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Cleaning Validation of Equipments in Bulk Drug Manufacturing Facility for Lignocaine Hydrochloride by using HPLC

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In most pharmaceutical manufacturing facilities, the effectiveness of a cleaning process is determined by monitoring the residues of only one compound (active ingredient). But in an 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 and highly reactive intermediates would not be a good compound to monitor. The choice of the chemical entity also depends on the accuracy and limit of detection and method of analysis of the particular depend *i.e.* it should be suitable according the acceptance criteria's. 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 it's 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.

Key Words: Lignocaine hydrochloride, Active pharmaceutical ingredients.

INTRODUCTION

Validation is a requirement that has always made sense from both a regulatory and quality perspective[1]. Validation should extend to those process steps determined to be critical to the quality and purity of the final product. Cleaning validation is a documented process that proves the effectiveness and consistency in cleaning of pharmaceutical equipment[2]. There is however more fundamental reason 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 the manufactured products from being contaminated. There are two types of contamination. Cross-contamination is usually thought of in terms of an active ingredient from one product carrying over into a subsequently manufactured product. However, carry over of other product components such as excipient can also be problematic and may degrade the final quality of product.

The second type of contamination is by foreign particles, which may be bacterial in nature or could represent parts of the equipment such as gasket or linings.

The objectives of equipment cleaning and cleaning validation effort in the API area are same as those in pharmaceutical production area.

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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 a API facility is one of the greatest challenges faced by the API manufacturers.

Contamination leads to inferior quality of final products produced and hence causes considerable loss to the company.

EXPERIMENTAL

The bulk drug manufactuirng faciltiy at Astra Zeneca Pharma India Limited manufacture mainly three main API's *viz.*, metaprolol tartarate, lignocaine hydrochloride and terbutaline sulphate. All these API are manufactured utilising a common facility. So it is neeeded to ensure that there 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].

Analytical method validation[4,5] for rinse and swab samples of lignocaine hydrochloride.

Chromatographic conditions:

Colum :	C-18, 5 µ, 250 × 4.6 mm
Detector:	276 nm, UV Detector
Flow rate:	1.2 mL/min
Injection volume:	20 mL
Stop time:	20 min

System suitability parameters:

Resolution:	NLT 1.4
Capacity factor:	Between 5.5 and 8.5
Theoretical plates:	NLT 3200.
Tailing factor:	NMT 2.5

Rinse method: The rinse method[6] was used to collect the samples from the equipments as mentioned below after the cleaning operation was completed using portable water and acetone. Each of the rinse that was got from the equipment was collected separately. The amount of solvent used for collecting the rinse samples were 5 L of acetone and 30 L potable water. The rinse samples were collected in a well-stoppered amber coloured bottle. After the samples were collected, the bottles were labeled immediately which stated the point from which the samples were collected and also specified the date of collection of the samples 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:

Maximum allowable carry over (MACO) for lignocaine hydrochloride

$$\text{MACO} = \frac{\text{Daily therapeutic dose of Lignocaine hydrochloride} \times \text{Worst case number of doses}}{\text{Safety factor}}$$

$$\text{Worst case number of dose} = \frac{\text{Smallest batch size of any other in the group}}{\text{Largest daily dose of any other product in the group}}$$

In case of lignocaine hydrochloride the smallest batch happens to be that of terbutaline sulphate, which has a batch size of 29.2 kg and a daily dose of 400 mg.

$$\text{Worst case number of doses} = \frac{29.2 \times 1000 \times 1000 \text{ mg}}{400 \text{ mg/dose}} = 73000 \text{ mg}$$

Hence taking into account the above information the MACO for lignocaine hydrochloride, taking the safety factor as 1000 is calculated

$$\text{MACO} = \frac{80 \text{ mg/dose} \times 73000 \text{ doses}}{1000}$$

MACO of lignocaine hydrochloride into the subsequent batches is = 5.84 g

Analysis of the rinse and swap samples[9]: In case of the rinse samples of water they are injected directly after filtering through 0.45 µ filter and the chromatograms were recorded and the calculations were done to determine the amount of active ingredient retained in equipment. In case of the rinse samples of acetone, 5 mL of acetone were taken in stoppered test tube and the acetone was evaporated by passing nitrogen gas through it. As a result of which any of the active ingredient in acetone was deposited on the inner walls of the test tube. 5 mL of mobile phase was added and the contents are mixed with a cyclomixer and the resulting solution was injected and the chromatograms were recorded. The calculations were done to determine the amount of active retained in equipment (Table-1).

TABLE-1
AMOUNT OF LIGNOCAINE HYDROCHLORIDE RETAINED IN THE EQUIPMENT

Equipment	Water rinse (ppm)	Acetone rinse (ppm)	Swab (ppm)	Water rinse (ppm)	Acetone rinse (ppm)	Swab (ppm)
Glass line reactor –101	17.442	77.542	19.4600	0.5620	4.4820	58.4365
Centrifuge – 101	48.272	83.578	1.7515	116.0571	161.6423	0.3114
Fluid bed drier (D-102)	5.835	–	10.0040	0.4720	–	0.9135
Sifter (S-102) dedicated	2.125	–	0.3600	0.1999	–	0.3876

The swabbing of all the equipments was performed at the selected areas. 10 mL of the mobile phase was added to the stoppered tubes containing the swab samples and then it was subjected to mixing with the help of a cyclomixer. The resulting solution was analyzed by the HPLC method, the chromatograms was recorded in each case and the concentration of lignocaine hydrochloride solution was calculated (Table-2).

TABLE-2
AMOUNT OF CARRY OVER OF LIGNOCAINE HYDROCHLORIDE

Equipment	Water rinse (ppm)	Acetone rinse (ppm)	Swab (ppm)	Water rinse (ppm)	Acetone rinse (ppm)	Swab (ppm)
Glass line reactor –101	179.198	13.277	125.67100	5.773	0.767	377.3780
Centrifuge – 101	495.945	14.311	0.06030	1192.367	27.678	0.0107
Fluid bed drier (D-102)	59.948	–	204.43900	4.849	–	18.6680
Sifter (S-102)	21.832	–	0.00056	2.054	–	0.0006

RESULTS AND DISCUSSION

The chromatogram of standard solutions and sample solutions 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 lignocaine hydrochloride was found to be 0.1 ppm. The ruggedness of the method was determined by carrying out the experiment on different instruments of HPLC (LC-10AT VP) & Shimadzu by different operators using different columns of similar type like Hypersil ODS and µ-Bondapak C18. 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 demonstrate that the method developed was rugged and robust (Table-3). Further, there was no interference due to excipients. The system suitability studies were also carried out to determine column efficiency, resolution and peak asymmetry.

TABLE-3
SUMMARIZED RESULTS OF ALIDATION METHOD OF LIGNOCAINE HYDROCHLORIDE

Parameters	Acceptance criteria	RSD (%)	Results
Accuracy	Percentage recovery should be between 98.0 and 102.0%.	-	The percentage recovery is found to be between 99.5 and 102.0%. The results are found to be well with in the acceptance limit
Precision	RSD should not be more than 2 %	1.21	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 0.9998. Percentage curve fitting is found to be 99.98. The results are found to be well within the acceptance limit

Parameters	Acceptance criteria	RSD (%)	Results
Specificity	The resolution between lignocaine hydrochloride and 2,6-dimethyl aniline is not less than 1.5. The number of theoretical plates determined for lignocaine hydrochloride is at least 1500. The capacity factor for lignocaine hydrochloride should be between 5.5 and 8.5. The tailing factor for lignocaine hydrochloride should be less than 2.5.	-	The resolution between lignocaine hydrochloride and 2,6-dimethyl aniline is found to be 2.98. The number of theoretical plates determined for lignocaine hydrochloride is 1500. The results are found to be well within the acceptance limits.
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 lignocaine hydrochloride is found to be more than 3:1
Limit of quantification (LOQ)	The signal to noise ratio should be more than 10 : 1	-	The signal –to-noise ratio of 0.5-ppm solution of lignocaine hydrochloride is found to be more than 10:1. The results are well within the acceptance limits. The limit of quantification is 0.5ppm
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 2.0% for 10-ppm solution
Robustness	Relative standard deviation of replicate injections under different conditions should be less than 2.0% for 10-ppm solution. The resolution between lignocaine hydrochloride and xylidine is not less than 1.4. The number of theoretical plates determined for lignocaine hydrochloride is at least 1500. The capacity factor for lignocaine hydrochloride should be between 5.5 and 8.5. The tailing factor for lignocaine hydrochloride should be less than 2.5.		Relative standard deviation of replicate injections under different conditions is found to be less than 2.0% for 10 ppm solution. The results are found to be well within the acceptance limit.

In case of lignocaine hydrochloride to determine the carry over of lignocaine hydrochloride the batch size to be considered is that of terbutaline sulphate which is 29.2 kg. The Table-3 depicted the carry over of lignocaine hydrochloride into the other products.

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