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Validation and Cleaning Validation of Equipments in Bulk Drug Manufacturing Facility for Terbutaline Sulphate by HPLC

K. KATHIRESAN*, K. KANNAN, N. KANNAPPAN, P. VENKATESAN, K.R.P. SHENOY† and R.MANAVALAN
Department of Pharmacy, Annamalai University, Annamalai Nagar-608 002, India
E-mail: kathiresan123@rediffmail.com

Validation is a requirement that has always made sense from both a regulatory and quality perspective. Cross contamination is one of the major problems faced in manufacture of bulk drugs, as cross contamination in one batch may lead to the contamination of several batches of pharmaceutical dosage forms. Hence, a cross contamination in active pharmaceutical ingredient facility is one of the greatest contamination leads to inferior quality of final products produced and causes considerable loss to the company. Hence, the relevance of the study about analytical method validation deals with the methods of analysis, definition and theory of method validation. Cleaning validation deals with the methods used for cleaning and sampling techniques. Cleaning validation in bulk drug plant and acceptance limits are fixed by using maximum allowable carry over calculation. The result of present study indicates that the method is suitable for successful implementation in the industry.

Key Words: Terbutaline sulphate, HPLC, Active pharmaceutical ingredients.

INTRODUCTION

Cleaning validation is a documented process that proves the defectiveness and consistency in cleaning of pharmaceutical equipment[1]. It is necessary to have effective cleaning programs for the regulatory and compliance requirement[2]. There is however more fundamental reasons and that is a moral requirement to produce products that are as pure and free from contamination to the extent that is possible and feasible. Cleaning programmers are necessary simply to prevent our manufactured products form being contaminated.

The efforts are necessary to prevent contamination of a future batch of another product. However work in active pharmaceutical ingredients

†Astra Zeneca Pharma India Ltd., Bangalore-560 024, India.

facility creates some challenges as it involves cleaning reactors, product transfer line and pumps, filters centrifuges and dryers, facilitates that they are very different form those in pharmaceutical production area, so one has to understand complexities to form an effective cleaning programme. Cleaning becomes more important in an API area because a cross contamination in a batch of API may end up in several batches of pharmaceutical dosage forms. A cross contamination problem in an API facility definitely has a potential for multiplying into a larger problem.

In a formulation area cleaning validation, many of the surfaces to be cleaned are within the reach of the operator. However, in most cases, an operator working in an API facility cannot reach the area that must be cleaned. This is especially true when large volume reactors are used. Bringing a person inside a reactor to scrub it would not be only impractical, but also complicated and risky. Transfer lines must be cleaned and they cannot be reached easily for scrubbing. The cleaning which is difficult to each surface is one of the most important consideration in API area cleaning efforts.

In the most pharmaceutical manufacturing facilities, the effectiveness of a cleaning process is determined by monitoring the residues of only one compound (active ingredient). But in a API facility unlike in pharmaceutical production, during which is stable and unchanged throughout the entire process, API manufacturing may involve different chemical entities. Therefore, it is very important to choose which chemical entities will be monitored to determine the effectiveness of the cleaning process, a short lived, highly reactive intermediates would not be a good compound to monitor. The choice of the chemical entity also depends on the accuracy and detection limit of method of analysis of the particular depend *i.e.*, it should be suitable according to the acceptance criteria.

The selection of the worst case should not always be made solely on the basis of potency and there should always be a logical, scientific and documented reason of selection.

In API manufacturing facility another area of concern is that most of the equipment comes in contact with intermediates for which no medical response levels are known and toxicity data is not available, hence its well advised to consider the potential levels of precursors and intermediates remaining on equipment. It recommended to identity precursors and intermediates and begins to study their levels carefully during the manufacturing process. Later, purification steps in manufacturing process remove many of these materials and hence they may not cause any problem.

EXPERIMENTAL

The bulk drug manufacturing facility at Astra Zeneca Pharma India Limited, Bangalore, manufacture mainly three main API, namely metoprolol tartarate, lignocaine hydrochloride and terbutaline sulphate. All these API are manufactured utilizing a common facility. So it is needed to ensure that thereis no carry over of these products. The cleaning validation studies of the equipment in the bulk drug facilities was to be carried out for the terbutaline sulphate and lignocaine hydrochloride[3].

As the cleaning validation studies are carried out for terbutaline sulphate and lignocaine hydrochloride, it was needed to select analytical method to carry out the studies.

Analytical method validation[4,5] for rinse and swab samples of terbutaline sulphate.

Chromatographic conditions:

Column	: C-18, 5 micron, 250 × 4.6 mm
Detector	: 276 nm, UV Detector
Flow rate	: 1.2 mL/min
Injection Volume	: 20 µL
Stop time	: 20 min

Rinse method: The rinse method[6] was used to collect the samples from equipments as mentioned as below after the cleaning operation was completed using portable water and acetone. Each of the rinse form the equipment is collected separately. The amount of solvent used for collecting the rinse sample is 5 L of acetone and 300 L portable water. The rinse samples were collected in a well-stoppered amber colour bottle. Immediately after the bottles were labeled which stated the point from which the samples were collected and it specified the data of collection of the sampled and the samples collected were stored in a cool place.

Establishing limits and acceptance criteria[7,8]: The limit established must be such that they are practical and achievable and have scientific basis. The limits can be established based on the factor determined as the maximum allowable carry over the calculations for determining these factors are as described below:

$$\text{Maximum allowable carry over for lignocaine hydrochloride} = \frac{\text{Daily therapeutic dose of lignocaine hydrochloride} \times \text{Wart case number of doses}}{\text{Safety factor}}$$

Analysis of the rinse samples[9]: In case of the rinse samples of water they are injected directly after filtering through 0.45 micron filter and the chromatograms are recorded and the calculations are done to determine the amount of active ingredients retained in equipment. In case of the rinse

samples of acetone 5 mL of acetone is taken in stoppered test tube and the acetone is evaporated by passing nitrogen gas through it, as a result of which any of the active ingredient in acetone is deposited on the inner walls of the test tube. 5 mL of mobile phase is added and the contents are mixed with a cyclo mixer and the resulting solution is injected and the chromatograms are recorded, the calculations done to determine the amount of active ingredient retained in equipment.

RESULTS AND DISCUSSION

The chromatogram of standard solutions and sample solution were recorded. The accuracy of the method was determined by recovery studies. The recovery studies were carried out and the percentage recovery was calculated. From the data obtained, recoveries for the standard drugs were considered sufficiently accurate. The precision data shows that the reproducibility of the assay procedure was satisfactory. The calibration curve shows linear response over the range of concentration used in the assay procedure. The calibration curve passes through the origin, which justifies the use of single point calibration and the proximity of all points to the calibration line demonstrated that the method has adequate linearity to the concentration of the analyte. The limit of detection (LOD) for terbutraline sulphate and lignocaine hydrochloride was found to be 1 and 0.1 ppm, respectively. The ruggedness of the method was determined by carrying out the experiment on different instruments of HPLC (LC-10AT VP) and Shimadzu by different operators using different columns similar type like Hypersil ODS and u-Bondapak C 18. Robustness of the method was determined by making slight changes in the chromatographic conditions. The ruggedness and robustness of the method showed that there were no marked changed in the chromatographic parameters, which demonstrates that the method developed is rugged and robust. Further, there is no interference due to excipients. The system suitability studies were also carried out to determine column efficiency, resolution and peak asymmetry. The proposed HPLC methods are simple, accurate, precise, linear, rugged and rapid. Hence, this method is suitable for analysis of the rinse and swab samples.

In this cleaning validation programme, mainly four equipments were selected from the cross contamination point. Likewise, among the four bulk drugs manufactured in the facility. Lignocaine hydrochloride IP and terbutaline sulphate teken into account for which the cleaning validation studies were to be carried out. Then the acceptance limits were established to check the quantity of carryover of the API, from the previous product to the next product having the smallest batch size among all the APIs produced in the premises. Terbutaline sulphate was found to have the minimum possible batch size (*i.e.* 29.2 kg) among the four bulk drugs.

TABLE-1
AMOUNT OF TERBUTALINE SULPHATE WHICH IS RETAINED IN THE EQUIPMENT AS CALCULATED FROM THE RINSE SAMPLES

Equipment	Water rinse (ppm)	Acetone rinse (ppm)	Swab (ppm)	Water rinse (ppm)	Acetone rinse (ppm)	Swab (ppm)
Glass line reactor (R-101)	5.151	3.675	0.0978	0.642	0.0154	0.0386
Centrifuge (C-101)	35.452	13.252	0.0458	1.643	0.886	0.0339
Rotocone drier (D-103) (dedicated)	0.2887	–	0.588	0.0885	–	0.134
Sifter (S-102) (dedicated)	–	–	6.241	–	–	10.872

TABLE-2
SUMMARIZED RESULTS OF METHOD VALIDATION OF TERBUTALINE SULPHATE

Parameters	Acceptance criteria	RSD (%)	Results
Accuracy	Percentage recovery should be between 98.0- 102.0%.	-	The percentage recovery is found to be between 99.0- 101.0%. The results are found to be well with in the acceptance limit
Precision	RSD should not be more than 2 %	0.31	The results are found to be well within the acceptance limit
Linearity & Range	Correlation coefficient should be not less than 0.99. Percentage curve fitting should be not less than 99.7	-	Correlation coefficient is found to be 0.9992. Percentage curve fitting is found to be 99.92. The results are found to be well within the acceptance limit
Limit of Detection (LOD)	The signal to noise ratio should be more than 3 : 1	-	Signal-to-noise ratio of 0.1-ppm solution of terbutaline sulphate is found to be more than 3:1
Limit of Quantitation (LOQ)	The signal to noise ratio should be more than 10 : 1		The signal –to-noise ratio of 0.5-ppm solution of terbutaline sulphate is found to be more than 10:1
Ruggedness	Relative standard deviation of replicate injections under different conditions should be less than **2.0%** for **10-ppm** solution	-	Relative standard deviation of replicate injections under different conditions is found to be less than **1.0** for **10-ppm** solution

Parameters	Acceptance criteria	RSD (%)	Results
Specificity	The resolution between Terbutaline sulphate and 3,5-dihydroxy-w-t-butyl amino acetophenone should not less than 1.4. The number of theoretical plates determined for Terbutaline sulphate should be at least 3200 The capacity factor for Terbutaline sulphate should be between 5.5- 8.5. The tailing factor for terbutaline sulphate should be less than 2.5.	-	The resolution between Terbutaline sulphate and 3,5-dihydroxy-ω-*t*-butyl amino acetophenone is found to be 1.49. The number of theoretical plates determined for Terbutaline sulphate is 4296. The capacity factor forTerbutaline sulphate is found to be 6.06. The tailing factor for terbutaline sulphate is found to be 1.0. The results are found to be well within the acceptance limits.
Robustness	Relative standard deviation of replicate injections under different conditions should be less than **2.0%** for **10-ppm** solution. The resolution between terbutaline and 3,5-dihydroxy-W-t-butyl amino acetophenone is not less than 1.4. The number of theoretical plates determined for Terbutaline sulphate should be between 5.5 and 8.5. The tailing factor for terbutaline sulphate should be less than 2.5.	-	Relative standard deviation of replicate injections under different conditions is found to be less than 1.0 for 10-ppm solution. The resolution between Terbutaline sulphate and 3,5-dihydroxy-ω-*t*-butyl amino acetophenone is not less than 1.4. The number of theoretical plates determined for terbutaline sulphate is at least 3200. The capacity factor for terbutaline sulphate should be between 5.5 and 8.5. The tailing factor for terbutaline sulphate should be less than 2.5. The results are found to be well within the acceptance limit.

Equipments like Reactor-101 were founded to be the common points, for the production of fine chemicals like lignocaine hydrochloride, terbutaline sulphate and metoprolol tartaurate. Then the rinse and swab samples were collected from both reactor-101 and centrifuge-101. Likewise the Rotocone drier D-103, driver-102 (fluidized bed drier - 102) and sifter -101 & 102 (s-101 & 102 were taken into consideration for the cleaning validation programme.

Before carrying out the cleaning validation programme, the method of analysis was appraised. The method used for analysis selected for lignocaine hydrochloride and terbutaline sulphate were the in house methods developed. The methods were validated for estimation of swab and rinse samples.

It was ensured that the methods chosen could detect the levels of the drugs is in ppm. All the equipment being rinsed with respective solvents and ultimately the amount of API to the next product were found within the acceptance limit. Hence, the object of the company to have an effective cleaning programme was well documented and ultimately the desired results were achieved.

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