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Original article

Validation of Swab Sampling and HPLC Methods for Determination of Meloxicam Residues on Pharmaceutical Manufacturing Equipment Surfaces for Cleaning Validation

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The swab sampling and HPLC methods for residual estimation of meloxicam in swab samples from equipment surfaces after manufacturing of Mobicam 15 mg (meloxicam 15 mg) uncoated tablets were developed and validated. The swab sampling method was developed and optimized in order to obtain a suitable recovery (>90 %). Polyester swabs were moistened with diluent - a mixture of methanol, 1 M sodium hydroxide solution and water 28:2:20, v/v/v. The HPLC method was developed using Luna C18(2) 150 × 4.6 mm, 5 µm column with a mobile phase - a mixture of solution A and solution B (63 : 37); the flow rate – 0.8 mL/min; the column temperature - 40°C; the detector wavelength - 254 nm; the injection volume – 25 µL. The calibration curve is linear (the r^2=1.00000) over a concentration range 0.11–88 µg/mL; the limit of detection and the limit of quantitation are 0.11µg/mL and 0.014 µg/mL, respectively; no interference from swab solution was observed and samples were stable for 24 h. The determined concentration varying 0.016 – 5.8 µg/mL are well below the calculated limit of contamination. So the proposed validated HPLC method with appropriate swab wipe procedure could be applicable for cleaning validation on residues of meloxicam.

Keywords: Residual estimation, Swab sampling, Cleaning validation, HPLC

Sürüntü Örnekleme Validasyonu ve Temizlik Validasyonu için Farmasötik Üretim Ekipman Yüzeyinde Meloksikam Artığı Tayini için YPSK Metodları

Kaplanmamış Mobicam 15 mg (meloksikam 15 mg)'tabletlerinin üretiminden sonra ekipman yüzeyinden alınan sürüntü örneklerinde meloksikamın artık değerlendirmesi için sürüntü örnekleme ve YPSK metodları geliştirildi ve valide edildi. Sürüntü örnekleme metodu geliştirildi ve uygun geri kazanım (>%90%) elde edilmesi için optmize edildi. Poliester bezler diluent -metanol, 1 M sodium hidroksit çözeltisi ve su karışımı: 28:2:20, h/h/h ile nemlendirildi. YPSK metodu, Luna C18(2) 150 × 4.6 mm, 5 µm kolonu kullanılarak, A ve B çözeltisi karışımı (63:37, h/h) mobil fazı ile, 0.8 mL/min akış hızı ile, , 40 C° kolon sıcaklığı, 254 nm dedektör dalga boyu, 25 µL injeksiyon hacmi ile geliştirildi. Kalibrasyon eğrisi 0.11–88 µg/mL konsantrasyon aralığında lineerdir (r^2=1.00000) ve teşhis sınırı ve tayin alt sınırı sırasıyla 0.11µg/mL ve 0.014 µg/mL dir; sürüntü çözeltisinden herhangi bir etkileşim gözlenmedi ve örnekler 24 saat stabildi. Belirlenen konsantrasyon 0.016 – 5.8 µg/mL arasında, hesaplanan kontaminasyon limitinin oldukça altındaydı. Bu yüzden önerilen valide edilmiş YPSK metodu uygun sürüntü alma işlemiyle meloksikam artıklarında temizlik validasyonu için geçerli olabilir.

Anahtar kelimeler: Artık tahmini, Sürüntü örnekleme, Temizlik validasyonu, YPSK

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INTRODUCTION

In pharmaceutical manufacturing industries, it is well established that equipment and production areas must be cleaned after each manufacturing process and regulatory authorities recommend validation of the procedure used. Cleaning validation is a critical analytical responsibility of quality system in pharmaceutical industry and the process of ensuring the cleaning procedure which effectively removes the residues from the manufacturing equipment and facilities below a predetermined level. This is necessary not only to ensure the quality of the next batch of different products but also to prevent cross-contamination; it is also a FDA (Food and Drug Administration)/GMP (Good Manufacturing Practice) requirement. Cleaning validation consists of two separate activities: development and validation of the cleaning procedure used to remove the drug from the manufacturing equipment surfaces and development and validation of the methods used to quantify the residues on the surfaces of manufacturing equipment.

Residues have a significant cross-contamination potential. Residual estimation requires development of selective and sensitive methods capable of quantitative estimation of traces remaining over the surface of manufacturing equipment after cleaning procedure. It involves identification of numerous sampling points in the manufacturing lane to demonstrate a complete removal of residues. The sampling, therefore a very important parameter, since the conclusion of the cleaning procedure is based on the sample results. According to the FDA guide, two different methods of sampling are generally admitted for performing a cleaning control: the direct surface sampling, using the swabbing technique and the indirect sampling based on the analysis of solutions used for rinsing the equipment.

The acceptance limit (AL) for residues in the equipment is not established in the current regulations. According to the FDA, the limit should be based on logical criteria, involving the risk associated with residues of determined products. Calculation of an acceptable limit of residues and a maximum allowable carryover (MAC) for active pharmaceutical ingredient (API) in the production equipment should be based on therapeutic doses, toxicity and a general limit (10 ppm). Several mathematical formulas were proposed to establish the acceptable residual limit (1-7).

Mobicam 15 mg - a non-steroidal anti-inflammatory drug of the oxicams group. It has an anti-inflammatory, analgesic and antipyretic action. Expressed anti-inflammatory action of meloxicam is confirmed on all standard models of inflammations. The action mechanism of meloxicam is caused by its ability to inhibit the synthesis of prostaglandins – one of the main components of an inflammation. In vivo meloxicam inhibits synthesis of prostaglandins in the inflammatory focus more intensively than in mucous membrane of stomach and kidneys. These distinctions are connected with more selective inhibition of Cyclooxigenase-2 (COX-2) in comparison with Cyclooxigenase-1 (COX-1). The inhibition of COX-2 causes therapeutic effect of NSAIDs whereas the inhibition of COX-1 causes their collateral actions from a stomach and kidneys. One tablet contains 15 mg meloxicam.

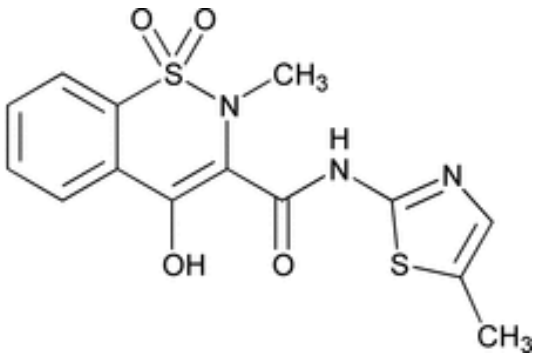

Figure 1. Chemical structure of meloxicam.

Meloxicam ($C_{14}H_{13}N_3O_4S_2$,Mr=351.40, 4-Hydroxy- 2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide (CAS registry number: 71125-38-7) is

pale yellow powder, soluble in dimethylformamide, slightly soluble in acetone, very slightly soluble in methanol and in alcohol, practically insoluble in water (8).

The aim of this study was to demonstrate the applicability of HPLC method for determination the residues of meloxicam in cleaning control swab samples from manufacturing surfaces after production (primary packaging) of Mobicam 15 mg uncoated tablets and the efficiency of the cleaning procedure. This product was evaluated as the worst case. The API namely meloxicam is practically insoluble in water and very adherent to surfaces. The analytical method was validated with respect to system suitability test, specificity, linearity-range, robustness, limit of detection (LOD) and quantitation (LOQ). The stability of solutions of meloxicam was also studied. These studies were performed in accordance with established guidelines (9-11). Also, the swabbing procedure was optimized in order to obtain a suitable recovery of active ingredient. The cleaning validation was performed on three consecutive batches of finished product – Mobicam 15 mg (meloxicam 15 mg) uncoated tablets.

MATERIAL AND METHODS

The certified reference standard of meloxicam was supplied by USP. The HPLC grade methanol, 2-propanol and analytical grade phosphoric acid, ammonium phosphate dibasic, sodium hydroxide were purchased from Sigma-Aldrich (Germany). The HPLC grade water was prepared using Milli Q Adventage A10 purification system (Millipore, France). Polyester microswabs (3×2.5×10 mm) for sampling were purchased from ITW Texwipe (USA). Cleaning procedure was performed using Microbac Forte 1 % solution as a disinfectant/detergent which was purchased from Bode Chemie (Germany).

The chromatographic analysis was performed using Ag 1260 Infinity (AG Technologies, USA). The output signal was monitored and processed using Chemstation software. The pH of the solutions was measured by a pH meter S40 Sevenmulti (Mettler-Toledo, Switzerland). SONOREX™ Digital 102P Ultrasonic bath DK 102 (Germany), Shaker 3056 IKA SH 501 DIGITAL Werke (Germany), Analytical balance CPA 232S Sartorius (Germany), GFL water bath (Germany) were used for sample preparation. All the measuring equipment was qualified.

The method was developed using a Luna C18 (2) 150×4.6 mm, 5 µm column with an isocratic mobile phase containing a mixture of solution A (2 g of ammonium phosphate dibasic dissolved in 1000 mL of water HPLC grade and adjusted pH of 7.0±0.05 with phosphoric acid) and solution B (a mixture of 650 mL of methanol and 100 mL of 2-propanol) (63 : 37 v/v); The mobile phase was filtered through Durapore PVDF, 0.45 µm membrane filters and degassed. The flow rate of the mobile phase was 0.8 mL/min. The column temperature was maintained at 40 °C and the eluted compound was monitored at the wavelength of 254 nm. The sample injection volume was 25 µL (12).

Preparation of standard solution

22 mg of meloxicam standard was weighed, transferred accurately to 25 mL volumetric flask and was added 1 mL of 1 M sodium hydroxide and 15 mL methanol, sonicated until it becomes completely dissolved and diluted to volume with methanol diluent, mixed well. Then it was filtered through Durapore PVDF 0.45 µm membrane filter, discarding the first 5 ml of the filtrate (Stock solution). 1mlofthis solution was transferred to a 10 ml volumetric flask, diluted to volume with diluent – a mixture of methanol, 1 M sodium hydroxide and water (28 : 2 : 20) and was mixed well (0.088 mg/mL).

Preparation of sample solution (extraction procedure)

Rinse and swab are two sampling methods available to demonstrate cleaning validation. Swab technique is a preferred technique by FDA (13-19). The swabbing process is a subjective manual process that involves physical interaction between the swab and the surface and thus may vary from operator to operator. So, a standardized motion protocol is required to establish reproducible recoveries. A

swab was immersed in extraction solution and folded diagonally. Excess solution was squeezed to avoid unnecessary dilution of drug. The surface was wiped horizontally, starting from outside toward the center. Fresh surface was exposed and repeatedly wiped to extract the maximum residue. Finally the swab was secured in a closed and labeled container for estimation.

It has been used swab sampling method. The selected surfaces (the worst case sampling places evaluated based on risk analysis using HACCP) of stainless steel of equipment (5 × 5 cm^2) previously cleaned using disinfectant/detergent and dried. The surface was successively wiped with one swab moistened with extraction solution (diluent – a mixture of methanol, 1 M sodium hydroxide and water (28 : 2 : 20). The swabs were placed in the 5 mL screw-cap test tubes containing 1 mL extraction solution. Subsequently, the tubes were placed in an ultrasonic bath for 5 min and the solutions were analyzed by HPLC.

Recovery rate of swab sampling from stainless steel surfaces

In parallel with swab sampling of residues of active ingredient, for the positive swab control, checking sampling procedure and determination of recovery (three individual determination) of swab sampling and analytical method combination, the selected surfaces of stainless steel (5 × 5 cm^2) were sprayed with 100 µL of standard stock solution and the solvent was allowed to evaporate. Then swab sampling was performed according to swab wipe procedure as described in sample solution preparation.

The calculation formula of recovery, %:

$$\text{Rec},\% = \frac{\text{Au} \times 100}{\text{As}} (1)$$

where, A_u - Peak area of meloxicam obtained from swab sample solution; A_s- Peak area of meloxicam obtained from standard solution.

Quantitative estimation of meloxicam residues

The calculation formula of the concentration (mg/mL) of meloxicam residues:

$$X = \frac{\text{Au} \times W \times 1 \times P}{\text{As} \times 25 \times 10 \times 100} (2)$$

where, A_u - Peak area meloxicam obtained from the chromatogram of swab sample solution; A_s- Peak area of meloxicam obtained from the chromatogram of standard solution;W – Mass of weighed meloxicam standard, mg; P - Purity of standard, % (Assay , %).

Establishing cleaning limits

The acceptable limit for the drug residue must ensure the absence of cross-contamination for subsequent batches manufactured in the affected equipment. FDA's guidance for determining residue limits requires a logical, practical, achievable and verifiable determination practice (2-5).

The basic principle of cleaning validation is that the patient should not take more than 0.1 % of the standard therapeutic dose (effective dose). The calculation formula is based on the dosage criteria:

$$\text{MAC} = \frac{\text{TD} \times \text{SF} \times \text{BS}}{\text{LDD}} (4)$$

where, MAC is the maximum allowable carryover (mg), TD is the API minimal therapeutic dose of previous product (mg), SF is a safety factor (1/1000), BS is the smallest batch size of the subsequent product (mg) and LDD is the largest daily dose of the subsequent product (mg).

The acceptable limit for residues in swab solution is expressed in mg/mL:

$$\text{AL} < \frac{\text{MAC} \times \text{Rec} \times \text{As} \times \text{F}}{\text{At} \times \text{V}} (5)$$

where, AL is the acceptance limit (mg), A_s is the sampling area (cm^2), Recis the recovery rate of the sampling method and A_t is the total production line area (cm^2), V – the volume of swab sample (mL).

Method Validation

Specificity

The ability of this method to separate and accurately measure the peak of interest indicates the specificity of the method. The specificity of the method was checked by injecting standard solution, the background control and the negative swab control samples.

Linearity and range

The linearity of an analytical method is its ability to elicit results that are directly or by a well-defined mathematical transformation, proportional to the concentration of the analyte in a sample within a given range.

From standard solution of meloxicam (0.88 mg/mL) working solutions were prepared at six different concentration levels ranging from 0.00011 mg/mL to 0.088 mg/mL. Six replicate injections (n=6) were performed at each concentration of meloxicam. The linearity was checked by the correlation coefficient (acceptance criteria: >0.99), the square of correlation coefficient (acceptance criteria: >0.98), the relative standard deviation (RSD) of peak areas (acceptance criteria: <2.0 %), the RSD, % of retention times (acceptance criteria: <1.0 %).

Limit of quantitation (LOQ) and limit of detection (LOD)

The LOD is the smallest quantity of the targeted substance that can be detected but not accurately quantified in the sample. The LOQ of method is the lowest amount of the targeted substance, which can be quantitatively determined under the experimental conditions prescribed with included inside the acceptance limits over the concentration range investigated. The signal-to-noise ratio (s/N) of method was adopted for the determination of the lower limit of quantitation. The limit of quantitation is estimated to be ten times the s/N ratio; the limit of detection is estimated to be three times of s/N ratio (acceptance criteria). The quantitation limit was achieved by injecting a series of possible dilute solutions of component and the precision was established at the quantitation level. The RSD, % of peak areas should not be more than 10 % (acceptance criteria).

System suitability test

The system suitability parameters were measured to verify the chromatographic system performance. System suitability was checked by six replicate injections (n=6) of standard solution. Main parameters including: the RSD, % of peak areas (acceptance criteria: <2.0 %), the RSD, % of retention times (acceptance criteria: <1.0 %), the tailing factor (acceptance criteria: 0.8-1.2), the number of theoretical plates (acceptance criteria: >2000) were measured.

Accuracy

The accuracy of the method was assessed by comparing the analyte amount determined versus the known amount spiked at three different concentration levels (0.0088, 0.00044, 0.00011mg/mL) with three replicates (n=3). The accuracy is expressed as percentage of standard recovered from spiked solution (placebo+standard)with correspondingRSD, %. The main recovery should be within 85.0 – 115.0 % and the RSD, %ofpercentage recovery should be <5.0 %for each concentrationlevel of spiked sample solution (acceptance criteria). The recovery for each concentration level of spiked solution was calculated by the following formula:

$$\text{Rec},\% = \frac{\text{Arec} \times 100}{\text{Asp}} \quad (6)$$

where, A_{rec} - Peak area of meloxicam obtained from swab sample solution (recovered amount); A_{sp}- Peak area of meloxicam obtained from spiked solution (amount added).

Precision

The precision of an analytical method is the degree of agreement among the individual test results obtained, when the method is repeated with multiple samples from the same homogeneous sample mix. It was estimated by measuring repeatability (intraday precision) and

time-dependent intermediate precision (interday) on six replicate injections of standard solution and on six individual determinations of meloxicam in swab sample solution at the same concentration. The validation parameter was studied during the determination of the recovery rate of swab sampling. Swab sample solutions were prepared in the way as described in the recovery rate of swab sampling from stainless steel surfaces. The precision was checked by the RSD, % of determined concentrations (mg/mL) for six individual determinations of meloxicam which should not be more than 5.0 %, also by the percentage difference, % between two inter day determinations which should not be more than 5.0 % (acceptance criteria). The concentration of meloxicam in sample solution was calculated by the formula (2).

Robustness

The robustness test examines the effect that operational parameters have on the analysis results. For determination of a method's robustness a number of method parameters, for example standard solution stability are varied within a realistic range and the quantitative influence of the variables is determined. If the influence of the parameter is within a previously specified tolerance, the parameter is said to be within the method's robustness range. In this study, only one factor was evaluated which was standard solution stability. The standard solution stability was evaluated at room temperature during 48 hours. The stability of the solution was studied initially, after 6, 24 and 48 hours against freshly prepared standard solution. The stability was checked using two standard solutions and by the percentage difference between peak areas of standard solutions stored at room temperature and freshly prepared which should not be more than 3.0 % (acceptance criteria). Similarity factor between two standard solutions should be within 0.98-1.02 (acceptance criteria).

The influence of swab material

For study the influence of swab material (polyester) on the concentration of meloxicam residues in swab samples, standard solution and extracted swab solution added standard of the same concentration were injected. The influence was evaluated quantitatively by the calculated percentage difference between peak areas obtained from standard solution and extracted swab solution added standard which should not be more than 3.0 % (acceptance criteria).

RESULTS AND DISCUSSION

Calculation of acceptance limits

Swab sampling of areas hardest to clean was done from equipment used in the manufacturing and residues were found in mg/mL. The smallest batch sized subsequent products were selected for calculating the values of the maximal allowable carryover. The lowest obtained values of maximum allowable carryover of both APIs were used to calculate the acceptance limits. The lowest was obtained when 0.1 % dose limit criteria was used for the total equipment which was justified by the principle API at a concentration of 1/1000 of its lowest therapeutic dose will not produce any adverse effects. The less the batch size of subsequent product and the API minimal daily dose of previous product, the less the acceptance limit of residues and the risk of cross-contamination increases. The calculated AL of meloxicam is 0.02951 mg/mL .For residual estimation the determined concentration of meloxicam residues in swab sample solution should not be more than the AL (acceptance criteria).

The main recovery rate of swab sampling from stainless steel surfaces is 91.25 % (three individual determinations).

System suitability test

During performing the system suitability test, in all cases the RSD of the peak areas, the RSD of the retention times, the number of theoretical plates per column and the tailing factor comply with acceptance criteria. The results are summarized in Table 1.

Table 1. System suitability test results

Injection number	Peak area	Retention Time, min	Number of theoretical plates	USP Tailing factor
1	3342.33765	8.268	3296	0.89
2	3344.19849	8.265	3308	0.90
3	3343.16602	8.260	3312	0.91
4	3341.95166	8.247	3309	0.90
5	3342.14063	8.248	3311	0.90
6	3341.76660	8.234	3317	0.91
Average	3342.59351	8.254	3309	0.90
RSD, %*	0.028	0.157	0.212	0.835

*RSD, % = Percentage relative standard deviation

Linearity and range

Linearity of the method was studied by analyzing standard working solutions at six different concentration levels ranging from 0.00011 to 0.088 mg/mL for meloxicam. The calibration curve was constructed by plotting the response area against the corresponding concentration injected. The high value of the correlation coefficient indicates very good linearity. The linearity concentration and regression statistics are shown in Table 2. Figure 2 shows the linearity graph.

Limit of quantitation (LOQ) and limit of detection (LOD)

The determined limits of quantitation and detection for API are presented in Table 3. The LOQ of the method was estimated to be equal to 0.00011 mg/mL and 0.000014 mg/mL could be considered as the LOD according to the acceptance criteria.

Specificity

The specificity study was shown that there is no interference from the extracted blank swab

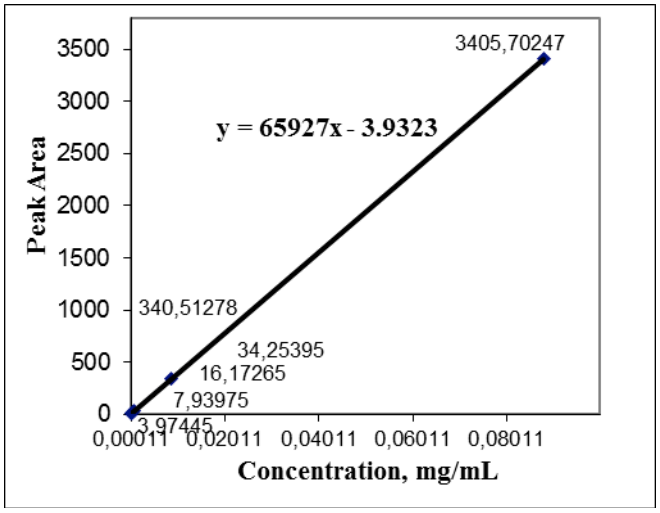

Figure 2. Linearity graph

and the extraction solvent at the retention time of analyte peak.

into extraction solution – diluent as described in the preparation of sample solution. Swabbing was performed with six individual

Table 2. The linear regression data for meloxicam.

Level	Concentration, mg/mL	Average peak area	RSD of peak areas, % (n=6)
I	0.088	3405.70247	0.048
II	0.0088	340.51278	0.204
III	0.00088	34.25395	0.882
IV	0.00044	16.17265	3.538
V	0.00022	7.93975	5.583
VI	0.00011	3.97445	4.013
Correlation coefficient (r)		1.00000	
Square of correlation coefficient (r^2)		1.00000	

Table 3. LOQ and LOD of the method.

Parameter	Value
LOQ*, mg /mL	0.00011
LOD*, mg /mL	0.000014
RSD of peak areas, % for LOQ (n=6)	4.013
RSD of peak areas, % for LOD (n=6)	12.131
s/N* for LOQ	17
s/N for LOD	7

*LOQ = Limit of Quantitation, LOD = Limit of Detection, s/N = signal-to-noise ratio

Accuracy

The accuracy of method was studied by using three spiked solutions (placebo + standard) with different concentration 0.0088, 0.00044, 0.00011 mg/mL. The accuracy results are shown in Table 4.The percentage of recovery obtained (0.506 %, 0.525 % and 1.241 %) and the RSD, % of percentage recovery calculated (91.01 %, 88.92 % and 88.15 %) is well within limit so acceptance criteria which indicate the accuracy of the method.

Precision

The precision repeatability (intraday precision) was determined by performing swabbing, which involved spiking meloxicam on stainless steel surface, recovering the meloxicam with swabs and desorbing the swabs

determinations using the meloxicam concentration – 0.088 mg/mL. The precision repeatability was performed in the same manner as in the accuracy study. The data of Table 5 shows that the average results of precision repeatability within limit so acceptance criteria. The RSD, % of determined concentrations (mg/mL) for six individual determinations of meloxicam was less than 5.0 %. The intermediate precision (inter day) was carried out on a different day. The intermediate precision results were accordance with acceptance criteria. The percentage difference, % between two inter day determinations is equal to 0.877 % which indicates a good precision.

Table 4. The accuracy results.

Theoretical concentration of spiked sample solution, mg/mL	Concentration, mg/mL		Peak area	The percentage recovery	The main recovery, %	RSD of percentage recovery, % (n=3)
	Amount added	Amount recovered				
0.0088	0.00901	0.00824	304.79599	91.47	91.01	0.506
		0.00820	303.21436	91.00		
		0.00816	301.72482	90.55		
0.00044	0.00041	0.000366	14.85566	89.17	88.92	0.525
		0.000366	14.86219	89.21		
		0.000362	14.72437	88.38		
0.00011	0.000113	0.000098	3.62763	87.10	88.15	1.241
		0.000101	3.71856	89.28		
		0.0000995	3.66790	88.06		

The influence of swab material

The calculated percentage difference between peak areas of standard solution and extracted swab solution added standard is 1.07 %. Hence, the swab material does not effect on the determination of meloxicam residues.

Robustness

The stability of the standard solutions was tested by storing them at room temperature for 48 hours. Two standard solutions were injected after 6, 24 and 48 hours. Standard solutions of meloxicam stored at room temperature are stable within 48 hours. The percentage difference between peak areas of standard solutions stored at room temperature within 6, 24 and 48 hours and freshly prepared is 0.25, 098 and 1.56 %, respectively. This gives the confidence that API residues are stable and the residues concentration do not change in swab sample solutions during cleaning validation.

Residual estimation of meloxicam in swab samples collected from equipment surfaces

After manufacturing of three consecutive batches of Mobicam 15 mg uncoated tablets and cleaning of equipment swab samples were collected from different sampling points of surfaces (25 cm^2). The equipment surfaces were rinsed with water for several times in order to remove extraction solution – diluent and the last rinsed samples were checked on pH value compared with water pH. In laboratory swab samples were tested immediately for residual estimation of meloxicam using the validated HPLC method. The results are shown in Table 6. Figure 3, 4 shows chromatogram obtained from standard solution and swab sample solution, respectively.

The determined concentration of residues of meloxicam in swab sample solutions taken from the sampling areas (25 cm^2) of equipment surfaces varies from 0.000016 mg/mL to 0.005839 mg/mL (0.016 – 5.839 µg/mL) which is well below the calculated limit of cross-contamination. In spite of Mobicam 15 mg uncoated tablet containing both insoluble and very adherent APIis the worst case from the point of 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.

Table 5. The precision results

Standard solution				
The number of injection	**Precision repeatability (intraday)**		**Intermediate precision (inter day)**	
	Peak area		**Peak area**	
1	3348.49609		3427.65649	
2	3349.51978		3430.29297	
3	3349.42822		3431.02539	
4	3350.04150		3431.13403	
5	3352.14844		3431.46387	
6	3354.90356		3431.33325	
Average	3350.75627		3430.48433	
RSD	0.071		0.042	
Sample solution				
Sample solution #	**Precision repeatability (intraday)**		**Intermediate precision (inter day)**	
	Peak area	**Concentra tion, mg/mL**	**Peak area**	**Concentra tion, mg/mL**
1	3048.44043	0.08042	3133.50439	0.08092
2	3012.90991	0.07948	3158.27490	0.08156
3	3264.32910	0.08611	3252.54419	0.08400
4	3141.25342	0.08286	3378.08105	0.08724
5	3053.73877	0.08056	3149.05811	0.08132
6	3064.80176	0.08085	3079.33398	0.07952
Average	3097.57890	0.08171	3191.79944	0.08243
RSD	2.969	2.969	3.357	3.357
	The percentage difference, %			0.877

Table 6. Swab samples analysis results, mg/mL.

Sampling point number	**Concentration of meloxicam residues, mg/mL**		
	Batch 01	**Batch 02**	**Batch 03**
1	0.000161	0.000200	0.000242
2	0.005839	0.001472	0.000852
3	0.000340	0.000428	0.000093
4	0.000422	0.000225	0.000016
Average	0.0001691	0.000581	0.000301

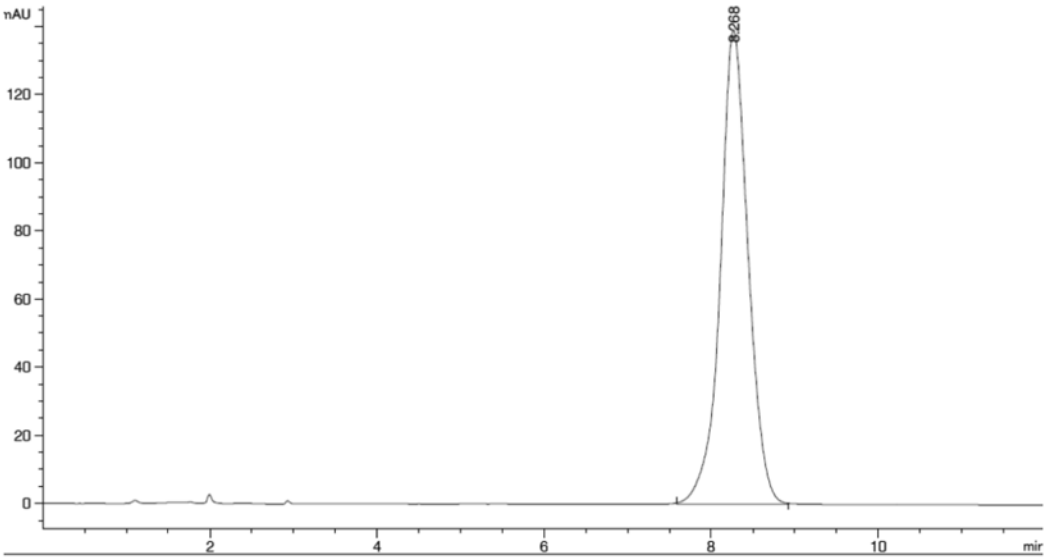

Figure 3. The chromatogram of standard solution

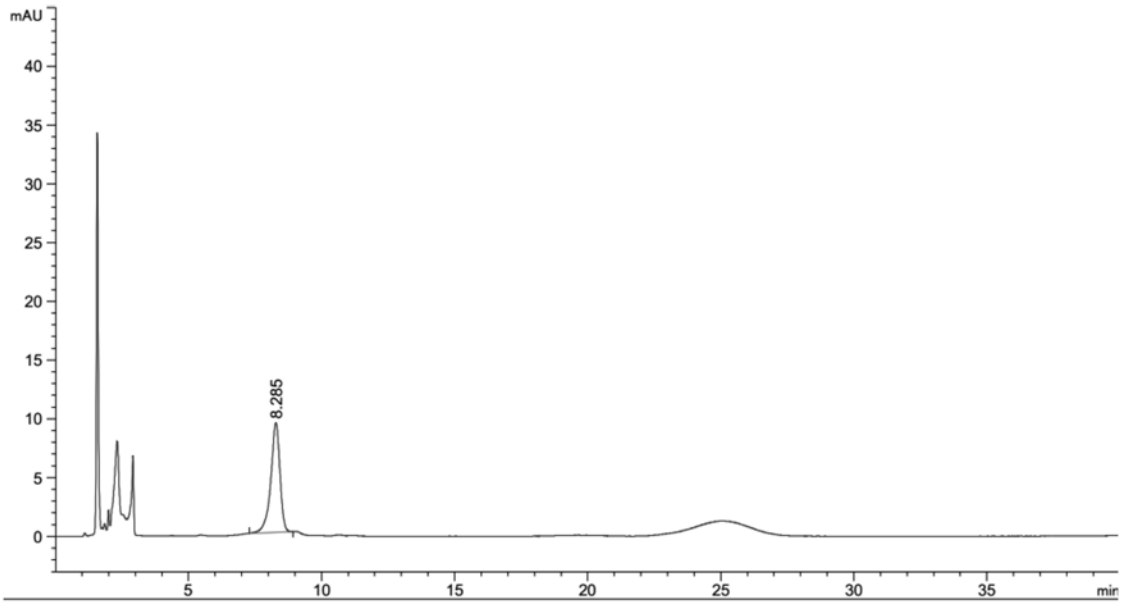

Figure 4. The chromatogram of swab sample solution.

CONCLUSION

Swab sampling and HPLC methods were developed and validated for quantitative estimation of meloxicam residues on stainless steel surfaces of plant equipment after manufacturing of Mobicam 15 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.Theswab sampling and HPLC validated methods can be used in other pharmaceutical quality control laboratories to apply successfully in cleaning validation for quantitative estimation of meloxicam residues after manufacturing of meloxicam uncoated tablets.

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