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Research Article

TECHNIQUE DEVELOPMENT OF CLEANING VALIDATION FOR CHLORDIAZEPOXIDE IP TABLETS DOSAGE FORM

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Abstract

Carefully designed cleaning validation and its evaluation can ensure that residues of active pharmaceutical ingredient will not carry over and cross-contaminate the subsequent product. Chemical inspection method was developed and validated for the verification and determination of chlordiazepoxide in the production area and to confirm the efficiency of the cleaning procedure as per CGMP regulations. First all equipments, used in the production of chlordiazepoxide, were visually inspected for the cleanliness and were found visually clean. Chemical inspection was done on basis of 10 ppm criteria. Range of chemical residue was 1.48-9.89 ppm in dispensing booth, 0.31-9.28 ppm in granulation room, 0.00 to 9.94 in sifter, 0.00 to 4.03 in sifter cum multimill, 0.00 to 7.01 in rapid mixer granulator, 2.48 to 8.06 in fluidized bed dryer, 0.00 to 8.01 in conta blender, 0.00 to 9.44 in compression cubicle and compression machine, 0.00 to 3.01 in coating room and coating machine and 0.00 to 9.85 in blister packing room and blister packing machine. Result indicated that calculated limit of chemical residue was not exceeded over prescribed limit during three consecutive batches of production after cleaning procedure. Hence, it can be said that this cleaning method validation on solid dosage forms of chlordiazepoxide can be used in routine cleaning to avoid the risk of cross contamination.

Keywords: Chlordiazepoxide , validation

INTRODUCTION

Carefully designed cleaning validation and its evaluation can ensure that residues of active pharmaceutical ingredient will not carry over and cross-contaminate the subsequent product. The manufacturing process of an active pharmaceutical ingredient (API) typically consists of various chemical reaction and purification steps followed by physical changes. In general early steps undergo further processing and purification and so potential carryover of the previous product would be removed. The amount or as we will call it here, level of cleaning required in order to ensure that the API is free from unacceptable levels of contamination by previous substances varies depending on the step solvent can be readily made. Critical data such as being cleaned and the next substance being manufactured in the same piece of equipment (train).

CHEMICAL INVESTIGATION METHOD

OBJECTIVE AND SCOPE:

To check the residue/traces on cleaned machinery and equipments used for manufacturing of product at each stage. This procedure is applicable for cleaning validation only.

PROCEDURE:

RINSE PROCEDURE:

Equipment was cleaned as per individual

equipment cleaning procedure. Equipment was rinsed with 5 litre of purified water thoroughly. Steps were taken to ensure the uniformity of the residual material in the rinse prior to sample.Sufficient holding time was allowed to ensure uniformity due to diffusion of the active ingredient residues. This water was taken as the rinse sample. After that, 100 ml of rinse sample was taken in cleaned bottle for checking residue. Bottle was analyzed in chemical laboratory.

VISUAL INSPECTION METHOD

The equipment including "Hard to clean areas" should appear clean with no traces of product when observed in wet and dry condition of the surface. The standard of visually clean shall be used for purposes of both validation and monitoring. The dividing line between visually clean and visually dirty is regarded as presence of residual levels of active ingredient.

Test:A representative portion of the sample was transferred to a Nesslers cylinder and view in diffused light.

Calculation of result: Sample should be clear in appearance in Nessler cylinder.

RESULT & DISCUSSION

Validation considerations for new products and existing product lines have both fundamental differences and similarities. Both may require cycle development and optimization activities prior to validation. They both may also require the development and validation of low level analytical detection methods for the active ingredient, detergent or cleaning solvent, and possibly excipients. For new products, the cycle development and optimization steps are more readily accomplished in the process development phase. At this point the choice of detergent or solvent can be readily made. Critical data such as solubility, conductivity, and pH of the active in the detergent or solvent can be easily developed. Such data can be helpful in the design and development of the process and equipment for the production scale[10-13]All critical monitoring instrumentation such as thermocouples or RTDs, pressure gauges, flow meters, conductivity sensors or pH meters must be identified andcalibrated. The function of each monitoring device must be clearly understood. This is particularly true in an automated system, where individual devices may have a controlling influence over particular phases of the process. When specifying equipment to be used for cleaning, it is helpful to select equipment with multiple monitoring devices as they help to establish a reproducible cleaning process. All personnel must be trained and each operator must understand the cleaning steps and process. In order to establish a validated cleaning procedure, whether manual, semi-automated or fully automated, it is generally useful to perform cycle development studies in order to establish the parameters which are to be validated. Proper development of the cleaning cycle provides confirmation of the safety of the process, economic savings, confidence in the validation starting point and experience with the test and sampling methods. At the conclusion of cycle development, it is possible to finalize standard operating procedures (SOPs) for the correct operation and monitoring of the cleaning system. The critical factors which influence the cleaning cycle to be developed include: the equipment, the cleaning agents, cleaning parameters, product or formulation, cleaning procedures, documentation and training. It is important not only that operator training occur, but also that the training be well documented. Without proper documentation, it is impossible to prove that the training was actually accomplished. Operators should be retrained each time a cleaning procedure is changed and the new training must be documented, just as in the case of a change to a manufacturing procedure[1-6].

Organoleptic techniques (i.e., visual, smell, touch) used as a component of the cleaning program and, additionally, as one of the testsuseful for the validation of the cleaning procedure.Visual examination of equipment for cleanliness immediately before use is required by the CGMP regulations.Visual examination is a combination of sampling and analysis, where the observer makes an immediate determination of equipment cleanliness. Visual examination of equipment, in particular, is utilized by the majority of pharmaceuticals both as a means of evaluating cleaned surfaces during the cleaning validation stage and after cleaning validation is complete as part of an ongoing monitoring of the cleaning process. In some instances this method has been shown to have a high sensitivity. The visual examination of equipment enhanced by simply passing an ultraviolet "black" light over the surfaces of the equipment. This use of an

ultraviolet light would be effective for residues which fluoresce when irradiated with ultraviolet light. Another means of visual enhancement is the use of dyes which form colored complexes with certain residues such as proteins producing a colored residue much easier to observe visually than the uncomplexed free residue. For example, methylene blue can detect anionic detergent residues and proteins remaining on equipment but here used the uv lamp for examination of the surfaces of equipments and their parts/components and found visually clean after cleaning procedure which is efficient to clean the equipments and their parts effectively[14-17].All the equipments, used in the production of chlordiazepoxide, were visually inspected for the cleanliness during production of three successive batches. In dispensing booth floor, walls, door-I and II, platform balance, reverse laminar air flow, scoops and other utensils were inspected and found clean as shown in Table 1.

	Areas for visual observation	Visually clean Yes/ No		
		Batch No.		
		Batch – I	Batch – II	Batch - III
1	Floor	Yes	Yes	Yes
2	Walls	Yes	Yes	Yes
3	Door – I	Yes	Yes	Yes
4	Doors – II	Yes	Yes	Yes
5	Platform Balance	Yes	Yes	Yes
6	Reverse Laminar Air Flow	Yes	Yes	Yes
7	Scoops	Yes	Yes	Yes
8	Other Utensils	Yes	Yes	Yes

In sifter sieves, blades of multi mill, feed hopper, dischsrge chute and screw conveyer were inspected and found clean as shown in Table 2.

Table 2 Visual inspection results of sifter (after cleaning)

	Areas for visual observation	Visually clean Yes/ No		
		Batch No.		
		Batch – I	Batch – II	Batch - III
1	Sieves	Yes	Yes	Yes
2	Blades of Multil Mill	Yes	Yes	Yes
3	Feed Hopper	Yes	Yes	Yes
4	Discharge Chute	Yes	Yes	Yes
5	Screw Conveyor	Yes	Yes	Yes

In rapid mixer granulator discharge chute, view glass-I and II, impeller, chopper, near discharge chute and RMG lid were inspected and found clean as shown in Table 3.

Table 3 Visual inspection results of rapid mixer granulator (after cleaning)

	Areas for visual observation	Visually clean Yes/ No		
		Batch No.		
		Batch – I	Batch – II	Batch - III
1	Discharge Chute	Yes	Yes	Yes
2	View Glass – I	Yes	Yes	Yes
3	View Glass – II	Yes	Yes	Yes
4	Impeller	Yes	Yes	Yes
5	Chopper	Yes	Yes	Yes
6	Near discharge chute	Yes	Yes	Yes
7	RMG lid	Yes	Yes	Yes

In fluidized bed dryer FBD bowl product container, bottom pan, retarding chamber and inner side of view glass were inspected and found clean as shown in Table 4.

Table 4 Visual inspection results of fluidized bed dryer (after cleaning)

	Areas for visual observation	Visually clean Yes/ No		
		Batch No.		
		Batch – I	Batch – II	Batch - III
1	FBD bowl product container	Yes	Yes	Yes
2	Bottom Pan	Yes	Yes	Yes
3	Retarding Chamber	Yes	Yes	Yes
4	Inner side of view glass	Yes	Yes	Yes

In conta blender its lid and inner surface were inspected and found clean as shown in Table 5.

Table 5 Visual inspection result of conta blender (after cleaning)

	Areas for visual observation	Visually clean Yes/ No		
		Batch No.		
		Batch – I	Batch – II	Batch - III
1	Lid of conta blender	Yes	Yes	Yes
2	Inner surface of conta blender	Yes	Yes	Yes

In compression cubicle and compression machine section floor, ceiling, walls, doors, electric panels, hopper, feed frame, turret, discharge chute, metal detector and discharge chute of metal detector were inspected and found clean as shown in Table 6.

Table 6 Visual inspection result of compression cubicle and compression machine (after cleaning)

	Areas for visual observation	Visually clean Yes/ No		
		Batch No.		
		Batch – I	Batch – II	Batch - III
1	Floor	Yes	Yes	Yes
2	Ceiling	Yes	Yes	Yes
3	Walls	Yes	Yes	Yes
4	Doors	Yes	Yes	Yes
5	Electric panels	Yes	Yes	Yes
6	Hopper	Yes	Yes	Yes
7	Feed Frame	Yes	Yes	Yes
8	Turret	Yes	Yes	Yes
9	Discharge Chute	Yes	Yes	Yes
10	Metal Detector	Yes	Yes	Yes
11	Discharge Chute of Metal Detector (VO-RCM-06)	Yes	Yes	Yes

In coating area and coating machine section floor, ceiling, walls, doors, electric panels and coating pan-I, II, III, IV and V were inspected and found clean as shown in Table 7.

Table 7 Visual inspection results of coating area and coating machine (after cleaning)

:

	Areas for visual observation	Visually clean Yes/ No		
		Batch No.		
		Batch – I	Batch – II	Batch - III
1	Floor	Yes	Yes	Yes
2	Ceiling	Yes	Yes	Yes
3	Walls	Yes	Yes	Yes
4	Doors	Yes	Yes	Yes
5	Electric panels	Yes	Yes	Yes
6	Coating Pan I	Yes	Yes	Yes
7	Coating Pan II	Yes	Yes	Yes
8	Coating Pan III	Yes	Yes	Yes
9	Coating Pan VI	Yes	Yes	Yes
10	Coating Pan V	Yes	Yes	Yes

In blister packing room and blister packing machine floor, walls, doors, hopper, spiral bowl, chute, feed box, machine door, de-blistering machine chute were inspected and found clean as shown in Table 8.

Table 8 Visual inspection results of blister packing room and blister packing machine (after cleaning)

	Areas for visual observation	Visually clean Yes/ No		
		Batch No.		
		Batch – I	Batch – II	Batch - III
1	Floor	Yes	Yes	Yes
2	Walls	Yes	Yes	Yes
3	Doors	Yes	Yes	Yes
4	Hopper	Yes	Yes	Yes
5	Spiral Bowl	Yes	Yes	Yes
6	Chute	Yes	Yes	Yes
7	Feed Box	Yes	Yes	Yes
8	Machine Door	Yes	Yes	Yes
9	De-blistering machine chute	Yes	Yes	Yes

After visual examination all equipments were inspected by chemical method as discussed below- The results of the chemical tests sampled from the dispensing booth and its components, mentioned in Table 9 and Figure 1, were within the acceptance criteria and indicated the effective cleaning for the dispensing booth as per defined procedure.

Table 9 Chemical inspection results of dispensing booth (after cleaning)

Swab Sampled Area : 10 × 10 cm^2. **Swab Medium :** Purified Water

Serial No.	Sampled Area / Locations	Active drug content (10 ppm criteria)		
		Batch–I	Batch-II	Batch-III
1	Floor Sample – I	1.48	2.03	1.78
2	Floor Sample- II	4.35	3.50	4.02
3	Wall Sample – I	5.64	5.48	6.20
4	Wall Sample – II	5.93	5.80	6.11
5	Door Sample – I	5.93	6.01	6.20
6	Door Sample – II	3.86	3.65	4.11
7	Side Wall RLAF – I	6.38	6.30	5.96
8	Side Wall RLAF – II	6.70	6.35	5.86
9	Side Wall RLAF – III	7.34	8.20	7.35
10	Platform Balance – I	9.89	9.62	9.50
11	Platform Balance – II	7.02	7.65	7.20
12	Platform Balance - III	4.47	5.12	4.80
13	Scoop - I	4.47	4.80	5.01
14	Scoop - II	9.89	8.80	7.96

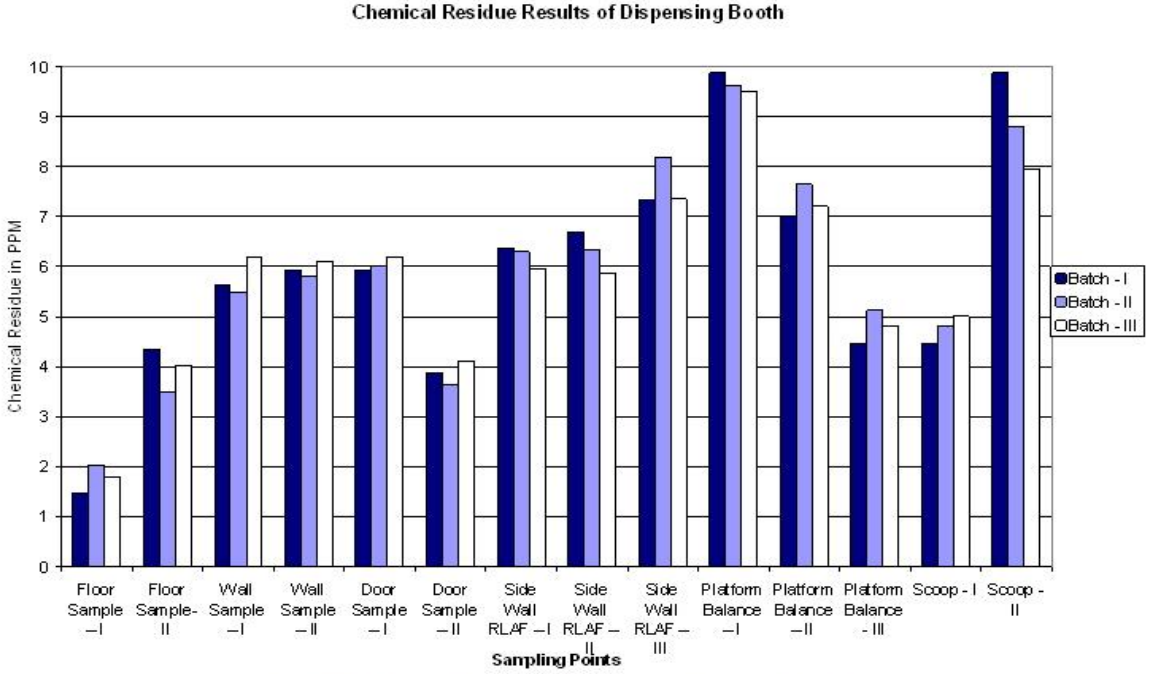

Figure 1 Chemical residue results of dispensing booth.

The results of chemical test sampled from the granulator and its components after cleaning for three batches, mentioned in Table 10 and Figure 2, were within the acceptance criteria.

Table 10 Chemical inspection results of granulation room (after cleaning)

Swab Sampled Area : 10 × 10 cm^2. **Swab Medium :** Purified Water

Serial No.	Sampled Area / Locations	Active drug content (10 ppm criteria)		
		Batch–I	Batch-II	Batch-III
1	Floor Sample – I	6.21	2.86	4.96
2	Floor Sample- II	2.17	5.80	5.22
3	Wall Sample – I	9.28	9.12	9.01
4	Wall Sample – II	0.31	2.11	0.96
5	Door Sample – I	1.24	2.45	3.01
6	Door Sample – II	2.48	2.87	3.56

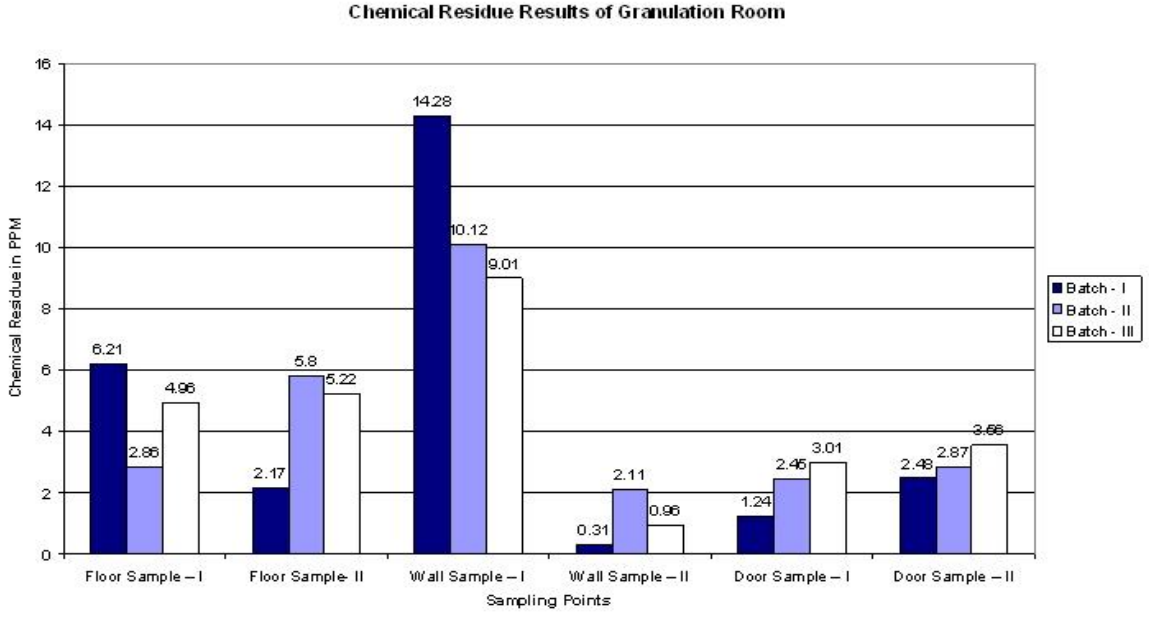

Figure 2 Chemical residue results of granulation room.

The results of chemical test sampled from sifter and its components after cleaning for three batches, mentioned in Table 11 and Figure 3, were within the acceptance criteria.

Table 11 Chemical inspection results of sifter (after cleaning)

Swab Sampled Area : 10 × 10 cm^2. **Swab Medium :** Purified Water

Rinse Volume : 100 ml. **Rinse Medium :** Purified Water

Serial No.	Sampled Area / Locations	Active drug content (10 ppm criteria)		
		Batch–I	Batch-II	Batch-III
1	Discharge Chute	0.93	1.20	1.45
2	Discharge Chute (Rinse)	0.00	2.01	1.11
3	Feed Bowl – I	9.94	8.96	9.20
4	Feed Bowl – II	1.24	3.45	4.01
5	Sieve – I	2.79	3.22	2.23
6	Sieve – II	1.24	1.86	2.36
7	Sieve – III	1.86	2.24	1.80

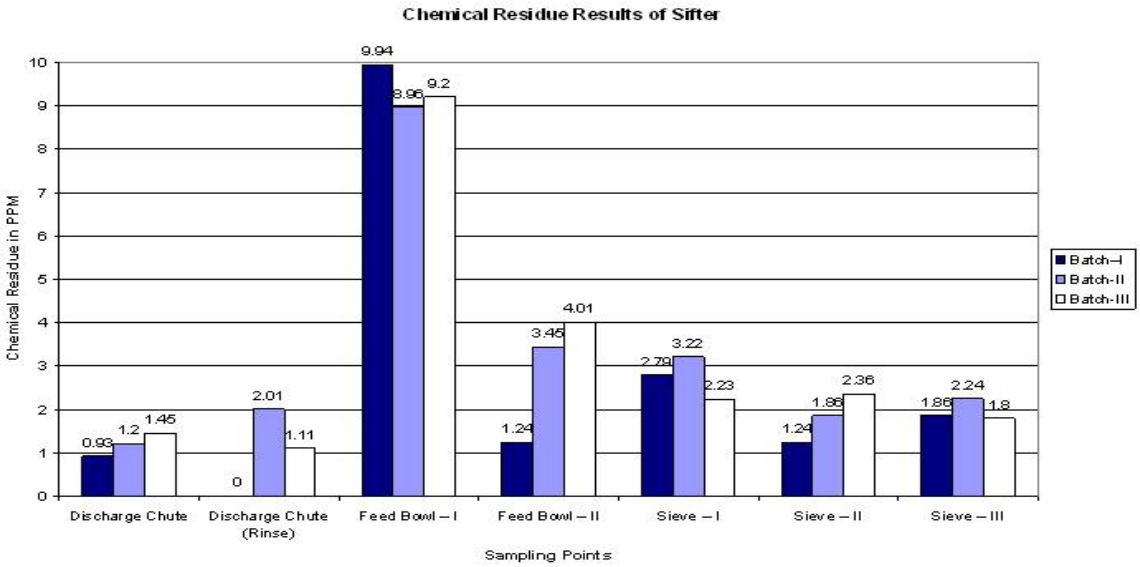

Figure 3 Chemical residue results of sifter.

The results of chemical test sampled from sifter cum multimill and its components after cleaning for three batches, mentioned in Table 12 and Figure 4, were within the acceptance criteria.

Table 12 Chemical inspection results of sifter cum multimill (after cleaning)

Swab Sampled Area : 10 × 10 cm^2. **Swab Medium :** Purified Water

Rinse Volume : 100 ml. **Rinse Medium :** Purified Water

Serial No.	Sampled Area / Locations	Active drug content (10 ppm criteria)		
		Batch–I	Batch-II	Batch-III
1	Discharge Chute	1.55	1.50	2.01
2	Discharge Chute (Rinse)	0.00	0.35	0.05
3	Feed Hopper – I	3.42	3.05	2.10
4	Feed Hopper – II	3.73	2.86	3.50
5	Multmill Screen	1.55	2.11	1.32
6	Screw Conveyor	3.42	4.03	3.12

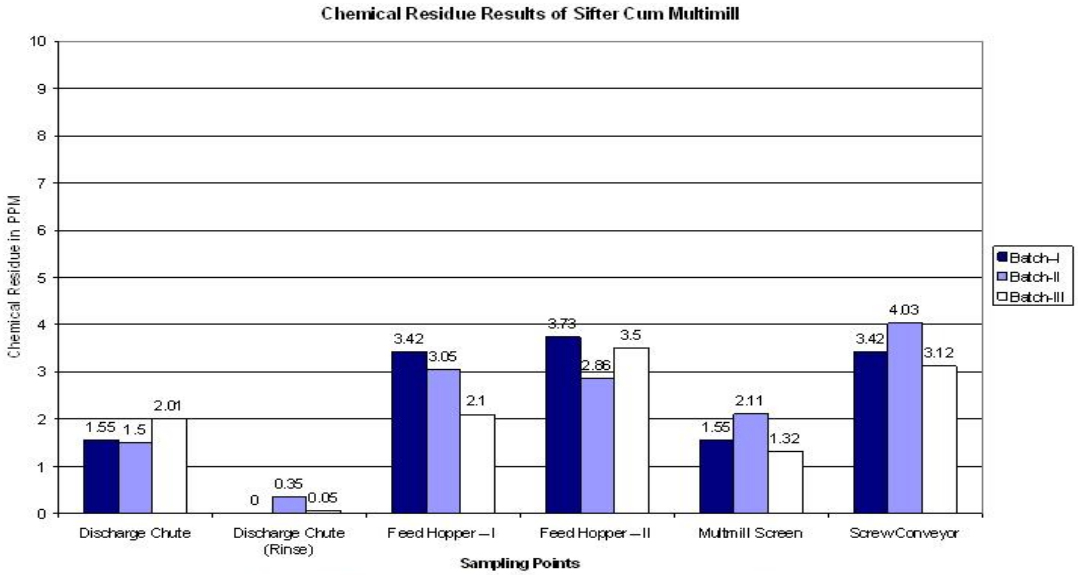

Figure 4 Chemical residue results of sifter cum multimill.

The results of chemical test sampled from rapid mixer granulator and its components after cleaning for three batches, mentioned in Table 13 and Figure 5, were within the acceptance criteria.

Table 13 Chemical inspection results of rapid mixer granulator (after cleaning)

Swab Sampled Area : 10 × 10 cm^2. **Swab Medium :** Purified Water

Rinse Volume : 100 ml. **Rinse Medium :** Purified Water

Serial No.	Sampled Area / Locations	Active drug content (10 ppm criteria)		
		Batch–I	Batch-II	Batch-III
1	Discharge Chute	3.73	4.46	3.30
2	Discharge Chute (Rinse)	0.30	0.00	0.45
3	Bottom RMG Bowl – I	3.42	4.50	2.01
4	Bottom RMG Bowl– II	6.52	7.01	4.86
5	Bottom RMG Bowl-III	4.97	4.45	2.86
6	Side wall of RMG Bowl	2.48	3.01	2.78
7	Impeller Center	2.17	2.96	3.01
8	Impeller Rear	1.86	2.11	1.65
9	Chopper Bottom	3.42	4.35	3.80
10	Lid of RMG	2.05	1.85	1.32

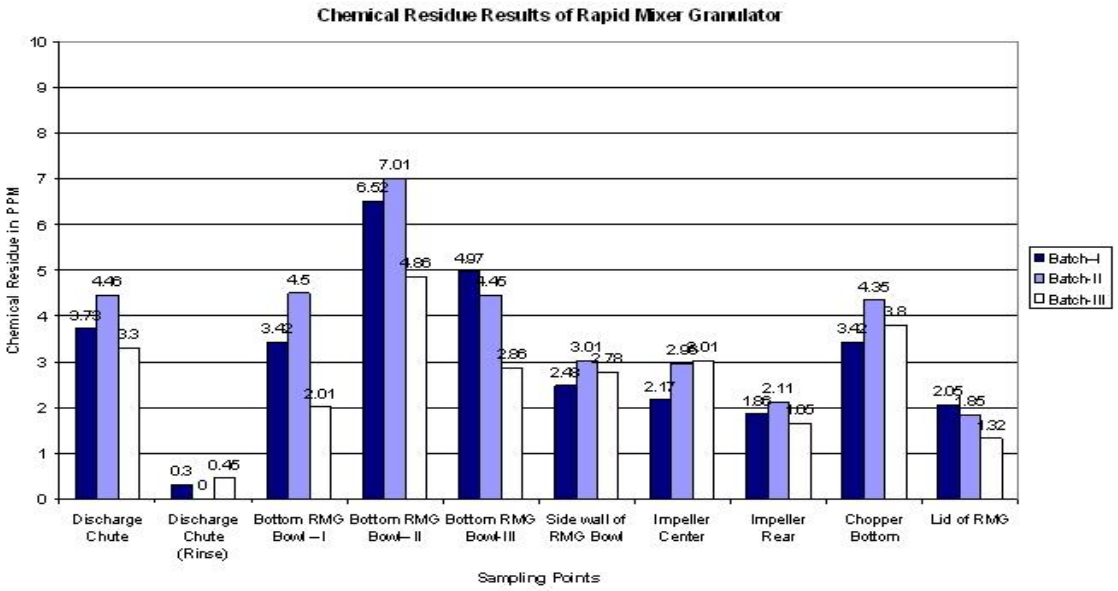

Figure 5 Chemical residue results of rapid mixer granulator.

The results of chemical test sampled from fluidized bed dryer and its components after cleaning for three batches, mentioned in Table 14 and Figure 6, were within the acceptance criteria.

Table 14 Chemical inspection results of fluidized bed dryer (after cleaning)

Swab Sampled Area :10 × 10 cm^2. Swab Medium : Purified Water

Sr. No.	Sampled Area / Locations	Active drug content (10 ppm criteria)		
		Batch–I	Batch-II	Batch-III
1	Retarding chamber - I	7.76	8.06	5.96
2	Retarding chamber – II	4..97	7.75	6.80
3	Side wall of FBD Bowl	3.11	2.80	3.22
4	Bottom wall of FBD bowl - I	4.97	5.80	4.65
5	Bottom wall of FBD bowl - II	2.48	4.08	3.85
6	Bottom wall of FBD bowl - III	2.48	2.50	3.60
7	Center of FBD Bowl	6.83	7.82	5.96

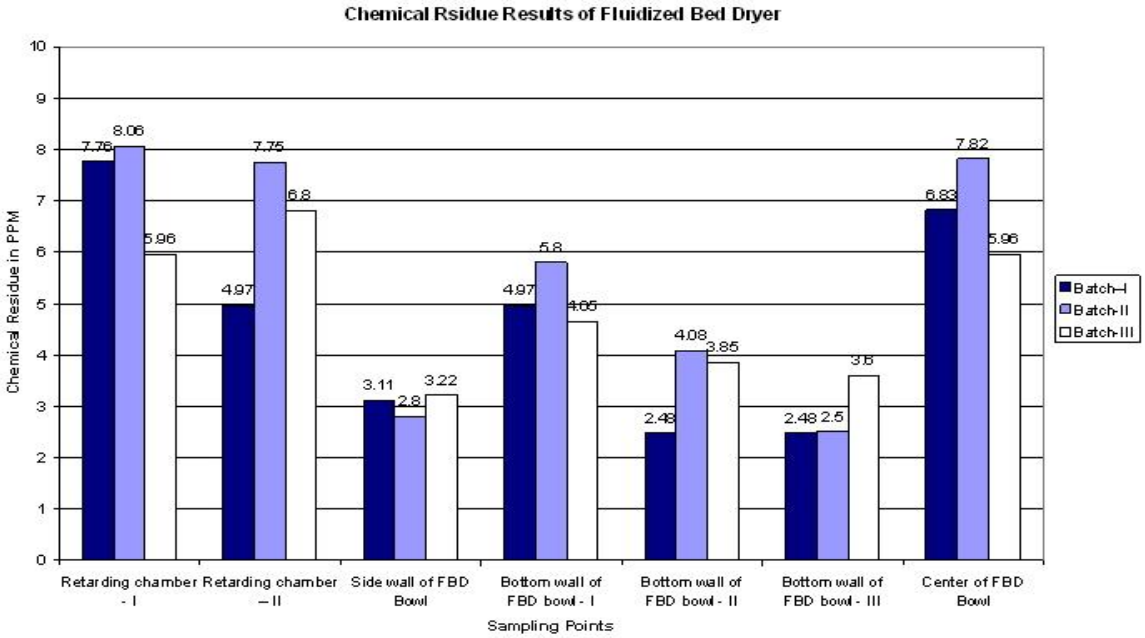

Figure 6 Chemical residue results of fluidized bed dryer.

The results of chemical test sampled from conta blender and its components after cleaning for three batches, mentioned in Table 15 and Figure 7, were within the acceptance criteria.

Table 15 Chemical inspection results of conta blender (after cleaning)

Swab Sampled Area :10 × 10 cm^2. Swab Medium : Purified Water

Rinse Volume : 100 ml. Rinse Medium : Purified Water

Serial No.	Sampled Area / Locations	Active drug content (10 ppm criteria)		
		Batch–I	Batch-II	Batch-III
1	Conta Bin Wall – I	4.08	5.60	3.80
2	Conta Bin Wall – II	7.22	6.96	8.01
3	Conta Bin Wall – III	2.51	3.36	2.86
4	Conta Bin Wall – IV	3.45	4.65	5.78
5	Conta Bin Wall – V	5.02	3.35	5.65
6	Conta Bin Lid	3.14	2.80	2.95
7	Conta Bin (Rinse)	0.80	0.35	0.00

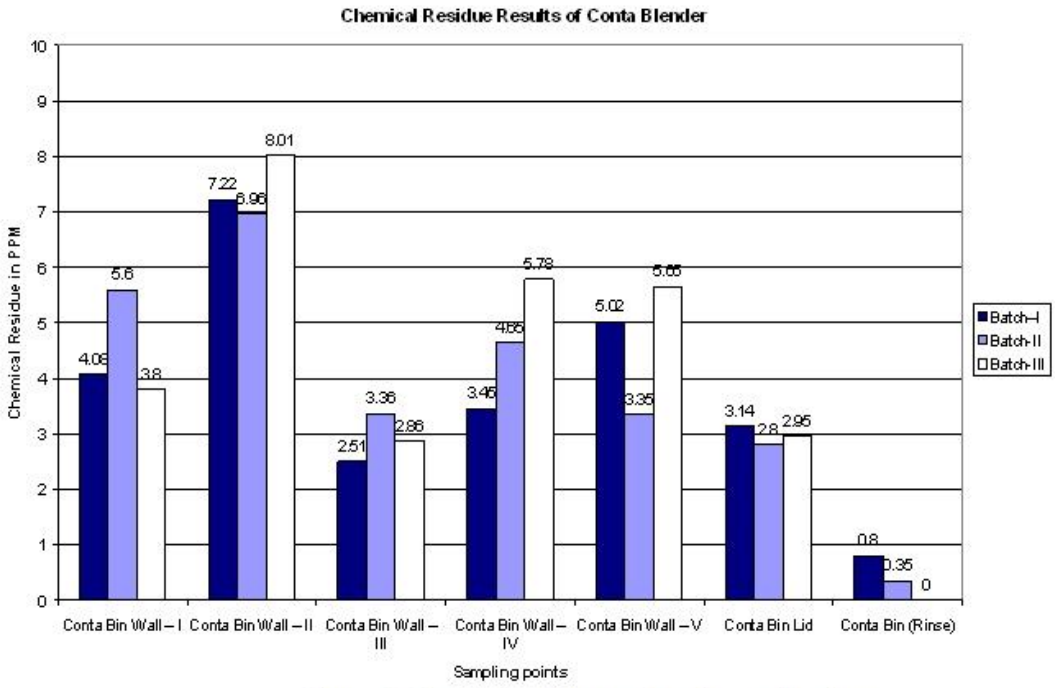

Figure 7 Chemical residue results of conta blender.

The results of chemical test sampled from compression cubicle and compression machine and its components after cleaning for three batches, mentioned in Table 16 and Figure 8, were within the acceptance criteria.

Table 16 Chemical inspection results of compression cubicle and compression machine (after cleaning)

Swab Sampled Area : 10 × 10 cm^2. **Swab Medium :** Purified Water

Rinse Volume : 100 ml. **Rinse Medium :** Purified Water

Sr. No.	Sampled Area / Locations	Active drug content (10 ppm criteria)		
		Batch–I	Batch-II	Batch-III
1	Floor Sample - I	4.72	5.85	7.30
2	Floor Sample – II	4.72	6.10	4.85
3	Wall Sample – I	7.24	8.65	7.86
4	Wall Sample – II	4.09	3.96	5.65
5	Door Sample – I	4.09	5.88	6.03
6	Door Sample – II	3.78	4.10	4.16
7	Feed Hopper – I Top	3.46	4.01	3.85
8	Feed Hopper – I Bottom	4.41	5.03	6.71
9	Feed Hopper – II Top	3.46	4.35	3.30
10	Feed Hopper – II Bottom	3.46	2.90	3.85
11	Feed Frame – I	9.44	7.60	6.96
12	Feed Frame – II	5.35	5.80	4.98
13	Feed Frame – III	4.41	4.46	5.01
14	Feed Frame – IV	2.83	3.35	4.20
15	Turret – I	7.55	8.10	9.22
16	Turret – II	7.94	6.95	7.30
17	Discharge Chute – I	3.15	4.60	4.11
18	Discharge Chute – II	2.83	3.35	2.96
19	Discharge Chute – I (Rinse)	0.60	0.80	1.30
20	Discharge Chute – II (Rinse)	0.00	1.11	0.55
21	Discharge Chute Metal Detector – I	8.96	8.65	6.45
22	Discharge Chute Metal Detector – II	8.18	5.96	4.96
23	Y– Chute (Rinse) Arm – I	1.21	0.80	0.35
24	Y– Chute (Rinse) Arm – II	0.20	0.65	0.00
25	De-dusting Unit-I (Rinse)	0.68	0.03	0.92
26	De-dusting Unit-II (Rinse)	0.88	0.75	0.55

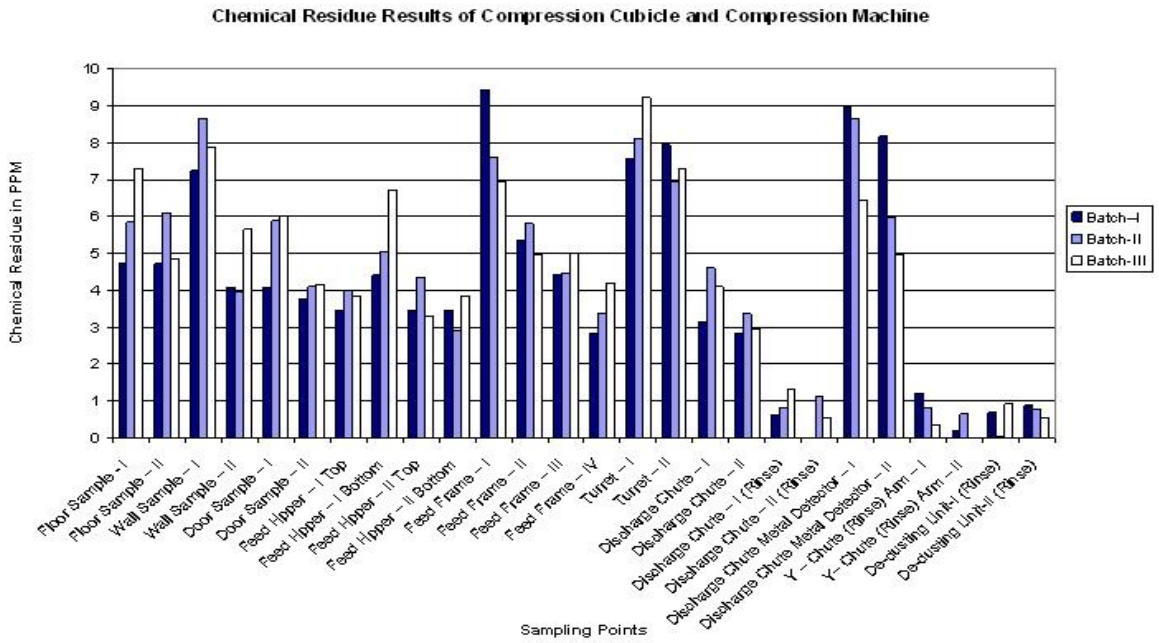

Figure 8 Chemical residue results of compression cubicle and compression machine.

The results of chemical test sampled from coating room and coating machine and its components after cleaning for three batches, mentioned in Table 17 and Figure 9, were within the acceptance criteria.

Table 17 Chemical inspection results of coating room and coating machine (after cleaning)

Swab Sampled Area : 10 × 10 cm^2. **Swab Medium :** Purified Water

Rinse Volume : 100 ml. **Rinse Medium :** Purified Water

Sr. No.	Sampled Area / Locations	Active drug content (10 ppm criteria)		
		Batch–I	Batch-II	Batch-III
1	Floor Sample - I	2.82	3.01	2.89
2	Floor Sample – II	0.31	2.11	2.60
3	Wall Sample – I	0.00	0.21	0.30
4	Wall Sample – II	0.00	0.00	0.11
5	Door Sample – I	2.82	1.85	2.03
6	Door Sample – II	0.31	2.60	0.65
7	Coating Pan – I Top	0.31	1.20	0.60
8	Coating Pan – I Bottom	0.63	0.21	0.80
9	Coating Pan – I Side	0.00	0.11	0.81
10	Coating Pan – I Lid	0.63	0.35	0.00
11	Coating Pan – I (Rinse)	0.03	0.35	0.41
12	Coating Pan – II Top	0.00	1.20	0.36
13	Coating Pan – II Bottom	0.00	0.00	0.21
14	Coating Pan – II Side	0.31	0.22	0.81
15	Coating Pan – II Lid	0.00	0.11	0.23
16	Coating Pan – II (Rinse)	0.10	0.30	0.00
17	Coating Pan – III Top	0.00	0.23	0.41
18	Coating Pan – III Bottom	0.00	0.12	0.71
19	Coating Pan – III Side	0.31	0.45	0.24
20	Coating Pan – III Lid	0.31	0.35	0.62
21	Coating Pan – III (Rinse)	0.31	0.00	0.13
22	Coating Pan – IV Top	0.94	0.91	1.21
23	Coating Pan – IV Bottom	0.31	0.45	0.26
24	Coating Pan – IV Side	0.63	0.31	0.55
25	Coating Pan – IV Lid	0.31	0.36	0.21
26	Coating Pan – IV (Rinse)	0.00	0.00	0.11
27	Coating Pan – V Top	0.63	0.71	0.85
28	Coating Pan – V Bottom	0.00	0.17	0.19
29	Coating Pan – V Side	0.63	0.81	0.56
30	Coating Pan – V Lid	0.00	0.23	0.00
31	Coating Pan – V (Rinse)	0.13	0.00	0.23

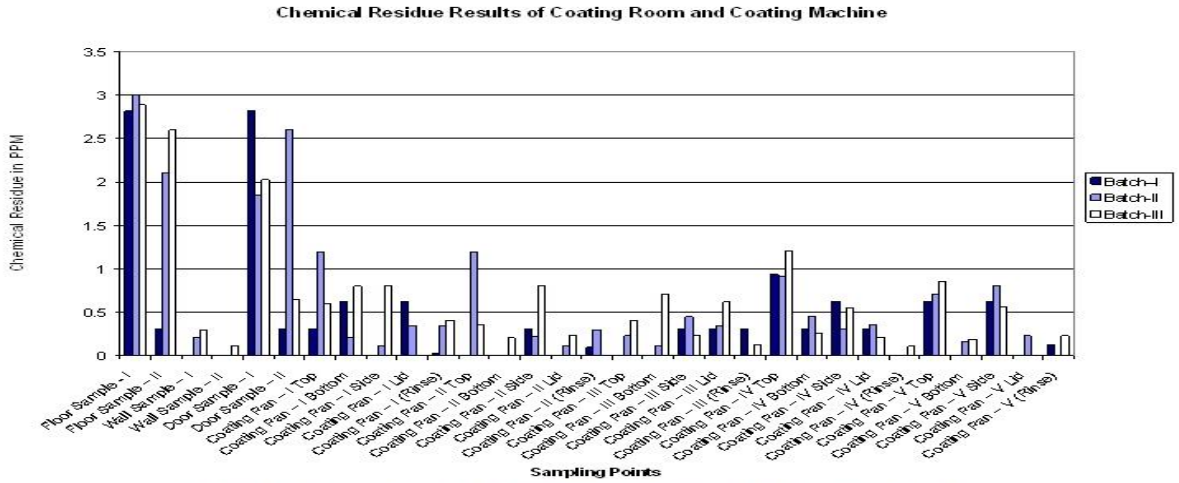

Figure 9 Chemical residue results of coating room and coating machine.

The results of chemical test sampled from blister packing room and blister packing machine and its components after cleaning for three batches, mentioned in Table 18 and Figure 10, were within the acceptance criteria.

Table 18 Chemical inspection results of blister packing room and blister packing machine (after cleaning)

Swab Sampled Area : 10 × 10 cm^2 **Swab Medium :** Purified Water

Rinse Volume : 100 ml. **Rinse Medium :** Purified Water

Sr. No.	Sampled Area / Locations	Active drug content (10 ppm criteria)		
		Batch–I	Batch-II	Batch-III
1	Floor Sample - I	0.62	3.35	0.85
2	Floor Sample – II	2.15	0.32	0.21
3	Wall Sample – I	6.77	0.12	0.11
4	Wall Sample – II	9.08	9.96	8.50
5	Door Sample – I	1.23	6.50	0.86
6	Door Sample – II	1.54	12.06	9.85
7	Feed Hopper	1.54	1.65	2.11
8	Spiral Bowl	0.62	0.32	0.12
9	Chute	1.54	1.55	0.81
10	Hopper (Rinse)	0.03	0.06	0.35
11	Feed Box – I	0.31	0.25	0.36
12	Feed Box – II	0.62	0.86	0.21
13	Machine Door – I	0.00	0.31	0.00
14	Machine Door – II	1.23	0.96	0.78
15	Pass Box	1.23	2.21	1.85
16	De-blistering M/C Chute – I	7.08	5.06	4.46
17	De-blistering M/C Chute – II	0.21	0.56	0.38
18	De-blistering M/C Chute – I (Rinse)	0.62	0.92	0.46
19	De-blistering M/C Chute – II (Rinse)	0.00	0.31	0.11

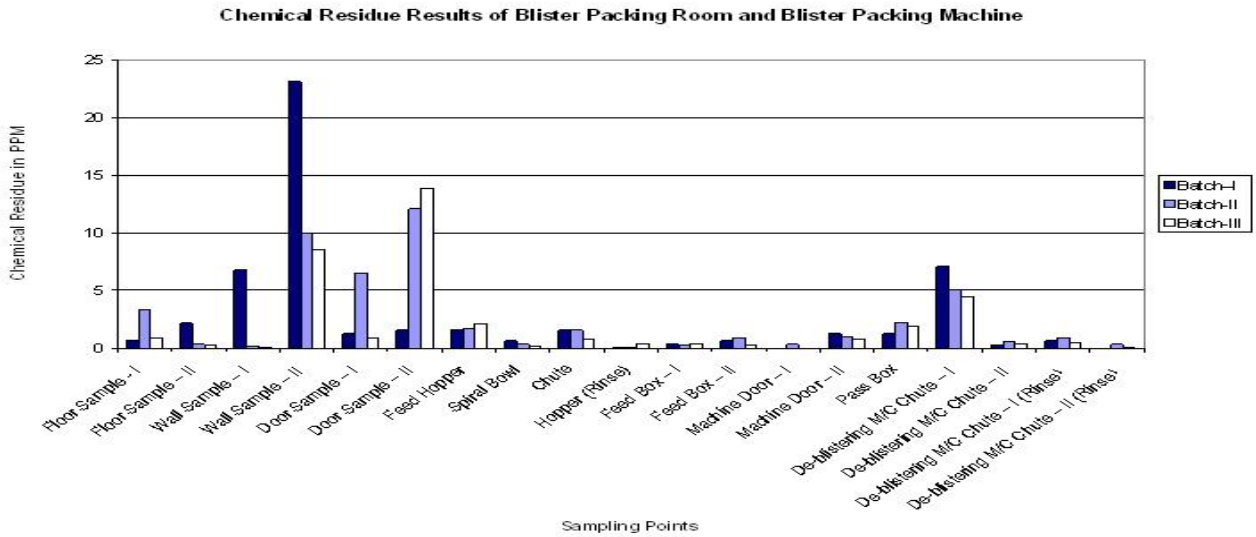

Figure 10 Chemical residue results of blister packing room and blister packing machine.

Results for all the equipments, used in the production of chlordiazepoxide, and production section, were found within the pre determined limits on chemical inspection during three successive batches study.

CONCLUSION

The Final Conclusion has been drawn on the basis of the results obtained during execution of the cleaning validation on solid dosage forms at the manufacturing facility of Cheryl Laboratories established standard equipment cleaning procedures. Only product to product change over (B- type cleaning) cleaning method has been validated.All the qualification studies, calibrations and analytical method validation have been conducted prior to this cleaning validation as a prerequisite. All the results were evaluated against the acceptance criteria mentioned in cleaning validation master plan, i.e. NMT 10 ppm and NMT 100 ppm for residue limits of direct contact surfaces and non contact surfaces, respectively. By thorough compilation of the obtained results, we can conclude that chemical residue are well under pre-determined acceptance criteria. The chemical residues of Chlordiazepoxide at all product contact equipment surfaces (critical equipment sufaces) were lies below 10 ppm. The highest chemical residue of 9.89 ppm was observed at dispensing booth which is still satisfy the 10 ppm criteria. This particular point can be considered as the hot spot of the entire equipments train and shall be subjected to routine verification of post cleaning inspection. The three times repetition of the same results indicates the consistency of the existing cleaning method for achieving expected cleanliness. The worst case approach intensifies the ruggedness of the cleaning method. This risk based study also take care the safety of the products manufactured in this multi product manufacturing facility. This cleaning method validation meets all criteria to satisfy the regulatory requirements on its part. Hence, it can be said that this cleaning method validation on solid dosage form has successfully been completed and can be used in routine cleaning to avoid the risk of cross contamination.

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Pvt.Ltd. Altogether three consecutive batches of Chlordiazepoxide IP 10 Tablets (Clordiazepoxide 10 mg) were taken under cleaning validation study to prove the effectiveness and consistency of the pre-

REFERENCES

1. Agalloco JP,Brame W,Ferenc B, Hall WE,Jenkins K,LaMagna JT,Madsen RE,Mullen MV,Wagenknecht D, Wagner CM. Points to consider for cleaning validation: PDA Technical Report No. 29. PDA J Pharm Sci Tech, 1998; 52, November – December Supplement: pp. 7-53.
2. Human Drugs CGMP Notes In: A Memo on Current Good Manufacturing Practice Issues on Human Use Pharmaceuticals, 1997; volume 5, Number 3..
3. Equipment Cleaning and Maintenance, Department of Health and Human Services, CFR 21, Part 211, Subpart 211.67.
4. "Guide to Inspection of Validation of Cleaning Procedures", US FDA, 1993.
5. "Guide to Inspection of Bulk Pharmaceutical Chemicals", US FDA 1994.
6. Harpaz D, Berry IR. Validation of Bulk Pharmaceutical Chemicals, Interpharm press Inc., Illinois, 1997.
7. LeBlanc DA. Pharm Tech, 1998; 22(5): 66 – 74.
8. LeBlanc DA. Pharm Tech, 1996; 20(1):84-92.
9. Chudzik GM. J Val Tech, 1998; 5(1): 77-81.
10. Forsyth RJ, Haynes DV. Pharm Tech, 1998; 22(9): 104-112.
11. Thomas JA. J. Val Tech, 2000; 6(2): 522-530.
12. Hall WE, J Val Tech, 1997; 4(1).
13. Fourman GL, Mullen MV. Pharm Tech, 1998; 17(4):54-60.
14. LeBlanc DA. Pharm Tech, 1998; 19(5):136-148.
15. Agalloco JP. Points to consider in the validation of equipmentscleaning procedure, J ParenterSciTechnol, 1992; 46(5).
16. Baffi R, Dolch G, Garnick R, Huang YF, Mar B, Matsuhiro D, Niepelt B, Parra C, Stephan M. J ParenterSciTechnol, 1991; 45(1), 13-19.