Journal of
Chemical Engineering & Process Technology

Bhattacharya et al, J Chem Eng Process Technol 2014, 5:6
DOI: 10.4172/2157-7048.1000211

Research Article Open Access

Process Validation of Ceftriaxone and Sulbactam Dry Powder Injection

Shiv Sankar Bhattacharya[1]*, Naveen Bharti[1] and Subham Banerjee[2]

[1]School of Pharmaceutical Sciences, IFTM University, Moradabad, Uttar Pradesh, India
[2]Division of Pharmaceutical Technology, Defence Research Laboratory, Tezpur, Assam, India

Abstract

In the present work Process validation of Ceftriaxone and Sulbactam as a dry powder injection was carried out. As the manufacturing process of dry powder injection is mainly dependent on blending process. In the present investigation, blending process was validated at different speeds of blender and the % assay was estimated by HPLC method. The octagonal blender was operated at 13, 17 and 20 rpm samples were taken from 10 different locations inside the blender. At 13 rpm there is much variation in assay results, at 17 rpm there is very less variation and also at 20 rpm there is slight variation occurs with reference to the acceptable ranges of assay {i.e. 90-110 %}. The obtained results clearly indicated that the optimum rpm is often necessary for the proper mixing of the drug. Therefore, 17 rpm was considered for the proper mixing at blending stage and it can be successfully employed to manufacture of dry powder injections for further manufacturing. The content uniformity of the net filled content was found to be in ± 5 % of average net content. Hence, it was concluded that process stands validated for the preparation of dry powder injection.

Keywords: Process validation; Ceftriaxone; Sulbactam; Dry powder injection; Good Manufacturing Practices (GMP); Blending

Introduction

Validation is a concept that has been evolving continuously since its formal appearance in the United States in 1978 [1]. According to the FDA's current Good Manufacturing Practices (cGMP) control procedure shall be established to monitor output and to validate performance of the manufacturing processes that may be responsible for causing variability in the characteristics of In-process materials and the drug product [2-4]. Validation is documented evidence that provides a high degree of assurance that a specific process will consistently produce a product that meets its predetermined specifications and quality attribute. Validation study *in evitably* leads to process optimization, better productivity and lower manufacturing cost. The investment made in validation, similar to the investment made in qualified people can only provide an excellent return [5]. The concept of validation has expanded through the years to encompass a wide range of activities from analytical methods used for the quality control of drug substances and drug products, to equipment's, facilities and process for the manufacture of drug substances and drug products to computerized systems for clinical trials, labeling or process control. Validation studies are essential part of Good Manufacturing Practices (GMP) and should be conducted in according with predefined protocols. A written report summarizing results and conclusions should be recorded, prepared and stored. Validation has become one of the pharmaceutical industry's most recognized and discussed subjects. It is a critical success factor in product approval and ongoing commercialization. The objective of the present work is a) to provide documented evidence for the operation sequencing and scheduling of manufacturing processes and to determine the critical parameters of the manufacturing process of dry powder injection. b) to provide assurance that manufacturing process is suitable for intended purpose and consistently meets its predetermined specifications and quality attributes, as per Master Formula Record (MFR) and c) to systematically conduct the validation studies pertaining to the manufacturing activities of Ceftriaxone and Sulbactam dry powder injection and to conclude on a high degree of assurance that manufacturing process, consistently meets the predetermined specifications and quality attributes. Hence the quality product output can be increased, leading to increase in quality, productivity and decrease the need of reprocessing [3,6].

Experimental

List of raw materials

Ceftriaxone Sodium (IP) was from Nectar Lifesciences Ltd, Chandigarh, India and Sulbactam Sodium (USP) was procured from Aurobindo Pharma Ltd, Hyderabad, Telangana, India.

List of packaging materials

Glass Vial 5 ml (Type III) was collected from Neutral Glass & Allied Industries, Surat, Gujrat, India. Grey Bromo Butyl Rubber Bung (20 mm) was purchased from Bharat Rubber Works Pvt. Ltd. Mumbai, Maharashtra, India and Flip Off seal (20 mm, white) was from HBR Packaging Mumbai, Maharashtra, India.

List of equipment's used

All equipment's are perfectly qualified as per Design Qualification, (DQ), Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ) acceptance criteria (Table 1).

Batch operation

The batch operation validation approach means a plan to conduct process validation on different products manufactured with the same processes using the same equipment. The validation process using these approaches must include batches of different strengths or products which should be selected to represent the worst case conditions or scenarios to demonstrate that the process is consistent for all strengths or products involved. In process validation three consecutive batches

***Corresponding author:** Shiv Sankar Bhattacharya, School of Pharmaceutical Sciences, IFTM University, Delhi Road, Moradabad-244 001, Uttar Pradesh, India, Tel: 0341-2313120; E-mail: shivsankar.bhattacharya@gmail.com

Received October 10, 2014; **Accepted** October 28, 2014; **Published** October 31, 2014

Citation: Bhattacharya SS, Bharti N, Banerjee S (2014) Process Validation of Ceftriaxone and Sulbactam Dry Powder Injection. J Chem Eng Process Technol 5: 211. doi: 10.4172/2157-7048.1000211

Name of the Equipment's	DQ	IQ	OQ	PQ
Bung Processor & Autoclave	Complies	Complies	Complies	Complies
Vial Washing Machine	Complies	Complies	Complies	Complies
Sterilization & Depyrogenation Tunnel	Complies	Complies	Complies	Complies
Vial Filling & Bunging Machine	Complies	Complies	Complies	Complies
Blender	Complies	Complies	Complies	Complies
LAF (Filling)	Complies	Complies	Complies	Complies
LAF (Cooling zone)	Complies	Complies	Complies	Complies
LAF (Blending area)	Complies	Complies	Complies	Complies
LAF (Mount stand)	Complies	Complies	Complies	Complies

Table 1: Equipment qualification details.

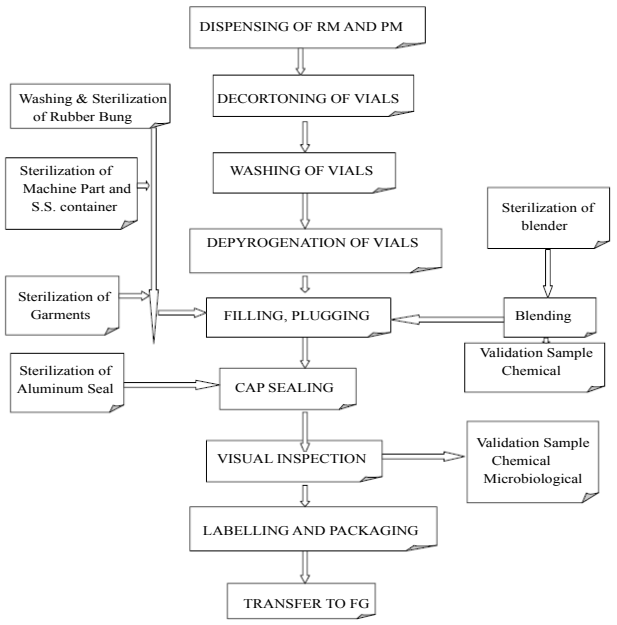

Figure 1: Flow diagram for manufacturing of DPI.

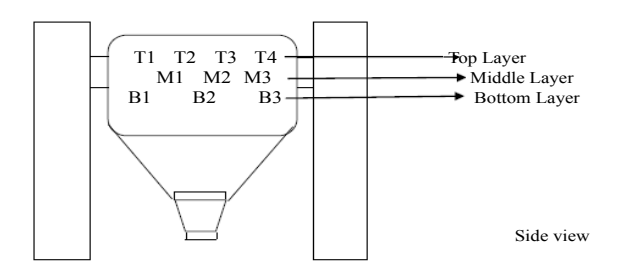

Figure 2: Diagram of octagonal blender with sampling locations. Where **T1** = Top Left, **T2** = Top Front, **T3** = Top Right, **T4** = Top Rear, **B1** = Bottom Left, **M1** = Middle Left, **B2** = Bottom Center, **M2** = Middle Center, **B3** = Bottom Right, **M3** = Middle Right.

are used for manufacturing operation these batches are of the size which will be produced during the routine marketing of the product. The given process flow diagram is for manufacturing DPI, to be performed in various stages (Figure 1) and points indicated different sampling locations (Figure 2). Sampling analysis report was reported in terms of assay, uniformity of weight, pH, particulate matter, uniformity of content by weight at various intervals at different operations as per the sampling plan at blending stage. The following rotational variations were investigated at 13, 17 and 20 rpm for a fixed blending time of 60 min according to the master production control record.

Results and Discussion

The process validation was started at the qualification of instrument all the instrument was qualified at the time of process validation. Environmental condition monitoring of manufacturing area is critical process parameter for process validation. In environmental monitoring critical parameter like, temperature, relative humidity, and differential pressure, viable or non-viable particles are generally monitored. The maximum and minimum temperature was found to be 26°C and 24°C respectively in different processing area. The maximum and minimum % relative humidity was found 45% and 30%, respectively in different processing area. The differential pressure was found to be not more than (NMT) 10 Pascal. The viable particles were not found during observation. The maximum non-viable particles of ≥ 0.5 µ were found NMT 3520 per m^3 in sterile filling area. Similarly, the maximum non-viable particles of ≥ 5.0 µ were found to be NMT 29 per m^3 in sterile filling area. The visible and non-visible particulate matter was checked during vial washing, sterilization and filling stages, the particulate matter was found to be as per acceptance criteria. During vial filling and stoppering the weight variation and content uniformity of dosage unit was also calculated/checked. The result was found under acceptance criteria (Table 2). Sealing integrity test was performed after vial sealing with the help of sealing integrity test apparatus no defects was observed in this test. Analytical test and sterility test of finished product was performed by quality control and microbiology department both test were complies. In the process validation of dry powder for injection, the main focus was done on Blending stage. The dry powder for both the drugs i.e. Ceftriaxone and Sulbactam was blended in the octagonal blender at various revolutions per minute (13 or 17 or 20 rpm) for 60 minutes according to the master production control record (Figures 3-5). The comparison of % assay of Ceftriaxone and sulbactam at different rpm were represented in Figures 6 and 7 respectively. The above results and graph showed that more consistent % assay values were found at 17 rpm. The results obtained at 13 rpm were not complying with the acceptance limits of 90.0-110.0% because the values were found to be less than 90.0%. It may be due to the incomplete or improper blending occurrence at the 13 rpm. The results at 20 rpm were also inconsistent in their % assay values and the values were found to be greater than 100.0% either due to segregation or improper mixing. The results at

Parameters	Area	Acceptance criteria	Observation comply / not comply
Temperature (°C)	Vial filling area Cooling zone Vial washing room Vial sealing room	NMT 24°C NMT 24°C NMT 26°C NMT 26°C	comply
Relative Humidity (%)	Vial filling area Cooling zone	NMT 30% NMT 45%	comply
Differential Pressure (mm)	Vial filling vs Vial washing Vial filling vs Cooling zone Vial filling vs Air lock	NLT 10 pascal NLT 10 pascal NLT 10 pascal	comply
Sterile Filling Area Particle Count	Viable particle count Non-viable particle coun	1 CFU/m^3 ≥ 0.5 µ=NMT 3520/m^3 ≥ 5 µ= NMT 29/m^3	comply
Area Adjacent to Sterile Area Particle Count	Viable particle count Non-viable particle count	2 CFU/m^3 ≥ 0.5 µ=NMT 352000/m^3 ≥ 5 µ= NMT 2900/m^3	comply

Table 2: Environmental Condition of Manufacturing Area.

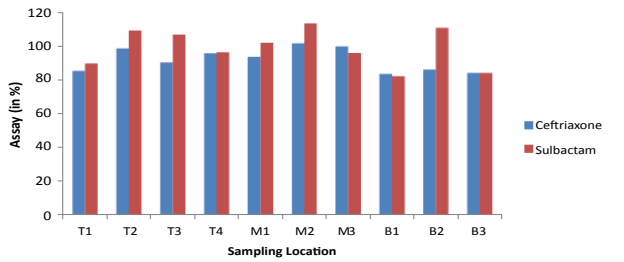

Figure 3: Comparative assay (in %) of Ceftriaxone and Sulbactam at 13 RPM.

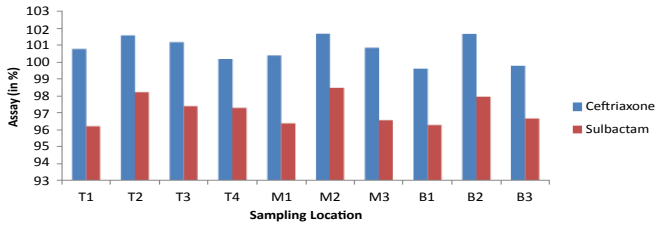

Figure 4: Comparative assay (in %) of Ceftriaxone and Sulbactam at 17 RPM.

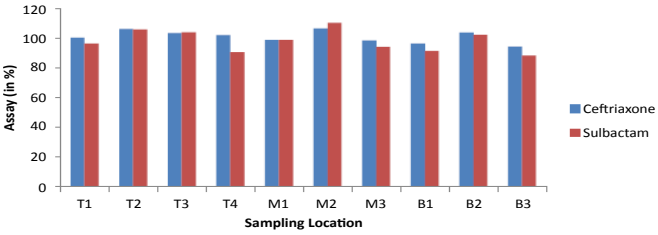

Figure 5: Comparative assay (in %) of Ceftriaxone and Sulbactam at 20 RPM.

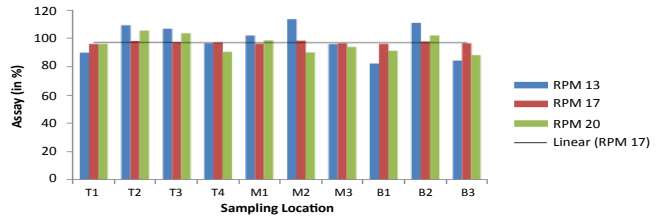

Figure 6: Showing comparison of % assay of Ceftriaxone at different rpm. The graph also indicates that assay of Ceftriaxone at RPM 17 show consistent result (due to linearity).

17 rpm were found to be consistent and also graphically showed the linearity indicating that at this rpm the process stands validated and the results are reproducible. The results for uniformity of content by weight were observed in Figure 8. The above results of % content uniformity by weight for all the 10 vials sampled were found to be in acceptance criteria range of 85-115% which indicates that filling of powder process was producing reproducible results of acceptance limits. The uniformity of weight was also found to comply with the acceptable range limits i.e. ± 5% of average net content. The pH of the finished sample was done and found to be 6.45 i.e. in limits of 4.5-9.0. The particulate matter test was also complying with the acceptance criteria (Table 3).

So the data of all three batches were complying with its acceptance criteria. Hence the product can be successfully manufactured at the commercial scale and the sterile manufacturing process is validated.

Conclusion

From the present study, following conclusion can be drawn i) blending stage of the Process Validation play key role in the manufacturing of dry powder injections, ii) rpm was a critical parameter at blending stage of process validation which governs proper & uniform mixing and thus responsible for good assay results, iii) drug content in all the vials was within the limit and iv) attempts were made in present study to prepare a stable composition of dry powder injection of Ceftriaxone & Sulbactam combination. These results clearly reflect that the prepared dry powder injections of Ceftriaxone & Sulbactam offers good assay results and within limit. Thus, Optimum blending speed i.e. 17 rpm at blending stage can be successfully employed to manufacture Dry Powder Injections for further scale up. Finally, all the test result was found to be as per acceptance criteria or compiled. Based on observation of three batches it was concluded that the product can be successfully manufactured and the sterile manufacturing process is validated.

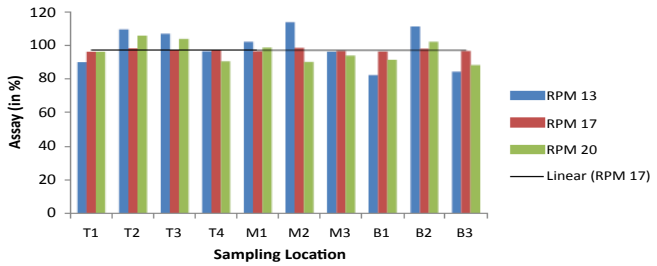

Figure 7: Showing comparison of assay of Sulbactam at different RPM. The graph also indicates that assay of Sulbactam at RPM 17 show consistent result (due to linearity).

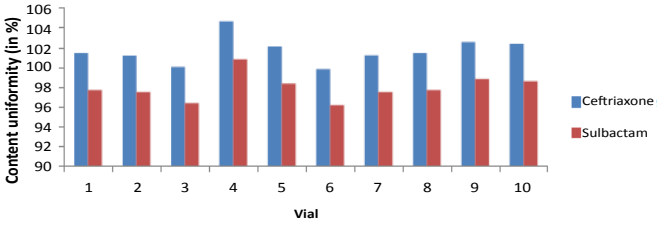

Figure 8: Comparison of % content uniformity of Ceftriaxone and Sulbactam.

Test parameter	Acceptance criteria	Observation comply / Not comply
Assay	As per monograph	comply
Uniformity of weight	Individual weight ± 5% of target fill weight	comply
pH	4.5 to 9.0	comply
Particulate matter	Vials should be essentially free from visible particulate matter. Sub-visible particulate matter: ≥ 10 µ: NMT 3000/vial ≥ 25 µ: NMT 300/vial	comply
Uniformity of dosage units (By weight variation)	Meets the requirement, (NMT ±15.0%)	comply
Sealing of vials	No. defects should be observed.	comply

Table 3: Observation Report.

References

1. US FDA (1987) Guideline on General principles of process validation. Center for Drug Evaluation and Research (CDER), Rockville, MD.
2. Chows SC (1997) Pharmaceutical validation and process control in drug development. Drug Information Journal 31: 1195-1201.
3. WHO (1992) Good Manufacturing Practices for Pharmaceutical Products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. 32nd Report, WHO Technical Report Series no.823, Geneva 14-96.
4. Potdar MA (2007) Pharmaceutical Quality Assurance. 2nd edition, Nirali Prakashan.
5. Chaloner-Larsson G, Anderson R, Egan A (1997) A WHO guide to GMP requirements: Part 2: Validation, guide to Good Manufacturing Practice. World Health Organization, Geneva.
6. Haider SI (2006) Pharmaceutical Master Validation Plan. 1st edition, CRC Press LLC, 2-6.