



PROCESS VALIDATION OF AMOXICILLIN TRIHYDRATE AND POTASSIUM CLAVULANATE ORAL SUSPENSION

Darshna K Barot, Sweetu Patel, Divya Patel, Prasanna K Pradhan*, Umesh Upadhyay

Sigma Institute of Pharmacy, Baroda, Gujarat, India.

ABSTRACT

The aim of this work was to study prospective process validation of Amoxicillin trihydrate and Potassium clavulanate oral suspension. Three initial process validation batches of same size, method, equipment and validation criteria were taken. The critical parameters involved in sifting, mixing and filling were identified and evaluated as per validation master plan. Uniformity of mixing is optimum in 30 minutes as standard deviation is between ± 0.29 to ± 0.30 . Drying time of 240 min is suitable for obtaining moisture content within 0.4 -0.6 %. The drug content of reconstituted liquid suspension on day 1 and day 7 were within the limits of 90 % to 120 %. The outcome indicated that data obtained by process validation of three batches provides high degree of assurance that manufacturing process of Amoxicillin trihydrate and Potassium clavulanate oral suspension produces product meeting its predetermined specifications and quality attributes.

Keywords: Amoxicillin trihydrate (ACT), Potassium clavulanate (PSC), Oral Suspension, Prospective Process Validation, Uniformity of Blending.

INTRODUCTION

The concept of validation came in mid 1970's in order to improve quality of pharmaceuticals.

Validation is an essential part of GMP and required to be done as per predetermined specifications. Prospective Process validation is carried out during the product development phase in which the production process should be broken down into individual steps. These are then evaluated on the basis of past experience or theoretical considerations to determine the critical process parameters that may affect quality of finished product. The trial batches are taken, evaluated and overall assessment is made. If the results are unacceptable after evaluation then the process must be modified and improved until satisfactory results are obtained. This present work deals with the process validation ACT and PSC oral suspension [1-4].

Validation: The word Validation simply means "Assessment of validity" or action of "proving effectiveness". According to European community for medicinal products.

Types of Validation:

- Prospective Validation
- Retrospective Validation
- Concurrent Validation

Prospective Validation: The Prospective 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 and 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. 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.

In practice, it may take some considerable time to accumulate these data. Amongst these should be the use of different lots of active raw materials and major recipients, batches produced on different shifts, the use of different equipment and facilities dedicated for commercial production, operating range of the critical processes, and a thorough analysis of the Process data in case of Requalification and Revalidation. Limits, frequencies and actions to be taken in the event of the limits being exceeded should be specified.

MATERIALS AND METHODS

ACT (DSM Anti infective Ind.), PSC (China), sodium citrate I.P.(Amijal chemicals.), carboxymethyl cellulose sodium (Posy Pharmachem Pvt.Ltd.), colloidal silicone dioxide(Cabot Sanmar Ltd.), aspartum I.P.(China), Citric Acid (Anhydrous) I.P. (Vasa Pharma.), Propyl Paraben Sodium I.P (Salicylatesand chemicals Pvt.Ltd.), Methyl Paraben Sodium I.P (Nebula Healthcare.), American Ice Cream dry flavours HIS (Vital Flavours and Fragrances.), Mannitol I.P (China) were used in these formulation. All raw materials used were of I.P grade and all the chemicals used for analysis were of analytical grade.

Equipments and machineries

Weighing Balance (5,10,15 kg, JalaramElectronics,Bombay), pH meter(ANA Lab.),Double cone blender (10,25,50 kg,Kishore and co.), Tray Dryer (48 trays, Veldon Engineers), Induction cap sealing machine (Sevana), HPLC (Agilent Technologies), I.R.moisture balance (5 gm, Rajdhani scientific Instrument co, New Delhi), Karl fischer apparatus (Vigo-Matic-MD), Sieve Shaker (20# to 120#,Preeti Instruments), and Bulk density apparatus (Campbell electronics), Mechanical Shifter (40#,Unimek) were used for process validation of ACT and PSC oral suspension.

Manufacturing process (Sifting, mixing, filling and sealing)

Oral suspension was manufactured by using ingredients shown in Table 1.During manufacturing, temperature $27^{\circ}\text{C}\pm 2^{\circ}\text{C}$ and RH NMT 45 % was maintained by using dehumidifier and air conditioner. Mannitol drying was done at 65°C for four hour in tray dryer till moisture content reaches to NMT 0.6%. All the raw materials except ACT and PSC were sifted through sieve #40. All the sifted raw materials,ACTans PSC were then mixed in the double cone blender for 30 minutes and the weight was checked and recorded. After approval from Q.C. department, filling of bottles started by taking weight. Then sealing of bottles with the help of induction cap sealing machine [5].

Analysis

ACT and PSC were estimated by using HPLC at 220 nm. Quantity equivalent to 50 mg of ACT and 20 mg of PSC were accurately weighed in 100ml of volumetric flask, dissolved in water and dilute to 100ml with the same solvent.

Process validation stage, control variables and measuring justification

In sifting, sieve integrity before and after sifting was tested while for mixing uniformity, the samples are withdrawn as shown in Figure 1 and analyzed. During Mannitol drying stage the samples are withdrawn as shown in Figure 2 and the moisture content was determined at 120, 180 ,240 and 300 minutes. Representative samples were selected for evaluation of percentage of moisture content, particle size and bulk density. At the filling stage the parameters evaluated are appearance, uniformity of weight, viscosity, particle size, weight per ml, water content , assay, stability and pH .The results of all the parameters are shown in Table no. 2, 3, 4, 5 and 6 [6-9].

Fig 1. Illustrative diagram double cone blender and sampling location

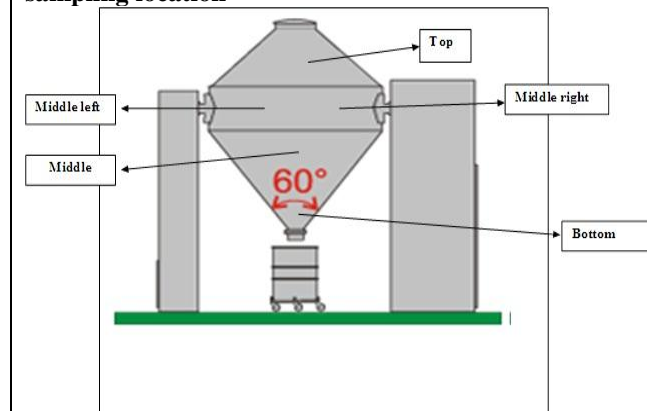


Fig 2. Illustrative diagram tray dryer and sampling location

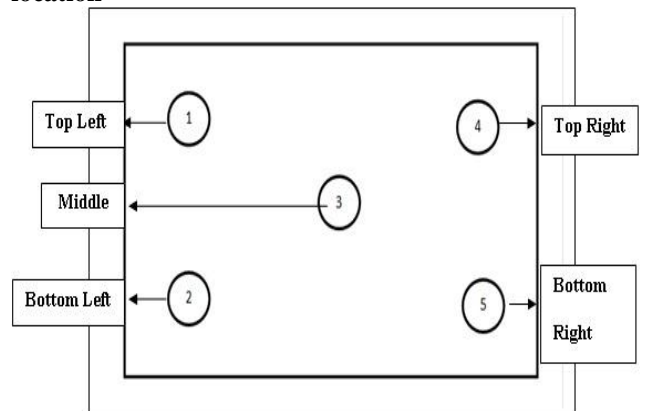


Table 1. Composition Of Various Process Validation Batches

Ingredient	Quantity Taken	Mesh
Amoxicillin Trihydrate I.P.	2.205 kg	40
Potassium Clavunate + syloid(1:1) I.P.	0.789 kg	40
Sodium Citrate I.P.	0.054 kg	40
Colloidal silicone Dioxide I.P.	0.180 kg	40
CMC Sodium I.P.	0.180 kg	40
Aspartame I.P.	0.090 kg	40
Citric Acid (Anhydrous) I.P.	0.036 kg	40
Propyl Paraben Sodium I.P.	0.008 kg	40
Methyl Paraben Sodium I.P.	0.015 kg	40
American Ice Cream Dry Flavour HIS	0.135 kg	40
Mannitol I.P.	3.773 kg	40

All three batches (ACL-044, ACL-045, ACL-046) taken for process validation were of same size.

Table 2. Results Of Sifting Stage

Batch No.	Moisture content(%w/w)	pH	Bulk density(g/ml)	Tapped density(g/ml)
ACL 044	0.43	4.99	0.53	0.75
ACL 045	0.43	5.03	0.53	0.75
ACL 046	0.43	5.02	0.54	0.75

Table 3. Results Of Sugar Drying Stage

Batch No.	Moisture content (%w/w)											
Time	120 min			180 min			240 min			300 min		
Layer	T	M	R	T	M	R	T	M	R	T	M	R
ACL 044	3.4	2.4	3.5	1.2	1.4	1.1	0.5	0.4	0.4	0.4	0.5	0.4
ACL 045	3.1	2	3.2	1.2	1.3	1	0.4	0.5	0.4	0.4	0.4	0.5
ACL 046	3.5	2.6	3.3	1.4	1.2	1.2	0.5	0.4	0.4	0.4	0.5	0.4

T= Top left, M= Middle, R= Right

Table 4. Results Of Blending Stage Of ACT

Batch No	%RSD			
Blending Time(Minutes)	10	20	30	40
ACL 044	4.77	3.23	0.29	0.44
ACL 045	4.37	2.43	0.29	0.31
ACL 046	4.52	2.81	0.29	0.34

% RSD was calculated by taking mean of assay of all 5 locations as shown in fig. 1

Table 5. Results of blending stage of PSC

Batch No	%RSD			
Blending Time(Minutes)	10	20	30	40
ACL 044	5.63	3.91	0.47	0.88
ACL 045	6.12	3.71	0.71	0.91
ACL 046	5.62	3.91	0.56	0.84

% RSD was calculated by taking mean of assay of all 5 locations as shown in fig. 1

Table 6. Results of filling stage

Batch no.	Moisture Content(%w/w)	Weight variation(g)
ACL 044	0.43	5.03
ACL 045	0.43	5.02
ACL 046	0.43	5.03

Table 7. Finished product testing results

Parameter	Standards	ACL 044	ACL 045	ACL 046
Description/Identification	White or off white colored, free flowing powder.	Complies	Complies	Complies
Uniformity of Weight (%)	5.0 gm \pm 5%	5.035 gm (+0.035)	5.02 gm (+0.029)	5.031 gm (+0.031)
pH	3.80 to 6.60	4.99	5.03	5.02
Weight per ml(gm/ml)	1.06 \pm 5	1.05	1.05	1.05
Water Content (%)	NMT 7.5	5.97	5.88	5.93
Assay (Amoxicillin) (%w/v)	Between 90 to 120	103.45	103.63	103.63
Assay (Clavulanic Acid) (%w/v)	Between 90 to 125	120.76	121.1	121.1
Yield of Batch (%)	100	98.02	97.6	97.9

RESULTS AND DISCUSSION

ACT and PSC oral suspension were evaluated for process validation parameters like sifting, drying, mixing and filling. Sifting: sifting process evaluation involves measurement of moisture content, pH, bulk density and tapped density observed. Integrity of sieve before and after sifting the material was found to be satisfactory for all 3 batches. The selected sieve of 40# was suitable for sifting the material. Sifting evaluation parameters shows acceptable pH, moisture content, bulk density and tapped density. Drying: At drying stage the % moisture content obtained at different locations and different time intervals. Drying time of 240 minutes is suitable for obtaining moisture content of 0.4- 0.6 %. Mixing (Blending): Uniformity of mixing was checked by assay of 5 locations for all 3 batches of each drug and % RSD was calculated by mean assay of all locations thus uniformity of mixing is optimum in 30 minutes . Filling: During filling stage the parameters are evaluated. Filling stage evaluation parameters shows satisfactory result. Finished product testing results are shown in Table no.7. Finished product testing shows satisfactory results.

CONCLUSION

Based on the results of all three batches at each stage it is concluded prospective process validation of ACT and PSC oral suspension produces the batches with acceptable results and no significant deviation from reported documented evidence. Thus it provides high degree of assurance that manufacturing process of Amoxicillin Trihydrate and Potassium Clavunate oral suspension produces product meeting its predetermined specifications and quality attributes.

ACKNOWLEDGEMENT

The authors are grateful to Kaptab Pharmaceuticals for providing necessary facilities to carry out this work.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. ICH Q7. Good manufacturing practice guide for active pharmaceutical ingredients, 2000, 25-26.
2. Guidelines for process Validation of Pharmaceutical Dosage Forms, Saudi Food & Drug Authority Kingdom of Saudi Arabia, 2010, 9-15.
3. <http://home.interkom.com>
4. <http://www.drugs.com>
5. Rohokale BS, Jadhav VM and Kadam VJ. Studies in Prospective process validation of Metformin HCl tablet dosage formulation. *International Journal of PharmTech Research*, 2(3), 2010, 1673-1678.
6. Kathiresan K, Moorthi C, Prathyusha Y, Reddy BG, Reddy MB and Manavalan R. An overview of pharmaceutical validation. *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, 1(4), 2010, 1026-1035.
7. <http://www.pharmainfo.net/reviews/validation-essential-quality-assurance-tool-pharma-industries>.
8. Mohammed IZ and Medgyesi I. Increased Importance Of The Documented Development Stage In Process Validation. *Saudi Pharmaceutical Journal*, 20(3), 2012, 283-285.
9. David F. Development a Sound Process Validation. *BioPharma International.com*, 20, 2007, 1-12.