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DEVELOPMENT AND CLEANING VALIDATION OF METFORMIN HCL TABLET BY SWAP TECHNIQUE

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ABSTRACT:
In the present work, an industrial project procedure has been taken in Cassel research laboratory Chennai. The project was identified to be validated as cleaning validation of Metformin tablets. 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 metformin tablets. The research work was carried out by swap cleaning method and the test has been performed on various equipments which are used for metformin tablet manufacturing of a particular batch. The cleaning solution was analyzed by UV spectroscopy at 232nm. The different changeover of total residue carry over metformin in ppm by swab method was found to be 0.21166. All the results were found to be well within the acceptance criteria of 1.8752 ppm and it's finally concluded that 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.

Keywords: Metformin, Validation, Swap technique.

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INTRODUCTION

"A validated manufacturing process is one, which has been provided to do what it purpose to or is represented to do. The proof of validation is obtained through the collection and evaluation of data, preferably, beginning from the process development phase and continued through into the production phase. Validation necessarily includes process qualification but it also includes the control of the entire process for repeated batches or runs[1]."

Cross-contamination is a significant risk to patients. This is true whether through direct administration to a patients or in the case of in vitro diagnostics through the performances of a test on a patient samples. Cleaning and cleaning validation are two activities that have the largest opportunity to prevent patient risk by assuring that no cross contamination can occur. Cleaning validation is becoming more and more important as we work with increasingly potent, increasingly complicated drug substances and increasingly complex biotechnology products. Our products have greater and greater risks of interaction with one another resulting in harmful effects to patients. To truly limit this risk, scientific approaches must be taken in all aspects of the cleaning and cleaning validation program[2].

Cleaning Procedures

Written cleaning procedures for each piece of equipment and process must be prepared. It is vital that the equipment design is evaluated in detail in conjunction with the product residues to be removed, the available cleaning agents and cleaning techniques when determining the optimum cleaning procedure for the equipment [3,4].

Reason for Cleaning Validation

The objectives of equipment cleaning and cleaning validation in an Active Pharmaceutical Ingredient (API) area are same as those in pharmaceutical production area. In both these areas efforts are necessary to prevent contamination of a future batch with the previous batch material.

The cleaning of 'difficult to reach' surface is one of the most important consideration in equipment cleaning

validation. Equipment cleaning validation in an API facility is extremely important as cross contamination in one of the pharmaceutical dosage forms, will multiply the problem. Therefore, it is important to do a step-by-step evaluation of API process to determine the most practical and efficient way to monitor the effectiveness of the cleaning process.

It is necessary to validate cleaning procedures for the following reasons

1. It is a prime customer requirement since it ensures the purity and safety of the product.
2. It is a regulatory requirement in Active Pharmaceutical Ingredient product manufacture.
3. It also assures the quality of the process through an internal control and compliance[5].

Types of Contaminations

1. Cross contamination with active ingredients: Contamination of one batch of product with significant levels of residual active ingredients from a previous batch cannot be tolerated. In addition to the obvious problems posed by subjecting consumers or patients to unintended contaminants, potential clinically significant synergistic interactions between pharmacologically active chemicals are a real concern.

2. Contamination with unintended materials or compounds: While inert ingredients used in drug products are generally recognized as safe or have been shown to be safe for human consumption, the routine use, maintenance and cleaning of equipments provide the potential contamination with such items as equipment parts, lubricants, chemical cleaning agents and pieces of cleaning tools such as brushes and rags.

3. Microbiological contamination: Maintenance, cleaning and storage conditions may provide adventitious micro organisms with the opportunity to proliferate within the processing equipment[6].

Sampling Technique

Generally there are two types of sampling that are accepted. The most desirable is the direct method of sampling the surface of the equipment, another method being the use of rinse sampling.

1. Direct surface sampling: It involves the determination of the type of sampling material used and its impact on the test data to check the interference of the sampling material with the test. Therefore, early in the validation programme, it is crucial to assure the sampling medium and solvent if they are satisfactory and be readily used. Advantages of direct sampling are that, areas hardest to clean and which are reasonably accessible can be evaluated, leading to establishing a level of contamination or residue per given surface area. Additionally, residues that are "dried out" or are insoluble can be sampled by physical removal.

2. Swab sampling: After cleaning the equipment, product contact surfaces could be swabbed to evaluate surface cleanliness. Swabs used should be compatible with the active ingredients and should not interfere with the assay. They should not cause any degradation of the compound. The solvent used for swabbing should provide good solubility for the compound and should not encourage degradation.

3. Rinse sampling: Sampling and testing of rinse samples for residual active ingredient is a commonly adopted method to evaluate cleanliness. This is a fairly convenient method in many cases and requires control over the solvent used for rinsing, the contact time and the mixing involved. The solvent used should be selected based on the solubility of the active ingredient and should either simulate a subsequent batch of product or at least provide adequate solubility.

A disadvantage of rinse samples is that the residue or contaminant may not be soluble or may be physically occluded in the equipment. An analogy that can be used is the "dirty pot." In the evaluation of cleaning of a dirty pot, particularly with dried out residue, one does not look at the rinse water to see that it is clean; one looks at the pot[7-13].

MATERIALS AND METHODS

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”.

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.

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

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
LD50: Lethal Dose 50 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).

(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.
CONC: Concentration (kg/kg or ppm) of "Previous" substance in the next batch. Based on MACO calculated from therapeutic doses and / 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:

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

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.

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: 30cm2)[14].

CLEANING VALIDATION IN DISPENSING BOOTH

Dispensing booth is used to perform dispensing operations in pharmaceutical industries. The equipments serve as safety equipment to operator doing the dispensing operation. In dispensing booth big packing of dangerous chemicals are dispensed to small packing by operator under class 100 environments and 10% exhaust system adopted. Dispensing unit is always a negative pressure unit and air is circulated from outside to inside of the equipment. Hence during dispensing operation powder is always sucked at pre filter given at the bottom of the cabinet so that chemicals do not affect the operator.

Table. 1: Cleaning validation in dispensing booth

S.No	Name of the Component	Description
1	Cabinet	Body is made up of SS 304 sheets hair line fi nish of grit 160 and thickness 1.0 mm
2	Side frame	Puf filled sandwich panel of SS 304 sheets
3	Motor	R4e-225-cc 01-023pc made in germany
4	Blower	Dynamically balanced al blower with high static pressure low vibration level
5	Switch	Electric switch made in china -03nos
6	Tube light	Philips make -30 watts|cfl|-2nos
7	Magnehelic guage	Dwyer make magnehelic gauge are used to measure the pressure drop across hepa filter 0-500pa
8	Front door	Front door flexible curtain(vynle) 3mm thickness-01nos

Dispensing will generate fine dust. That might eventually cause risk to operators and also products. One should have a cleaning process to prevent any cross contamination and product exposure. Dispensing tools must be separate. We cannot have a separate LAF but scoops and other utensils must be separate. It's essential to clean dispensing area and validate.

Procedure

The main objective of this procedure is to establish a procedure for swab sampling for validation of test surface to evaluate cleaning efficacy.

Making of swap stick: swap sticks are prepared by using sterile cotton.

Transport container: Capped test tubes made of glass.

Sampling solvent: Water/ as mentioned in the validation protocol of analytical method used for analysis of swab samples of respective active ingredients.

Instrument for measuring absorbance: Ultra Violet spectroscopy: Pipette out 10ml of sampling solvent in transport container. Remove a swab from its protective bag using a clean latex hand glove. Avoid touching the swab head to prevent its contamination. Transfer the swab in transport container (test tube) containing 10ml of sampling solvent and allow the swab to soak completely. Take out the swab from sampling solvent and squeeze the tip against inner surface of test tube to remove excess solvent in such a manner that excess sampling solvent drips inside the test tube.

Hold the stem of swab without touching the head of the swab. Using moistened swab wipe the test surface of 30cm². (horizontal strokes). At the end of each stroke, lift the swab carefully. Turn the swab over to its other side, wipe the test surface 30cm² (vertical). At the end of each stroke, lift the swab carefully. Hold the steam of the swab without touching the head of the swab and let the swab drop into the transport container. Cap the transport container and send for analysis after labeling the same. Calculate the content of $C_4H_{11}N_5$,HCl taking 798 as the value of A(1%, 1 cm) at the maximum at about 232 nm.

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

Table. 2: Standard amount of 10ppm in 0.001% is 1mg.

S.No	Sample	Std absorbance	Test absorbance	Concentration in 30cm² (mg)
1	I	0.852	0.241	0.282
2	II		0.181	0.212
3	III		0.101	0.118

$$\text{Concentration of drug by 30cm}^2\text{ in sample 1} = \frac{0.241}{0.852} \times 1$$

$$= 0.282\text{mg}$$

$$\text{Concentration of drug by 30cm}^2\text{ in sample 2} = \frac{0.181}{0.852} \times 1$$

$$= 0.212\text{mg}$$

$$\text{Concentration of drug by 30cm}^2\text{ in sample 3} = \frac{0.101}{0.852} \times 1$$

$$= 0.118\text{mg}$$

$$\text{Average concentration of drug / 30cm}^2\text{ of the whole equipment} = \frac{0.282+0.212+0.118}{3}$$

$$= 0.204\text{mg}$$

$$\text{The amount of drug present in 5560cm}^2\text{ of Dispensing Booth} = \frac{0.204}{30} \times 5560$$

$$= 37.808\text{mg or } 0.03781 \text{ ppm}$$

CLEANING VALIDATION IN DISPENSING BALANCE

Make: omega
Model: OPW
Capacity: 500kg
Resolution: 100g
Procedure:
Making of swap stick: Swap sticks are prepared by using sterile cotton.
Transport container: Capped test tubes made of glass.
Sampling solvent: Water/ as mentioned in the validation protocol of analytical method used for analysis of swab samples of respective active ingredients.
Instrument for measuring absorbance: Ultra Violet spectroscopy
Check and ensure the cleanness of the dispensing balance before start validation process. Select test surface area 30cm² in dispensing balance. Remove a swab from its protective bag using a clean latex hand glove. Pipette out 10ml of sampling of water in transport container. Transfer the swab in transport container (test tube) containing 10ml of sampling solvent and allow the swab to soak completely. Using moistened swab wipe the test surface of dispensing balance 30cm². (horizontal strokes). Turn the swab over to its other side; wipe the test surface 30cm² (vertical). Hold the steam of the swab without touching the head of the swab and let the swab drop into the transport container. Cap the transport container and send for analysis after labeling the same. Calculate the content of $C_4H_{11}N_5$,HCl taking 798 as the value of A(1%, 1 cm) at the maximum at about 232 nm.

Table. 3: Cleaning validation in dispensing balance

S. No.	Sample	Std absorbance	Test absorbance	Concentration in 30cm² (mg)
1	I	0.852	0.189	0.221
2	II		0.201	0.239
3	III		0.078	0.091

$$\text{Concentration of drug by 30cm}^2\text{ in sample 1} = \frac{0.189}{0.852} \times 1$$
$$= 0.221\text{mg}$$
$$\text{Concentration of drug by 30cm}^2\text{ in sample 2} = \frac{0.201}{0.852} \times 1$$
$$= 0.239\text{mg}$$
$$\text{Concentration of drug by 30cm}^2\text{ in sample 3} = \frac{0.078}{0.852} \times 1$$
$$= 0.091\text{mg}$$
$$\text{Average concentration of drug / 30cm}^2\text{ of the whole equipment} = \frac{0.221+0.239+0.091}{3}$$
$$= 0.182\text{mg}$$
$$\text{The amount of drug present in 80.85cm}^2\text{ of Dispensing balance} = \frac{0.182}{30} \times 80.85$$
$$= 0.490\text{mg or } 0.00049\text{ppm}$$

CLEANING VALIDATION IN SIFTER

Making of swap stick: swap sticks are prepared by using sterile cotton
Transport container: Capped test tubes made of glass.
Sampling solvent: Water/ as mentioned in the validation protocol of analytical method used for analysis of swab samples of respective active ingredients.
Instrument for measuring absorbance: Ultra Violet spectroscopy
Check and record the temperature and relative humidity in processing area temperature, should be 25 ±2°C & RH 45±5%. Check and ensure visually all the equipment and equipment parts are cleaned. Remove a swab from its protective bag using a clean latex hand glove. Pipette out 10ml of sampling of water in transport container. Transfer the swab in transport container (test tube) containing 10ml of water and allow the swab to soak completely. Using moistened swab wipe the test surface of sifter 30cm². (horizontal strokes). Turn the swab over to its other side; wipe the test surface 30cm² (vertical). Hold the steam of the swab without touching the head of the swab and let the swab drop into the transport container. Cap the transport container and send for analysis after labeling the same. Calculate the content of $C_4H_{11}N_5$,HCl taking 798 as the value of A(1%, 1 cm) at the maximum at about 232 nm.

Table. 4: Cleaning validation in sifter

S. No	Sample	Std absorbance	Test absorbance	Concentration in 30cm² (mg)
1	I	0.852	0.115	0.176
2	II		0.228	0.267
3	III		0.072	0.084

$$\text{Concentration of drug by 30cm}^2\text{ in sample 1} = \frac{0.115}{0.852} \times 1$$
$$= 0.176\text{mg}$$
$$\text{Concentration of drug by 30cm}^2\text{ in sample 2} = \frac{0.228}{0.852} \times 1$$
$$= 0.267\text{mg}$$
$$\text{Concentration of drug by 30cm}^2\text{ in sample 3} = \frac{0.072}{0.852} \times 1$$
$$= 0.084\text{mg}$$
$$\text{Average concentration of drug by 30cm}^2\text{ of the whole equipment} = \frac{0.176+0.267+0.084}{3}$$
$$= 0.175\text{mg}$$
$$\text{The amount of drug present in 1350cm}^2\text{ of sifter} = \frac{0.175}{30} \times 1350$$
$$= 7.914\text{mg or } 0.00791\text{ppm}$$

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CLEANING VALIDATION IN RIBBON MIXER

Model- GU-660 Double Spiral Ribbon Blender,
Gross capacity ---226 gallons (858 liters),
Net capacity -174 gallons (660 liters),
Speed -30 rpm,.

After unloading of the selected validation production batch of metformin HCl tablet the mixer is washed as per its respective approved cleaning procedure. The special extended sampling should be executed from different locations/parts of the mixer. Remove a swab from its protective bag using a clean latex hand glove. Pipette out 10ml of sampling of water in transport container. Transfer the swab in transport container (test tube) containing 10ml of water and allow the swab to soak completely. Using moistened swab wipe the test surface of mixer 30cm². (horizontal strokes). Turn the swab over to its other side; wipe the test surface 30cm² (vertical). Hold the steam of the swab without touching the head of the swab and let the swab drop into the transport container. Cap the transport container and send for analysis after labeling the same. Calculate the content of $C_4H_{11}N_5$, HCl taking 798 as the value of A (1%, 1 cm) at the maximum at about 232 nm.

Table. 5: Cleaning validation in ribbon mixer

S. No.	Sample	Std absorbance	Test absorbance	Concentration in 30cm² (mg)
1	I	0.852	0.192	0.205
2	II		0.175	0.091
3	III		0.201	0.235

$$\text{Concentration of drug by 30cm}^2\text{ in sample 1} = \frac{0.192}{0.852} \times 1 = 0.225\text{mg}$$

$$\text{Concentration of drug by 30cm}^2\text{ in sample 2} = \frac{0.175}{0.852} \times 1 = 0.205\text{mg}$$

$$\text{Concentration of drug by 30cm}^2\text{ in sample 3} = \frac{0.201}{0.852} \times 1 = 0.235\text{mg}$$

$$\text{Average concentration of drug by 30cm}^2\text{ of the whole equipment} = \frac{0.225+0.205+0.235}{3} = 0.221\text{mg}$$

$$\text{The amount of drug present in 3352cm}^2\text{ of Ribbon mixer} = \frac{0.221}{30} \times 3352 = 24.69\text{mg or } 0.02469\text{ppm}$$

CLEANING VALIDATION IN TRAY DRYER

Cleaning procedure for tray dryer

Switch off the electrical main of tray dryer. Remove under use label and put to be cleaned label. Remove the dust from the body with dry duster. Open the door, remove all the trays and take it in washing room. Clean each tray by potable water followed by 0.1% Detergent solution using nylon scrubber. Clean each tray with potable water followed by purified water. Remove water with the help of compressed air; dry all the trays with a clean lint free cloth.

Remove a swab from its protective bag using a clean latex hand glove. Pipette out 10ml of sampling of water in transport container. Transfer the swab in transport container (test tube) containing 10ml of water and allow the swab to soak completely. Using moistened swab wipe the test surface of tray dryer 30cm². (horizontal strokes). Turn the swab over to its other side, wipe the test surface 30cm² (vertical). Hold the steam of the swab without touching the head of the swab and let the swab drop into the transport container. Cap the transport container and send for analysis after labeling the same. Calculate the content of $C_4H_{11}N_5$, HCl taking 798 as the value of A (1%, 1 cm) at the maximum at about 232 nm.

Table. 6: Cleaning validation in tray dryer

S. No.	Sample	Std absorbance	Test absorbance	Concentration in 30cm² (mg)
1	I	0.852	0.358	0.420
2	II		0.352	0.413
3	III		0.152	0.178

$$\text{Concentration of drug by 30cm}^2\text{ in sample 1} = \frac{0.358}{0.852} \times 1 = 0.420\text{mg}$$

$$\text{Concentration of drug by 30cm}^2\text{ in sample 2} = \frac{0.352}{0.852} \times 1 = 0.413\text{mg}$$

$$\text{Concentration of drug by 30cm}^2\text{ in sample 3} = \frac{0.152}{0.852} \times 1 = 0.178\text{mg}$$

$$\text{Average concentration of drug by 30cm}^2\text{ of the whole equipment} = \frac{0.420+0.413+0.178}{3} = 0.337\text{mg}$$

$$\text{The amount of drug present in 3017cm}^2\text{ of tray dryer} = \frac{0.337}{30} \times 3017 = 33.89\text{mg or } 0.0389\text{ppm}$$

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CLEANING VALIDATION IN CADMILL

Put OFF the electrical supply and cover motor, starter, with polythene bag. Remove hopper, blade chamber, screen and blades & clean with potable water. Further clean with 2.5% Teepol solution using scrubber. Rinse with potable water thoroughly.

Apply 20 lit of hot water to all the cleaned items and allow the water to drink. Finally rinse with about 30lit purified water. Wipe out with dry clean lint free cloth and with 70% IPA. Assemble the parts and affix cleaned. Remove a swab from its protective bag using a clean latex hand glove. Pipette out 10ml of sampling of water in transport container. Transfer the swab in transport container (test tube) containing 10ml of water and allow the swab to soak completely. Using moistened swab wipe the test surface of cadmill 30cm^2. (horizontal strokes). Turn the swab over to its other side, wipe the test surface 30cm^2 (vertical). Hold the steam of the swab without touching the head of the swab and let the swab drop into the transport container. Cap the transport container and send for analysis after labeling the same. Calculate the content of $C_4H_{11}N_5$, HCl taking 798 as the value of A (1%, 1 cm) at the maximum at about 232 nm.

Table. 7: Cleaning validation in cadmill

S. No.	Sample	Std absorbance	Test absorbance	Concentration in 30cm² (mg)
1	I	0.852	0.301	0.353
2	II		0.359	0.421
3	III		0.112	0.131

$$\text{Concentration of drug by 30cm}^2\text{ in sample 1} = \frac{0.301}{0.852} \times 1 = 0.353\text{mg}$$

$$\text{Concentration of drug by 30cm}^2\text{ in sample 2} = \frac{0.359}{0.852} \times 1 = 0.421\text{mg}$$

$$\text{Concentration of drug by 30cm}^2\text{ in sample 3} = \frac{0.112}{0.852} \times 1 = 0.131\text{mg}$$

$$\text{Average concentration of drug by 30cm}^2\text{ of the whole equipment} = \frac{0.353+0.421+0.131}{3} = 0.301\text{mg}$$

$$\text{The amount of drug present in 1050cm}^2\text{ of tray dryer} = \frac{0.301}{30} \times 1050 = 10.56\text{mg or } 0.01056 \text{ ppm}$$

CLEANING VALIDATION IN DOUBLE CONE BLENDER

Cleaning agents: Tap water

Cleaning equipments: Dry duster, 0.1% Teepol

Dismantle the safety guard of the blender, circular lid and gasket by unclamping the wing nuts Clean the outside of the blender with dry duster followed by moist duster and then with dry duster. Keep the butterly valve close and keep an SS container below it. Wash inside the blender with tab under and drain it through butterfly value. Clean inside surface with warm water 40°C to 50°C followed by 0.1% teepol solution. Then wash with plenty of water to remove the teepol completely, and then rinse with water. Wipe the different parts of the blender with clean lint free duster. Then assemble the dismantled parts. Dry clean the blender & lids with lint free duster and dedust the external surface with clean lint free duster.

Making of swap stick: swap sticks are prepared by using sterile cotton.

Transport container: Capped test tubes made of glass.

Sampling solvent: water/ as mentioned in the validation protocol of analytical method used for analysis of swab samples of respective active ingredients.

Instrument for measuring absorbance: UV

Pipette out 10ml of sampling solvent in transport container. Remove a swab from its protective bag using a clean latex hand glove. Avoid touching the swab head to prevent its contamination. Transfer the swab in transport container (test tube) containing 10ml of sampling solvent and allow the swab to soak completely. Take out the swab from sampling solvent and squeeze the tip against inner surface of test tube to remove excess solvent in such a manner that excess sampling solvent drips inside the test tube. Hold the stem of swab without touching the head of the swab. Using moistened swab wipe the test surface of 30cm^2. (horizontal strokes). At the end of each stroke, lift the swab carefully. Turn the swab over to its other side, wipe the test surface 30cm^2 (vertical). At the end of each stroke, lift the swab carefully. Hold the steam of the swab without touching the head of the swab and let the swab drop into the transport container. Cap the transport container and send for analysis after labeling the same. Calculate the content of $C_4H_{11}N_5$, HCl taking 798 as the value of A (1%, 1 cm) at the maximum at about 232 nm.

Table. 8: Cleaning validation in double cone blender

S. No	Sample	Std absorbance	Test absorbance	Concentration in 30cm² (mg)
1	I	0.852	0.221	0.259
2	II		0.323	0.379
3	III		0.342	0.401

$$\text{Concentration of drug by } 30cm^2 \text{ in sample 1} = \frac{0.221}{0.852} \times 1$$
$$= 0.259mg$$

$$\text{Concentration of drug by } 30cm^2 \text{ in sample 2} = \frac{0.323}{0.852} \times 1$$
$$= 0.379mg$$

$$\text{Concentration of drug by } 30cm^2 \text{ in sample 3} = \frac{0.342}{0.852} \times 1$$
$$= 0.401mg$$

$$\text{Average concentration of drug by } 30cm^2 \text{ of the whole equipment} = \frac{0.259+0.379+0.401}{3}$$
$$= 0.346mg$$

$$\text{The amount of drug present in } 3150cm^2 \text{ of double cone blender} = \frac{0.338}{30} \times 3150$$
$$= 36.36mg \text{ or } 0.0363 \text{ ppm}$$

VALIDATION IN COMPRESSION MACHINE

- Clean the parts using about 20 kg of potable water followed by scrubbing with nylon scrapper dipped in 0.1% Sodium Lauryl Sulphate solution.
- Wash the parts with about 20 kg of Potable water and finally rinse with about 20 kg of Purified Water.
- Remove all the upper punches, and lower punches collect them in a tray. Clean all the upper punches with the help of dry clean lint free cloth. Wiping with a lint free cloth dipped in 70% Isopropyl alcohol followed by dry lint free cloth.
- Place the dies one after another in to the die pockets, initially press with thumb and finally fix them till the upper surface of the dies flushes with turret surface.
- Insert the lower punch into the guide hole. Push the punch to its highest position and ensure it drops freely under its own weight. Insert the nylon plug into the lower punch-locking hole and fix the anti turning spring strip. Carefully rotate the turret and fix the remaining lower punches in the same way.
- Fix both the feed frames and hoppers properly and connect the dust extraction ports.

Table. 9: Validation in compression machine

S. No.	Sample	Std absorbance	Test absorbance	Concentration in $30cm^2$ (mg)
1	I	0.852	0.341	0.400
2	II		0.203	0.238
3	III		0.319	0.374

$$\text{Concentration of drug by } 30cm^2 \text{ in sample 1} = \frac{0.341}{0.852} \times 1$$
$$= 0.400mg$$

$$\text{Concentration of drug by } 30cm^2 \text{ in sample 2} = \frac{0.203}{0.852} \times 1$$
$$= 0.238mg$$

$$\text{Concentration of drug by } 30cm^2 \text{ in sample 3} = \frac{0.319}{0.852} \times 1$$
$$= 0.374mg$$

$$\text{Average concentration of drug by } 30cm^2 \text{ of the whole equipment} = \frac{0.400+0.238+0.374}{3}$$
$$= 0.337mg$$

$$\text{The amount of drug present in } 4900cm^2 \text{ of compression} = \frac{0.337}{30} \times 4900$$
$$= 55.04mg \text{ or } 0.055 \text{ ppm}$$

RESULT AND DISCUSSION

The cleaning validation for the equipment used in manufacturing process of Metformin 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 metformin 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 changeover of total residue carry over metformin in ppm by swab method was found to be 0.21166.

Table. 10: Results of all the validation procedure

S. No.	Equipment/ instrument	Avg conc of drug in $30cm^2$ (mg)	Total amt of drug present in whole equipment (ppm)	Acceptance limit (ppm)
1	Dispensing booth	0.240	0.03781	0.0612
2	Dispensing balance	0.182	0.00049	0.982
3	Sifter	0.175	0.00791	0.202
4	Ribbon mixer	0.221	0.02469	0.150
5	Tray dryer	0.337	0.0389	0.052
6	Cadmill	0.301	0.01056	0.284
7	Double cone blender	0.346	0.0363	0.082
8	Compression machine	0.337	0.055	0.062

All the results were found to be well within the acceptance criteria of 1.8752 ppm. 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 procedure has been taken in Cassel research laboratory Chennai. The project was identified to be validated as cleaning validation of Metformin tablets. 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 metformin tablets, consistently and concurrently yields the results not exceeding predetermined acceptance limit of the metformin tablets.

All the equipments were selected from cross contamination point of view based on the matrix approach. Likewise, among the tablets manufacturing facility, metformin tablet is predicted based on the worst case approach was developed.

The swab samples were taken from all the equipments but other samples were taken from excluding compression machine analysis. The results of cleaning validation were 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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