Int J Pharm Bio Sci 2012 Oct; 3(4): (P) 222 - 244

Research Article **Analytical Chemistry**

International Journal of Pharma and Bio Sciences **ISSN 0975-6299**

CLEANING VALIDATION OF ALBENDAZOLE TABLETS 400 MG

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ABSTRACT

The cleaning validation is to verify the effectiveness of the cleaning procedure for removal of product residues, degradation products, preservatives, excipients and cleaning agents so that the analytical monitoring may be reduced to a minimum in the routine phase. In addition one needs to ensure there is no risk associated with cross contamination of active ingredients. Cleaning validation is intended to address special consideration and issues pertaining to validation cleaning procedures for equipment used in the manufactured of pharmaceutical products, radiopharmaceuticals, and biological drugs. The document is also intended to establish inspection consistency and uniformity with respect to equipment cleaning procedures.

KEY WORDS: Acceptable residual level (ARL), Cleaning equipment, Swabs and Wipes Method, Rinse Method

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INTRODUCTION

As a result of any pharmaceutical unit process, a residual level of the drug substance remains on the equipment and facility even after clean up. This residual drug and possibly traces of cleaning agents may be carried over into the next product resulting in adulteration of the subsequent product. Hence, the cleaning methods developed should consistently lower the level of residual to the acceptable residual level (ARL). Formulation and Mullen of Eli Lilly Company established a method for finding out cleaning acceptance criteria limit for a multi drug facility in 1993. Pierre Rousseau introduced matrix approaches to the solved complex cleaning Validation Problems. Cleaning is a challenging task and the design of the cleaning system depending upon the equipment use (dedicated/multipurpose), manufacture (continuous/batch), cleaning equipment (manual/automated), preparation (commercial product/clinical supplies), product formulation i.e., type of materials being removed from the surface, drugs (low risk/high risk), sterile/non sterile, solids/liquids and solubility (soluble/insoluble) of active ingredients. An acceptable cleaning system should incorporate the following elements.

MATERIALS AND METHODS

SAMPLING PROCEDURE

In order to evaluate a cleaning method it is necessary to sample the product contact surfaces of the equipment and establish the level of residuals present.

i) Swabs and Wipes Method

Swabbing is the most widely used sampling technique. Swabs may be saturated with solvent such as water or alcohol, facilitating the solubilization and physical removal of surface residues.

Advantages

- Dissolves and physically remove sample.
- Adequate to a wide variety of surfaces
- Economical and widely available.
- Allows sampling of a defined area.

Limitations

- An invasive technique that may introduce fibers.
- Results may be technique dependent.
- Swab material and design may inhibit recovery and specificity of the method.
- Evaluation of large, complex and hard-to-reach areas difficult (e.g. crevices, pipes, valves, large vessels). In obtaining rinse samples, location, timing and volume are important considerations.

ii) Rinse Method

Advantages

- Adaptable to online monitoring.
- Easy to sample and non-intrusive.
- Allows sampling of a large surface area.
- Allows sampling of porous surfaces.

Limitations

- Residues may not be homogeneously distributed.
- Inability to detect location of residues.
- Rinse volume is critical to ensure accurate interpretation of results.

iii) Coupon sampling

Coupons of the same materials of construction as the item to be cleaned can be affixed to the equipment, spiked with the product, subject to the cleaning procedures and then submitted to the laboratory for direct analysis and recovery studies.

Advantages

- Allows for direct surface sampling.
- Useful in cleaning method development.
- Reduced variability in recovery.

- Useful in evaluation of equipment materials of construction.

Limitations

- Coupon may not be representative of equipment contamination or cleaning as it is separate from primarily surface.
- Invasive
- Might interfere with the cleaning process.

iv) Solvent sampling

This technique uses a solvent not normally employed in the cleaning process to maximize recovery residues.

Advantages

- Commonly used in bulk chemical facilities
- Applicable for actives, cleaning agents, excipients
- Less technique dependent than swabs.
- Usually affords more analytical specificity, less recovery loss than swabs.
- Allows sampling of a larger surface area.
- Allows sampling of porous and delicate surface
- Maximizes recovery to rinse.

Limitations

- May require operator protection and other safety and environmental protection measures.
- May require more than one sampling for broad spectrum analysis.
- Reduced physical sampling of the surface.
- May be difficult to accurately define the controlled area sampled, therefore usually used for rinsing an entire piece of equipment such as a vessel.
- May require the removal of solvent prior to equipment use for production.

v) Placebo and Product Sampling

Placebo sampling can be used to detect residues on equipment thorough the processing of a place to batch subsequent to the cleaning process. Product sampling is similar to placebo sampling except that it uses actual product.

Advantages

- Points of product contact identical for the two batches
- Applicable for hard to reach surfaces.
- Require no additional sampling steps.

Limitations

- Difficult to determine recovery
- Lowers analytical specificity and inhibits detectability
- Residues may not be homogenously distributed.
- No direct measurement of residues on product contact surfaces.

ACCEPTANCE CRIETRIA

Method of calculating Acceptance Criteria

i) Based on Therapeutic Daily Dose

The principle for the requirement is that the standard Therapeutic Daily Dose (TDD) of the following substance (contaminated substance, in this called “next”) may be contaminated by no more than a certain proportion (usually 1/1000 part) of the TDD of the substance investigated in the cleaning validation (contaminating substance, in this case called “Previous”). This method only applies when the therapeutic daily dose is known. It generally used for final product changeover API Process “A” to API process “B”.

Procedure

Establish the limit for Maximum Allowable Carryover (MACO) according to the following equation.

$$MACO = \frac{TDDprevious \times MBS}{SF \times TDDnext}$$

MACO Maximum Allowable Carryover: acceptable transferred amount from the investigation product (“Previous”)

$TDD_{previous}$ Standard therapeutic dose of the investigated product (in the same dosage form as: TDD
TDD_{next} Standard therapeutic dose of the daily dose for the next product.
MBS Minimum batch size for the next product(s) (where MACO can end up)
SF Safety factor (normally 1000 is used in calculations based on TDD).

ii) Based on Toxicology Data

In cases in which a therapeutic dose is not known (e.g. for intermediates and detergents), toxicity data may be used for calculating MACO.

Procedure

Calculate the so called NOEL number (No Observable Effect Level) according to the following equation and use the result for the establishment of MACO.

$$NOE = \frac{LD_{50}\ (g/kg) \times 70(kg\ a\ person)}{2000}$$

From the NOEL number a MACO can then be calculated according to

$$MACO = \frac{OEL \times MBS}{SF \times TDD_{next}}$$

MACO Maximum Allowable Carry over: acceptable transferred amount from the investigated product ("previous").
NOEL No Observed Effect Level
LD_{50} Lethal Dose 50 in g/kg animal. The identification of the animal (mouse, rat etc.,) and the way of entry (IV, oral etc.,) is important.
2000 2000 is an empirical constant
TDD_{next} Largest normal daily dose for the next product
MBS Minimum batch size for the next products (where MACO can end up)
SF Safety factor

The safety factor (SF) varies depending on the route of administration. Generally a factor of 200 is employed when manufacturing APIs to be administered in oral dosage forms. SF can vary depending on substance/dosage form according to (suppose tox values from oral administration) as for example as presented on the next page.

(iii) General Limit

If the calculation methods based on therapeutic doses or toxicological data result in unacceptably high or irrelevant carryover figures, or toxicological data for intermediates are not know, the approach of a general limit may be suitable. Companies may choose to have such an upper limit as a policy. The general limit is often set as an upper limit for the maximum concentration (MAXCONC) of a contaminating substance in a subsequent batch. The concentration (CONC) of the investigated substance which can be accepted in the next batch, according to dose related calculations, is:

$$CONC = \frac{MACO}{MBS}$$

MACO Maximum Allowable Carryover: acceptable transferred amount from the investigated product ("previous"). Calculated from therapeutic doses and /or tox data.
MACO$_{ppm}$ Maximum Allowable Carryover: acceptable transferred amount from the investigated product ("previous"). Calculated from general ppm limit.
CONCCconcentration (kg/kg or ppm) of "Previous" substance in the next batch. Based on MACO calculated from therapeutic doses and / or tox data.
MAXCONC General limit for maximum allowed concentration (kg/kg or ppm) of "Previous" substance in the next batch.
MBS Minimum batch size fir the next product(s) (where MACO can end up)

A general upper limit for the maximum concentration of a contaminating substance in a subsequent batch (MAXCONC) is often set to – ppm depending on the nature of products produced from the individual company (e.g. toxicity, pharmacological activity,) ppm in APIs is very frequent).
Note – If you decide to employ the concept of levels of cleaning may be used for different levels. Especially if the product cleaned out is within the same synthetic chain and covered by the specification of the API, much higher (qualified) levels are acceptable.

If the calculated concentration (CONC) of the previous (based on MACO calculation from therapeutic doses/tox data) exceeds the general upper limit (MAXCONC), then MAXCONC level will be limit.

Swab Limits
If homogenous distribution is assumed on all surfaces, a recommended value can be set for the content in a swab. This can be used as basic information for preparation of a method of analysis and detection limit.

Procedure
Establish the target value for swab limit for the whole equipment train, using the following equation:

$$\text{Target value } [\mu g/dm^2] = \frac{\text{MACO } [\mu g]}{\text{Total surface } [dm^2]}$$

Also other methods with different swab limits for different surfaces in a piece of equipment and/or equipment train can be used. Using this approach, the total amount found on the equipment train has to be below the MACO.

SAFETY FACTORS[2]

Typical products	**Applicable approach may be Cndd = normal daily dose**
Topical	1/10th to 1/100th of ndd
Oral	1/100th to 1/1000th of ndd
Injections, Ophthalmics	1/1000th to t/10000th of ndd
Research & investigational	1/10000th to 1/100000th of ndd

RESULTS AND DISSCUSSION

Swabbing is the most widely used sampling technique. Swabs may be saturated with solvent such as water or alcohol, facilitating the solubilization and physical removal of surface residues (Sampling area: 30cm^2).

(i) Albendazole tablets to Paracetamol tablets BP 100mg
Dispensing Booth

$$\text{Sensitivity level} = \frac{\text{Sample absorbance}}{\text{Standard absorbance}} \times \text{Standard amounts of 10ppm in 0.001\%}$$

Standard amount of 10ppm in 0.001% is 1mg.

$$\text{Concentration of drug by 30cm}^2\text{ in sample I} = \frac{0.112}{0.742} \times 0.1\text{mg}$$

$$= 0.1509\text{mg}$$

$$\text{Concentration of drug by 30cm}^2\text{ in sample II} = \frac{0.101}{0.742} \times 1\text{ mg}$$

$$= 0.1361\text{mg}$$

$$\text{Concentration of drug by 30cm}^2\text{ in sample III} = \frac{0.092}{0.742} \times 1\text{ mg}$$

$$= 0.1240\text{mg}$$

$$\text{Average concentration of drug / 30cm}^2\text{ of the whole equipment} = \frac{0.1509+0.1361+0.1240}{3}$$

$$= 0.137\text{mg}$$

$$\text{The amount of drug present in 5229cm}^2\text{ of Dispensing Booth} = \frac{0.137}{30} \times 5229$$

$$= 23.8793\text{mg (or) } 0.0238\text{ppm}$$

Dispensing Balance:

$$\text{Concentration of drug by } 30cm^2 \text{ in sample} = \frac{0.101}{0.742} \times 1 \text{ mg}$$

$$= 0.1375mg$$

$$\text{The amount of drug present in } 78.75cm^2 \text{ of Dispensing Balance } \frac{0.137}{30} x78.75$$

$$= 0.3609mg \text{ (or) } 0.000361ppm$$

Dispensing tools

$$\text{Concentration of drug by } 30cm^2 \text{ in sample} = \frac{0.027}{0.742} \times 1 \text{ mg}$$

$$= 0.0364mg$$

$$\text{The amount of drug present in } 60cm^2 \text{ of Dispensing Tools} = \frac{0.0364}{30} x60$$

$$= 0.0728mg \text{ (or) } 0.000073ppm$$

Sifter

$$\text{Concentration of drug by } 30cm^2 \text{ in sample I} = \frac{0.109}{0.742} \times 1 \text{ mg}$$

$$= 0.1469mg$$

$$\text{Concentration of drug by } 30cm^2 \text{ in sample II} = \frac{0.092}{0.742} \times 1 \text{ mg}$$

$$= 0.1240mg$$

$$\text{Average of Concentration of drug /}30cm^2 \text{ of the whole equipment.} = \frac{0.1469+0.1240}{2}$$

$$= 0.1354 \text{ mg}$$

$$\text{The amount of drug present in } 1227cm^2 \text{ of Sifter} = \frac{0.1354}{30} X1227$$

$$= 5.5378mg \text{ (or) } 0.00554 \text{ ppm}$$

Steam Jacketed Kettle

$$\text{Concentration of drug by } 30cm^2 \text{ in sample I} = \frac{0.084}{0.742} \times 1 \text{ mg}$$

$$= 0.1132 \text{ mg}$$

$$\text{Concentration of drug by } 30cm^2 \text{ in sample II} = \frac{0.092}{0.742} \times 1 \text{ mg}$$

$$= 0.1240 \text{mg}$$

$$\text{Average of Concentration of drug /}30cm^2 \text{ of the whole equipment} = \frac{0.1132 + 0.1240}{2}$$

$$= 0.1186 \text{ mg}$$

$$\text{The amount of drug present in } 904.2cm^2 \text{ of SJK} = \frac{0.1186}{30} \times 904.2$$

$$= 3.5746\text{mg (or) } 0.00358 \text{ ppm.}$$

RMG

$$\text{Concentration of drug by } 30cm^2 \text{ in sample I} = \frac{0.064}{0.742} \times 1\text{mg}$$

$$= 0.08625 \text{ mg}$$

$$\text{Concentration of drug by } 30cm^2 \text{ in sample II} = \frac{0.077}{0.742} \times 1 \text{ mg}$$

$$= 0.1038 \text{ mg}$$

$$\text{Concentration of drug by } 30cm^2 \text{ in sample III} = \frac{0.075}{0.742} \times 1 \text{ mg}$$

$$= 0.1011 \text{ mg}$$

$$\text{Average of Concentration of drug /}30cm^2 \text{ of the whole equipment} = \frac{0.08625+0.1030+0.1011}{3}$$

$$= 0.09705 \text{ mg}$$

$$\text{The amount of drug present in } 2101.8m^2 \text{ of RMG} = \frac{0.09705}{30} X2101.8$$

$$= 6.7993\text{mg (or) } 0.0068\text{ppm.}$$

FBD

$$\text{Concentration of drug by } 30cm^2 \text{ in sample I} = \frac{0.202}{0.742} \times 1 \text{ mg}$$

$$= 0.2722 \text{ mg}$$

$$\text{Concentration of drug by } 30cm^2 \text{ in sample II} = \frac{0.167}{0.742} \times 1 \text{ mg}$$

$$= 0.2251 \text{ mg}$$

$$\text{Concentration of drug by } 30cm^2 \text{ in sample III} = \frac{0.178}{0.742} \times 1 \text{mg}$$

$$= 0.2399 \text{ mg}$$

$$\text{Concentration of drug by } 30cm^2 \text{ in sample IV} = \frac{0.218}{0.742} \times 1 \text{mg}$$

$$= 0.2938 \text{mg}$$

$$\text{Average of Concentration of drug } /30cm^2 \text{ of the whole equipment} = \frac{0.2722+0.2251+0.2399+0.2938}{4}$$

$$= 0.2577 \text{ mg}$$

$$\text{The amount of drug present in } 4225.2 \text{ } cm^2 \text{ of FBD} = \frac{0.2577}{30} \times 4225.2$$

$$= 36.2945 \text{mg (or) } 0.0363 \text{ppm.}$$

Cadmill

$$\text{Concentration of drug by } 30cm^2 \text{ in sample I} = \frac{0.472}{0.742} \times 1 \text{ mg}$$

$$= 0.6361 \text{ mg}$$

$$\text{Concentration of drug by } 30cm^2 \text{ in sample II} = \frac{0.397}{0.742} \times 1 \text{mg}$$

$$= 0.5350 \text{ mg}$$

$$\text{Average of Concentration of drug } /30cm^2 \text{ of the whole equipment} = \frac{0.6361 + 0.5350}{2}$$

$$= 0.5855 \text{ mg}$$

The amount of drug present in 923.4 cm^2 of Cadmill = $\frac{0.5855}{30}$ x 923.4

= 18.0217mg or 0.018ppm.

Octogonal Blender

Concentration of drug by $30cm^2$ in sample I = $\frac{0.378}{0.742}$ x 1 mg

= 0.5094 mg

Concentration of drug by $30cm^2$ in sample II = $\frac{0.428}{0.742}$ x 1 mg

= 0.5768 mg

Concentration of drug by $30cm^2$ in sample III = $\frac{0.432}{0.742}$ x 1mg

= 0.5822 mg

Average of Concentration of drug /$30cm^2$ of the whole equipment = $\frac{0.5094 + 0.5768 + 0.5822}{3}$

= 0.5561 mg

The amount of drug present in 2721 cm^2 of Blender = $\frac{0.5561}{30}$ x 2721

= 50.4384mg (or) 0.05044ppm

Compression Machine

Concentration of drug by $30cm^2$ in sample I = $\frac{0.251}{0.742}$ x 1 mg

= 0.3383 mg

Concentration of drug by $30cm^2$ in sample II = $\frac{0.182}{0.742}$ x 1 mg

= 0.2453 mg

Concentration of drug by $30cm^2$ in sample III = $\frac{0.222}{0.742}$ x 1mg

= 0.2992 mg

$$\text{Concentration of drug by } 30cm^2 \text{ in sample IV} = \frac{0.191}{0.742} \times 1mg$$

$$= 0.2574 \text{ mg}$$

$$\text{Average of Concentration of drug /}30cm^2 \text{ of the whole equipment} = \frac{0.3383+0.2453+0.2992+0.2574}{4}$$

$$= 0.2850 \text{ mg}$$

$$\text{The amount of drug present in 4608 } cm^2 \text{ of Compression Machine } \frac{0.2850}{30} \times 4608$$

$$= 43.776mg \text{ (or) } 0.0438ppm$$

II. Albandazole tablets to Chloroquine phosphate tablets BP 100mg

S. No.	Equipment Name	Average Concentration of drug by $30cm^2$ (mg)	Equipment in totally present amount(ppm)	Acceptance Limit (ppm)
1	Dispensing Booth	0.137	0.0238	0.04615
2	Dispensing Balance	0.1375	0.000361	3.065
3	Dispensing tools	0.0364	0.000073	4.022
4	Sifter	0.1354	0.00554	0.1967
5	Steam jacketed kettle	0.1186	0.00358	0.2669
6	RMG	0.09705	0.0068	0.1148
7	FBD	0.2577	0.0363	0.05712
8	Cad mill	0.5855	0.018	0.2614
9	Octogonal Blender	0.5561	0.05044	0.0887
10	Compression Machine	0.2850	0.0438	0.0524

Dispensing Booth

$$\text{Sensitivity level} = \frac{\text{Sample absorbance}}{\text{Standard absorbance}} \times \text{Standard amounts of 10ppm in 0.001\%}$$

Standard amount of 10ppm in 0.001% is 1mg.

$$\text{Concentration of drug by } 30cm^2 \text{ in sample I} = \frac{0.126}{0.742} \times 0.1mg$$

$$= 0.1698mg$$

$$\text{Concentration of drug by } 30cm^2 \text{ in sample II} = \frac{0.089}{0.742} \times 1 \text{ mg}$$

$$= 0.1200mg$$

$$\text{Concentration of drug by } 30cm^2 \text{ in sample III} = \frac{0.102}{0.742} \times 1 \text{ mg}$$

$$= 0.1375mg$$

$$\text{Average concentration of drug / } 30cm^2 \text{ of the whole equipment} = \frac{0.1698+0.1200+0.1375}{3}$$

$$= 0.1424mg$$

$$\text{The amount of drug present in } 5229cm^2 \text{ of Dispensing Booth} = \frac{0.1424}{30} \times 5229$$

$$= 24.8205mg \text{ (or) } 0.02482ppm$$

Dispensing Balance

$$\text{Concentration of drug by } 30cm^2 \text{ in sample} = \frac{0.113}{0.742} \times 1 \text{ mg}$$

$$= 0.1523mg$$

$$\text{The amount of drug present in } 78.75cm^2 \text{ of Dispensing Balance } \frac{0.1523}{30} \times 78.75$$

$$= 0.3998mg \text{ (or) } 0.0003998ppm$$

Dispensing tools

$$\text{Concentration of drug by } 30cm^2 \text{ in sample} = \frac{0.042}{0.742} \times 1 \text{ mg}$$

$$= 0.0566mg$$

$$\text{The amount of drug present in } 60cm^2 \text{ of Dispensing Tools} = \frac{0.0566}{30} \times 60$$

$$= 0.1132mg \text{ (or) } 0.0001132ppm$$

Sifter

$$\text{Concentration of drug by } 30cm^2 \text{ in sample I} = \frac{0.122}{0.742} \times 1 \text{ mg}$$

$$= 0.1644mg$$

$$\text{Concentration of drug by } 30cm^2 \text{ in sample II} = \frac{0.088}{0.742} \times 1 \text{ mg}$$

$$= 0.1186mg$$

$$\text{Average of Concentration of drug /30cm}^2\text{ of the whole equipment.} = \frac{0.1644+0.1186}{2}$$

$$= 0.1415 \text{ mg}$$

$$\text{The amount of drug present in 1227cm}^2\text{ of Sifter} = \frac{0.1415}{30} X1227$$

$$= 5.7874\text{mg (or) } 0.0057874 \text{ ppm}$$

Steam Jacketed Kettle

$$\text{Concentration of drug by 30cm}^2\text{ in sample I} = \frac{0.102}{0.742} \times 1 \text{ mg}$$

$$= 0.1375 \text{ mg}$$

$$\text{Concentration of drug by 30cm}^2\text{ in sample II} = \frac{0.094}{0.742} \times 1 \text{ mg}$$

$$= 0.1267\text{mg}$$

$$\text{Average of Concentration of drug /30cm}^2\text{ of the whole equipment} = \frac{0.1375 + 0.1267}{2}$$

$$= 0.1321 \text{ mg}$$

$$\text{The amount of drug present in 904.2cm}^2\text{ of SJK} = \frac{0.1321}{30} x904.2$$

$$= 3.9815\text{mg (or) } 0.0039815 \text{ ppm.}$$

RMG

$$\text{Concentration of drug by 30cm}^2\text{ in sample I} = \frac{0.081}{0.742} \times 1\text{mg}$$

$$= 0.1092 \text{ mg}$$

$$\text{Concentration of drug by 30cm}^2\text{ in sample II} = \frac{0.102}{0.742} \times 1 \text{ mg}$$

$$= 0.1375 \text{ mg}$$

$$\text{Concentration of drug by 30cm}^2\text{ in sample III} = \frac{0.092}{0.742} \times 1 \text{ mg}$$

$$= 0.1240 \text{ mg}$$

Average of Concentration of drug /30cm^2 of the whole equipment $= \frac{0.1092+0.1375+0.1240}{3}$

$= 0.1235$ mg

The amount of drug present in 2101.8m^2 of RMG $= \frac{0.1235}{30} \times 2101.87$

$= 8.6525$mg (or) 0.0086525ppm.

FBD

Concentration of drug by 30cm^2 in sample I $= \frac{0.242}{0.742} \times 1$ mg

$= 0.3262$ mg

Concentration of drug by 30cm^2 in sample II $= \frac{0.210}{0.742} \times 1$ mg

$= 0.2830$ mg

Concentration of drug by 30cm^2 in sample III $= \frac{0.179}{0.742} \times 1$mg

$= 0.2412$ mg

Concentration of drug by 30cm^2 in sample IV $= \frac{0.184}{0.742} \times 1$mg

$= 0.2480$mg

Average of Concentration of drug /30cm^2 of the whole equipment $= \frac{0.3262+0.2830+0.2412+0.2480}{4}$

$= 0.2746$ mg

The amount of drug present in 4225.2 cm^2 of FBD $= \frac{0.2746}{30} \times 4225.2$

$= 38.6745$mg (or) 0.0386745ppm.

Cadmill

Concentration of drug by 30cm^2 in sample I $= \frac{0.412}{0.742} \times 1$ mg

$= 0.5553$ mg

Concentration of drug by 30cm^2 in sample II $= \frac{0.371}{0.742} \times 1$mg

$= 0.5$ mg

$$\text{Average of Concentration of drug /30cm}^2\text{ of the whole equipment} = \frac{0.5553+0.5}{2}$$

$$= 0.5276 \text{ mg}$$

$$\text{The amount of drug present in 923.4 cm}^2\text{ of Cadmill} = \frac{0.5276}{30} \times 923.4$$

$$= 16.2396\text{mg or } 0.016239\text{ppm.}$$

Octogonal Blender

$$\text{Concentration of drug by 30cm}^2\text{ in sample I} = \frac{0.412}{0.742} \times 1 \text{ mg}$$

$$= 0.5553 \text{ mg}$$

$$\text{Concentration of drug by 30cm}^2\text{ in sample II} = \frac{0.378}{0.742} \times 1 \text{ mg}$$

$$= 0.5094 \text{ mg}$$

$$\text{Concentration of drug by 30cm}^2\text{ in sample III} = \frac{0.431}{0.742} \times 1\text{mg}$$

$$= 0.5809 \text{ mg}$$

$$\text{Average of Concentration of drug /30cm}^2\text{ of the whole equipment} = \frac{0.5553+0.5094+0.5809}{3}$$

$$= 0.5485 \text{ mg}$$

$$\text{The amount of drug present in 2721 cm}^2\text{ of Blender} = \frac{0.5485}{30} \times 2721$$

$$= 49.7489\text{mg (or) } 0.0497489\text{ppm}$$

Compression Machine

$$\text{Concentration of drug by 30cm}^2\text{ in sample I} = \frac{0.262}{0.742} \times 1 \text{ mg}$$

$$= 0.3531 \text{ mg}$$

$$\text{Concentration of drug by 30cm}^2\text{ in sample II} = \frac{0.192}{0.742} \times 1 \text{ mg}$$

$$= 0.2588 \text{ mg}$$

$$\text{Concentration of drug by 30cm}^2\text{ in sample III} = \frac{0.212}{0.742} \times 1\text{mg}$$

$$= 0.2857 \text{ mg}$$

$$\text{Concentration of drug by } 30\text{cm}^2 \text{ in sample IV} = \frac{0.234}{0.742} \times 1\text{mg}$$

$$= 0.3154 \text{ mg}$$

$$\text{Average of Concentration of drug /}30\text{cm}^2 \text{ of the whole equipment} = \frac{0.3531+0.2588+0.2857+0.3154}{4}$$

$$= 0.3032 \text{ mg}$$

$$\text{The amount of drug present in 4608 cm}^2 \text{ of Compression Machine } \frac{0.3032}{30} \times 4608$$

$$= 46.5717\text{mg (or) } 0.0465717\text{ppm}$$

III. Albandazole tablets to Erythromycin Stearate tablets 500mg

S. No.	Equipment Name	Average Concentration of drug by 30cm^2 (mg)	Equipment in totally present amount(ppm)	Acceptance Limit (ppm)
1	Dispensing Booth	0.1424	0.02482	0.05151
2	Dispensing Balance	0.1523	0.0004	3.42
3	Dispensing tools	0.0566	0.0001132	4.49
4	Sifter	0.1415	0.00579	0.22
5	Steam jacketed kettle	0.1321	0.00398	0.298
6	RMG	0.1235	0.008653	0.128
7	FBD	0.2746	0.0387	0.0638
8	Cad mill	0.5276	0.01624	0.2917
9	Octogonal Blender	0.5485	0.0498	0.099
10	Compression Machine	0.3032	0.04657	0.05845

Dispensing Booth

$$\text{Sensitivity level} = \frac{\text{Sample absorbance}}{\text{Standard absorbance}} \times \text{Standard amounts of 10ppm in 0.001\%}$$

Standard amount of 10ppm in 0.001% is 1mg.

$$\text{Concentration of drug by } 30\text{cm}^2 \text{ in sample I} = \frac{0.097}{0.742} \times 0.1\text{mg}$$

$$= 0.1307\text{mg}$$

$$\text{Concentration of drug by } 30\text{cm}^2 \text{ in sample II} = \frac{0.087}{0.742} \times 1\text{ mg}$$

$$= 0.1173\text{mg}$$

$$\text{Concentration of drug by } 30cm^2 \text{ in sample III} = \frac{0.063}{0.742} \times 1 \text{ mg}$$

$$= 0.0849mg$$

$$\text{Average concentration of drug / } 30cm^2 \text{ of the whole equipment} = \frac{0.1307+0.1173+0.0849}{3}$$

$$= 0.1109mg$$

$$\text{The amount of drug present in } 5229cm^2 \text{ of Dispensing Booth} = \frac{0.1109}{30} \times 5229$$

$$= 19.3300mg \text{ (or) } 0.01933ppm$$

Dispensing Balance

$$\text{Concentration of drug by } 30cm^2 \text{ in sample} = \frac{0.141}{0.742} \times 1 \text{ mg}$$

$$= 0.1900mg$$

$$\text{The amount of drug present in } 78.75cm^2 \text{ of Dispensing Balance } \frac{0.19}{30} \times 78.75$$

$$= 0.4988mg \text{ (or) } 0.0005ppm$$

Dispensing tools

$$\text{Concentration of drug by } 30cm^2 \text{ in sample} = \frac{0.039}{0.742} \times 1 \text{ mg}$$

$$= 0.0526mg$$

$$\text{The amount of drug present in } 60cm^2 \text{ of Dispensing Tools} = \frac{0.0526}{30} \times 60$$

$$= 0.1052mg \text{ (or) } 0.0001052ppm$$

Sifter

$$\text{Concentration of drug by } 30cm^2 \text{ in sample I} = \frac{0.118}{0.742} \times 1 \text{ mg}$$

$$= 0.1590mg$$

$$\text{Concentration of drug by } 30cm^2 \text{ in sample II} = \frac{0.092}{0.742} \times 1 \text{ mg}$$

$$= 0.1240mg$$

Average of Concentration of drug /30cm^2 of the whole equipment. $= \frac{0.1590+0.1240}{2}$

$= 0.1415$ mg

The amount of drug present in 1227cm^2 of Sifter $= \frac{0.1415}{30} X1227$

$= 5.7874$mg (or) 0.0057874 ppm

Steam Jacketed Kettle

Concentration of drug by 30cm^2 in sample I $= \frac{0.090}{0.742} x \quad 1$ mg

$= 0.1213$ mg

Concentration of drug by 30cm^2 in sample II $= \frac{0.098}{0.742} x \quad 1$ mg

$= 0.1321$mg

Average of Concentration of drug /30cm^2 of the whole equipment $= \frac{0.1213+0.1321}{2}$

$= 0.1267$ mg

The amount of drug present in 904.2cm^2 of SJK $= \frac{0.1267}{30} x904.2$

$= 3.8187$mg (or) 0.003818 ppm.

RMG

Concentration of drug by 30cm^2 in sample I $= \frac{0.110}{0.742} x \quad 1$mg

$= 0.1483$ mg

Concentration of drug by 30cm^2 in sample II $= \frac{0.107}{0.742} x \quad 1$ mg

$= 0.1442$ mg

Concentration of drug by 30cm^2 in sample III $= \frac{0.101}{0.742} x \quad 1$ mg

$= 0.1361$ mg

Average of Concentration of drug /30cm^2 of the whole equipment $= \frac{0.1483+0.1442+0.1361}{3}$

$$= \quad 0.1428 \text{ mg}$$

$$\text{The amount of drug present in } 2101.8\text{m}^2 \text{ of RMG} = \frac{0.1428}{30} \text{x} 2101.87$$

$$= 10.0046\text{mg (or) } 0.010\text{ppm.}$$

FBD

$$\text{Concentration of drug by } 30\text{cm}^2 \text{ in sample I} = \frac{0.084}{0.742} \text{ x } 1 \text{ mg}$$

$$= \quad 0.1132 \text{ mg}$$

$$\text{Concentration of drug by } 30\text{cm}^2 \text{ in sample II} = \frac{0.077}{0.742} \text{ x } 1 \text{ mg}$$

$$= \quad 0.1038 \text{ mg}$$

$$\text{Concentration of drug by } 30\text{cm}^2 \text{ in sample III} = \frac{0.081}{0.742} \text{ x } 1\text{mg}$$

$$= \quad 0.1092 \text{ mg}$$

$$\text{Concentration of drug by } 30\text{cm}^2 \text{ in sample IV} = \frac{0.081}{0.742} \text{ x } 1\text{mg}$$

$$= \quad 0.1092\text{mg}$$

$$\text{Average of Concentration of drug } /30\text{cm}^2 \text{ of the whole equipment} = \frac{0.1132+0.1038+0.1092+0.1092}{4}$$

$$= \quad 0.1089 \text{ mg}$$

$$\text{The amount of drug present in } 4225.2 \text{ cm}^2 \text{ of FBD} = \frac{0.1089}{30} \text{x } 4225.2$$

$$= 15.34 \text{ mg (or) } 0.01534 \text{ ppm.}$$

Cadmill

$$\text{Concentration of drug by } 30\text{cm}^2 \text{ in sample I} = \frac{0.392}{0.742} \text{ x } 1 \text{ mg}$$

$$= \quad 0.5283 \text{ mg}$$

$$\text{Concentration of drug by } 30\text{cm}^2 \text{ in sample II} = \frac{0.401}{0.742} \text{ x } 1\text{mg}$$

$$= \quad 0.5404 \text{ mg}$$

$$\text{Average of Concentration of drug /30cm}^2\text{ of the whole equipment} = \frac{0.5283+0.5404}{2}$$

$$= 0.5343 \text{ mg}$$

$$\text{The amount of drug present in 923.4 cm}^2\text{ of Cadmill} = \frac{0.5343}{30} \times 923.4$$

$$= 16.4458\text{mg or } 0.01645\text{ppm.}$$

Octogonal Blender

$$\text{Concentration of drug by 30cm}^2\text{ in sample I} = \frac{0.223}{0.742} \times 1 \text{ mg}$$

$$= 0.3005\text{g}$$

$$\text{Concentration of drug by 30cm}^2\text{ in sample II} = \frac{0.234}{0.742} \times 1 \text{ mg}$$

$$= 0.31 \text{ mg}$$

$$\text{Concentration of drug by 30cm}^2\text{ in sample III} = \frac{0.22}{0.742} \times 1\text{mg}$$

$$= 0.2992 \text{ mg}$$

$$\text{Average of Concentration of drug /30cm}^2\text{ of the whole equipment} = \frac{0.3005+0.31+0.2992}{3}$$

$$= 0.3033 \text{ mg}$$

$$\text{The amount of drug present in 2721 cm}^2\text{ of Blender} = \frac{0.3033}{30} \times 2721$$

$$= 27.51\text{mg (or) } 0.02751\text{ppm}$$

Compression Machine

$$\text{Concentration of drug by 30cm}^2\text{ in sample I} = \frac{0.080}{0.742} \times 1 \text{ mg}$$

$$= 0.1078 \text{ mg}$$

$$\text{Concentration of drug by 30cm}^2\text{ in sample II} = \frac{0.086}{0.742} \times 1 \text{ mg}$$

$$= 0.1159 \text{ mg}$$

$$\text{Concentration of drug by } 30cm^2 \text{ in sample III} = \frac{0.082}{0.742} \times 1mg$$

$$= 0.1105 \text{ mg}$$

$$\text{Concentration of drug by } 30cm^2 \text{ in sample IV} = \frac{0.085}{0.742} \times 1mg$$

$$= 0.1146 \text{ mg}$$

$$\text{Average of Concentration of drug /}30cm^2 \text{ of the whole equipment} = \frac{0.1078+0.1159+0.1105+0.1146}{4}$$

$$= 0.1124 \text{ mg}$$

$$\text{The amount of drug present in 4608 } cm^2 \text{ of Compression Machine } \frac{0.1124}{30} \times 4608$$

$$= 17.26mg \text{ (or) } 0.01726ppm$$

S. No.	Equipment Name	Average Concentration of drug by $30cm^2$ (mg)	Equipment in totally present amount(ppm)	Acceptance Limit (ppm)
1	Dispensing Booth	0.1109	0.01633	0.017212
2	Dispensing Balance	0.1900	0.0005	1.143
3	Dispensing tools	0.0526	0.0001052	1.5
4	Sifter	0.1415	0.00579	0.07335
5	Steam jacketed kettle	0.1267	0.00382	0.09954
6	RMG	0.1428	0.01	0.04282
7	FBD	0.1089	0.01534	0.0213
8	Cad mill	0.5343	0.01645	0.09747
9	Octogonal Blender	0.3033	0.02751	0.03308
10	Compression Machine	0.1124	0.01726	0.01953

The cleaning validation for the equipment used in manufacturing process of Albendazole tablets was carried out to provide that documented evidence with high degree of assurance that the cleaning, when followed as per standard operating procedure, yields concurrently and consistently the results which will be well within the acceptance criteria. The cleaning validation is carried out on the equipment used for manufacturing of Albendazole tablets, after following the cleaning procedure as laid down in standard operating procedure for cleaning. Samples for the analysis were obtained by swab method. The different change over of total residue carry overs Albendazole in ppm by swab method was found to be 0.188694, 0.1950662,0.1373352. All the results were found to be well with in the acceptance criteria of 8.17117, 9.12046, 3.047302ppm. The swab method is found to be a better sampling technique when compared to acceptance limit to sampling amount. With the satisfactory completion of the cleaning validation, it was concluded that the cleaning procedure followed is appropriate and satisfactory.

CONCLUSSION

In the present work, an industrial project has[Delete] procedure has been taken in Global Remedies Ltd., (A subsidiary of Strides Arco Lab Ltd.,) Hosur. The project was identified to be validated as Cleaning Validation of Albendazole tablets 400 mg. The purpose of cleaning validation is to establish the documented evidence with high degree of assurance that the cleaning process followed as per standard operating procedure for cleaning the equipment used for the processing of Albendazole tablets, consistently and concurrently yields the results not exceeding predetermined acceptance limit of the Albendazole tablets. All the equipments were selected from cross contamination point of view based on the matrix approach. Like wise, among the tablets manufacturing facility, Albendazole tablet is predicted, based on the worst case approach was developed. Then the acceptance limit is established to check the quantity of carry over of the drug Albendazole. From the previous product to the next product having the smallest batch size among all the product producing in the premises. Chloroquine phosphate tablets are found to have the minimum possible batch size (202kg) among all the products. The Erythromycin Stearate tablets are found to have the maximum formulae single dose 500mg per tablet. The MACO is determined on the basis of smallest batch size and largest single dose.

The swab samples were taken from all the equipments but other samples were taken from excluding compression machine analysis. The results of cleaning validation is found to be good within the acceptance limit(Based on swab limit and MACO approach) deals with the results and discussion with representation of tablets. From this study, it may be concluded that the results of cleaning validation is found to be well within the acceptance limit and hence the objective of the company to have an effective cleaning programme is well documented and ultimately the results were achieved.

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