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Original Article

DEVELOPMENT AND VALIDATION OF ANALYTICAL METHOD FOR ESTIMATION OF ARIPIPRAZOLE IN SWAB SAMPLES ON PHARMACEUTICAL MANUFACTURING EQUIPMENT SURFACES FOR CLEANING VALIDATION

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ABSTRACT

Objective: To validate simple analytical method and its application in the determination of residual aripiprazole in production area equipment and to confirm the efficiency of cleaning procedure.

Methods: The swab sampling and UV method for residual estimation of aripiprazole in swab samples from equipment surfaces after manufacturing of three consecutive batches of aripiprazole 10 mg uncoated tablets were developed and validated.

Results: The swab sampling method was developed and validated in order to obtain the suitable recovery (>90%). The swabs were saturated with acetonitrile. The UV method was developed using UV-Vis spectrophotometer at 255 nm. The calibration curve was linear (r^2 =1.0000) over a concentration range of 1-30 µg/ml. The LOD and LOQ were 0.43 µg/ml and 1.32µg/ml, respectively. No interference from swab solution was observed and samples were stable for 24h. The determined concentration varying from 1.00-5.687µg/swab was well below the calculated limit of contamination i.e., 24.2µg/swab or 24.2 µg/25 cm^2.

Conclusion: The results obtained from cleaning procedure confirmed that the proposed procedure was able to remove aripiprazole from equipment surfaces below the value of 10 ppm criteria. So the proposed validated UV method with appropriate swab wipe procedure could be applicable for cleaning validation on residues of aripiprazole.

Keywords: Residual estimation, swab sampling, Cleaning validation, Aripiprazole, UV method

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INTRODUCTION

Cleaning validation is defined as providing a high degree of assurance that a cleaning process removes residues of the active pharmaceutical ingredients of the product manufactured in a piece of equipment, the cleaning aids utilized in the cleaning process and the microbial attributes [1, 2]. All residues are removed to predetermined levels to ensure the quality of the next product manufactured is not compromised by waste from the previous product and the quality of future products using the equipment, to prevent cross-contamination and as a GMP requirement. The U. S. food and drug administration (FDA) have strict regulation about the cleaning validation. For example, FDA requires firms to have written general procedures on how cleaning processes will be validated. Also, FDA expects the general validation procedures to address who is responsible for performing and approving the validation study, the acceptance criteria, and when revalidation will be required. FDA also requires firms to conduct the validation studies in accordance with the protocols and to document the results of studies. The valuation of cleaning validation is also regulated strictly, which usually mainly covers the aspects of equipment design, cleaning process written, analytical methods and sampling. Each of these processes has their related strict rules and requirements. Regarding the establishment of limits, FDA does not intend to set acceptance specifications or methods for determining whether a cleaning process is validated. But some limits that have been mentioned by industry include analytical detection levels such as 10 ppm, biological activity levels such as 1/1000 of the normal therapeutic dose and organoleptic levels [3-5].

Sampling sites is based on the difficult clean geometries of the equipment and these locations are inaccessible i.e. their inaccessibility makes them difficult to clean, therefore, before choosing for sampling sites one must be conscious in selecting the desired sampling locations [6]. For validation of cleaning procedure three methods of sampling that are considered to be acceptable, namely direct surface sampling (swab method), indirect sampling (use of rinse solution) and placebo sampling. A combination of the first two methods is generally the most desirable particularly in circumstances where accessibility of equipment parts can mitigate against direct surface sampling [7, 8].

The cleaning validation is documented evidence with a high degree of assurance that consistently removes the residue of the subjected product below the established acceptance criteria. For the acceptable residual limit, various mathematical formulas and calculations are done based on known daily dose or on toxicological data along with safety factors. Hence the cleaning validation involves three separate activities: (i) establishment of acceptable residue limits for drug, (ii) development and validation of assay method for determination of drug from equipment surfaces and (iii) the development and validation of cleaning procedure that is used to remove drug from the manufacturing surfaces [6, 9-14, 25].

Aripiprazole is an atypical antipsychotic drug. It is primarily used in the treatment of psychotic conditions such as schizophrenia and bipolar disorder. It is commercially available as a tablet or as an oral solution. Tablets are available in 10 mg, 15 mg, 20 mg and 30 mg. Due to low dose profile, it is necessary to prove that the equipment train and production area are clean prior to the development of next product, as per good manufacturing practice.

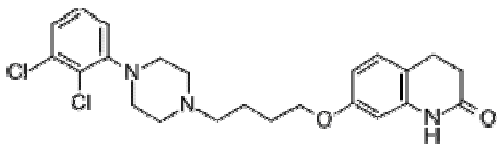

Fig. 1: Aripiprazole [29]

Aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$) m. wt 448.385, 7-{4-[4-(2, 3-dichloro-phenyl)-piperazin-1-yl] butoxy}-3, 4-dihydroquinolin-2(1*H*)-one (CAS registry number: 129722-12-9) is white to off-white crystalline powder, freely soluble in acetonitrile, ethanol, methanol, sparingly soluble in water [29].

The objective of this study was to demonstrate the applicability of UV method for estimation of the residues of aripiprazole in cleaning control swab samples from manufacturing surfaces after production of aripiprazole 10 mg uncoated tablets and the efficiency of the cleaning procedure. The analytical method was validated for linearity, accuracy, precision, robustness, ruggedness, LOQ, LOD. The stability of the solutions of aripiprazole was also studied. The studies were carried out as per the established guidelines [15-19, 26]. Also, the swabbing procedure was optimised in order to obtain a suitable recovery of the active ingredient. The cleaning validation was performed on three consecutive batches of finished product-aripiprazole 10 mg uncoated tablets.

MATERIALS AND METHODS

Chemicals and reagents

All the reagents were of analytical grade. Aripiprazole was obtained from Cadila Pharmaceuticals Ltd, Ahmadabad, India. Acetonitrile was obtained from Molychem, Mumbai, India. Swabs were obtained from Himedia Lab. Ltd. Mumbai, India. Stainless steel plates were used in this experimental work. Double distilled water was used throughout the study.

Equipment and instruments

Single rotary tablet compression machine (Shakti, India), UV Spectrophotometer model 1800 (Shimadzu, Japan).

Establishment of cleaning level acceptance criteria for aripiprazole

There are several approaches for the establishment of acceptable residual limit (ARL) calculation. ARL is calculated and compared with different approaches and minimum the value of ARL was selected [7, 8].

(i) Calculation of total carryover limit based on therapeutic or medical dose;

(ii) limit of calculation based on 10 ppm criteria (adulteration limit);

(iii) Limit of calculation based on visual inspection.

Calculation of total carryover limits based on therapeutic dosage

According to this approach, the safety factor is considered as a risk assessment factor. Many companies have chosen to use a standard safety factor of 1/1000 for all limits calculations. This means that any product, when administered at 1/1000 of its daily therapeutic dose (effective dose), will not cause any toxic effect to the patient if administered by the same route.

The basic principle of cleaning validation is that the patient should not take more than 0.1% of the therapeutic dose (effective dose). The lowest allowable residue level based on pharmacological activity is achieved by using the smallest dosage of the current product and the smallest batch size manufactured using the equipment train. The formula used for the calculation of the lowest allowable residue value is shown:

$$ARL = \frac{(STD x SBS x SF x M)}{(MDD x SSA)}$$

Where, ARL is the acceptance residual limit, STD is the API smallest therapeutic dose of previous product A (mg/unit dose), SBS is the smallest batch size of any subsequent product (mg) to be manufactured in the small equipment train, SF is the safety factor i.e. 1/1000 or 0.001, MDD is the maximum daily dose of the product to be manufactured in the same equipment train, M is the surface area/swab (25 cm^2), SSA is the shared equipment surface area.

Limit of calculation based on 10 ppm criteria

It is stated that not more than 10 ppm of the product will appear in the next batch of product. ARL was calculated on the basis of 10 ppm criterion according to below formula.

$$ARL = \frac{(10 x MBS x M)}{(SSA)}$$

Where ARL is the acceptance residual limit, MBS is the minimum batch size in kg of any subsequent product to be manufactured in the same equipment train. (Product B), M is the surface area/swab (25 cm^2), SSA is the shared equipment surface area.

Limit of calculation on the basis of visual inspection

Visually equipment surface area must appear clean with no traces of product or any extraneous matter. The VLOD (visually limit of detection) was determined by spiking 5 x 5 cm Stainless steel plates with known amount of drug. The lowest level of aripiprazole residue was visually detected.

Development and validation of UV procedure for assay of aripiprazole residues in swab collected from stainless steel plates

Calibration curve of aripiprazole

A primary stock solution of 1000µg/ml was prepared in acetonitrile by dissolving 10 mg of aripiprazole in 10 ml acetonitrile. For the preparation of different concentrations, aliquots of stock solution were transferred into series of 10 ml volumetric flasks and volume was made with acetonitrile. Different concentrations were prepared in a range of 1-30µg/ml of aripiprazole in acetonitrile and absorbance was measured at 255 nm for standard graph [20].

Validation of developed method as per ICH guidelines

The developed method for estimation of aripiprazole was validated as per ICH guidelines for validation parameters like accuracy, linearity, limit of detection (LOD), limit of quantification (LOQ), selectivity and robustness and ruggedness [18, 19, 28].

Linearity

In order to establish the linearity of the analytical method, a series of dilutions ranging from 1-30µg/ml were prepared. The absorbance values were noted at 255 nm. Linearity curve was plotted against corresponding concentration values. The compliance with beer's lamberts law (linearity) was found to be in concentration range and noted.

Accuracy

The accuracy of the method was estimated by determination of recovery for three concentrations (corresponding to 80, 100 and 120% of test solution concentration) covering the range of the method. For each concentration, three sets were prepared and absorbances were noted. The drug concentrations of aripiprazole were then calculated

Recovery study of drug from spiked stainless steel plates

Recovery study was prepared on spiked stainless steel plates [20-23] with a predefined 10 cm^2 surface area. 5 ml volume of different concentrations of 1, 5, 10, 15 and 20 µg/ml of aripiprazole was spiked onto stainless steel plates with five sets of the concentration of five plates each and was allowed to evaporate. The head of adsorbent swabs was saturated with acetonitrile. The total surface of the plates was successively wiped initially in a horizontal and then in a vertical fashion, starting from the outside towards the centre, with swabs moistened with the appropriate solvent. The head of the swabs was placed into a 10 ml volumetric flask containing 5 ml of the solvent (in which the swab was soaked). Then 5 ml of water was added to each volumetric flask. These volumetric flasks were capped and sonicated for 15 min. The absorbance of the solution was measured with UV-Vis spectrophotometer. The UV maxima in acetonitrile were found to be 255 nm.

Precision: Precision was considered at two levels:

Repeatability (Intra-day repeatability)

The intra-day repeatability was established by analysis 6 different concentrations with three replicates. In intra-day precision, all the replicate was prepared on the same day and

statistical validation was carried out. The data is represented as relative standard deviation (% RSD) and with low relative standard deviation (% RSD) values which indicate the good method precision.

Inter-day precision

Day to day precision was carried out by analysis 6 concentration with three replicates. In inter-day precision, all the linearity concentrations were prepared and absorbance was recorded. The low relative standard deviation (% RSD is ±2%) values which indicate the good method precision.

Robustness and ruggedness

Robustness and ruggedness were carried out to evaluate the influence of small but deliberate variations in the experimental conditions for the determination of aripiprazole. Robustness of the method was determined by changing the temperature and ruggedness of the method was determined by changing analyst.

LOD and LOQ

LOD and LOQ of the method were established using the following formulas as per ICH guideline:

$$LOD = \frac{3.3\sigma}{S}$$

$$LOQ = \frac{10\sigma}{S}$$

Where, σ is the mean standard deviation of y–intercepts of regression lines, S is the slope of the standard curve.

Optimization and validation of cleaning procedure for aripiprazole tablets on compression machine

The cleaning validation was done to demonstrate the effectiveness of the cleaning procedure for residues up to the predetermined acceptance level of aripiprazole in the equipment train [24].

Sampling procedure

To determine the residue of drug remaining in the equipment train after cleaning swab sampling procedure was used. For this procedure, sterile cotton swabs with polypropylene stick in HDPF bottle were used. Before collecting the samples the swabs were dipped in the acetonitrile and completely saturated for 15 min. For all sampling locations, 5 cm × 5 cm swab area was selected and swabbed in described swabbing pattern. The pattern of swabbing and pressure applied was such that it collected the maximum residue present in the selected area. All this operation was done with care and wearing powder free sterile gloves in hands. The swab wiped from selected area was placed in the sterile HDPF containing 5 ml of acetonitrile and capped securely. Each tube was sonicated for 5 min; the extract was collected and analyzed by developed method.

Chemical acceptance criteria

ARL (acceptable residual limit) used to calculate chemical acceptance criteria

$$Chemical\ acceptance\ criteria = \frac{(ARL x\ recovery\ from\ SS\ plate\ surface)}{100}$$

Sampling locations

It is important to include the swab samples from the most difficult to clean and worse case locations of the equipment, but the sampling locations were selected such that these were representative of all areas of equipment, even easy to clean surfaces.

In the given piece of equipment, 99% surface was readily accessible, easy to clean and visually friendly category. Only 1% or less equipment surface was hard to clean and it was assumed that the equipment was equally dirty as the hard to clean surface samples obtained.

Following sampling locations were selected for swab sampling of the residual drug from tablet machine after washing (fig. 2; table 1).

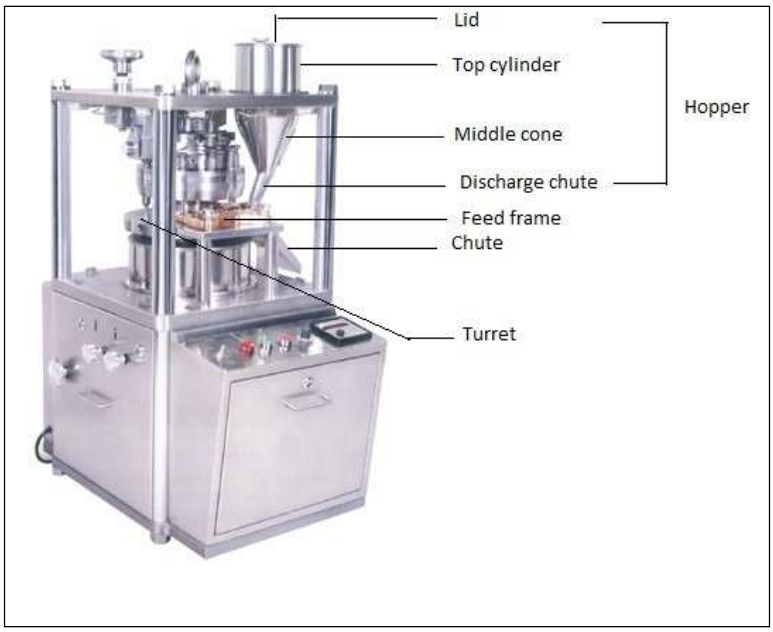

Fig. 2: Different sampling locations in the single rotary tablet compression machine [27]

Table 1: Different sampling locations in the single rotary tablet compression machine [27]

S. No.	Sampling point location	Sampling point name
1.	Hopper top cylinder	TCM-01
2.	Hopper middle cone	TCM-02
3.	Hopper discharge chute	TCM-03
4.	Turret	TCM-04
5.	Chute	TCM-05

Optimisation of cleaning procedure

After compression of the tablets of aripiprazole 10 mg the tablet machine was cleaned according to the general procedure used in the industry to clean the pharmaceutical equipment. The samples were collected with cotton swabs by wiping 5 cm×5 cm area of predefined sampling locations. Samples were analyzed and compared w. r. t the predetermined acceptance criteria [24].

Following steps were followed in the cleaning procedure of the tablet machine after compression of the aripiprazole 10 mg tablet.

- The main power supply of machine was switched off.
- The pressure was released which was applied on the roller of the machine during compression.
- Previous batch powders, containers and tablets were removed from manufacturing area.
- The loosely stuck powder was wiped from the machine using a dry cloth.
- Compression machine was dissembled as follows:
  - Remove the hopper from spindle by unscrewing the upper screws.
  - Doors of the machine were opened.
  - The feed frame was removed from die table by screwing the upper screws.
  - The screws of tablet discharge chute were loosened and removed it from the machine.
  - All above-dissembled parts were subjected to washing.
  - Bottom side cover was removed from the machine.
  - Upper punches were removed by removing upper punch guide and rotating the turret with the help of flying wheel.
  - The die locking screw was unlocked from the turret with allen key and dies were removed with the help of die driving road by pressing through the lower guide hole.
- Cleaning of die and punches
  - The adhered powder was removed from the punches with the help of the dry cloth.
  - Punches were cleaned with the help of clean wet dipped in purified water.
  - Dies were cleaned by inserting the wet cloth dipped in purified water through the bore. Dies were externally wiped with wet cloth dipped in purified water,
  - Cleaned punches and dies were placed into proper cabinet after visual inspection.
  - The die lock was cleaned with a clean wet cloth dipped in purified water.
  - Die lock was allowed to air dry after cleaning.
- Cleaning of machine
  - The top base of the machine, upper roller, an upper cam track and lower track were cleaned with a wet cloth dipped in purified water followed by cleaning with dry cloth clean.
  - All adhered material to turret was removed by means of the vacuum cleaner and then wiped with a clean cloth moistened in water followed by cleaning with a clean cloth soaked with IPA.
  - Shank of upper punch, lower punch and die pocket were cleaned with a dry clean cloth.
  - Other non-contact parts of the machine were cleaned with a clean dry cloth.
  - Doors were cleaned with a cloth moistened with purified water followed by dry clean cloth.
- Washing
  - Hopper, feed frame, liner take off the plate and discharge chute was cleaned by flushing with purified water for not less than 4 min to remove the adhered materials on SS surfaces.
- Final rinse and drying
  - Finally feed frames, hopper from the inner side, liner takes off the plate and discharge chute was rinsed with purified water not more than 4 min. Excess water was removed with dry clean cloth,
- Cleaned items were carried to machine area.
- The machine was labelled 'Ready to use'.

Validation of cleaning procedures

For validation of cleaning procedure on tablet machine, three consecutive batches of aripiprazole tablet 10 mg were prepared. This validation was done to prove the effectiveness and consistency of the cleaning procedure. Validation was also done to meet the regulatory requirement of the development method. After production of each batch the tablet compression machine was subjected to above cleaning procedure. Visual and chemically inspection results were recorded.

RESULTS AND DISCUSSION

Establishment of cleaning level acceptance criteria for aripiprazole

Swab sampling of area hardest to clean was done from equipment used in the manufacturing and residues were found in mg/ml. the smallest batch sized (SBS) subsequent products were selected for calculating the values of the maximal allowable carryover. ARL was calculated and compared with different approaches and minimum the value of ARL was selected.

Calculation of total carryover limits based on therapeutic dosage

The formula used for the calculation of the lowest allowable residue value is shown:

$$ARL = \frac{(STD x SBS x SF x M)}{(MDD x SSA)}$$

Where, ARL is the acceptance residual limit, STD is the smallest therapeutic dose of product A (mg/unit dose), SBS is the smallest batch size of any subsequent product to be manufactured in the small equipment train, SF is the safety factor i.e. 1/1000 or 0.001, MDD is the maximum daily dose of the product to be manufactured in the same equipment train, M is the surface area/swab (25 cm^2), SSA is the shared equipment surface area.

$$Smallest\ batch\ size = \frac{minimum\ working\ capacity\ in\ gram\ (A)}{Weight\ of\ the\ tablet}$$

A = (1.25L (25% capacity of hopper) x 425 gram/l(average bulk density of subsequent material)=531.25 gm

B = Tablet weight

SBS (number of dosage unit form/unit batch) = $\frac{531.25}{0.117} gm$

= 4540.5 tablets

Shared surface area of the tablet compression machine. Covering hopper, turret, discharge chute was calculated 5,484.64 cm^2 (table 2).

$$ARL = \frac{(STD x SBS x SF x M)}{(MDD x SSA)}$$

$$ARL = \frac{(30 x 4540.5 x 0.001 x 25)}{(10 x 5484.64)}$$

= 0.0620 mg/swab

= 62µg/swab or 62µg/25 cm^2

Table 2: Surface area calculation for tablet machine

S. No.	Part name	Geometric shape	L	B	R	H	Formula used	Surface area in cm²
1.	Hopper							
a.	Top cylinder	Cylinder			23	16	2Лrh	2311.04
b.	Middle cone	Double radius cone			r1=20.3 r2= 8.2	14	2Л(r1+r2)/2×h	1239.6
c.	Discharge chute	Cylinder			5.1	11.5	2Лrh	368.3
2.	Turret							
		Circular			r1=14 r2=9		Л(rl)²-Л(r2)²	361.1
3.	Feed frame							
		Rectangle	28	15				420
4.	Chute							
		C channel	20.5	8.8		6	Lb+2bh	286
5.	Lid of hopper							
		Circular			8		Лr²	200.96
Total								4986.04
(+ % of area)								498.6
Total								5484.64

L= length, B= breath, R= radius, H= height, Л= 3.14

Limit of calculation based on 10 ppm criteria

ARL was calculated on the basis of 10 ppm criterion according to below formula.

$$ARL = \frac{(10xMBSxM)}{(SSA)}$$

Where ARL is the acceptance residual limit, MBS is the minimum batch size in kg of any subsequent product to be manufactured in the same equipment train. (Product B), M is the surface area/swab (25 cm²), SSA is the shared equipment surface area.

$Minimum\ batch\ size =$ (1.25L (25% capacity of hopper) x 425 gram/l(average bulk density of subsequent material) = 531.25 gm

= 0.531Kg

$$ARL = \frac{(10xMBSxM)}{(SSA)}$$

$$ARL = \frac{(10x0.531x25)}{(5484.64)}$$

= 0.0242 mg/swab

=24.2µg/swab or 24.2µg/25 cm²

Limit of calculation on the basis of visual inspection

The VLOD (visually limit of detection) was determined by spiking 5 x 5 cm stainless steel plates with known amount of drug concentration (10-40µg/ml) after evaporation of the sample solution. The lowest level of aripiprazole residues which was visually detected is 40µg/25 cm².

Since ARL value of 24.2µg/swab was the lowest value out of three values obtained from 3 criterions. Hence 24.2µg/25 cm² was considered as the acceptable residual limit (ARL) for aripiprazole for residual estimation of the determined concentration of aripiprazole residues in swab sample solution should not be more than ARL (acceptance criteria).

Development and validation of UV procedure for assay of aripiprazole residues in swab collected from stainless steel plates

Calibration curve of aripiprazole in acetonitrile

The stock solution (1000µg/ml) was prepared in acetonitrile by dissolving 10 mg of aripiprazole in 10 ml acetonitrile. From the stock solution, various dilutions were prepared and absorbance was measured at 255 nm [22]. The calibration curve was constructed by plotting absorbance vs concentration with linear regression equation Y = 0.032+0.0006, regression coefficient r²equal to 1 (fig. 3, 4). The high value of correlation coefficient indicates good linearity.

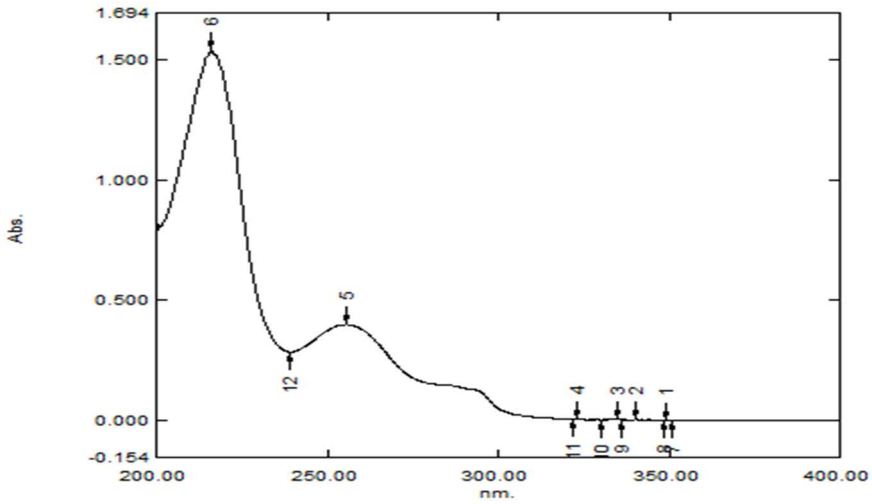

Fig. 3: UV spectrum of aripiprazole in acetonitrile showing absorption maxima at 255 nm

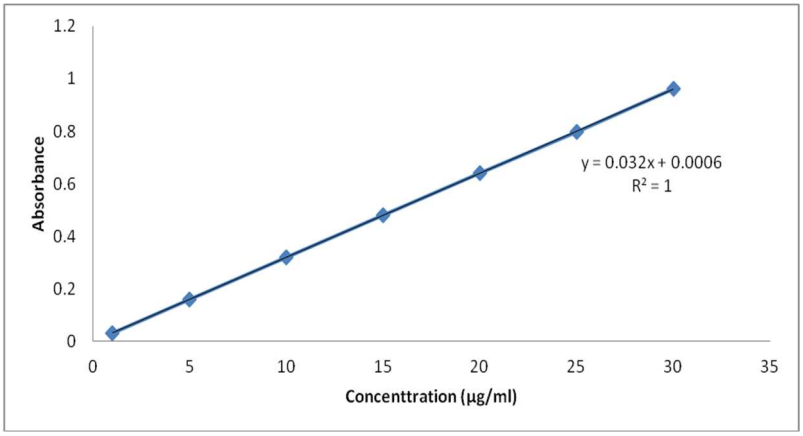

Fig. 4: Calibration curve for aripiprazole

Validation of developed method as per ICH guideline

Linearity

Different aliquots were taken from the stock solution and diluted with acetonitrile to prepare series of concentration ranging from 1-30µg/ml. The absorbance value was noted at 255 nm and plotted against corresponding concentration values. The linearity range was found to be 1-30µg/ml for aripiprazole. Each measurement was carried out in sextet (table 3).

Accuracy

The accuracy of the method was determined by calculating recovery of aripiprazole by standard addition method. A known amount of standard solution of aripiprazole (80, 100, and 120 %) added to pre-quantified separate (10µg/ml) respectively. The amount of aripiprazole was estimated (table 4).

The low value of standard deviation indicates that the proposed method is accurate. Results of recovery studies are given in table 4. The % recovery was found between 95.20%-98.82% which were within the limit of acceptable criteria which indicate indicates that the method has good accuracy for determining aripiprazole [22].

Recovery study of drug from spiked stainless steel plates

Recovery study was prepared on spiked stainless steel plates with a predefined 10 cm^2 surface area. 5 ml volume of different concentrations of 1, 5, 10, 15 and 20 µg/ml of aripiprazole was spiked onto stainless steel plates with five sets of the concentration of five plates each and was allowed to evaporate. The head of adsorbent swabs was saturated with acetonitrile.

The total surface of the plates was successively wiped initially in a horizontal and then in a vertical fashion, starting from the outside towards the centre, with swabs moistened with the appropriate solvent. The head of the swabs was placed into a 10-ml volumetric flask containing 5 ml of the solvent (in which the swab was soaked). Then 5 ml of water was added to each volumetric flask. These volumetric flasks were capped and sonicated for 15 min.

The absorbance of the solution was measured with UV-Vis spectrophotometer at 255 nm. The % recovery with spiked stainless steel plates was found between 88.75-98.12% which is well within the acceptance criteria with %RSD value well in limit i.e. less than 2%. Hence indicates method has good accuracy for determining aripiprazole (table 5).

Table 3: Linearity data for aripiprazole

Drug conc. (µg/ml)	mean±SD (n=6)	Drug recovered (µg)	% recovery
1	0.032±0.002	0.996	99.68
5	0.160±0.001	4.986	99.93
10	0.320±0.004	10	100
15	0.48±0.002	14.98	99.87
20	0.640±0.003	20	100
25	0.797±0.016	24.91	99.65
30	0.960±0.001	29.99	99.98
Mean			99.89
Standard Deviation			0.174
% Relative Standard Deviation			0.174

n=6 each measurement was repeated in sextet, Data is expressed in mean±SD.

Table 4: Recovery study for aripiprazol

Amt of sample (µg/ml)	Amt of std. drug added (µg/ml)	Mean (n=3)	SD	% RSD	Drug recovered (µg)	% Recovery
10	8	0.549	0.0005	0.105	17.13	95.20
10	10	0.629	0.0006	0.110	19.65	98.29
10	12	0.696	0.001	0.240	21.74	98.82
Mean						97.44
Standard Deviation						1.952
% Relative Standard Deviation						2

Each measurement was repeated three times independently, Data is expressed in mean±SD.

Table 5: Result obtained for the recovery of aripiprazole form spiked 180-grit stainless steel plate samples

Drug spiked (µg)	Absorbance (n=5)	Drug recovered (µg)	% Recovered
1	0.032	0.981	98.12
	0.031	0.95	95
	0.029	0.887	88.75
	0.03	0.918	91.87
	0.032	0.981	98.12
5	0.155	4.825	96.5
	0.153	4.762	95.25
	0.154	4.793	95.87
	0.152	4.731	94.62
	0.156	4.856	97.12
10	0.305	9.512	95.12
	0.309	9.637	96.37
	0.307	9.575	95.75
	0.311	9.7	97
	0.31	9.66	96.68
15	0.461	14.38	95.91
	0.464	14.48	96.54
	0.463	14.45	96.33
	0.465	14.51	96.75
	0.466	14.54	96.95
20	0.618	19.29	96.46
	0.615	19.2	96
	0.617	19.26	96.31
	0.619	19.32	96.62
	0.62	19.35	96.78
Mean			95.87
Standard Deviation			1.924
% Relative Standard Deviation			2

Each measurement was repeated five times. (n=5)

Precision

Precision was investigated by analyzing the different concentration of aripiprazole (20µg/ml) in independent replicates on the same day (intra-day) and on consecutive days (inter-day).

Repeatability

The intra-day and inter-day precisions of the proposed method was determined by performing swabbing which involved spiking aripiprazole on stainless steel surface, recovering the aripiprazole with swabs and desorbing the swabs into extraction solution diluent as described earlier in accuracy study and analyzing corresponding responses on the same day and on different days over a period of one week for different concentration of standard solution of aripiprazole (20µg/ml). Results were reported in table 6, 7. The results indicate that the % RSD values were 0.09 and 0.079 for Intraday and Interday precision respectively which were within the prescribed limits of ICH guidelines indicate good precision.

Table 6: Repeatability analysis of aripiprazole (Intraday precision)

Drug Conc (µg/ml)	Mean absorbance (n=3)	SD	% RSD	Drug recovered (µg)	% recovery
20	0.637	0.0005	0.090	19.90	99.54
20	0.637	0.0015	0.239	19.89	99.48
20	0.637	0.0005	0.090	19.90	99.54
20	0.637	0.001	0.156	19.88	99.43
20	0.638	0.001	0.156	19.91	99.59
20	0.638	0.0005	0.090	19.93	99.69
Mean					99.55
Standard Deviation					0.089
% Relative Standard Deviation					0.090

Each measurement was repeated three times. (n=3), Data is expressed in mean±SD.

Table 7: Repeatability analysis of aripiprazole (Interday precision)

Drug conc. (µg/ml)	Mean absorbance (n=3)	SD	% RSD	Drug recovered (µg)	% Recovery
20	0.640	0.002	0.331	19.99	99.95
20	0.639	0.0007	0.110	19.97	99.85
20	0.639	0.0007	0.110	19.95	99.75
20	0.64	0.0014	0.220	19.98	99.90
20	0.639	0.0014	0.221	19.97	99.85
20	0.640	0.0028	0.441	19.99	99.95
Mean					99.880
Standard Deviation					0.078
% Relative Standard Deviation					0.079

Each measurement was repeated three times. (n=3), Data is expressed in mean±SD.

Robustness and ruggedness

In robustness, the drug content was analyzed under the experimental variables like a slight change in the temperature (25˚C, 18˚C). In ruggedness analyst to analyst, variation was considered. As the % RSD values was found to less than 2%, so method proves its robustness and ruggedness (table 8-10). This gives the confidence that API residues are stable and the residues concentration do not change in swab solutions during cleaning validation.

LOD and LOQ

The sensitivity of the method for estimation was determined in terms of the limit of detection (LOD) and limit of quantitation (LOQ). The LOD value of LOD was found to be 0.43µg/ml and LOQ was found to be 1.32µg/ml (table 11).

Optimization and validation of cleaning procedure for aripiprazole tablets on compression machine

Cleaning procedure validation was done to check the effectiveness of cleaning procedure.

Chemical acceptance criteria

ARL (acceptable residual limit) used to calculate chemical acceptance criteria

$$Chemical\ acceptance\ criteria = \frac{(ARLx\ recovery\ from\ SS\ plate\ surface)}{100}$$

$$= \frac{(24.2x95.8)}{100}$$

= 23.18µg/cm^2

Table 8: Room temperature (25 ˚C) variation study for aripiprazole

Drug conc. (µg/ml)	Mean absorbance (n=3)	SD	% RSD	Drug recovered (µg)	% recovery
20	0.638	0.002	0.313	19.91	99.59
20	0.635	0.002	0.314	19.83	99.17
20	0.635	0.002	0.314	19.84	99.22
20	0.641	0.002	0.312	20.02	100.1
20	0.641	0.001	0.156	20.01	100.0
20	0.640	0.002	0.312	19.99	99.95
Mean					99.68
Standard Deviation					0.418
% Relative Standard Deviation					0.419

Each measurement was repeated three times independently. (n=3), Data is expressed in mean±SD.

Table 9: 18 ˚C temperature variation study for aripiprazole

Drug conc. (µg/ml)	Mean absorbance (n=3)	SD	% RSD	Drug recovered (µg)	% recovery
20	0.633	0.001	0.157	19.77	98.86
20	0.632	0.001	0.158	19.75	98.76
20	0.633	0.001	0.157	19.76	98.81
20	0.634	0.001	0.157	19.79	98.96
20	0.631	0.001	0.158	19.72	98.60
20	0.632	0.002	0.316	19.74	98.70
Mean					98.78
Standard Deviation					0.126
% Relative Standard Deviation					0.128

Each measurement was repeated three times independently. (n=3), Data is expressed in mean±SD.

Table 10: Analyst to analyst variation study for aripiprazole

Drug Conc. (µg/ml)	Mean absorbance (n=3)	SD	% RSD	Drug recovered (µg)	% recovery
20	0.636	0.0035	0.555	19.87	99.35
20	0.636	0.0007	0.111	19.87	99.35
20	0.634	0.0007	0.111	19.80	99.04
20	0.632	0.0007	0.111	19.74	98.73
20	0.637	0.0007	0.110	19.90	99.51
20	0.639	0.0014	0.221	19.95	99.75
Mean					99.29
Standard Deviation					0.357
% Relative Standard Deviation					0.360

Each measurement was repeated three times independently. (n=3), Data is expressed in mean±SD.

Table 11: Regression analysis data and summary of validation parameters for proposed method

Parameters	Aripiprazole
Linearity	1-30 (µg/ml)
Regression equation	Y=0.032x+0.0006
Slope	0.032
Intercept	0.0006
Correlation coefficient	1
LOD (limit of detection) (µg/ml)	0.43
LOQ (limit of quantitation) (µg/ml)	1.32
Precision (% RSD)	
Interday (n=6)	0.079
Intraday (n=6)	0.090

Optimization of cleaning procedure

Samples were analyzed and compared with respect to the pre-determined acceptance criteria.

Validation of cleaning procedure

For validation of cleaning procedure, the three consecutive batches of aripiprazole tablets 10 mg were formulated and evaluated (according to each cleaning level condition) by the developed analytical method. The level of drug residue obtained from visual inspection and chemical inspection was evaluated against the ARL level. The level of drug residue obtained after final washing (of three batches) was less than the pre-calculated ARL value hence, it was concluded that the established procedure is responsible to achieve the expected cleanliness. The concentration of drug was found to be highest at turret (5.166 µg/swab) but within the ARL value i.e., 24.2µg/swab (table 14, 15; fig. 4).

Table 12: Chemical inspection results of various steps and time of cleaning on turret

	Active drug content (µg/ml)			
Sampling location	**Initial after tablet production**	**After wiped with dry cloth**	**After wiped with clean cloth wetted with purified water**	**After wiped with clean soaked in IPA**
TCM-04	44.43	14.28	12.09	4.75
	45.68	14.90	13.81	5.687
	45.218	14.43	14.12	5.062
Avg. (n=3)	45.11	14.54	13.34	5.166

TCM-04= turret; IPA=isopropyl alcohol, each measurement was repeated three time independently. (n=3)

Table 13: Chemical inspection results of various steps and time of cleaning on different parts of tablet compression machine

	Active drug content (µg/ml)					
Sampling location	**Initial after tablet production**	**After wiped with dry cloth**	**After rinse with potable water**			**After rinse with purified water for 3 min**
			2 min	**4 min**	**6 min**	
	22.56	11.15	6	5.062	4.593	4.281
	23.34	13.18	6.312	7.25	4.281	2.406
	23.81	12.87	6.312	5.062	3.968	2.562
Average (n=3)	**23.23**	**12.40**	**6.208**	**5.791**	**4.280**	**3.083**
TCM-02	43.65	10.06	6.312	6	3.187	2.25
	44.59	10.84	6.156	5.531	3.5	2.875
	44.75	11.78	7.093	4.75	4.437	3.5
Average (n=3)	**44.33**	**10.89**	**6.520**	**5.427**	**3.708**	**2.875**
TCM-03	16.15	9.593	8.031	3.968	3.5	2.406
	17.25	11	9.125	3.968	3.812	1
	16.62	11.93	9.75	3.187	4.437	1.156
Average (n=3)	**16.67**	**10.84**	**8.968**	**3.707**	**3.916**	**1.520**
TCM-05	33.96	21	5.531	5.218	3.656	2.562
	34.28	22.40	6.468	4.437	3.343	3.031
	34.43	21.62	6	4.281	3.968	2.875
Average (n=3)	**34.22**	**21.67**	**5.999**	**4.645**	**3.655**	**2.822**

TCM-01= hopper top cylinder; TCM-02=hopper middle cone; TCM-03= hopper discharge chute; TCM-04= turret; TCM-05=chute, each measurement was repeated three time independently. (n=3)

Table 14: Visual inspection results of tablet compression machine after cleaning

S. No.	**Areas for visual observation**	**Visually clean: Yes/No (n=3)**		
		Batch-1	**Batch-2**	**Batch-3**
1.	Doors	Yes	Yes	Yes
2.	Hopper	Yes	Yes	Yes
3.	Turret	Yes	Yes	Yes
4.	Discharge chute	Yes	Yes	Yes

Each measurement was repeated three time independently. (n=3)

Table 15: Chemical inspection results of tablet compression machine after cleaning

S. No.	**Sampling location**	**Active drug content (µg/swab) (n=3)**		
		Batch-1	**Batch-2**	**Batch-3**
1.	TCM-01	4.281	2.406	2.562
2.	TCM-02	2.25	2.875	3.5
3.	TCM-03	2.406	1	1.156
4.	TCM-04	4.75	5.687	5.062
5.	TCM-05	2.562	3.031	2.875

TCM-01= hopper top cylinder; TCM-02=hopper middle cone; TCM-03= hopper discharge chute; TCM-04= turret; TCM-05=chute, each measurement was repeated three times independently. (n=3)

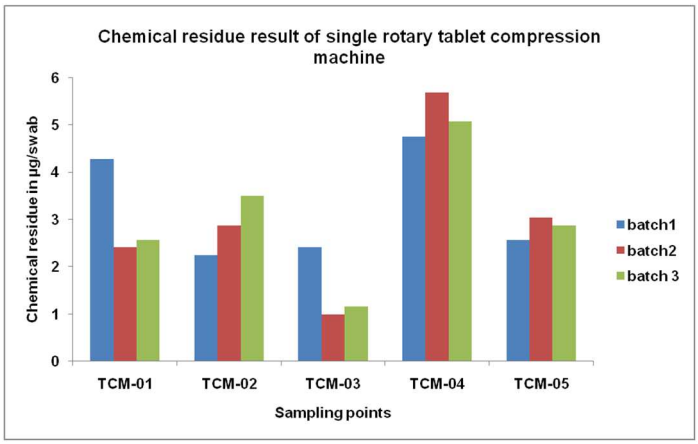

Fig. 5: Comparation of chemical residue content of three batches at various locations of tablet compression machine after cleaning, TCM-01= hopper top cylinder; TCM-02=hopper middle cone; TCM-03= hopper discharge chute; TCM-04= turret; TCM-05=chute

Hence the developed cleaning method removes even traces of residue of drug present on the instrument. Analytical method developed was found to be linear, precise, accurate and sensitive to detect even small quantity of drug residue in view of cleaning validation. Cleaning standard operating procedure provides sufficient removal of the residues from equipment surfaces and totally excludes the risk of cross contamination.

CONCLUSION

Cleaning procedure was optimized by changing the variables and determination of drug residues on different parts of tablet machine in different steps of cleaning. Cleaning validation was executed on tablet compression machine. Three consecutive batches of aripiprazole tablets were formulated for cleaning validation study. The chemical residue of the drug at various parts of the equipment surfaces was found within the predefined acceptance criteria.

Swab sampling and UV method were developed and validated for the quantitative estimation of aripiprazole residues on stainless steel surfaces of plant equipment after manufacturing of aripiprazole 10 mg uncoated tablets to demonstrate cleaning validation. Methods with appropriate swab wipe procedure were found to be selective, accurate, precise and linear. No interference from swab solution was observed and samples were stable during analysis for residual estimation. Hence, the results obtained confirm that the cleaning procedures used are able to remove residues from equipment surfaces and well below the calculated limit of contamination.

The swab sampling and UV method can be used in other pharmaceutical quality control laboratories to apply successfully in cleaning validation for quantitative estimation of aripiprazole residues after manufacturing of aripiprazole uncoated tablets.

CONTRIBUTION

Ms. Sukhpreet Kaur (Research Scholar) performed practical work. Ms. Indu Bala has supervised the practical work and compiled it. Dr. Anjoo Kamboj has helped in the compilation of results and prepared the manuscript. Dr. Upendra K Jain has worked as an overall supervisor.

CONFLICT OF INTERESTS

Declared none

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