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Cleaning Validation of Liquid Orals

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The manufacture of pharmaceutical products, active ingredients and medical devices has only one aim, safe products that consistently meet high Quality Standards. Validation provides documented evidence that processes are under control and that consistent product quality is assured. The overall objective of any cleaning validation is to assure that intermediates, excipients, cleaning agents and most importantly active drug ingredients from the previous production batch do not contaminate the product. Taking the example of two liquid oral preparations, it was developed and proved that three consecutive washes with demineralised water (DM) were better than any soap/chemical washes to prevent cross-contamination in subsequent batches.

Validation detects and analyses optimization potential and supports implementation. Pharmaceutical manufacturers often make a large number of product types in one facility. Often there are several different strengths prepared of the same product. The cleaning problems include large number of processes and product types manufactured within one facility. The number of cleaning methods, assays and types of equipment to be tested are often staggering[1,2]. FDA considered the potential of cross contamination to be significant and to pose a serious health risk to the public. FDA expects firms to have written procedures called Standard Operating Procedures (SOPs), detailing the cleaning processes used for various pieces of equipments.

Several questions need to be addressed while evaluating the cleaning process, for e.g. at what time does a piece of equipment/system become clean? Depending upon the limits set by FDA for potent and non-potent drugs[6], the equipment tends to be clean when the limit of active ingredients and excipients in ppm is below the permissible limit. Does it have to be scrubbed by hand? Depending upon the nature of material processed and the type of reactor, scrubbing using a brush and scrapping by hand may be required. What is accomplished by hand scrubbing rather than just solvent wash? Solvent washes at times may form chemical complexes with the drug/excipients used. It may go undetected and can be harmful for the next batch to be processed. How different are manual cleaning processes from batch to batch and product to product? Nature of the product plays a vital role for cleaning processes to be selected and validated e.g. sticky materials may require compressed air, steam and vacuum application for thorough cleaning. The answers to these questions are important to the inspection and evaluation of the cleaning process since one must determine the overall effectiveness of the process. As the industry continues to battle the rising cost of doing business, the potential for unnecessary product scrap or loss becomes a serious matter[3].

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MATERIALS AND METHODS

Two liquid syrups prepared and marketed by Juggat Pharma, Bangalore were taken for the present study. These are Panthor syrup comprising of sodium acid phosphate IP, chlorpheniramine maleate IP and ammonium chloride IP. Cidazole suspension contains albendazole as the active ingredient.

Cleaning procedure and validation studies with panthor syrup:

Once the batch was over thorough rinsing with mild scrubbing using DM water was carried out. About 5 l of DM water washes in three wash solutions were collected from

the outlet of the reactor. The jacketed reactor was of 2100 l capacity, made up of stainless steel with a lid on top and outlet at the bottom. It had a four-armed stainless steel propeller. After each wash, cotton swabs were used to rub on the sidewalls of the reactor and collected thereafter. They were dissolved in water and subjected to further analysis.

Methods of analysis:

Sodium acid phosphate was assayed using the procedure of IP[5] with a slight modification, which is as follows. Ten millilitres of the sample was pipetted into a clean 100 ml volumetric flask and made up to the mark with water and mixed. Five millilitres of this solution was pipetted out and made up to 200 ml with water in a volumetric flask. One millilitre of this solution was used for analysis by colorimetry at 493 nm. Ammonium chloride was also assayed using IP[5] procedure. The results of the analysis are shown in Table 1 and Table 2, respectively.

HPLC method of analysis was developed to detect the presence of chlorpheniramine maleate (CPM) in the DM water washes by the following procedure using reverse phase liquid chromatography principle[4]. The instrument conditions are listed in Table 3.

The sample and standard solutions were made alkaline with 2 M sodium hydroxide solution. The bases (any impurities) were extracted with chloroform. The chloroform layer was evaporated and the bases were dissolved in the acidic medium of the mobile phase and injected into liquid chromatograph. Mobile phase used was a mixture of water (HPLC grade), methanol (HPLC grade) and glacial acetic acid (AR) in the ratio of 70:30:1.The solution was filtered through 0.45 µm membrane filter and sonicated for 15-20 min. The working reference standard was prepared by weighing 22.3 mg of the drug and dissolving in 100 ml of water in a volumetric flask. Two millilitres of 2 M sodium hydroxide solution was added to both standard and sample solutions till alkaline, 3x25 ml portions of chloroform (AR) was used for extraction. The chloroform layers were collected in another separator and washed with about 10 ml of water. The chloroform layer was then transferred into a dry 100 ml volumetric flask through anhydrous sodium sulphate. Twenty millilitres of chloroform was used to wash the anhydrous sodium sulphate into the same volumetric flask. Volume was made up with chloroform and mixed. Five millilitres of the standard and sample chloroform solutions were accurately transferred into a dry stoppered test tube, which was marked as SP and EP respectively. The chloroform was evaporated

TABLE 1: CONTENT OF SODIUM ACID PHOSPHATE IN PANTHOR SYRUP, WASHES.

	mg/100 ml*	ppm**	Standard Deviation
I Wash	49.8	498	0.001
II Wash	4.4	44	0.002
III Wash	0.9	09	0.004
I Swab	5.7	57	0.004
II Swab	4.4	44	0.006
III Swab	0.9	09	0.006

* Indicates average of three determinations and ** denotes parts per million.

TABLE 2: CONTENT OF AMMONIUM CHLORIDE IN PANTHOR SYRUP, WASHES.

	mg/100 ml*	ppm**	Standard Deviation
I Wash	240	2400	0.002
II Wash	7.8	78	0.003
III Wash	0.521	5.21	0.003
I Swab	6.7	67	0.004
II Swab	2.08	20.8	0.005
III Swab	1.04	10.4	0.005

* Indicates average of three determinations and ** denotes parts per million.

TABLE 3: SHIMADZU LIQUID CHROMATOGRAPH CONDITIONS.

Pump	LC 10 As
Flow	1 ml/min
Detector	SPD–10 A
Wave length	280 nm
Integrator	C – R7A
Chart speed	0.50 (cm/min)
Injector	10/20 µl loop
Column	C 18, 4.6 x 100 mm symmetry

TABLE 4: THE ESTIMATED AMOUNT OF CPM BY HPLC IN PANTHOR SYRUP.

	From the Chart EA***	SA*	SW** (mg)	Drug Content
[STD – CPM]	1436653	1454154	-	98.5%
Sample Wash I	179151	1436653	22.3	27.8 ppm
Sample Wash II	2857	1436653	22.3	0.44 ppm
Swab I	25543	1436653	22.3	3.95 ppm
Swab II	21352	1436653	22.3	3.3 ppm

*SA represents respective standard areas, ** SW denotes respective standard weights taken and ***EA represents respective sample areas.

and 5 ml of the mobile phase was added to the residue. Ten microlitres each of SP (standard) and EP (sample) solutions were injected into the liquid chromatograph. The retention time of CPM is approximately two minutes. From the respective peak areas obtained in the standard and sample chromatograms, contents were calculated using the formula (EA/SA)x(SW/100)x(10/100)x100x5. The results showing the drug content are given in Table 4.

Studies with cidazole suspension:

To concentrate only on the presence/absence of active ingredient for cleaning validation, cidazole suspension was chosen as it had about 200 mg of the active ingredient. The drug content present in the washes was estimated as per the IP procedure[5]. The results are given in Table 5.

RESULTS AND DISCUSSION

The results obtained clearly indicate the need for uniformity in the cleaning process which was eventually achieved by proper scrubbing to reduce the level of sodium acid phosphate to below 10 ppm as stated by US FDA[6] for any batch contents after washes. Usage of various detergents and chemicals can be avoided as they form some unknown complexes. Formation and detection of new chemical complexes is a cause of concern and thus DM water wash with occasional scrubbing are suggested.

TABLE 5: THE ESTIMATED AMOUNT OF ALBENDAZOLE IN CIDAZOLE SUSPENSION, WASHES.

	mg/100 ml*	ppm**	Standard Deviation
I Wash	5.7	1140	0.003
II Wash	1.7	340	0.001
III Wash	-	-	0.002
I Swab	0.8	168	0.005
II Swab	-	-	0.003
III Swab	-	-	0.004

* Indicates average of three determinations and ** denotes parts per million.

From the results obtained with panthor syrup, the following observations could be made. In case of ammonium chloride the third wash showed permissible 5.21 ppm of ammonium chloride whereas the third swab showed almost double i.e., 10.4 ppm indicating more adherence of the material on the side walls of the reactor which was properly scrubbed during the cleaning process to bring down the ppm of ammonium chloride to well below the stated US FDA limits. Minimal amount of diluted chlorpheniramine maleate (CPM) present failed to answer the usual assay procedure. The active ingredient is 2 mg in 5 ml in comparison to sodium acid phosphate and ammonium chloride which are 300 and 100 mg/5 ml respectively which answer the test procedure successfully. HPLC method developed for detecting CPM, even in traces (Table 4) indicates the absence of CPM in the second wash and second swab, thus avoiding even the third wash and third swab analysis.

In case of cidazole suspension, the negative absorbance obtained after third wash and third swab analysis as shown in Table 5 prove the validation of cleaning process with DM water. When the amount of active ingredient present is high like in case of albendazole or if it is a potent drug, it is advisable to thoroughly rinse and scrub the reactor so that the amount of the active constituent in each wash will fall within the limit permissible by FDA.

It can thus be concluded that the use of harsh chemicals and detergents should be avoided and cleaning method should be validated by using a proper technique with DM

water wash and scrubbing if required. This will prevent the cross contamination of products from batch to batch and also prevent the formation of any new chemical complexes , which are thus difficult to detect and may cause problems.

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