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Studies in Prospective Process Validation of Cefpodoxime proxetil Oral Suspension I.P.

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Abstract: The aim of this work was to study prospective process validation of cefpodoxime proxetil 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 60 minutes as standard deviation is between ±0.31 to ±0.37. Drying time of 60 min is suitable for obtaining moisture content within 0.3-.06 %. The drug content of reconstituted liquid suspension on day 1 and day 7 were within the limits of 90 % to 110 %. The outcome indicated that data obtained by process validation of three batches provides high degree of assurance that manufacturing process of cefpodoxime proxetil oral suspension produces product meeting its predetermined specifications and quality attributes.

Key words: Cefpodoxime Proxetil, Oral Suspension, Prospective Process Validation, Uniformity of Mixing.

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[1]. Prospective process validation is carried out during the product development phase in which the production process should be broken down into individual steps[2]. 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[3]. 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[4]. This present work deals with the process validation of cefpodoxime proxetil (CP) oral suspension.

Materials and methods:

Cefpodoxime Proxetil (Aurobindo Pharma Ltd. ,Ahmadabad, India); sodium benzoate ,xanthan gum (Ker Take Health Care Pvt. Ltd.,Baroda, India); sodium citrate, citric acid, carboxymethylcellulose sodium, colloidal silicone dioxide, aspartame, sodium lauryl sulphate (Vishal Pharma,Ahmedabad, India); dry mix babul gum (Pratmi Life science, Baroda, India) and sugar pharma grade (Navkar Sugar's,Mumbai,India) was used in this formulation.

All raw materials used were of I.P grade and all the chemicals used for analysis were of analytical grade.

Equipments and machineries:

Double cone blender (50 kg, Kishore and co.), Tray Dryer (48 Trays, Veldon Engineers), Induction cap sealing machine (Campbell electronics), HPLC (Agilent Technologies), I.R.moisture balance (Rajdhani scientific), Karl fischer apparatus (Systronics), Sieve Shaker (Lequitron), pH meter (Analab instruments), Brookfield Viscometer (Brookfield viscometer lab.) and Bulk density apparatus (Campbell electronics) were used for process validation of CP oral suspension.

Manufacturing process (Sifting, mixing, filling and sealing):

Oral suspension was manufactured by using ingredients shown in **Table 1.** During manufacturing, temperature 27ºC±2ºC and RH NMT 45 % was maintained by using dehumidifier and air conditioner. Sugar drying was done at 65ºC for one hour in tray dryer till moisture content reaches to NMT 0.4%. All the raw materials except CP were sifted through sieve #40. All the sifted raw materials and CP were then mixed in the double cone blender for 2 hours and the weight was checked and recorded. After approval from Q.C. department, filling of bottles started followed by sealing with the help of induction cap sealing machine.

Analysis: [7]

CP was estimated by using HPLC at 235 nm. Quantity equivalent to 50 mg of CP was accurately weighed and dispersed in 10 ml water. Acetonitrile, 20 ml, was added to this, sonicated for 15 min and volume was made to 100 ml with solvent mixture containing 60 volume of water and 40 volume of acetonitrile and then filtered. Reference solution was prepared by dissolving CP in solvent mixture to obtain solution of 30 µg/ml. Mobile phase consist of 60 volume of 0.02M ammonium acetate and 40 volume of acetonitrile and the flow rate was set at 2 ml/min.

Process validation stage, control variables and measuring justification: [5-10]

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 sugar drying stage the samples are withdrawn as shown in figure 2 and the moisture content was determined at 20, 40 and 60 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 2, 3, 4 and 5.

Table No. 1: Composition of Various Process Validation Batches

Ingredient	Quantity Taken	Mesh
Cefpodoxime proxetil	1.326Kg	40
Sodium citrate	0.060Kg	40
Sodium benzoate	0.180kg	40
Colloidal silicone dioxide	0.240Kg	40
Carboxy methyl Sodium	0.180Kg	40
Citric acid (anhydrous)	0.210Kg	40
Sodium	0.045Kg	40
Aspartum	0.180Kg	40
Dry mix babulgum	0.225Kg	40
Xanthan gum	0.180Kg	40
Sugar pharma grade	51.204Kg	40

All three batches (MAR-7112, MAR-7113, MAR-7114) taken for process validation were of same size.

Table No. 2 Results of sifting stage

Batch No.	Moisture content (%w/w)	Particle size (µm)	Bulk density(g/ml)	Tapped density(g/ml)
MAR-7112	0.35	220	0.8403	0.9167
MAR-7113	0.2	225	0.8334	0.9092
MAR-7114	0.2	218	0.8350	0.9109

Table No 3 Results of sugar drying stage

Batch No.	Moisture content (%w/w)								
Time	20 min			40 min			60 min		
Layer	T	M	B	T	M	B	T	M	B
MAR-7112	3.4	2.45	3.5	1.2	0.98	0.99	0.6	0.4	0.4
MAR-7113	2.1	2	3.2	1.2	0.9	1	0.45	0.41	0.4
MAR-7114	2	2.5	2.9	0.98	0.98	1.1	0.4	0.3	0.41

T= Top left, M= Middle, B= Bottom right

Table No. 4: Results of Blending Stage:

Batch No.	% Drug content (±S.D)		
Blending time	30 minutes	60 minutes	90 minutes
MAR-7112	97.80(±1.01)	99.51(±0.34)	99.09(±0.91)
MAR-7113	100.42(±1.55)	98.22(±0.31)	96.76(±0.90)
MAR-7114	100.22(±1.45)	101.26(±0.37)	97.98(±0.90)
Standard Deviation(S.D) was calculated by taking mean of assay of all 10 locations as shown in fig. 1			

FIG NO 1: ILLUSTRATIVE DIAGRAM OF DOUBLE CONE BLENDER AND SAMPLING LOCATIONS.

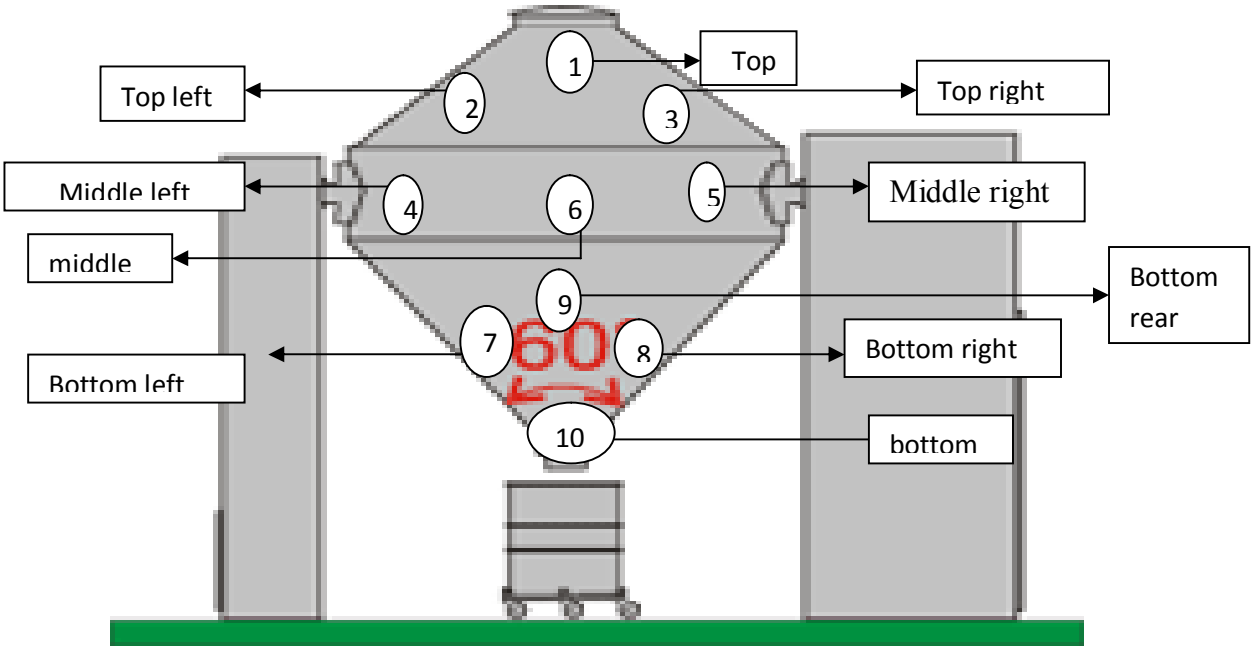


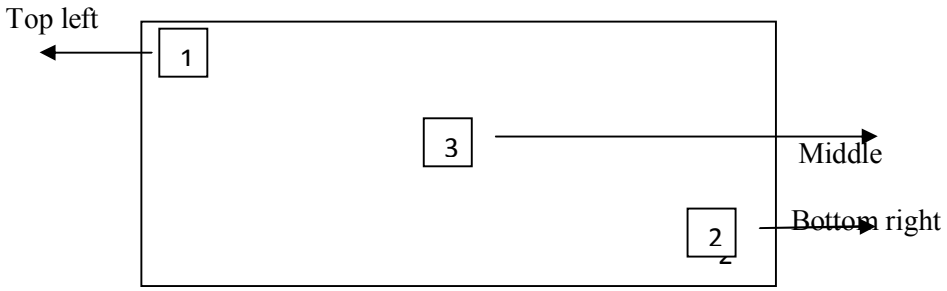
Table No. 5 Results of filling stage

Batch no.	Moisture Content (%w/w)	Weight variation(g)± S.D.
MAR-7112	0.6	18.014±0.032
MAR-7113	0.45	18.016±0.041
MAR-7114	0.61	18.01±0.054

Table No. 6: Finished product testing results

Parameter	Standards	MAR-7112	MAR-7113	MAR-7114
Identification	White to off white colored, free flowing powder.	complies	Complies	Complies
Uniformity of weight (%)	18g±10%	±0.047	±0.043	±0.065
pH	4.0-5.5	4.43	4.40	4.42
Viscosity (cp)	Should be pourable	10000	10000	10000
Particle size (µm)	220±5%	220	220	220
Weight per ml	1.9 ± 5%	1.947	1.950	1.947
Water content (%)	NMT 1.5	1.35	1.32	1.29
Assay (%w/v)	90-110	101.51	101.73	101.40
Stability (% w/v)	90-110	98.97	98.77	98.03
Yield of batch (%)	100	98.03	97.60	97.90

FIG NO 2: ILLUSTRATIVE DIAGRAM OF TRAY DRYER AND SAMPLING LOCATIONS.



Results and discussion:

CP oral suspension was evaluated for process validation parameters like sifting, drying, mixing and filling.

Sifting: sifting process evaluation involves measurement of moisture content, particle size, bulk density and tapped density as observed from table no 2. 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 particle size, moisture content, bulk density and tapped density.

Drying: At drying stage the % moisture content obtained at different locations and different time intervals as shown in table no 3. Drying time of 60 min is suitable for obtaining moisture content of 0.3- 0.6 %.

Mixing: Uniformity of mixing was checked by assay of 10 locations for all 3 batches and SD was calculated by mean assay of all locations thus uniformity of mixing is optimum in 60 minutes because standard deviation was between ± 0.31 to ± 0.37

Filling: During filling stage the parameters evaluated are shown in table no 5. Filling stage evaluation parameters shows satisfactory result. Finished product testing results are shown in table no.6. 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 CP 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 cefpodoxime proxetil oral suspension produces product meeting its predetermined specifications and quality attributes.

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