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CLEANING VALIDATION OF ACETAMINOPHEN TABLETS

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ABSTRACT

Cross contamination is one of the major problems focused in manufacturing of drugs utilizing common facility which leads to inferior quality of final product and cause considerable loss to the company. Contamination of one batch product with significant levels of residual active ingredients from a previous batch and contamination by microorganisms are the real concern. The cleaning validation is a documented process that proves the effectiveness and consistency cleaning of pharmaceutical equipments to meet the regulatory requirements. Manufacturing of Acetaminophen tablets and Diphenhydramine Hydrochloride tablet utilizing common facility, where Acetaminophen could be a possible cross contaminant. Hence the present study was carried out to validate the cleaning activity from both regulatory and quality prospective. Visual inspection, Swab sampling for chemical residue and for microbiological analysis were carried out to validate cleaning activity and results from all methods were complying with acceptance criteria.

Keywords: Acetaminophen; Diphenhydramine Hydrochloride; Cross contamination; Cleaning validation.

INTRODUCTION

Cross contamination with active ingredients is a real concern. The Code of Federal Regulations states that "Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official, or other established requirements. Cleaning validation is a documented process that proves the effectiveness and consistency in cleaning of pharmaceutical equipment. It is necessary to have effective cleaning programs in place because of the regulatory requirements. However, more fundamental reason and that is a moral requirement to produce products that are as pure and free from contaminations to the extent that is possible and feasible. Cross contamination and contamination by a foreign material are two types of contamination. Cross contamination is usually through an active ingredient from one product carrying over into subsequent manufactured product. However, carryover of other product components such as excipients can also be problematic and may degrade the final quality of product. Contamination of one batch of product with significant levels of residual active ingredients from a previous batch obvious problems posed by subjecting consumes or patients to unintended contaminants. Potential clinically significant synergistic interaction between pharmacologically active chemicals is a real concern. Inert ingredients used in drug product are generally recognized as safe or have been shown to be safe for human consumption, the routine use; maintenance and cleaning of equipment provide the potential for contamination with such items as equipment parts and lubricants. Chemical cleaning agents and piece of cleaning tools such as brushes or rags can cause problems ranging from poor pharmaceutical elegance to exceeding acceptable levels of particulate matter in parental products to inadvertent inclusion of toxic compounds in the product. In addition, some actives are adversely affected by trace contaminants and may exhibit change in stability or bioavailability if exposed to such contamination. The second type of contamination is by foreign material these may be bacterial in nature or could represent parts of the equipment such as gasket or linings. Maintenance, cleaning and storage condition may provide adventitious microorganisms with the opportunity to proliferate with in processing equipment. This could pose obvious problems for sterile products manufacture (generation of high levels of pyrogens, decreasing

the assurance of sterility achieved by equipment sterilization procedures etc.) It can also be a serious problem for the manufacture of non sterile dosage form, particularly unpreserved products which support microbial growth. Manufacturing of Acetaminophen tablets 500 mg and Diphenhydramine Hydrochloride tablet 25 mg utilizing common facility, where Acetaminophen could be a possible cross contaminant. Hence the present study was carried out to validate the cleaning activity from both regulatory and quality prospective.[1-5]

EXPERIMENTAL

This study was conducted at GRANULES INDIA LTD., Hyderabad. All chemicals and reagents used for this study were of analytical grade.

Cleaning of equipments

The equipments were cleaned with purified water as cleaning agent as the Diphenhydramine HCl is freely soluble and Acetaminophen is sparingly soluble in water. Hence the residue level of product changeover for above products was considered to Acetaminophen with respect to dosage strength and solubility criteria.

Visual inspection[6]

Equipments were cleaned using water and after cleaning, equipments were visually checked for presence of residues.

SWAB Samplling for chemical residue[7-9]

After cleaning, equipments were visually inspected before any sampling and swab was collected using 15 parallel and 15 horizontal strokes from the surface of the equipments. Swab sampling was done from pre-determined measured locations. The swab area was around 10 cm x 10 cm. Swabs were analyzed using validated analytical method for estimation of residue. Acceptance criteria was calculated using 0.001 dose criterions and 10 ppm criterions. The maximum allowable carryover obtained was 34.88 ppm/swab and 158. 3 ppm/ swab by 0.001 dose criterions and 10 ppm criterions respectively. The minimum/low level value (34.88 ppm/swab) obtained was taken as an acceptable limit for residue carryover after manufacturing of Acetaminophen 500mg and Diphenhydramine HCL 25 mg Tablets.

SWAB Sampling for microbiological analysis[8, 9]

Sterile swab was used for swabbing. Swab samples were collected from the measured surface areas of the equipments which was different from area for chemical residue testing. The swab area was around 10 cm x 10 cm. After swab sampling, each swab sample was placed inside a properly labeled and sealed sterile test tube and analyzed for aerobic microbes, mold, yeast and pathogens using established methods. After swab sampling, swab area was sanitized with 70% isopropyl alcohol.

RESULTS AND DISCUSSION

Visual inspection

Visual inspection was done after cleaning of the equipments shows that there was no visual evidence of the residues.

SWAB Sampling for chemical residue

The maximum and minimum carryover of acetaminophen was found to be 8.77 ppm / swab and 1.30 ppm / swab respectively which were less than acceptance criteria. The results of chemical residue were tabulated in Table 1.

SWAB Sampling for microbiological analysis

The maximum and minimum total aerobic microbial count was found to be 7 CFU / swab and 3 CFU / swab respectively which were less than acceptance criteria. Total combined molds and yeast count was found to be nil and pathogens were absent at all sampling points. The results of microbiological analysis were tabulated in Table 2.

CONCLUSION

The cleaning validation studies of Acetaminophen 500 mg tablet was observed by Visual inspection, swab sampling for chemical residue and swab sampling for microbiological analysis. The result revealed that (1) There were no visual residues on the equipments (2) Chemical residues were below acceptance

criteria (3) Total aerobic microbial count were below acceptance criteria (4) Total combined molds and yeast count was nil and (5) Pathogens were absent. Upon the compiled data, it was concluded that the train of equipments in tablet manufacturing block is completed and the results were found to be satisfactory and there is no cross contamination of acetaminophen to next product.

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Table-1: Result of chemical residue

S.No.	Equipments	Sampling Point	Observations (ppm / swab)
1.	Sejong Rotary Tablet Press Machine (30 station)	Turret (location - I)	2.06
		Turret (location - II)	4.74
		Discharge port - I	4.14
		Feeder frame - I	3.52
		Hopper - I	4.04
		Inner Surface-Hose pipe - 1 (White)	4.06
2.	Tablet Deduster Machine (Make: Kramer)	Charging port	4.38
		Spiral assembly	4.40
		Discharge port	2.77
		Inner Surface - Hose pipe - II (White)	1.56
3.	Metal Detection Machine	Discharge chute	1.30
		Inlet chute	2.55
4.	Sejong Automatic Tablet Coating Equipment	Baffle - I	5.10
		Baffle - II	3.61
		Inside Surface Area of Coating pan	3.62
		Discharging assembly	7.93
		Unloading device	8.77
5.	Multi Solution preparation tank	Stirrer assembly	3.62
		Inside surface area	5.09
6.	Press fit machine	Product Hopper - 1	1.65
		Product Hopper - 2	5.06
		Vibrating Feed Hopper - 1	4.18
		Vibrating Feed Hopper - 2	3.12
		Vibration tablet Hopper with Level Controller - 1	3.40
		Vibration tablet Hopper with Level Controller - 2	4.31
		Tablet Feed plates - 1	3.21
		Tablet Feed plates - 2	4.22
		Tablet Insertion Unit - 1	3.60
		Tablet Insertion Unit - 2	4.17

Table-2: Result of Microbiological analysis

S.No.	Equipments	Sampling Point	Observations (CFU / Swab) [TAMC]	TCMY and Pathogens
1	Sejong Rotary Tablet Press Machine (30 station)	Turret (location-I)	04	NIL
		Turret (location-II)	04	NIL
		Discharge port-I	03	NIL
		Feeder frame-I	06	NIL
		Hopper-I	07	NIL
		Inner Surface-Hose Pipe-1 (White)	04	NIL
2	Tablet Deduster Machine	Charging port	05	NIL
		Spiral assembly	06	NIL
		Discharge port	03	NIL
		Inner Surface-Hose Pipe-II (White)	04	NIL
3	Metal Detection Machine	Discharge chute	07	NIL
		Inlet chute	07	NIL

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