Research Article

Cleaning validation Study for Common Equipments used in Paracetamol Suspension Pediatric 120mg/5ml and Simple Linctus BP

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ABSTRACT

The contamination of pharmaceutical product with other pharmaceutically active ingredients and microorganisms are the real concerned which questions the integrity and safety of the pharmaceutical product. In most cases contamination of pharmaceutical products occurs when a common facility is utilized to manufacture many products. Regulatory agencies established requirements for cleaning of such common instruments/ facility and validation of such process which is documented evidence with a high degree of assurance that one can consistently clean a system to predetermined and acceptable limits. Production of Paracetamol Suspension Pediatric 120mg/5ml and Simple Linctus BP in a common facility, where Paracetamol and Simple Linctus could be a possible cross contaminant. Hence the present study was carried out to validate the cleaning activity of Paracetamol and Simple Linctus. The instruments in the common facility were cleaned with purified water after production of Paracetamol and the validation of cleaning activity was done by visual inspection, swab sampling for chemical residue and swab sampling for microbiological analysis. The study result revealed the following (a) There were no visual residues on the equipments after cleaning, (b) Chemical residues were below the acceptance criteria, (c) Total aerobic microbial count were below the acceptance criterial. Upon the compiled data, it was concluded that there were no cross contamination of Paracetamol and Simple Linctus to next product.

Keywords: Cleaning validation, contamination, paracetamol, simple linctus

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INTRODUCTION

Contamination of pharmaceutical product with other pharmaceutically active ingredients and microorganisms are the real concern which questions the integrity and safety of the pharmaceutical product. Drug tragedy of sulfanilamide elixir which killed over 100 people is a classical example of pharmaceutical contamination. In most cases contamination of pharmaceutical products occurs when a common facility is utilized to manufacture many products. Hence regulatory agencies such as the Unites States Food and Drug Administration (USFDA), European Medicinal Evaluation Agency (EMEA), Australia's Therapeutic Goods Administration (TGA) established requirements for cleaning of such instruments/ facility. For example, Code of Federal Regulations (CFR) Title 21, Volume 4, Section 211.67, states: 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" and additionally, Section 211.182 requires that cleaning procedures must be documented appropriately, and that a cleaning and use log should be established [1,2].

The most common and practical solvent is water being non-toxic, economical, environment friendly and does not leave

any residues. Alkaline and acidic solvents are sometimes preferred as it enhances the dissolution of the material, which are difficult to remove; detergent which acts in four ways as wetting agent, solubilizer, emulsifier and dispersant in removing the residues and contaminants from the equipment; and chemical reaction which refers to oxidation and hydrolysis reaction which chemically breaks the organic residues and contaminant to make them readily removable from the equipment. Cleaning should be followed by validation which is documented evidence with a high degree of assurance that one can consistently clean a system or a piece of equipment to predetermined and acceptable limits and ensure no risks are associated with cross contamination of active ingredients or detergent [2,3].

The production of Paracetamol Suspension Pediatric 120mg/5ml and Simple Linctus BP are in common facility, where Paracetamol and Simple Linctus could be a possible cross contaminant. Hence the rationale behind the present study was to validate the cleaning activity of Paracetamol and Simple Linctus.

MATERIALS AND METHODS

All chemicals and reagents used for cleaning validation were of analytical grade. The instruments in the common facility were cleaned with purified water after production of Paracetamol and Simple Linctus. However, Paracetamol is sparingly soluble in water freely soluble in alcohol and Simple Linctus is very soluble in water and freely soluble in alcohol. Hence the residue level of products changeover for above products were considered to be both Paracetamol and Simple Linctus with respect to dosage strength and solubility criteria and the validation of cleaning activity was carried out by visual inspection, swab sampling for chemical residue and swab sampling for microbiological analysis.

Visual inspection [3-5]

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

Acceptance criteria for visual inspection

No quantity of residue should be visible on equipment after cleaning procedure. Spiking studies of drugs have been determined using 100 mcg of drugs in which most products are visible.

Swab sampling for chemical residue [5-7]

After cleaning, equipments were visually inspected before sampling. As the Paracetamol and Simple Linctus are freely soluble in alcohol, swabs were soaked in methanol and samples were 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 (4 inch square). The drug content of the swab samples were analyzed using validated analytical method.

Acceptance criteria for chemical residue [8,13,14]

The maximum allowable carryover obtained was 638.083 mg/swab and 19.940 mg/swab by 0.001 dose criterions and 10 ppm criterions respectively. The minimum/low level value (19.940 mg/swab) obtained was taken as an acceptable limit for residue carryover after manufacturing of Paracetamol Suspension Pediatric 120mg/5ml.

Swab sampling for microbiological analysis [7,8,12]

Sterile swabs were used for sampling during microbiological testing. 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 total viable count using established methods. After swab sampling, swab area was sanitized with 70% isopropyl alcohol.

Acceptance criteria for microbiological analysis [9-11]

Total Aerobic Microbial Count (TAMC) should not be more than 50 Colony Forming Unit (CFU) per swab

RESULTS AND DISCUSSION

Visual inspection

Visual inspection was done after cleaning of the equipments and there were no visual evidence of the residues and complies with the acceptance criteria. Summary of visual inspection observations are listed in (**Table 1**).

Table 1: Summary of visual inspection observation

Sr. No.	Equipments	Sampling point	Observation
1	50L SS vessel	Inner side bottom corner of 50 L vessel	No visual residue
2	10 KL Manufacturing Tank	Side wall corner of materiel addition port of tank	No visual residue
		Manufacturing Tank outlet valve	No visual residue
3	Ventury	Inside the valve (before Ventury and after pump)	No visual residue
		Ventury station from inside	No visual residue
4	Product Transfer line from manufacturing to holding	After basket filter neat triclover clamp from inside	No visual residue
5	Lobe pump	Inside the lobe pump	No visual residue
6	600 µm Filter Bag	From the 600µ filter bag net.	No visual residue
7	750 liter tank	Outlet valve of 750 L tank from inside	No visual residue
8	Silverson Mixer – GX -10	Inner bottom side of Work head of Silverson mixer GX -10	No visual residue
9	10 KL holding Tank	Side wall of 10 KL holding tank near tank opening	No visual residue
		10 KL Holding Tank outlet valve	No visual residue
10	Product Transfer line from holding to filling	10 KL Holding Tank bottom flexible hose near TC joint from inside	No visual residue
		Transfer Line corner near TC clamp.	No visual residue
11	Filling machine product buffer tank	Product Buffer tank Below stirrer blades	No visual residue
12	Product tank header	Inside the header	No visual residue
13	Chevron ring of filling piston	Chevron ring of filling piston	No visual residue
14	Filling Needle /nozzle	Filling needle hose pipe	No visual residue
15	Flexible hose connection part (above filling needle)	Inside the flexible hose connection part (above filling needle)	No visual residue

Swab sampling for chemical residue

All the samples are collected and analyzed as per validated procedure and results of all the comman equipments are bellow limit of quantification. Limit of quantification for paracetamol is 8.92µg/ml. Hence the swab sampling for chemical residue complies with the acceptance criteria and found satisfactory. Summary of swab sampling for chemical residue observations are listed in (**Table 2**).

Swab sampling for microbiological analysis

The maximum total aerobic microbial count was found to be 26 CFU/ swab at after basket filter neat triclover clamp from inside in product transfer line from manufacturing to holding and the minimum total aerobic microbial count was found to be 10 CFU/ swab at inside the header in product tank header. Hence the swab sampling for microbiological analysis complies with the acceptance criteria and found satisfactory. Summary of swab sampling for microbiological analysis observations are listed in (**Table 3**).

CONCLUSION

The cleaning validation of Paracetamol Suspension Pediatric 120mg/5ml and Simple Linctus BP were observed by visual inspection, swab sampling for chemical residue and swab sampling for microbiological analysis. Upon the compiled data, it was concluded that the train of equipments in Liquid manufacturing block is completed and the results were found to be satisfactory and there is no chance of cross contamination with Paracetamol Suspension Pediatric 120mg/5ml and Simple Linctus BP to next product.

Table 2: Summary of swab sampling for chemical residue observation

Sr. No.	Equipments	Sampling point	Residue in mg/swab
1	50L SS vessel	Inner side bottom corner of 50 L vessel	Bellow LOQ
2	10 KL Manufacturing Tank	Side wall corner of materiel addition port of tank	Bellow LOQ
		Manufacturing Tank outlet valve	Bellow LOQ
3	Ventury	Inside the valve (before Ventury and after pump)	Bellow LOQ
		Ventury station from inside	Bellow LOQ
4	Product Transfer line from manufacturing to holding	After basket filter neat triclover clamp from inside.	Bellow LOQ
5	Lobe pump	Inside the lobe pump	Bellow LOQ
6	600 µm Filter Bag	From the 600µ filter bag net.	Bellow LOQ
7	750 liter tank	Outlet valve of 750 L tank from inside	Bellow LOQ
8	Silverson Mixer – GX -10	Inner bottom side of Work head of Silverson mixer GX -10	Bellow LOQ
9	10 KL holding Tank	Side wall of 10 KL holding tank near tank opening	Bellow LOQ
		10 KL Holding Tank outlet valve	Bellow LOQ
10	Product Transfer line from holding to filling	10 KL Holding Tank bottom flexible hose near TC joint from inside	Bellow LOQ
		Transfer Line corner near TC clamp.	Bellow LOQ
11	Filling machine product buffer tank	Product Buffer tank Below stirrer blades.	Bellow LOQ
12	Product tank header	Inside the header	Bellow LOQ
13	Chevron ring of filling piston	Chevron ring of filling piston	Bellow LOQ
14	Filling Needle /nozzle	Filling needle hose pipe	Bellow LOQ
15	Flexible hose connection part (above filling needle)	Inside the flexible hose connection part (above filling needle)	Bellow LOQ

Table 3: Summary of swab sampling for microbial analysis observation

Sr. No.	Equipments	Sampling point	TAMC CFU/swab
1	50L SS vessel	Inner side bottom corner of 50 L vessel	13
2	10 KL Manufacturing Tank	Side wall corner of materiel addition port of tank	22
		Manufacturing Tank outlet valve	12
3	Ventury	Inside the valve (before Ventury and after pump)	13
		Ventury station from inside	17
4	Product Transfer line from manufacturing to holding	After basket filter neat triclover clamp from inside	10
5	Lobe pump	Inside the lobe pump	22
6	600 µm Filter Bag	From the 600µ filter bag net	18
7	750 liter tank	Outlet valve of 750 L tank from inside	24
8	Silverson Mixer – GX -10	Inner bottom side of Work head of Silverson mixer GX -10	20
9	10 KL holding Tank	Side wall of 10 KL holding tank near tank opening	13
		10 KL Holding Tank outlet valve	14
10	Product Transfer line from holding to filling	10 KL Holding Tank bottom flexible hose near TC joint from inside	24
		Transfer Line corner near TC clamp.	18
11	Filling machine product buffer tank	Product Buffer tank Below stirrer blades.	19
12	Product tank header	Inside the header	26
13	Chevron ring of filling piston	Chevron ring of filling piston	17
14	Filling Needle /nozzle	Filling needle hose pipe	22
15	Flexible hose connection part (above filling needle)	Inside the flexible hose connection part (above filling needle)	23

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