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Short communication

Cleaning validation of electronic counting machine with two different cleaning agents

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Introduction

The objective of cleaning validation as documented evidence is to prove that the equipment is consistently cleaned of product, cleaning agent and microbial residues to an acceptable level, to prevent possible contamination and cross-contamination (Raj, 2014). Cleaning validation can be performed between batches of same products and strengths and ascending strength or it can be performed during change-over of products with different APIs, color, flavor, descending strength and post maintenance of contact parts (Goswami et al., 2013).

Materials and methods

Materials: Active substance ingredient: Ketoprofen (BEC Chemicals Private Limited, India).

Excipients: cellulose mycrocristalline (JRS Pharma, Germany), lactose monohydrate (Meggle, Germany), povidone (BASF, Germany), croscarmellose sodium (JRS Pharma, Germany), silica, colloidal anhydrous (Evonik, Germany), sodium laurilsulfate (BASF, Germany).

Cleaning agents (mildly alkaline): Deconex CIP wash-x (Borer Chemie, Germany) contains: alkalis, dispersing agents, complexing agents, solubilizer, surfactants, wetting agents; COSA CIP 90 (Ecolab, USA) contains: octanoic acid, alcohol ethoxylate, alkylamine ethoxylates, sodium salt triethanolamine.

Methods: Cleaning validation of the electronic counting machine CPE 6 (MultiGel, Italy) was done.

Swab sampling was done from the most critical areas. A predetermined area (5x5 cm^2) was wiped with a swab moistened with a previously selected solvent. The swab was then immersed into a standard quantity of suitable diluent and further tests were done according to chromatographic analytical method. A HPLC system was used - Chromatographic column: stationary phase-charger C18, 125 x 4 mm, 5 µm; Mobile phase: 50% (20 mM KH2PO4 pH 3.5):50% ACN; Flow: 1.1 ml/min; Wavelength detection: 254 nm; Injection volume: 20 µl. Samples are dissolved in: 50% CH_3OH:50% H_2O. The HPLC method is validated in relation to parameters: selectivity, linearity, precision, accuracy, sensitivity in relation to detection limit and quantification limit.

In rinse sampling method, a predetermined area of clean surface of the machine was rinsed with purified water and 200 ml sample was tested for residues of the cleaning agent. The parts of the machine were dismantled and immersed in purified water for 10 minutes. A 200 ml sample was further analyzed.

Swab sampling for microbiological control was done the same way as the swab sampling for residues of API was done. A physiological solution was used as a solvent. Samples for microbiological testing are taken 8 hours after disinfection of the machine (Deconex Solarsept from Borer Chemie, Germany; Klercide 70/30 from Ecolab, Germany) in order to establish time limit between equipment cleaning and reuse and to ensure that the equipment remains clean till the next use.

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Results and discussion

The cleaning validation was done according to Master Validation Plan and encompassed 3 consecutive successful replicates which confirm the procedure is reproducibly effective. Selection of Ketoprofen caps. 50 mg as a worst case for the cleaning validation study, shown on the Table 1., was based on the lowest solubility of the active ingredient, median lethal dose (LD_{50}) and cleanability.

Table 1. Assessment (scoring) of Ketoprofen caps. 50 mg

Risk factor	Ketoprofen status	Degree of risk
Solubility	Practically insoluble	High: 6
LD_{50}	Very toxic (50-500)	High: 4
Cleanability	Easy cleanable	Low: 1
Total		High: 11

Table 2. Acceptance criteria and type of testing for cleaning validation

Test Type	Acceptance criteria
Visual check	No visible residues of API/ cleaning agent
Residues of API Ketoprofen on the machine	10.01 µg/ cm^2
Residues of cleaning agent	33.33 ppm (Deconex CIP wash-x) 54.02 ppm (COSA CIP 90)
Microbiological purity	25 cfu/ 25 cm^2 (Alarm limit) 50 cfu/ 25 cm^2 (Action limit)
Absence of	E.coli, P.aeruginosa, S.aureus

Table 3. Cleaning validation with Deconex CIP wash-x

Machine part	API residues (µg/ cm^2)	*Deconex CIP wash-x residues	Total viable count (cfu/25 cm^2)
Hopper	0.0038	no residues	0
	0.0264	no residues	0
	no residues	no residues	10
Rotating glass part	0.0415	/	/
	0.0038	/	/
	no residues	/	/
Hopper exit	/	no residues	0
	/	no residues	0
	/	no residues	0

The acceptance criteria for the cleaning validation testing are shown on the Table 2. The acceptance limit for chemical residues can be calculated and expressed as: MACO - Maximum Allowable Carry Over, NOEL - No observed effect level, etc. (Maurya S. et al., 2016). The cleaning validation with both cleaning agents showed good results within the established limits of acceptance. The results for cleaning validation with the cleaning agents Deconex CIP wash-x and COSA CIP 90 are shown on the Table 3. and Table 4. respectively.

Table 4. Cleaning validation with COSA CIP 90

Machine part	API residues (µg/ cm^2)	*COSA CIP 90 residues	Total viable count (cfu/25 cm^2)
Hopper	0.0038	no residues	<10
	0.0264	no residues	<10
	no residues	no residues	10
Rotating glass part	0.0415	/	/
	0.0038	/	/
	no residues	/	/
Hopper exit	/	no residues	<10
	/	no residues	10
	/	no residues	<10

Conclusion

The efficacy of the cleaning procedure is confirmed with the results gained from the samples testing. The results for residues of Ketoprofen and both cleaning agents were within the limits of acceptance. The time limit between machine cleaning and reuse, established according to the results form microbiological testing, was 8 hours. The cleaning validation of the machine CPE 6 has been done successfully, in accordance to the Validation Protocol and in compliance with the EU GMP Guidelines (EudraLex, Volume 4, Annex 15, 2015).

References

EudraLex, Volume 4, EU Good Manufacturing Practice (GMP) guidelines, Annex 15: Qualification and Validation (into operation since 1 October 2015)

Goswami, D., Rathore, K. S., Mishra, A., 2013. Introduction and General Overview of Cleaning Validation: A Review. Int. Journal of Pharmaceutical Erudition 3 (1), 57-68.

Maurya, S., Goyal, D., Verma, C., 2016. Cleaning Validation in Pharmaceutical Industry- An Overview. PharmaTutor 4 (9), 14-20.

Raj, A., 2014. Cleaning validation in pharmaceutical industries. J.Atoms and Molecules 4 (4), 779-783.