International Journal of PharmTech Research
CODEN (USA): IJPRIF, ISSN: 0974-4304
Vol.7, No.1, pp 139-147, 2014-2015

Pharmaceutical Prospective Process Validation Of Chloroquiune Tablets

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Abstract: The purpose of the research investigation was to study prospective process validation of Chloroquine tablets 150 mg. The basic principle of quality assurance is: A drug should be manufactured which is fitfor its intended use. Quality cannot be adequately assured by in-process and/ or finished product inspections and testing, but it should be built into the manufacturing process. Each step of a manufacturing process iscontrolled to assure that the finished product meets all quality attributes including specifications. Therefore, building of quality requires careful attention to a number of factors, such as the selection of raw materials, product, equipment, instruments, process design, control variables, in-process control and finished product testing. The critical process parameters were identified and evaluated by challenging the lower and upper release specifications. It has been known that facilities and processes involved in pharmaceutical production impact significantly on the quality of the products. The process controls are mandatory in good manufacturing practices. The purpose is to monitor the on-line and off-line performance of the manufacturing process, and hence, validate it. Thus, validation is an integral part of quality assurance. Three initial process validation batches of same batch size, manufacturing procedure, equipment& validation criteria were taken. The critical parameters involved in dry mixing, preparation of granulating agent, wet mixing, wet milling, drying, sizing, lubrication & compression stages were identified and evaluated as per validation protocol. The outcome indicated that this process validation data provides high degree of assurance that manufacturing process produces product meeting its predetermined specifications and quality attributes. This overview examines the need for pharmaceutical validation, the various approaches and steps involved, and other pertinent considerations.
Key words –Quality assurance, process validation, chloroquine tablets and critical process parameters.

Introduction

The main objective of all pharmaceutical plants is to manufacture products of requisite attribute and quality consistently, at the lowest possible cost. Although validation studies have been conducted in the pharmaceutical industry for a long time, the concept of validation has expanded through the years to embrace a wide range of activities from analytical methods used for the quality control of drug substances and drug products to computerized systems for clinical trials, labeling or process control. Validation is founded on, but not prescribed by regulatory requirements and is best viewed as an important and integral part of cGMP. This paper provides an overview of pharmaceuticals validation and process controls in drug development. The validation concept can be applied to new drugs, new dosage forms and generic drug development. FDA has the authority and responsibility to inspect and evaluate process validation performed by manufacturers. The CGMP regulations for validating pharmaceutical (drug) manufacturing require that drug products be produced with a high degree of assurance of meeting all the attributes they are intended to possess (21 CFR 211.100(a) and 211.110(a)).

A. Process validation and Drug Quality

Effective process validation contributes significantly to assuring drug quality. The basic principle of quality assurance is that a drug should be produced that is fit for its intended use. This principle incorporates the understanding that the following conditions exist:

1. Quality, safety and efficacy are designed or built in to product.
2. Quality cannot be adequately assured merely by in-process and finished-product inspection or testing.
3. Each step of a manufacturing process is controlled to assure that the finished product meets all quality attributes including specifications [3].

B. Approach to process validation

For purposes of this paper, process validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process validation involves a series of activities taking place over the lifecycle of the product and process. This describes process validation activities in three stages.

Stage 1–Process Design: The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.

Stage 2–Process Qualification: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

Stage 3–Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.

Before any batch from the process is commercially distributed for use by consumers, a manufacturer should have gained a high degree of assurance in the performance of the manufacturing process such that it will consistently produce APIs and drug products meeting those attributes relating to identity, strength, quality, purity, and potency. The assurance should be obtained from objective information and data from laboratory-, pilot-, and/or commercial-scale studies. Information and data should demonstrate that the commercial manufacturing process is capable of consistently producing acceptable quality products within commercial manufacturing conditions.

Successful validation program depends upon information and knowledge from product and process development. This knowledge and understanding is the basis for establishing an approach to control of the manufacturing process that result in products with the desired quality attributes. Manufacturers should:

- Understand the sources of variation
- Detect the presence and degree of variation
- Understand the impact of variation on the process and ultimately on product attributes
- Control the variation in a manner commensurate with the risk it represents to the processand product

Each manufacturer should judge whether it has gained sufficient understanding to provide a high degree of assurance in its manufacturing process to justify commercial distribution of the product. Focusing exclusively on qualification efforts without also understanding the manufacturing process and associated variations may not lead to adequate assurance of quality. After establishing and confirming the process, manufacturers must maintain the process in a state of control over the life of the process, even as materials, equipment, production environment, personnel, and manufacturing procedures change. Manufacturers should use ongoing programs to collect and analyze product and process data to evaluate the state of control of the process. These programs may identify process or product problems or opportunities for process improvements that can be evaluated and implemented through some of the activities described in Stages 1 and 2.

Process validation views and terms:

Capability of a process: Ability of a process to produce a product that will fulfill the requirements of that product. The concept of process capability can also be defined in statistical terms. (ISO 9000:2005).

Commercial manufacturing process: The manufacturing process resulting in commercial product (i.e., drug that is marketed, distributed, and sold or intended to be sold). For the purposes of this guidance, the term commercial manufacturing process does not include clinical trial or treatment IND material.

Concurrent release: Releasing for distribution a lot of finished product, manufactured following a qualification protocol, that meets the lot release criteria established in the protocol, but before the entire study protocol has been executed.

Continued process verification: Assuring that during routine production the process remains in a state of control.

Performance indicators: Measurable values used to quantify quality objectives to reflect the performance of an organization, process or system, also known as performance metricsin some regions. (ICH Q10).

Process design: Defining the commercial manufacturing process based on knowledge gained through development and scale-up activities.

Process qualification: Confirming that the manufacturing process as designed is capable of reproducible commercial manufacturing.

Process validation: The collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality products [3,4].

Quality: The degree to which a set of inherent properties of a product, system, or process fulfils requirements. (ICH Q9).

Types of Process Validation

- Prospective validation
- Concurrent validation
- Retrospective validation
- Re-validation

Process validation:

The objective of the prospective validation is to prove or demonstrate that the process will work in accordance with validation protocol prepared for the pilot production trials. Prospective validation should normally be completed prior to the distribution and sale of the medicinal product. In Prospective Validation, the validation protocol is executed before the process is put into commercial use. During the product development phase the production process should be broken down into individual steps. Each step should be evaluated on the basis of experience or theoretical considerations to determine the critical parameters that may affect the quality of the finished product. A series of experiments should be designed to determine the criticality of these factors. Each experiment should be planned and documented fully in an authorized protocol[5].

All equipment, production environment and the analytical testing methods to be used should have been fully validated. Master batch documents can be prepared only after the critical parameters of the process have been identified and machine settings, component specifications and environmental conditions have been determined. Using this defined process a series of batches should be produced. In theory, the number of process runs carried out and observations made should be sufficient to allow the normal extent of variation and trends to be established to provide sufficient data for evaluation. It is generally considered acceptable that three consecutive batches/runs within the finally agreed parameters, giving product of the desired quality would constitute a proper validation of the process [6].

Process Validation Protocol:

A written approved should be prepared that how validation will be conducted, including test parameters, product characteristics, production and packaging equipment, and decision points on what constitutes acceptable test results. This document should give details of critical steps of the manufacturing process that should be measured, the allowable range of variability and the manner in which the system will be

tested. In the case where a protocol is altered or modified after its approval, appropriate reasoning for such a change must be documented. The validation protocol should be prepared for three consecutive batches [7].

Materials and method

Materials

Chloroquine was obtained from IPCA labs, Avicel PH 102 andPVPK30 was obtained from Signet Chemical Corporation, Mumbai. Aerosil 200 was obtained from Evonik Mumbai, Magnesium stearate and Crosscarmalose sodium was obtained from S Zaveri Mumbai.

Methods

Chloroquine tablets were prepared by wet granulation method. Compositions of formulations is shown in Table 1. The tablet of chloroquine were prepared using Avicel PH 102 as filler and PVPK30 as binding agent.

Chloroquine and Avicel were sifted through 40 mesh and loaded 3L RMG. Materials were mixed for 10 minutes at 600RPM. Weighed 100 g purified water in glass beaker, PVPK 30 added in weighed quantity of purified water and stirred for 30 minutes to get clear solution. Binder solution water was added in dry mixed materials at 300RPM of impeller in 2 minutes followed by kneading for 2 more minutes at 300RPM of impeller and 2800 RPM of chopper. Granulated material passed through 8# mesh. Passed materials were dried at 60 ◦c till % LOD was NMT 1 %. Dried granules were blended with Crosscarmalose sodium and Aerosil for 10 minutes at 15 RPM. Further blended materials lubricated with magnesium stearate for 3 minutes at 15 RPM.

Table 1 Formulation composition of chloroquine.

Ingredients	PV1	PV2	PV3
Chloroquine	150	150	150
Avicel PH 102	100	100	100
PVPK30	20	20	20
Crosscarmalose sodium	20	20	20
Aerosil Pharma 200	10	10	10
Magnesium stearate	10	10	10
Total	310	310	310

Critical Process Parameters in process validation:

1. Dry Mixing
2. Drying
3. Blending
4. Lubrication
5. Compression

Dry Mixing:

The dry mixing step involves mixing of active ingredients with other additives using Rapid Mixer Granulator (RMG). The BUA of Chloroquine in the dry mixed materials was tested to validate dry mixing.

Drying:

Drying of wet granules for 1 to 2 hours at 60°Ctemperaturetill the loss on drying is NLT % w/w at105°C. (Outlet temperature would be approx.40ºCto 44°C).The level of moisture in the granules is important factor. If level of moisture is more in granules then blend will have poor flow &distribution characteristics. If level of moisture in blend is less it will produce tablet with capping, high friability and chipping problems. During drying the desired LOD will be maintained in the granules which will influence the quality parameters like tablet hardness, flow properties, physical properties during compression. Drying of granules in Tray dryer controls the level of moisture.

Lubrication:

This step involves mixing of Lubricating agent with drug granules & other blending material. The purpose of blending is to get a uniform distribution of granules and lubricating agent.

Evaluation of pre compression parameters

Bulk and Tapped density

Before final compression of tablets, powdered mixture was subjected to pre compression parameters such as bulk density, tapped density, angle of repose, powder compressibility and Hausner ratio. All the experiments were done in triplicates and expressed as mean± SD.

Bulk Density

Bulk density was determined by measuring the volume of the predetermined or preweighed mass of the powder blend according to the protocol described.

Bulk Density (Db) = (M) / (Vo) [12, 13]
Where,
M = Mass or weight of the powder blend
Vo = Apparent volume of the powder blend into the cylinder

Tapped Density

Tapped density was achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder was mechanically tapped and volume readings were taken until little further volume change was observed. The mechanical tapping was achieved by raising the cylinder and allowing it to drop under its own weight from a specified distance

Tapped density (Dt) = (M) / (Vf) [12, 13]
Where,
M = Mass or weight of the powder blend
Vf = Final volume of the powder blend into the cylinder.

Carr's Index or Compressibility Index (I)

This was calculated by the formula and expressed as percentage (%)
I = Dt -Db / Dt ×100% [12, 13]
Where
Db = Bulk density,
Dt = Tapped density.

Hausner Ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula-
Hausner Ratio = Dt/Db [12, 13]
Where,
Db = Bulk density,
Dt = Tapped density.

Angle of Repose

The determination of angle of repose of powder blend was carried out by employing fixed funnel method

Angle of Repose = $\tan^{-1}$ (H/R), [12, 13]
Where,
H = height of the pile,
R = radius of the pile.

Evaluation of post compression

These tests are as following:-

- Appearance
- Thickness
- Hardness
- Weight variation
- Friability
- Dissolution
- Drug content
- Stability studies

Appearance

The general appearance of tablet is its visual identity and all over elegance, shape, color, surface textures. These all parameters are essential for consumer acceptance. Tablets have smooth, clean surface, round concave shaped, white color tablet with pleasant taste.

Thickness:

The thickness of the tablets was determined by using vernier calipers. Randomly 10 tablets selected were used for determination of thickness that expressed in Mean± SD and unit is mm.

Weight variation:

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. The total weight of 20 tablets randomly from whole batch was determined and the average was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated.

Friability test:

Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface during transportation or handling. Roche friabilator was employed for finding the friability of the tablets. For tablets with an average weight of 0.65 g or less take a sample of whole tablets corresponding to about 6.5 g and for tablets with an average weight of more than 0.65 g take a sample of 10 whole tablets. Roche friabilator is rotated at 25rpm for 4 minutes for 100rounds. The tablets were dedusted and weighed again. The percentage weight loss was calculated using the formula.

$$\%f = \frac{W0 - W1}{W0} \times 100$$

Here, %f = Percentage friability
W0 = Initial weight (Before test)
W1 = Final weight (After test)

Drug content:

10 tablets were powdered and 100mg drug equivalent powder dissolved in suitable media 0.1N HCl. Volume of the solution made up to 100ml by that media. Solution was filtered and diluted 100times and analyzed spectrophotometrically and further calculation carried out to determine drug content in one tablet.

In vitro dissolution studies

The drug release study was performed using USP I basket apparatus at 37ºC±1ºC and100 rpm using 900 ml of is phosphate buffer (pH 1.2) Sample of 5 ml were withdrawn at predetermined time interval and filter through 0.45 micron membrane filter, diluted suitable and analyzed at 225nm.Percentage drug dissolved at different time intervals was calculated using Beers Lambert's law equation. [13].

Stability Study:

The stability of samples was monitored upto 3-month at ambient temperature and relative humidity (30°C/65% RH). Periodically, samples were removed and characterized for disintegration time, hardness, drug-content and dispersion time.

Results and Discussion

Table 2: Dry Mixing Chloroquine (Bua)

Batch No	PV1	PV2	PV3
Sr. No			
1	98.5	99.9	99.8
2	99.4	100.1	99.8
3	100.0	100.6	99.5
4	99.5	100.1	99.8
5	99.6	99.8	99.6
6	99.5	99.9	98.8
7	99.8	100.0	99.7
8	99.7	99.9	99.7
9	99.5	100.1	100.4
10	99.5	100.1	99.5
Mean	99.5	100.1	99.7
RSD	0.4	0.2	0.4
Max.	100.0	100.6	100.4
Min.	98.5	99.8	98.8

Blend uniformity results found to be satisfactory

Table 3: Bua of Lubricated Blend:

Batch No	PV1	PV2	PV3
Sr. No			
1	98.8	100.9	101.4
2	102.5	101.1	100.0
3	100.5	101.2	101.0
4	99.7	99.9	99.3
5	100.5	100.4	100.5
6	100.1	102.0	101.2
7	100.0	100.1	99.9
8	99.8	100.2	99.0
9	100.4	99.8	99.6
10	100.6	100.9	97.5
Mean	100.3	100.7	99.9
RSD	0.9	0.7	1.2
Max.	102.5	102.0	101.4
Min.	98.8	99.8	97.5

Blend uniformity results found to be satisfactory

Flow Properties of Granules:

Angle of Repose of Granules: All batches were evaluated for flow property. The results of all the batches were shown in table 3.

Table 4: Angle of repose of granules of batch F1 to F6

Batch No.	Angle of Repose(θ)	Carr's Index (%)	Hausner's Ratio(%)
PV1	27.65	11.2	1.13
PV2	27.98	10.8	1.10
PV3	27.85	10.43	1.14

From the results of flow properties of the all batches, it is concluded that all batches had good flow property.

Post compression parameters

The powder blend was compressed using 4 station compression machine. Tablets prepared by using mentioned formula have been found to be good, without any chipping, capping and sticking. Various physical parameters like thickness, hardness, weight variation, friability, hardness, dissolution were measured to evaluate tablets. All the formulations have therefore thought to show the acceptable physical parameters of tablets.

Table 5: Post Compression parameters

Batch No.	Weight variation	Thickness	Hardness	Friability
PV1	310±0.65	3.65±0.12	88±0.60	0.058±0.11
PV2	310±0.78	3.83±0.25	85±0.15	0.049±0.25
PV3	310±0.55	3.62±0.34	90±0.52	0.060±0.11

Table 6: Post Compression Evaluation

Batch No	PV1	PV2	PV3
Sr. No			
1	98.4	96.2	100.8
2	98.6	100.6	100
3	96.6	100.2	100.8
4	98.2	94.1	98
5	98.0	99.7	100.9
6	102.2	100.1	100.4
7	100.3	99.6	99.4
8	97.1	100.6	98.5
9	98.4	97.6	100.4
10	100.1	99.9	100.1
Mean	98.8	98.9	99.9
RSD	1.7	2.2	1.0
Max.	102.2	100.6	2.4
Min.	96.6	94.1	100.8
AV	4.08	5.2	100

In-vitro drug release:

Dissolution parameter: Medium: pH 7.4 Phosphate buffer
Volume: 900 ml
Apparatus: USP Type I
Speed: 50 rpm
Time Point: 1,2,4,8 and 12 hours.
Temperature: 37ºC
Identification: At 225.1 nm in UV-Visible spectrophotometer

Table 7: In-vitro drug release profile of batches F1 to F6

Time in min	Cumulative % drug release		
Batch no	F1	F2	F3
5min	101	101	100
10min	103	101	101
15min	102	101	101
30min	102	101	101
45min	102	101	101

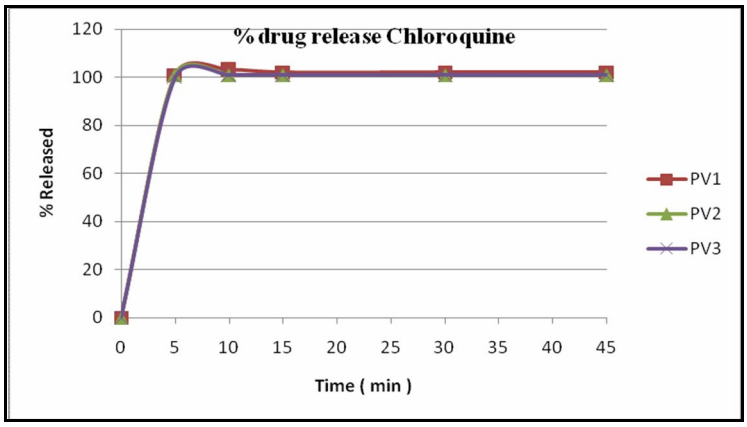

Figure 1 In-vitro drug release of Chloroquinebatches PV1 to PV3

Conclusion

Dry mixing results obtained of all three batches were found satisfactory. BUA results of lubricated blend of three process validation batches were found satisfactory. Post compression parameters like hardness, friability, thickness, content uniformity and dissolution results were found satisfactory. Based on results, it was concluded that process has given reproducible results.

Stability study:

Six months stability study at ambient temperature and relative humidity (40°C / 65% RH) of all three batches was performed, all formulation were found stable and there were no significant changes observed for hardness, drug content and disintegration time. Hence, the results of stability studies reveal that the process is validation and confirmed and has good stability.

References

1. Mahajan, H.S, Vilas S Jadhav Mouth dissolving tablets by melt granulation: A novel drug delivery system. Pharma tech.
2. Kuchekar, B. S., Atul, B.C., Mahajan, H.S.: Mouth dissolving tablets: A novel drug delivery system. Pharma times. 2014, 0974-4304
3. Guidelines on General Principles of Process Validation, Food and Drug Administration, Maryland, 1993;60-74.
4. A WHO guide to good manufacturing practice requirements, part: 2 validation 2 to 6,9.
5. Validation of solid dosage forms the FDA view, 1989;15(6-7):1119-1133
6. FDA, (CBER), Validation of Procedures for Processing of Human Tissues Intended for Transplantation, guidance for industry, May 2002.
7. FDA, (CDER),Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production, guidance for industry, October 2006.
8. D.A.: New drugs of 2003. J. Am. Pharm. Assoc. 2004,44, 168–206.
9. Porst, H., Padma-Nathan, H., Giuliano, F., Anglin, G., Varanese, L.,Rosen, R.: Efficacy of tadalafil for the treatment of erectile dysfunction at 24 and 36 hours after dosing: a randomized controlled trial. Urology.2003; 62, 121–126.
10. Padma-Nathan, H.: Efficacy and tolerability of tadalafil, a novel phosphodiesterase 5 inhibitor, in treatment of erectile dysfunction, Am. J. Cardiol. 2003;92, 19M–25M.
11. Higuchi, T., Connors, K.A.: Phase-solubility techniques Adv.Anal.Chem.Instr., 1965;4,117-122.
12. LachmmanL,LibermanHA,KonigJl.The theory & practice of industrial pharmacy,3rd Edn,Vargheese publishing house, Bombay,1991:297-300.
13. Indian Pharmacopoeia Government of India 2010.

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