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VALIDATION OF FLUIDIZED BED DRYER

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ABSTRACT

The present study is undertaken to validate pharmaceutical equipment, fluidized bed dryer (FBD), for ensuring quality products as well as processes. After study of design qualification (DQ), installation qualification (IQ), Operational qualification (OQ) and performance qualification (PQ), it is found that machine is working satisfactorily and its design and drawing reveal that the machine is according to the order of the company. The drug chosen for this study is cephalexin and it is observed that steam heating is more efficient than heat banks. It is found that as the drying time increases, the percentage of fines in the granules get increased. So shorter drying time will produce desired granules with fewer fines.

KEY WORDS: fluidized bed dryer, cephalexin.

INTRODUCTION

Validation, as it is known today, has developed from the need to maintain quality, consistency, and above all, public safety. The foundation of validation, the methodology behind validation, and the need for validation will likely remain a key aspect of the industry we work in (1). Validation is an essential part of good manufacturing practices (GMP). It is, therefore, an element of the quality assurance programme associated with a particular product or process. It is by design and validation that a manufacturer can establish confidence that the manufactured products will consistently meet their product specifications (2).The key idea of validation is to provide a high level of documented evidence that the equipment and the process conform to a written standard. The level (or depth) is dictated by the complexity of the system or equipment. The validation package must provide the necessary information and test procedures required to provide that the system and process meet specified

requirements (3).Pharmaceutical Equipment Evaluation provides hands-on techniques of qualifying pharmaceutical equipment to achieve FDA compliance. As such, it is a vital resource and one you need on your bookshelf and at your fingertips every working day (4) Fluid bed drying is most widely used technique for drying pharmaceutical powders and granules. The direct contact between particles and air/gas is possible in fluid bed system. They can be designed in either batch or continuous type fluid bed dryer. Here any type of inert gas or air is used (5). Cephalexin is a semi synthetic cephalosporin β lactum antibiotic intended for oral administration used to treat urinary tract infections, respiratory tract infections, skin and soft tissue infections (6). Cephalexin is a semisynthetic antibiotic derived from cephalosporin C and is almost completely absorbed from the gastrointestinal tract, with a bioavailability of 95%. Cephalexin has a half-life of around 1.1 h. (7, 8, 9). To maintain therapeutic range, the drug should be administered 3–4 times a day, which leads to sawtooth kinetics and resulting in ineffective therapy (10).Technical systems in a pharmaceutical production have to be validated. A system is critical or not may be known through a risk analysis. The impact on product quality makes a system to be validated. FBD is important equipment used for drying of granules in pharmaceutical industry. By using the granules of cephalexin, in present study, performance of FBD installed is evaluated and validated. DQ is not a legal necessity but it is introduced to the qualification process through implementation of Annex 15 to the EC guide on good manufacturing practices for medical products. It seems that regulatory bodies have interest to implement DQ of engineering and quality management. Now quality consciousness is the way of pharmaceutical production. In this regard present study is taken for validation of FBD using cephalexin granules.

MATERIALS AND METHODS

Materials

The following materials and reagents were mainly used for formulating of granules and testing for validation work. Cephalexin (Sun Pharmaceuticals, Madras), magnesium stearate (S.B. Impex, Bangalore), area (Nap Chemi), microcrystalline cellulose GR. PH 102 (Reliance cellulose, Hyderabad), lactose (Lactose India, Boroda), crosspovidone, Kollidon CL (BASF Germany), sodium starch glycolate, talc (Sheetal chemicals, Bombay), and Karl Fischer reagent (Qualigen Fine Chemicals, Bombay) were procured from commercial sources and used as received.

Methods

DQ

S. No	Specification	Demanded	Obtained
1	Unit rating of the equipment	Batch	Batch
2	Output capacity of the equipment	100-120 kg	100-120 kg
3	Material used for product container	S.S-316	S.S-316
4	Material used for blower:	S.S. Steel	S.S. Steel
5	Total volume of the product container	567 Ltrs	567 Ltrs
6	Rubber gasket material used	20X40 "D" type of silicon	20X40 "D" type of silicon
7	Capacity/No of heaters	30" long, 2k.w, and S.S. made	30" long, 2k.w, and S.S. made
8	Blower motor horse power/revolution	1.5 hp/3000r.p.m	1.5 hp/3000r.p.m
9	Finger bag chamber Diameter Height Total volume	S.S. 316 1310mm 820mm 806mm^3	S.S. 316 1310mm 820mm 806mm^3
10	Retarding chamber Diameter Height Total volume	 1310 mm 515 mm 402 mm^3	 1310 mm 515 mm 402 mm^3
11	Observation window (finger bag & retarding chamber) I.D O.D Glass thickness	 200 mm 290 mm 222 X 10 mm (toughened)	 200 mm 290 mm 222 X 10 mm (toughened)
12	Wire rope (length and thickness)	1 ½ mts & 5/16	1 ½ mts & 5/16
13	Blower	Aluminium	Aluminium
14	Blower diameter	560	560
15	No of Blades	8	8
16	Blower CFM	5500m^3/hr	5500m^3/hr
17	Heating media	Steam cum electric	Steam cum electric
18	No of steam coil	1 no's, S.S. 304	1 no's, S.S. 304
19	Electric load	60 K.W	60 K.W
20	Steam Pressure	3.5-5 kg/cm^2	3.5-5 kg/cm^2
21	Model	GMP model BF-100	GMP model BF-100

IQ

In installation qualification, the three have to be validated,

They are 1. Mechanical 2. Electrical and 3.General

1. Mechanical

S. No	Name of the parameter	Acceptance criteria
1	Moving parts and pinch points adequately guarded.	Yes
2	Machine suitably embedded (grounded).	Yes
3	All service lines properly connected	Yes
4	Change parts correctly fittings	Yes

2. Electrical

S. No	Name of the parameter	Acceptance criteria
1	All electrical wiring connected within machine body	Yes
2	Electrical earthing proper	Yes
3	Safety cut outs/interlocks working	Yes
4	Limit switches connected	Yes

3. General

S. No	Name of the parameter	Acceptance criteria
1	Adequate working space around the machine	Yes
2	Lightning arrangements adequate	Yes
3	Ventilation adequate	No
4	Preventive maintenance procedure and schedule prepared	Yes

OQ

S. No	Name of the parameter	Observation
1	Machine when puts on starts working. a. Noted the sequence to put on the machine	Yes
2	Machine when puts off stops working b. Noted the sequence to put off the machine	Yes
3	Emergency stop switch puts off maintenance even during mid sequence	Yes

Machine "ON"

S. No	Name of the parameter	Observation
1	All signal lamps/indicators lit	Yes
2	Directions of run correct	Yes
3	Sequence of operation proper	Yes

4	Conveyer/vee belts movement smooth	Yes
5	R.P.M. of motor, gearbox and other parts proper	Yes
6	All measuring instruments are working and calibrated. Thermometer Pressure gauge Electrical motors Temperature recorders	 Yes Yes Yes Yes
7	Noise level of running machine as per specifications	Yes
8	Vibration of machine within tolerance	Yes

Machine "Off"

S. No	Name of the parameter	Observation
1	All signal lamp/indicators off	Yes
2	No jamming of product when machine is put off in mid sequence	Yes
3	Inching switch in working order	Yes

PQ

Active Ingredient: Cephalexin.

Performance qualification is done using empty load and with load to check the performance of the machine. It is done as follows.

1. Timer calibration – to ensure timer performs as per specifications
2. Shaker validation – to ensure shaker is functioning as per set specifications.
3. Empty load validation to check the performance of heat bank 1,2,3 & 1,2 & 3 at different temperatures.
4. Empty load validation to check the performance of steam at different temperatures.
5. Empty load validation to check the performance of heat bank 1,2,3 & 1,2 & 3 at varying time interval.
6. Empty load validation to check the performance of steam at varying time interval.
7. Load validation to check the reduction in moisture content of the product at different temperatures (45°C, 50°C, & 60°C) using both steam and heat banks.
8. The analysis is done by Karl Fisher method

$$\text{K.F. Formula} = \frac{\text{Titre value} \times \text{K.F. Factor}}{\text{weight of substance taken} \times 10}$$

9. Load validation to check the particle size during drying using both steam and heat banks at different temperature (45°C, 50°C, & 60°C).

RESULTS AND DISCUSSION

It is found that description given for DQ is suitable and not varying. IQ is validated for mechanical, electrical and general. Its results show that mechanical, electrical and general arrangements and parameters are to the mark required. OQ is found suitable and fulfilling all requirements in on and off condition. In PQ study first timer calibration is studied. During timer calibration of FBD, the digital timer of FBD is compared with that of actual timer i.e stop clock. At 5 minutes intervals, readings are taken and duration of observation is allowed for 30 minutes. It is found that digital timer of FBD is in accordance with stop clock and hence timer need not be calibrated. During shaker validation of FBD, the digital timer of FBD is set for a duration of 30 minutes. The shaking time and drying time are adjusted in seconds. The drying time is set at an interval of 300 seconds (5minutes) and shaking time is set at 10 seconds. As soon as FBD is on, the drying time and shaking time are monitored FBD showed satisfactory results for drying time and shaking time, hence shaker is validated. The performance of heat banks (1, 2, 3 & 1,2 & 3) in empty load condition at 40°c, 50°c,60°c,70°c and 80°c at time intervals of 5 minutes, 10 minutes and 15 minutes is validated. During the period of validation, as soon as desired temperature is reached, cut off is noted. It is found well controlled. During the period of validation, the shaker programmer (drying and shaking) is functioning satisfactorily. The rise in temperature in all heat banks is uniform and heaters are validated. Empty load validation of steam performance at 40°C, 50°C, 60°C 70°C and 80°C at time intervals of 5 minutes, 10 minutes and 15 minutes, using 3.6- 4 kg/cm^2 steam pressure are studied and found suitable. Correlation between steam and heat banks are studied at 40°C, 50°C, 60°C 70°C and 80°C using steam of 4kg/ cm^2 and found that steam heating is more efficient to reach the same temperature. The empty load validation of heat banks (1,2,3 and 1,2&3) at varying time intervals of 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes and 30 minutes are performed using minimum temperature 40°C and maximum temperature 80°C to know the time taken for rise in temperature at 40°C and 80°C. It has been observed that in heat bank 1, 2,3 and 1,2,&3, the rise in temperature at each temperature is similar and performance of heat bank is satisfactory. In the same way empty load validation for steam heat performance by using steam of 3.6-4 kg/cm^2 is performed and found satisfactory correlation of this study between heat banks and steam (4kg/cm^2) show that steam is more efficient. Load validation for reduction in moisture content of product at 45°C, 50°C and 60°C are performed. Initial moisture content is 39.9% at top, 40.7 % at middle and 40.28% at the bottom. At 45°C after

15 minutes, 60 minutes, 75 minutes and 90 minutes, moisture content is found 31.02% at top, 33.01% at middle and 34.28% at bottom, 23.06% at top, 25.06% at middle and 25.55% at bottom, 12.88% at top, 15.45% at middle and 8.45% at bottom, 5.26% at top, 6.48% at middle and 6.63 at bottom and 1.7% at top, 1.9% at middle and 2.4% at bottom respectively. These are the average values collected from samples from facing towards earthings, towards temperature control panel, site opposite to earthings, site opposite to temperature control panel and from centre of the product bowel. The same way study is conducted for 50°C and 60°C. Moisture content is determined by Karl Fischer methods. For cephalexin bolus, the moisture content should be less than 2.5%. Thus it is concluded that 60°C is optimum temperature for 60 minutes for load of 65kgs using, heat banks. Load validation for reduction in moisture content of the product at 45°C, 50°C and 60°C using steam is performed in the same way as described for heat banks and found that 45 minutes at 60°C is optimum for a load of 65 kg. Thus steam heating is more efficient that heat banks. Load validation for particle size during drying process using, heat banks at 45°C, 50°C and 60°C is performed. Sieves of mesh size 10, 20, 30, 40, 50, 60, 70, 80, 90 and 100 are used. % of fines are calculated. Sampling is done as it is done for moisture content study. It is found that as the drying time increases, the percentage of fines in the granules gets increased. In the same way load validation for particle size during drying process using steam at 45°C, 50°C and 60°C are studies. It is considered that particles passing through mesh number 60 are fines. In this case also as the drying time increases, the percentage of fines in granules gets increased. So shorter drying time will produce desired granules which will be having less fines.

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