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Cleaning validation of Ibuprofen and Methocarbamol tablets

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Abstract

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. 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 tablet with Ibuprofen 200 mg and Methocarbamol 500 mg in a common facility, where Ibuprofen and Methocarbamol could be a possible cross contaminant. Hence the present study was carried out to validate the cleaning activity of Ibuprofen and Methocarbamol. The instruments in the common facility were cleaned with purified water after production of Ibuprofen 200 mg and Methocarbamol 500 mg 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, total combined molds and yeast count were below the acceptance criteria and (d) Pathogens were nil. Upon the compiled data, it was concluded that there were no cross contamination of Ibuprofen and Methocarbamol to next product.

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Ibuprofen, Methocarbamol, Cross Contamination, Cleaning Validation.

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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].

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/sanitizer [2, 3].

Production of tablet with Ibuprofen 200 mg and Methocarbamol 500 mg in a common facility, where Ibuprofen and Methocarbamol could be a possible cross contaminant. Hence the present study was carried out to validate the cleaning activity of Ibuprofen and Methocarbamol.

Material 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 Ibuprofen 200 mg and Methocarbamol 500 mg. However, Ibuprofen is highly soluble in alcohol and Methocarbamol is sparingly soluble in water. Hence the residue level of products changeover for above products were considered to be both Ibuprofen and Methocarbamol 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 [4, 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, 6]

After cleaning, equipments were visually inspected before sampling. As the Ibuprofen and Methocarbamol are highly 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

The maximum allowable carryover obtained was 541.24 ppm/swab and 129.9 ppm/swab by 0.001 dose criterions and 10 ppm criterions respectively. The minimum/low level value (129.9 ppm/swab) obtained was taken as an acceptable limit for residue carryover after manufacturing of Ibuprofen 200 mg and Methocarbamol 500mg tablets.

Swab sampling for microbiological analysis [5, 7]

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 aerobic microbes, mold, yeast and pathogens using established methods. After swab sampling, swab area was sanitized with 70% isopropyl alcohol.

Acceptance criteria for microbiological analysis

Total Aerobic Microbial Count (TAMC) should not be more than 50 Colony Forming Unit (CFU) per swab and Total Combined Molds and Yeast Count (TCMY) should not be more than 50 CFU per swab. Testing for pathogens should be nil.

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.

Swab sampling for chemical residue

The maximum residual content was found to be 9.98 ppm / swab at Spiral chute of matcon bin and minimum residual content was found to be 0.51 ppm/ swab at charging port of tablet deduster machine. 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 14 CFU/ swab at external surface area of matcon bin and the minimum total aerobic microbial count was found to be 3 CFU/ swab at discharge chute of metal detection machine. Total combined molds and yeast count and pathogens were found to be nil. 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 Ibuprofen and Methocarbamol tablets 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 tablet manufacturing block is completed and the results were found to be satisfactory and there is no chance of cross contamination with Ibuprofen and Methocarbamol to next product.

Table 1: Summary of visual inspection observations

Equipment	Sampling Point	Observation
Sejong Rotary Tablet Press Machine (49 station)	Turret (location - I)	No visual residue
	Turret (location - II)	No visual residue
	Discharge port - I	No visual residue
	Discharge port - II	No visual residue
	Feeder frame - I	No visual residue
	Feeder frame - II	No visual residue
	Hopper - I	No visual residue
	Hopper - II	No visual residue
	Conveyer belt - 1 (front side)	No visual residue
	Conveyer belt - 1 (rear side)	No visual residue
	Conveyer belt - 2 (front side)	No visual residue
	Conveyer belt - 2 (rear side)	No visual residue
	Conveyer belt - 3 (front side)	No visual residue
	Conveyer belt - 3 (rear side)	No visual residue
	Inner Surface - Hose Pipe - I	No visual residue
Tablet Deduster Machine	Charging port	No visual residue
	Spiral assembly	No visual residue
	Discharge port	No visual residue
	Inner Surface - Hose Pipe - II	No visual residue
Metal Detection Machine	Discharge chute	No visual residue
	Inlet chute	No visual residue
Sejong Automatic Tablet Coating Equipment	Baffle - I	No visual residue
	Baffle - II	No visual residue
	Inside surface area of coating pan	No visual residue
	Discharging assembly	No visual residue
	Unloading device	No visual residue
Matcon bin unloading conveyer	Conveyer belt	No visual residue
Matcon bin Unloading device	Inside surface unloading device	No visual residue
Multi Solution Preparation Tank	Stirrer assembly	No visual residue
	Inside surface area	No visual residue
Tablet capsule Inspection Machine	Product hopper	No visual residue
	Product hopper	No visual residue
	Discharge chute	No visual residue
	Discharge chute	No visual residue
	Belt	No visual residue
	Belt	No visual residue
Matcon Bin	Inside surface area	No visual residue
	External surface area	No visual residue
	Spiral chute	No visual residue
	SS cone	No visual residue

Table 2: Summary of swab sampling for chemical residue observations

Equipment	Sampling Point	Residue in ppm/swab	
		Ibuprofen	Methocarbamol
Sejong 49 station Rotary Tablet Press Machine	Turret (location - I)	6.14	7.63
	Turret (location - II)	6.27	7.50
	Discharge port - I	7.51	3.84
	Discharge port - II	7.64	3.53
	Feeder frame - I	7.57	3.78
	Feeder frame - II	7.88	8.07
	Hopper - I	8.43	7.82
	Hopper - II	8.57	7.58
	Conveyor Belt - 1 (Front side)	8.91	7.45
	Conveyor Belt - 1 (Rear side)	8.48	7.98
	Conveyor Belt - 2 (Front side)	9.41	7.84
	Conveyor Belt - 2 (Rear side)	8.52	2.23
	Conveyor Belt - 3 (Front side)	6.71	1.80
	Conveyor Belt - 3 (Rear side)	6.73	1.32
	Inner Surface Hose Pipe - I (white)	6.78	5.61
Tablet Deduster Machine	Charging port	6.82	**0.51**
	Spiral assembly	7.30	0.80
	Discharge port	7.44	0.83
	Inner Surface Hose Pipe - II (white)	7.92	3.63
Metal Detection Machine	Discharge chute	8.92	4.02
	Inlet chute	8.97	3.69
Sejong Automatic Tablet Coating Equipment	Baffle - I	9.19	3.18
	Baffle - II	9.24	2.59
	Inside surface area of coating pan	3.99	2.52
	Discharging assembly	4.00	2.58
	Unloading device	4.18	4.06
Sejong Automatic Tablet Coating Equipment	Baffle - I	5.41	3.60
	Baffle - II	7.51	3.38
	Inside surface area of coating pan	8.20	3.66
	Discharging assembly	4.05	4.39
	Unloading device	4.00	4.91
Matcon Bin Unloading Device	Conveyer belt	6.13	6.10
	Inside surface unloading device	6.06	5.53
Multi solution preparation tank	Stirrer assembly	5.99	7.36
	Inside surface area	6.04	8.72
Multi solution preparation tank	Stirrer assembly	7.04	6.00
	Inside surface area	6.59	5.61
Tablet Capsule Inspection Machine	Product hopper	6.39	5.64
	Discharge chute	7.61	7.83
	Belt	4.49	7.04
	Product hopper	7.52	8.43
	Discharge chute	8.09	7.55
	Belt	6.02	6.53
Matcon Bin	Inside surface	8.05	6.86
	External surface area	9.62	5.35
	Spiral chute	**9.98**	5.39
	SS cone	6.74	5.09

Table 3: Summary of swab sampling for microbiological analysis observations

Equipment	Sampling Point	TAMC (CFU/swab)	TCMY and Pathogens
Sejong 49 station Rotary Tablet Press Machine	Turret (location - I)	11	NIL
	Turret (location - II)	10	NIL
	Discharge port - I	08	NIL
	Discharge port - II	05	NIL
	Feeder frame - I	08	NIL
	Feeder frame - II	05	NIL
	Hopper - I	06	NIL
	Hopper - II	11	NIL
	Conveyor Belt - 1 (Front side)	05	NIL
	Conveyor Belt - 1 (Rear side)	07	NIL
	Conveyor Belt - 2 (Front side)	08	NIL
	Conveyor Belt - 2 (Rear side)	04	NIL
	Conveyor Belt - 3 (Front side)	04	NIL
	Conveyor Belt - 3 (Rear side)	08	NIL
	Inner Surface Hose Pipe - I (white)	04	NIL
Tablet Deduster Machine	Charging port	06	NIL
	Spiral assembly	07	NIL
	Discharge port	06	NIL
	Inner Surface Hose Pipe - II (white)	05	NIL
Metal Detection Machine	Discharge chute	**03**	NIL
	Inlet chute	06	NIL
Sejong Automatic Tablet Coating Equipment	Baffle - I	06	NIL
	Baffle - II	04	NIL
	Inside Surface Area of Coating pan	04	NIL
	Discharging assembly	07	NIL
	Unloading Device	06	NIL
Sejong Automatic Tablet Coating Equipment	Baffle - I	06	NIL
	Baffle - II	07	NIL
	Inside Surface Area of Coating pan	08	NIL
	Discharging assembly	09	NIL
	Unloading device	07	NIL
Unloading Device	Conveyer Belt	08	NIL
Multi solution preparation tank	Stirrer assembly	08	NIL
	Inside surface area	09	NIL
Multi solution preparation tank	Stirrer assembly	08	NIL
	Inside surface area	05	NIL
Tablet Capsule Inspection Machine	Product Hopper	11	NIL
	Discharge Chute	12	NIL
	Belt	09	NIL
	Product Hopper	06	NIL
	Discharge Chute	05	NIL
	Belt	07	NIL
Matcon Bin	Inside Surface	09	NIL
	External Surface Area	**14**	NIL
	Spiral Chute	08	NIL
	SS Cone	10	NIL

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