



INTERNATIONAL JOURNAL  
OF PHARMA AND BIO SCIENCES

## ***Internationally Indexed Journal***

Indexed in Chemical Abstract Services(USA),Index Copernicus ,Ulrichs Directory of Periodicals,Google scholar ,Cabi ,DOAJ ,PSOAR, EBSCO ,SCOPUS, EMBASE etc.



## ***Rapid Publishing***

**The International Journal of Pharma and Bio Sciences (IJPBS) is an international journal published quarterly. The Aim of IJPBS is to publish peer reviewed research and review articles in less time without much delay in the developing field of Pharmaceutical and Biological sciences. One week from the date of manuscript submission author gets the decision of acceptance and if accepted the manuscript will be processed within 3 weeks (approx.) for publication.**

### **Pharmaceutical Sciences**

#### **Branches**

- Pharmaceutics
- Novel drug delivery sys
- Nanotechnology
- Pharmacology
- Pharmacognosy
- Analytical chemistry
- Pharmacy practice
- Pharmacogenomics
- Polymer sciences
- Biomaterial sciences
- Medicinal chemistry
- Natural chemistry
- Biotechnology
- Pharmacoinformatics
- Biopharmaceutics

### **Biological Sciences**

#### **Branches**

- Biochemistry
- Biotechnology
- Bioinformatics
- Cell biology
- Microbiology
- Allied Sciences
- Molecular biology
- Neurobiology
- Cytology
- Pathology
- Immunobiology



**Impact Factor 0.47\***

*\*Refer Instruction to authors available at  
[www.ijpbs.net](http://www.ijpbs.net)*



Indexed In Elsevier Bibliographic Database  
(SCOPUS, EMBASE and Sciverse)

Journal Home page  
[www.ijpbs.net](http://www.ijpbs.net)

FOR INSTRUCTION TO AUTHORS VISIT  
[www.ijpbs.net](http://www.ijpbs.net)

FOR ANY QUERIES EMAIL TO

- [editorofijpbs@yahoo.com](mailto:editorofijpbs@yahoo.com)
- [editorijpbs@rediffmail.com](mailto:editorijpbs@rediffmail.com)
- [prasmol@rediffmail.com](mailto:prasmol@rediffmail.com)



## CLEANING VALIDATION OF ALBENDAZOLE TABLETS 400 MG

M.JEYBASKARAN<sup>1</sup>, \*BODAVULA SAMBA SIVA RAO\* AND Y.SURENDRANATH REDDY<sup>2</sup>,

*\*I/C Principal, Department of Pharmacy, khammam college of pharmacy, khammam.*

*<sup>1</sup>Assoc. Professor, Brown's college of pharmacy, khammam.*

*<sup>2</sup>Principal, Brown's college of pharmacy, khammam.*

### 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 manufacture 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



**BODAVULA SAMBA SIVA RAO**

I/C Principal, Department of Pharmacy, khammam college of pharmacy, khammam.

*\*Corresponding author*

## 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.

### **Procedure**

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

$$\text{MACO} = \frac{\text{TDD}_{\text{previous}} \times \text{MBS}}{\text{SF} \times \text{TDD}_{\text{next}}}$$

**MACO** Maximum Allowable Carryover: acceptable transferred amount from the investigation product ("Previous")

### **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 CRITERIA**

#### **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".

<b>TDD<sub>previous</sub></b>	Standard therapeutic dose of the investigated product (in the same dosage form as: TDD)
<b>TDD<sub>next</sub></b>	Standard therapeutic dose of the daily dose for the next product.
<b>MBS</b>	Minimum batch size for the next product(s) (where MACO can end up)
<b>SF</b>	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.

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

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

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

<b>MACO</b>	Maximum Allowable Carry over: acceptable transferred amount from the investigated product (“previous”).
<b>NOEL</b>	No Observed Effect Level
<b>LD<sub>50</sub></b>	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.
<b>2000</b>	2000 is an empirical constant
<b>TDD<sub>next</sub></b>	Largest normal daily dose for the next product
<b>MBS</b>	Minimum batch size for the next products (where MACO can end up)
<b>SF</b>	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 known, 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<sub>ppm</sub>** Maximum Allowable Carryover: acceptable transferred amount from the investigated product (“previous”). Calculated from general ppm limit.

**CONC** Concentration (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 for 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:

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

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<sup>2</sup>**

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

## RESULTS AND DISCUSSION

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<sup>2</sup>).

### (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:**

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample} &= \frac{0.101}{0.742} \times 1 \text{ mg} \\ &= 0.1375\text{mg} \end{aligned}$$

$$\begin{aligned} \text{The amount of drug present in } 78.75\text{cm}^2 \text{ of Dispensing Balance} &= \frac{0.137}{30} \times 78.75 \\ &= 0.3609\text{mg (or) } 0.000361\text{ppm} \end{aligned}$$

**Dispensing tools**

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample} &= \frac{0.027}{0.742} \times 1 \text{ mg} \\ &= 0.0364\text{mg} \end{aligned}$$

$$\begin{aligned} \text{The amount of drug present in } 60\text{cm}^2 \text{ of Dispensing Tools} &= \frac{0.0364}{30} \times 60 \\ &= 0.0728\text{mg (or) } 0.000073\text{ppm} \end{aligned}$$

**Sifter**

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample I} &= \frac{0.109}{0.742} \times 1 \text{ mg} \\ &= 0.1469\text{mg} \end{aligned}$$

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample II} &= \frac{0.092}{0.742} \times 1 \text{ mg} \\ &= 0.1240\text{mg} \end{aligned}$$

$$\begin{aligned} \text{Average of Concentration of drug / } 30\text{cm}^2 \text{ of the whole equipment.} &= \frac{0.1469+0.1240}{2} \\ &= 0.1354 \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{The amount of drug present in } 1227\text{cm}^2 \text{ of Sifter} &= \frac{0.1354}{30} \times 1227 \\ &= 5.5378\text{mg (or) } 0.00554 \text{ ppm} \end{aligned}$$

**Steam Jacketed Kettle**

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample I} &= \frac{0.084}{0.742} \times 1 \text{ mg} \\ &= 0.1132 \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample II} &= \frac{0.092}{0.742} \times 1 \text{ mg} \\ &= 0.1240\text{mg} \end{aligned}$$

$$\begin{aligned} \text{Average of Concentration of drug /}30\text{cm}^2 \text{ of the whole equipment} &= \frac{0.1132 + 0.1240}{2} \\ &= 0.1186 \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{The amount of drug present in } 904.2\text{cm}^2 \text{ of SJK} &= \frac{0.1186}{30} \times 904.2 \\ &= 3.5746\text{mg (or) } 0.00358 \text{ ppm.} \end{aligned}$$

**RMG**

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample I} &= \frac{0.064}{0.742} \times 1 \text{ mg} \\ &= 0.08625 \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample II} &= \frac{0.077}{0.742} \times 1 \text{ mg} \\ &= 0.1038 \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample III} &= \frac{0.075}{0.742} \times 1 \text{ mg} \\ &= 0.1011 \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{Average of Concentration of drug /}30\text{cm}^2 \text{ of the whole equipment} &= \frac{0.08625+0.1030+0.1011}{3} \\ &= 0.09705 \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{The amount of drug present in } 2101.8\text{m}^2 \text{ of RMG} &= \frac{0.09705}{30} \times 2101.8 \\ &= 6.7993\text{mg (or) } 0.0068\text{ppm.} \end{aligned}$$

**FBD**

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample I} &= \frac{0.202}{0.742} \times 1 \text{ mg} \\ &= 0.2722 \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample II} &= \frac{0.167}{0.742} \times 1 \text{ mg} \\ &= 0.2251 \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample III} &= \frac{0.178}{0.742} \times 1 \text{ mg} \\ &= 0.2399 \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample IV} &= \frac{0.218}{0.742} \times 1 \text{ mg} \\ &= 0.2938 \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{Average of Concentration of drug / } 30\text{cm}^2 \text{ of the whole equipment} &= \frac{0.2722+0.2251+0.2399+0.2938}{4} \\ &= 0.2577 \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{The amount of drug present in } 4225.2 \text{ cm}^2 \text{ of FBD} &= \frac{0.2577}{30} \times 4225.2 \\ &= 36.2945 \text{ mg (or) } 0.0363 \text{ ppm.} \end{aligned}$$

**Cadmil**

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample I} &= \frac{0.472}{0.742} \times 1 \text{ mg} \\ &= 0.6361 \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample II} &= \frac{0.397}{0.742} \times 1 \text{ mg} \\ &= 0.5350 \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{Average of Concentration of drug / } 30\text{cm}^2 \text{ of the whole equipment} &= \frac{0.6361 + 0.5350}{2} \\ &= 0.5855 \text{ mg} \end{aligned}$$

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

$$= 18.0217\text{mg or } 0.018\text{ppm.}$$

### ***Octagonal Blender***

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

$$= 0.5094 \text{ mg}$$

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

$$= 0.5768 \text{ mg}$$

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

$$= 0.5822 \text{ mg}$$

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

$$= 0.5561 \text{ mg}$$

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

$$= 50.4384\text{mg (or) } 0.05044\text{ppm}$$

### ***Compression Machine***

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

$$= 0.3383 \text{ mg}$$

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

$$= 0.2453 \text{ mg}$$

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

$$= 0.2992 \text{ mg}$$

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample IV} &= \frac{0.191}{0.742} \times 1\text{mg} \\ &= 0.2574 \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{Average of Concentration of drug /} 30\text{cm}^2 \text{ of the whole equipment} &= \frac{0.3383+0.2453+0.2992+0.2574}{4} \\ &= 0.2850 \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{The amount of drug present in } 4608 \text{ cm}^2 \text{ of Compression Machine} &= \frac{0.2850}{30} \times 4608 \\ &= 43.776\text{mg (or) } 0.0438\text{ppm} \end{aligned}$$

## II. Albandazole tablets to Chloroquine phosphate tablets BP 100mg

S. No.	Equipment Name	Average Concentration of drug by 30cm <sup>2</sup> (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

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

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

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample I} &= \frac{0.126}{0.742} \times 0.1\text{mg} \\ &= 0.1698\text{mg} \end{aligned}$$

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample II} &= \frac{0.089}{0.742} \times 1 \text{ mg} \\ &= 0.1200\text{mg} \end{aligned}$$

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample III} &= \frac{0.102}{0.742} \times 1 \text{ mg} \\ &= 0.1375\text{mg} \end{aligned}$$

$$\begin{aligned} \text{Average concentration of drug / } 30\text{cm}^2 \text{ of the whole equipment} &= \frac{0.1698+0.1200+0.1375}{3} \\ &= 0.1424\text{mg} \end{aligned}$$

$$\begin{aligned} \text{The amount of drug present in } 5229\text{cm}^2 \text{ of Dispensing Booth} &= \frac{0.1424}{30} \times 5229 \\ &= 24.8205\text{mg (or) } 0.02482\text{ppm} \end{aligned}$$

### ***Dispensing Balance***

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample} &= \frac{0.113}{0.742} \times 1 \text{ mg} \\ &= 0.1523\text{mg} \end{aligned}$$

$$\begin{aligned} \text{The amount of drug present in } 78.75\text{cm}^2 \text{ of Dispensing Balance} &= \frac{0.1523}{30} \times 78.75 \\ &= 0.3998\text{mg (or) } 0.0003998\text{ppm} \end{aligned}$$

### ***Dispensing tools***

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample} &= \frac{0.042}{0.742} \times 1 \text{ mg} \\ &= 0.0566\text{mg} \end{aligned}$$

$$\begin{aligned} \text{The amount of drug present in } 60\text{cm}^2 \text{ of Dispensing Tools} &= \frac{0.0566}{30} \times 60 \\ &= 0.1132\text{mg (or) } 0.0001132\text{ppm} \end{aligned}$$

### ***Sifter***

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample I} &= \frac{0.122}{0.742} \times 1 \text{ mg} \\ &= 0.1644\text{mg} \end{aligned}$$

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample II} &= \frac{0.088}{0.742} \times 1 \text{ mg} \\ &= 0.1186\text{mg} \end{aligned}$$

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

$$= 0.1415 \text{ mg}$$

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

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

### **Steam Jacketed Kettle**

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

$$= 0.1375 \text{ mg}$$

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

$$= 0.1267\text{mg}$$

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

$$= 0.1321 \text{ mg}$$

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

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

### **RMG**

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

$$= 0.1092 \text{ mg}$$

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

$$= 0.1375 \text{ mg}$$

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

$$= 0.1240 \text{ mg}$$

$$\text{Average of Concentration of drug} = \frac{0.1092+0.1375+0.1240}{3}$$

/30cm<sup>2</sup> of the whole equipment

$$= 0.1235 \text{ mg}$$

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

$$= 8.6525\text{mg (or) } 0.0086525\text{ppm.}$$

**FBD**

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

$$= 0.3262 \text{ mg}$$

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

$$= 0.2830 \text{ mg}$$

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

$$= 0.2412 \text{ mg}$$

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

$$= 0.2480\text{mg}$$

$$\text{Average of Concentration of drug} = \frac{0.3262+0.2830+0.2412+0.2480}{4}$$

/30cm<sup>2</sup> of the whole equipment

$$= 0.2746 \text{ mg}$$

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

$$= 38.6745\text{mg (or) } 0.0386745\text{ppm.}$$

**Cadmil**

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

$$= 0.5553 \text{ mg}$$

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

$$= 0.5 \text{ mg}$$

$$\begin{aligned} \text{Average of Concentration of drug} &= \frac{0.5553+0.5}{2} \\ /30\text{cm}^2 \text{ of the whole equipment} & \\ &= 0.5276 \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{The amount of drug present in } 923.4 \text{ cm}^2 \text{ of Cadmill} &= \frac{0.5276}{30} \times 923.4 \\ &= 16.2396\text{mg or } 0.016239\text{ppm}. \end{aligned}$$

### **Octagonal Blender**

$$\begin{aligned} \text{Concentration of drug} &= \frac{0.412}{0.742} \times 1 \text{ mg} \\ \text{by } 30\text{cm}^2 \text{ in sample I} & \\ &= 0.5553 \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{Concentration of drug} &= \frac{0.378}{0.742} \times 1 \text{ mg} \\ \text{by } 30\text{cm}^2 \text{ in sample II} & \\ &= 0.5094 \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{Concentration of drug} &= \frac{0.431}{0.742} \times 1 \text{ mg} \\ \text{by } 30\text{cm}^2 \text{ in sample III} & \\ &= 0.5809 \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{Average of Concentration of drug} &= \frac{0.5553+0.5094+0.5809}{3} \\ /30\text{cm}^2 \text{ of the whole equipment} & \\ &= 0.5485 \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{The amount of drug present in } 2721 \text{ cm}^2 \text{ of Blender} &= \frac{0.5485}{30} \times 2721 \\ &= 49.7489\text{mg (or) } 0.0497489\text{ppm} \end{aligned}$$

### **Compression Machine**

$$\begin{aligned} \text{Concentration of drug} &= \frac{0.262}{0.742} \times 1 \text{ mg} \\ \text{by } 30\text{cm}^2 \text{ in sample I} & \\ &= 0.3531 \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{Concentration of drug by} &= \frac{0.192}{0.742} \times 1 \text{ mg} \\ 30\text{cm}^2 \text{ in sample II} & \\ &= 0.2588 \text{ mg} \end{aligned}$$

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

$$= 0.2857 \text{ mg}$$

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

$$= 0.3154 \text{ mg}$$

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

$$= 0.3032 \text{ mg}$$

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

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

### III. Albendazole tablets to Erythromycin Stearate tablets 500mg

S. No.	Equipment Name	Average Concentration of drug by 30cm <sup>2</sup> (mg)	Equipment in totally present amount(ppm)	Acceptance (ppm)	Limit
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

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

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

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

$$= 0.1307\text{mg}$$

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

$$= 0.1173\text{mg}$$

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample III} &= \frac{0.063}{0.742} \times 1 \text{ mg} \\ &= 0.0849\text{mg} \\ \text{Average concentration of drug / } 30\text{cm}^2 \text{ of the whole equipment} &= \frac{0.1307+0.1173+0.0849}{3} \\ &= 0.1109\text{mg} \end{aligned}$$

$$\begin{aligned} \text{The amount of drug present in } 5229\text{cm}^2 \text{ of Dispensing Booth} &= \frac{0.1109}{30} \times 5229 \\ &= 19.3300\text{mg (or) } 0.01933\text{ppm} \end{aligned}$$

### ***Dispensing Balance***

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample} &= \frac{0.141}{0.742} \times 1 \text{ mg} \\ &= 0.1900\text{mg} \end{aligned}$$

$$\begin{aligned} \text{The amount of drug present in } 78.75\text{cm}^2 \text{ of Dispensing Balance} &= \frac{0.19}{30} \times 78.75 \\ &= 0.4988\text{mg (or) } 0.0005\text{ppm} \end{aligned}$$

### ***Dispensing tools***

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample} &= \frac{0.039}{0.742} \times 1 \text{ mg} \\ &= 0.0526\text{mg} \end{aligned}$$

$$\begin{aligned} \text{The amount of drug present in } 60\text{cm}^2 \text{ of Dispensing Tools} &= \frac{0.0526}{30} \times 60 \\ &= 0.1052\text{mg (or) } 0.0001052\text{ppm} \end{aligned}$$

### ***Sifter***

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample I} &= \frac{0.118}{0.742} \times 1 \text{ mg} \\ &= 0.1590\text{mg} \end{aligned}$$

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample II} &= \frac{0.092}{0.742} \times 1 \text{ mg} \\ &= 0.1240\text{mg} \end{aligned}$$

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

$$= 0.1415 \text{ mg}$$

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

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

### **Steam Jacketed Kettle**

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

$$= 0.1213 \text{ mg}$$

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

$$= 0.1321 \text{mg}$$

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

$$= 0.1267 \text{ mg}$$

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

$$= 3.8187 \text{mg (or) } 0.003818 \text{ ppm.}$$

### **RMG**

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

$$= 0.1483 \text{ mg}$$

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

$$= 0.1442 \text{ mg}$$

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

$$= 0.1361 \text{ mg}$$

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

$$= 0.1428 \text{ mg}$$

$$\begin{aligned} \text{The amount of drug present in } 2101.8\text{m}^2 \text{ of RMG} &= \frac{0.1428}{30} \times 2101.87 \\ &= 10.0046\text{mg (or) } 0.010\text{ppm.} \end{aligned}$$

**FBD**

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

$$= 0.1132 \text{ mg}$$

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

$$= 0.1038 \text{ mg}$$

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample III} &= \frac{0.081}{0.742} \times 1 \text{ mg} \end{aligned}$$

$$= 0.1092 \text{ mg}$$

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample IV} &= \frac{0.081}{0.742} \times 1 \text{ mg} \end{aligned}$$

$$= 0.1092\text{mg}$$

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

$$= 0.1089 \text{ mg}$$

$$\begin{aligned} \text{The amount of drug present in } 4225.2 \text{ cm}^2 \text{ of FBD} &= \frac{0.1089}{30} \times 4225.2 \end{aligned}$$

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

**Cadmil**

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample I} &= \frac{0.392}{0.742} \times 1 \text{ mg} \end{aligned}$$

$$= 0.5283 \text{ mg}$$

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample II} &= \frac{0.401}{0.742} \times 1 \text{ mg} \end{aligned}$$

$$= 0.5404 \text{ mg}$$

$$\begin{aligned} \text{Average of Concentration of drug} &= \frac{0.5283+0.5404}{2} \\ /30\text{cm}^2 \text{ of the whole equipment} & \\ &= 0.5343 \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{The amount of drug present in } 923.4 \text{ cm}^2 \text{ of Cadmill} &= \frac{0.5343}{30} \times 923.4 \\ &= 16.4458\text{mg or } 0.01645\text{ppm.} \end{aligned}$$

### **Octogonal Blender**

$$\begin{aligned} \text{Concentration of drug} &= \frac{0.223}{0.742} \times 1 \text{ mg} \\ \text{by } 30\text{cm}^2 \text{ in sample I} & \\ &= 0.3005\text{g} \end{aligned}$$

$$\begin{aligned} \text{Concentration of drug} &= \frac{0.234}{0.742} \times 1 \text{ mg} \\ \text{by } 30\text{cm}^2 \text{ in sample II} & \\ &= 0.31 \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{Concentration of drug} &= \frac{0.22}{0.742} \times 1\text{mg} \\ \text{by } 30\text{cm}^2 \text{ in sample III} & \\ &= 0.2992 \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{Average of Concentration of drug} &= \frac{0.3005+0.31+0.2992}{3} \\ /30\text{cm}^2 \text{ of the whole equipment} & \\ = 0.3033 & \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{The amount of drug present in } 2721 \text{ cm}^2 \text{ of Blender} &= \frac{0.3033}{30} \times 2721 \\ &= 27.51\text{mg (or) } 0.02751\text{ppm} \end{aligned}$$

### **Compression Machine**

$$\begin{aligned} \text{Concentration of drug} &= \frac{0.080}{0.742} \times 1 \text{ mg} \\ \text{by } 30\text{cm}^2 \text{ in sample I} & \\ &= 0.1078 \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{Concentration of drug by} &= \frac{0.086}{0.742} \times 1 \text{ mg} \\ 30\text{cm}^2 \text{ in sample II} & \\ &= 0.1159 \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample III} &= \frac{0.082}{0.742} \times 1\text{mg} \\ &= 0.1105 \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{Concentration of drug by } 30\text{cm}^2 \text{ in sample IV} &= \frac{0.085}{0.742} \times 1\text{mg} \\ &= 0.1146 \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{Average of Concentration of drug /} 30\text{cm}^2 \text{ of the whole equipment} &= \frac{0.1078+0.1159+0.1105+0.1146}{4} \\ &= 0.1124 \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{The amount of drug present in } 4608 \text{ cm}^2 \text{ of Compression Machine} &= \frac{0.1124}{30} \times 4608 \\ &= 17.26\text{mg (or) } 0.01726\text{ppm} \end{aligned}$$

S. No.	Equipment Name	Average Concentration of drug by 30cm <sup>2</sup> (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 within 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.

## CONCLUSION

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.

## REFERENCES

1. British Pharmacopoeia, Vol. 1, 1993, 365,611.
2. Cleaning validation Interpretation of the ICH guidelines for API, Sec-12.7, Cleaning Validation.
3. Constance J.A., "Why some dust control system Don't work", Pharm Eng., Jan-Feb, 24-26(1983).
4. Destin A. LeBlanc, "Cleaning Validation Technologies Technical Consulting Services" August 2002.
5. FDA, Guide to Inspections of Validation of Cleaning Processes, 1993
6. Fourman, G.L. and Mullen, M.V., "Determining cleaning validation acceptance limits for pharmaceutical manufacturing operations," Pharm Technol. 17(94), 54-60 (1993).
7. Gary L. Pourman and Michael V. Mullen, "Determining Cleaning Validation Acceptance Limits for Pharmaceutical Manufacturing Operations, Pharmaceutical Technology International, Jun 1993.
8. Gerald K. McEvoy, Kathy Litvak, M.S., Olin H. Welsh, J., et al., AHFS Drug information, pub: American society of health-system pharmacists, 54, 2001.
9. Harder S.W., "The Validation of cleaning procedures", Pharm. Technol. 8(5), 29-34 (1984).
10. Jenkins K.M., A.J. Vanderwielen, Ph.D., Cleaning validation an overall perspective in Pharmaceutical Technology, Apr 1994.
11. Martin Dale, The extra pharmacopoeia, 20<sup>th</sup> edition, 86.
12. McCormick, P.Y. and Cullen, L.F., in pharmaceutical Process Validation, 2<sup>nd</sup> Ed. Edited by I.R. Berry and R.A. Nash, 319-349 (1993).

13. Mead.W.J., "Maintenance its interrelationship with Drug Quality", Pharm Eng7(3), 29-33 (1987).
14. Pharmaceutical Inspection Convention Draft Document, Recommendations on Validation, Master Plan, Installation and Operational Qualification, Non-sterile Process Validation and Cleaning Validation, 1998.
15. Rodehamel J., "Cleaning and Maintenance", Pgs 82-87, University of Wisconsin's Control Procedures in Drug Production Seminar, July 17-22, 1966, William Blockstein, Editor, Published by the University of Wisconsin, L.O.C. #66-64234.
16. Smith J.A., "A modified Swabbing Technique for Validation of Detergent Residues in Clean – in place systems", Pharm. Technol. 16(1), 60-66 (1992).
17. USP 25 & NF 2002, 54.
18. Practice of Validation and Principles by K.Kathresan and K.K.Suresh.. American publishing house.