Core and Coated Tablet

Assay of core tablet was performed according to the method give in the USP 35-NF30 (USP35–NF30).

Content Uniformity Test of Core and Coated Tablet

Content uniformity test was performed for hydrochlorothiazide only as required by USP pharmacopeia that when the quantity of API in the finished pharmaceutical is in the limit of <25 mg or <25% (USP35–NF30). Assay of core tablet was performed according to the method give in the USP 35-NF30 USP35–NF30.

RESULTS AND DISCUSSIONS

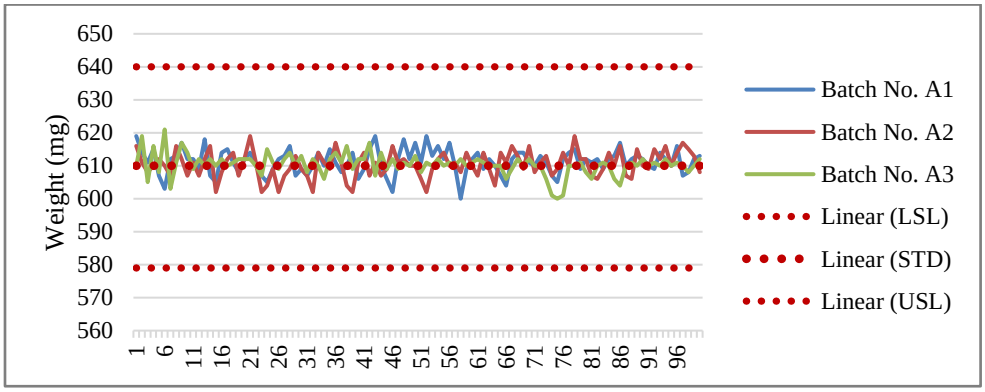
For the validation all the three batches were critically monitored at each steps and the results were recorded. At the granulation stage the loss on drying (LOD) of the granules were determined and recorded as 1.75%, 1.70% & 1.80% for all the three batches. It showed that results found within specification of 1.5–2.5%. After the final blending, the granules were checked for the uniformity of the mixing and the results are presented in the table.

Weight variation of core tablets of all three batches were evaluated and found within the limit (579.50 - 640.50mg), as shown in figure

Assay of Irbesartan & Hydrochlorothiazide (HCTZ) at granulation stage

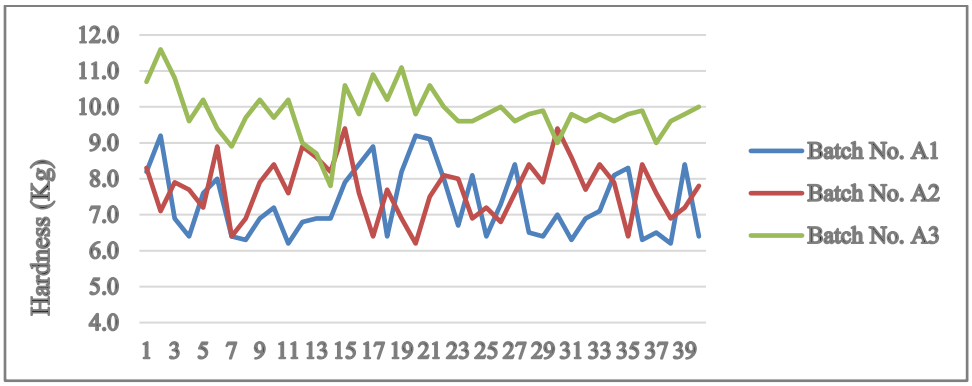
Sampling	Irbesartan			Hydrochlorothiazide		
	Batch No. A1	**Batch No. A2**	**Batch No. A3**	**Batch No. A1**	**Batch No. A2**	**Batch No. A3**
Top Left layer	97.300%	98.430%	102.022%	96.507%	97.789%	105.122%
Top Right layer	97.552%	101.951%	98.484%	96.581%	102.427%	101.652%
Middle Left layer	99.802%	103.39%	103.665%	98.963%	104.383%	106.376%
Middle Right layer	100.558%	99.785%	97.540%	98.301%	99.904%	101.130%
Bottom	97.305%	99.010%	97.204%	98.277%	98.913%	104.090%
Mean	*98.503%*	*100.483%*	*99.783%*	*97.726%*	*100.683%*	*103.674%*
COV ≤ 5.0%	*1.58%*	*2.03%*	*2.90%*	*1.14%*	*2.67%*	*2.16%*

Weight Variation of the Tablet Batch No. A1, A2 & A3



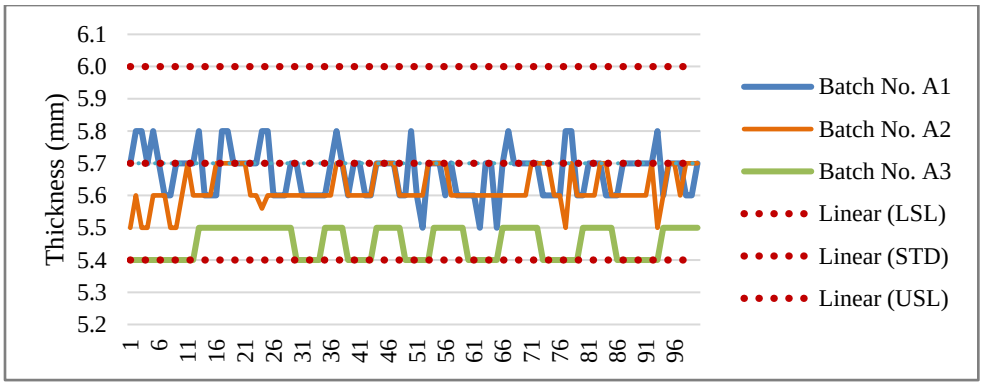
The hardness of core tablets of all three batches were measured and the results were within the limits (NLT 4.0 Kg) as shown in figure

Hardness Variation of the Tablet Batch No. A1, A2 & A3



Thickness of core tablets were measured with the help of calibrated digital Vernier caliper and results were found within the limit (5.30 ~ 5.90mm) as shown in figure

Thickness Variation of the Tablet Batch No. A1, A2 & A3



The friability test were conducted for all three batches and results are given in table

Table 3: Friability test

Sample No.	Batch No. A1	Batch No. A2	Batch No. A3
1	0.392%	0.316	0.116
2	0.344%	0.341	0.142
3	0.346%	0.353	0.090
Mean	0.361	0.336%	0.116%

Disintegration test

Disintegration test also performed at the start, middle and at the end of the each batch and the results of disintegration time met the acceptance criteria of NMT 15 minutes. The results are tabulated in table

Table 4: Disintegration test

Sample No.	Batch No. A1	Batch No. A2	Batch No. A3
1	02 Minutes	2.5 Minutes	02 Minutes
2	02 Minutes	2.5 Minutes	02 Minutes
3	02 Minutes	02 Minutes	2.5 Minutes
Mean	*02 Minutes*	*2.33 Minutes*	*2.33 Minutes*

Assay of Core Tablet

To ensure the uniform mixing at the compression stage of the API and excipients used, the core tablets were subjected to the chemical analysis and the results were within the

specified limit (90 – 110%) are recorded in table

Assay of Irbesartan & Hydrochlorothiazide (Core Tablet)

Sample No.	Irbesartan			Hydrochlorothiazide		
	Batch No. A1	Batch No. A2	Batch No. A3	Batch No. A1	Batch No. A2	Batch No. A3
1	97.764%	99.583%	98.111	99.764	99.583	100.179
2	97.885%	99.170%	98.189	99.885	99.170	100.510
3	100.497%	99.468%	98.429	100.497	99.468	100.728
4	101.148%	100.079%	99.371	101.148	100.079	97.082
5	98.038%	100.133%	98.428	98.038	100.133	9.967
Mean	99.066%	99.687%	98.506	98.60	99.16	99.63
COV ≤ 2.5%	1.64	0.41	0.51	1.69	0.51	1.49

Assay, Dissolution & Content Uniformity in Coated Tablet

Finely the coated tablet analyzed for the chemical analysis and the assay, dissolution & content uniformity for hydrochlorothiazide only was determined and the results are shown in tables

Assay of Irbesartan & Hydrochlorothiazide (Coated Tablet)

Sample No.	Irbesartan			Hydrochlorothiazide		
	Batch No. A1	Batch No. A2	Batch No. A3	Batch No. A1	Batch No. A2	Batch No. A3
1	98.701	103.976	101.551	102.225	101.453	103.818
2	98.453	103.633	101.703	101.945	100.869	103.986
Mean	98.577	103.850	101.627	102.085	101.161	103.902

Dissolution of Irbesartan & Hydrochlorothiazide (Coated Tablet)

Sample No.	Irbesartan			Hydrochlorothiazide		
	Batch No. A1	Batch No. A2	Batch No. A3	Batch No. A1	Batch No. A2	Batch No. A3
1	87.196	100.186	96.874	86.272	98.974	97.407
2	87.542	97.499	97.568	86.397	99.725	98.884
3	91.452	96.143	93.341	87.214	98.948	96.300
4	91.832	99.262	95.708	86.292	99.315	94.288
5	89.128	97.121	97.070	85.484	99.925	97.267
6	87.765	97.545	96.984	85.887	98.545	96.572
Mean	89.095	97.96	96.257	86.257	99.238	96.786

Content Uniformity Test of Hydrochlorothiazide (Coated Tablet)

Sample No.	Batch No. A1	Batch No. A2	Batch No. A3
1	97.806	99.632	99.548
2	98.357	91.677	97.426
3	99.920	91.364	101.496
4	95.782	92.573	98.673
5	98.012	101.366	101.469
6	99.417	96.315	99.552
7	99.031	99.834	104.917
8	97.588	94.663	101.824
9	98.827	96.928	102.843
10	99.031	101.572	99.982
Mean	98.38	96.59	100.77

From the above discussion it is concluded that the process for the manufacturing of tablet containing Irbesartan 300mg and Hydrochlorothiazide 12.5mg has been validated and will produce consistently quality product until there is no change in the process and the equipment used.

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