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VINCAMINE RESIDUES ANALYSIS USING HPLC AND ESTABLISHING LIMITS OF CROSS-CONTAMINATION IN SUPPORT OF CLEANING VALIDATION

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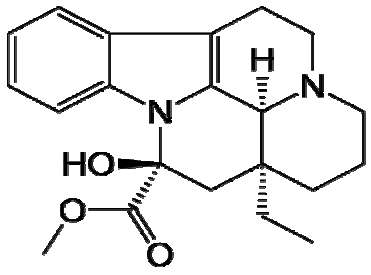
The current study demonstrates the applicability of a selective and rapid HPLC method for quantitative estimation of vincamine residues in samples collected from pharmaceutical manufacturing equipment surfaces and the efficiency of the developed cleaning procedure. The swab sampling method was developed in order to obtain a suitable recovery (>90 %). The surface (Sampling area – 25 cm^2) was successively wiped with one micro polyester swab moistened with diluent – methanol. The rinse samples were collected from equipment surfaces by rinsing with the fixed volume of the selected diluent. The method was developed using liquid chromatography system "Agilent 1 260 Infinity" and Luna C18(2) 150 × 4.6 mm, 5 µm column with a mobile phase containing a mixture of 0.1 M aqueous ammonium acetate solution and acetonitrile (40 : 60); The flow rate of mobile phase was 1.0 mL/min, The diode array detector wavelength was 280 nm and the injected volume was 50 µL. The method was validated with respect to system suitability parameters, specificity, linearity, accuracy, precision, limit of detection (LOD) and quantitation (LOQ). The stability of vincamine solutions in methanol was also studied. The calibration was linear $r^2 = 999$ over a concentration range 0.005–5 µg/mL; LOD – 0.005 µg/mL and LOQ – 0.025 µg/mL; The concentration of vincamine residues in sample solutions varies from 0.0069 - 11.60 µg/mL which is well below the limit of cross-contamination of the next product.



INTRODUCTION

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 to ensure the quality of the next batch of different pharmaceutical products and to prevent cross-contamination; it is also a FDA (Food and Drug Administration)/GMP (Good Manufacturing Practice) requirement.[1-2] 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. Residues 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 line to demonstrate a complete removal of residues. The sampling therefore is a very important parameter, since the efficacy of the

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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.[3] The acceptance limit (AL) for residues on 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 in the manufacturing equipment should be based on therapeutic doses, toxicity and a general limit (10 ppm). Several mathematical formulae were proposed to establish the acceptable limit.[4-5]

Vincamine is an active pharmaceutical ingredient, a nootropic agent to combat the effects of aging, or in conjunction with other nootropics for a variety of purposes. Vincamine is a peripheral vasodilator that increases the blood flow to the brain.

Vincamine – $C_{21}H_{26}N_2O_3$, Mw = 354.443, Methyl (3-alpha,14-beta,16-alpha)-14-hydroxy-14,15-dihydroeburnamenine-14-carboxylate (CAS registry number: 1617-90-9) is the principal alkaloid of *Vinca minor L.*, corresponding to 25–65% of the indole alkaloids in this plant (Figure 1). It is also found in the plant species *Catharanthus roseus*, and consists in a white or yellow crystalline powder, soluble in dimethyl formamide, chloroform and methylene chloride, slightly soluble in alcohol and methanol, insoluble in water.

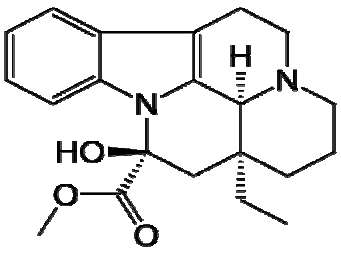

Fig. 1 – Chemical structure of vincamine.

There are some interesting studies in developing assay methods for Vincamine by different analytical methods. These include derivative-ratio spectrophotometry, ratio-subtraction spectrophotometry, chemometric-assisted spectrophotometry, thin-layer chromatography and liquid chromatography. [6-12]

The aim of this study was to develop and demonstrate the applicability of a selective and rapid HPLC method for determination of the residues of vincamine in cleaning control samples collected from manufacturing equipment surfaces after manufacturing of Glatan 30 mg uncoated tablets (One tablet contains 30 mg of vincamine) and the efficiency of the cleaning procedure. The analytical method was validated with respect to system suitability parameters, specificity, linearity-range, limit of detection (LOD) and quantitation (LOQ). The stability of standard solution of vincamine in methanol was also studied. These studies were performed in accordance with established guidelines.[13-16] Swab and rinse sampling procedures were optimized and developed in order to obtain a suitable recovery of the active ingredient. The cleaning validation was performed on three consecutive batches of finished product – Glatan 15 mg uncoated tablets.

EXPERIMENTAL

Reagent and chemicals

The certified reference standard of vincamine was supplied by LGC Standards. The HPLC grade acetonitrile, methanol and analytical grade ammonium acetate was purchased from Sigma-Aldrich.

Instrumentation

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). The cleaning procedure was performed using Lisoformin 3000 0.25 % solution as a disinfectant/detergent which was purchased from Lisoform (Germany).

The chromatographic analysis was performed using an Agilent 1260 Infinity system (Agilent Technologies, USA). The output signal was monitored and processed using Chemstation software. 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 appropriately calibrated and qualified.

Chromatographic system and conditions

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 0.1 M aqueous ammonium acetate solution and acetonitrile (40 : 60 v/v) filtered through Durapore Polyvinylidene difluoride, 0.45 µm membrane filters and degassed; The flow rate of mobile phase was 1.0 mL/min, the UV detector wavelength was 280 nm and the injected volume was 50 µL; The column temperature was maintained at 25 °C.

Method validation

The developed method was validated with respect to standard solution stability and filter compatibility test, system

suitability parameters, specificity, linearity-range, accuracy, precision, limit of detection (LOD) and quantitation (LOQ) according to ICH guideline and statistical assessment was performed using Microsoft Excel 2010.[14]

Preparation of standard solution

12.5 mg of vincamine reference standard was weighed, transferred accurately in a 50 mL volumetric flask and 35 mL of methanol were added, sonicated until it becomes completely dissolved and diluted to volume with the same diluent, mixed well. Then it was filtered through Durapore Polyvinylidene difluoride (PVDF) 0.45 µm membrane filter, discarding the first 5 mL of the filtrate. 2 mL of this solution was transferred to a 20 mL volumetric flask, diluted to volume with diluent – methanol and mixed well (Stock solution – 25 µg/mL). 1 mL of obtained solution was transferred to a 5 mL volumetric flask, diluted to volume with diluent – methanol and mixed well (5.0 µg/mL).

Preparation of sample solution (extraction procedure)

Rinse and swab are two sampling methods available to demonstrate cleaning validation. Swab technique is the preferred technique by FDA. The swabbing process is a subjective manual process that involves physical interaction between the swab and the surface, 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. The both sampling methods were used. The selected stainless steel 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, were considered. The surface was successively wiped with one swab moistened with extraction solution (diluent – methanol). 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 2–3 minutes and the solutions were analyzed by HPLC. The rinse samples from uneven surfaces (plastic brush) were collected by rinsing with the fixed volume of the selected diluent. [17-20]

Recovery rate of swab sampling from stainless steel surfaces

The sampling procedure was checked and recovery (three individual determinations) of the combined swab sampling and analytical method was determined. The selected surfaces of stainless steel (5×5 cm^2), were sprayed with 200 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 samples were diluted with the same diluent to 1 mL. The recovery, % was calculated by the formula: Rec, % = $R_u \times 100/R_s$, where Ru - Peak area of vincamine obtained from swab sample solution; Rs - Peak area of vincamine obtained from standard solution.

Quantitative estimation of vincamine residues

The concentration (µg/mL) of vincamine residues was calculated by the formula:

$$X = R_u \times W \times D \times 1\,000 \times P/R_s \times 100$$

where Ru is peak area vincamine obtained from the chromatogram of swab sample solution; Rs is peak area of vincamine obtained from the chromatogram of standard solution; W – Mass of vincamine standard substance, mg; D – Dilution factor; P – Purity of the standard compound, % (Assay , %).

RESULTS AND DISCUSSION

Establishing cleaning limits

The acceptable limit for the drug residues 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 minimum therapeutic dose of the active pharmaceutical ingredient (API) of the previous product in the largest daily dose of the subsequent product (The dosage criteria). This will not produce any adverse effects.

The calculation formula is based on the dosage criteria: MAC=TD×SF×BS/LDD, where MAC is the maximum allowable carryover (mg), TD is the minimal therapeutic dose of the studied API of the control product (mg), SF is a safety factor –1/1000 for solid oral dosage form, BS is the smallest batch size of the subsequently processed product's batch (mg) and LDD is the largest daily dose of the subsequently processed product's API (mg).[4,5] The acceptable limit for residues in sample solution is expressed in µg/mL.

For swab sample solution:

$$AL < MAC \times 1\,000 \times Rec \times A_s \times F/A_t \times V$$

For rinse sample solution:

$$L < MAC \times 1\,000/V$$

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

Swab sampling of areas hardest to clean was done for an equipment used in the manufacturing process and residues were expressed in µg/mL. The smallest batch size of the subsequent processed products was selected for calculating the values of the maximal allowable carryover. The

lowest obtained value of maximum allowable carryover of active ingredient – vincamine was used to calculate the acceptance limit. The less the batch size of the subsequent product and the minimal daily dose of the studied product, the less the acceptance limit of residues and the risk of cross-contamination increases. The calculated AL of vincamine for swab sample solution is 12.3 μg/mL, for rinse sample solution – 36 μg/mL. To estimate the determined concentration of vincamine residues in sample solution should not be more than the AL (acceptance criteria). The main recovery rate of swab sampling from stainless steel surfaces is 94.94 % (three individual determinations).

Optimization of chromatographic system conditions

The final chromatographic conditions were determined by optimizing the system operational parameters: wavelength for detection, composition of the mobile phase, flow rate, nature of stationary phase and checking the system suitability parameters: theoretical plates, tailing factor, peak purity. The calibration curve showed good linearity for trace level quantitative estimation at 280 nm.

Optimization of sampling method

The swab sampling method was developed in order to obtain a suitable recovery. The surface (sampling area – 5â × 5 cm^2) was successively wiped with one micro polyester swab (3 × 2.5 × 10 mm) moistened with diluent – methanol. The swabs were spiked with different quantities of vincamine. The optimal conditions were achieved when methanol was used as diluent (easy to remove from surfaces by deionized water after sampling and to control its residues using gas chromatography; vincamine is freely soluble in methanol) and sonication time of 2–3 minutes.

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, spiked swab sample solution and the negative control (placebo) sample solution (blank). The specificity study has shown that there is no interference from the extracted blank and the extraction solvent at the retention time of analyte peak. The vincamine peak was pure (Figure 2). Purity factor (999.8) was more than purity threshold (990.0). Figures 3, 4, 5 show the chromatogram obtained from standard solution, the negative control swab sample solution and spiked swab sample solution respectively.

Linearity and range

The response function 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 the standard solution of vincamine (5 μg/mL) working solutions were prepared at seven different concentration levels ranging from 5 μg /mL to 0.005 μg/mL. Six replicate injections (n = 6) were performed at each concentration level. The linearity was checked by the correlation coefficient (acceptance criteria: >0.990), the determination coefficient (acceptance criteria: >0.98), the relative standard deviation (RSD) of peak areas (acceptance criteria: <2.0 %) at all concentration levels, the RSD, % of retention times (acceptance criteria: <1.0 %). The calibration curve was constructed by plotting the response area against the corresponding concentration of the injected solutions. A value closer to unit of the correlation coefficient indicates a good linearity. The calibration plot and the corresponding statistic parameters of the regression are shown in Table 1. Figure 6 shows the linearity plot.

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, which included inside the acceptance limits over the concentration range investigated. The signal-to-noise ratio (s/N) 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 stepwise diluted solutions and precision

was established at the specific determined level. The RSD, % of peak area values should not be more than 10% (acceptance criteria). The determined limits of quantitation and detection for vincamine are presented in Table 2. The s/N for the determined LOQ level is around 19 and around 4 at the LOD level; The LOQ of the method was estimated to be equal to 0.025 µg/mL and 0.005 µg/mL could be considered as the LOD according to the acceptance criteria.

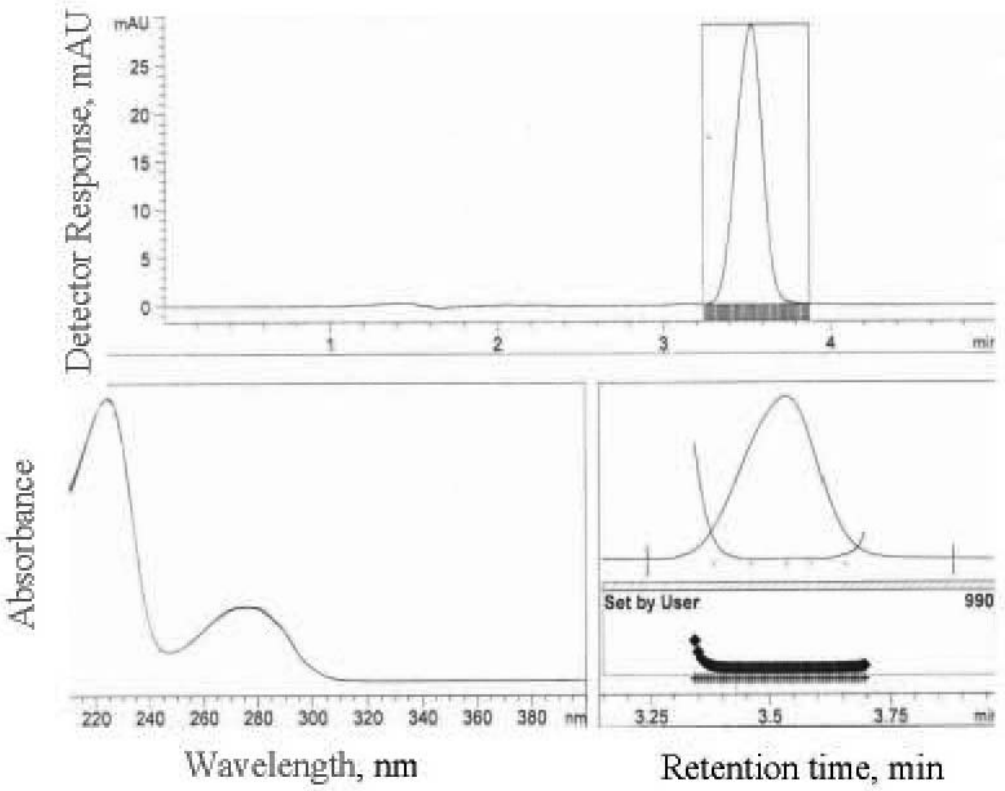

Fig. 2 – Spectral purity of the vincamine peak in the chromatogram of a standard solution.

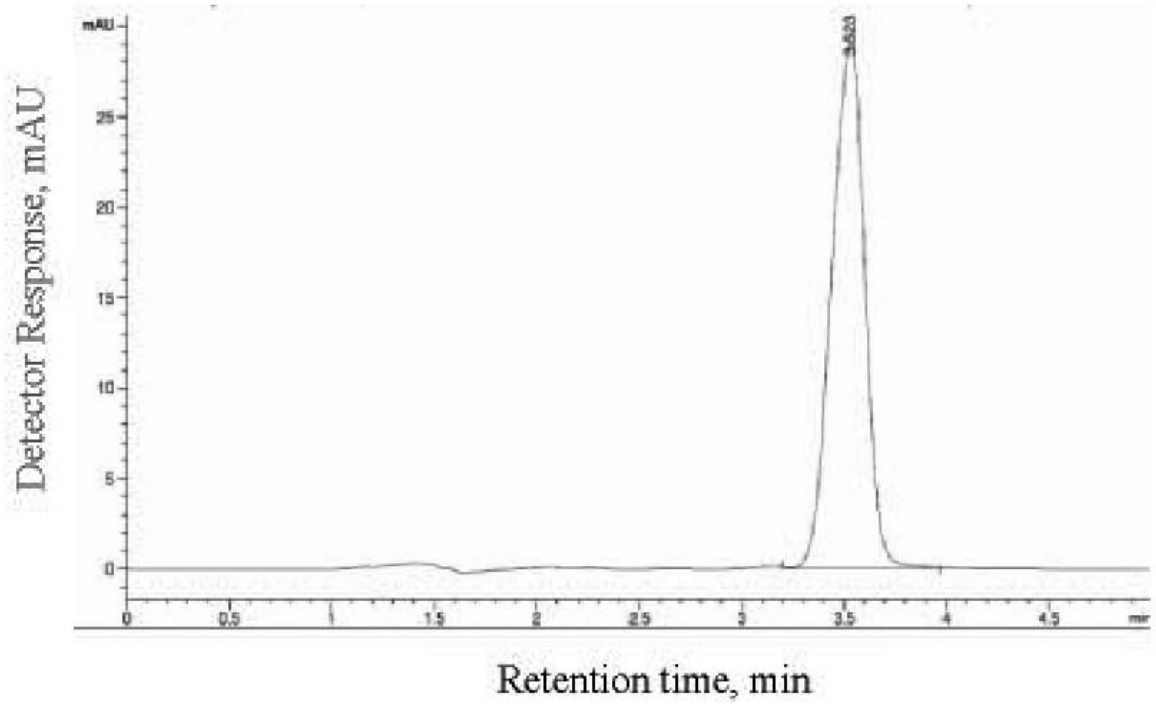

Fig. 3 – Chromatogram of standard solution.

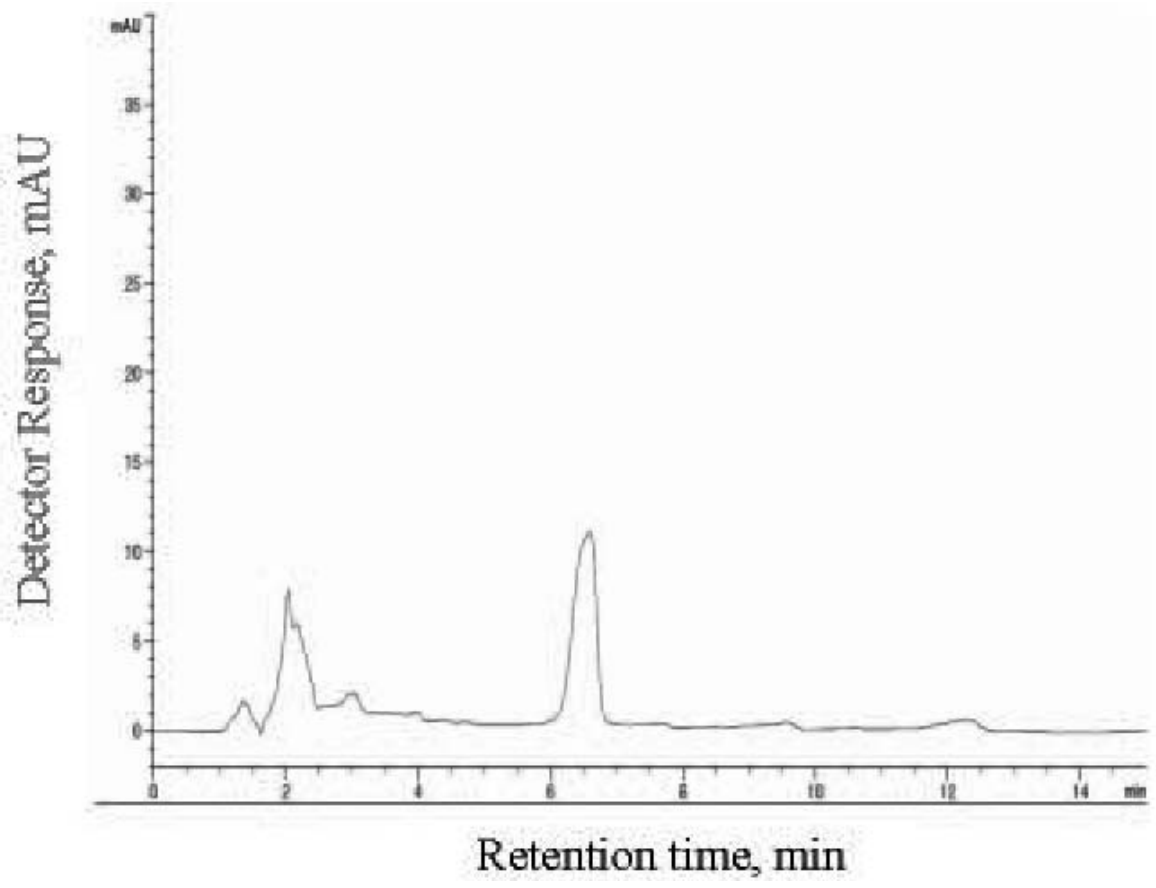

Fig. 4 – Chromatogram of negative control swab sample solution.

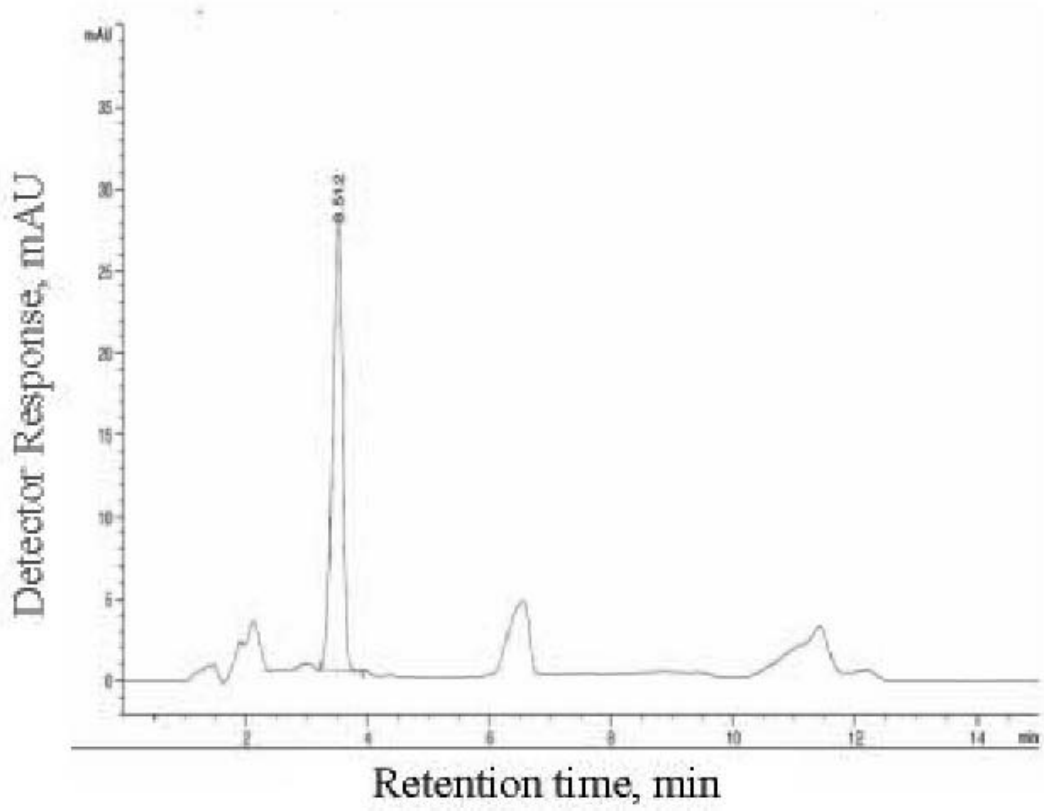

Fig. 5 – Chromatogram of spiked swab solution.

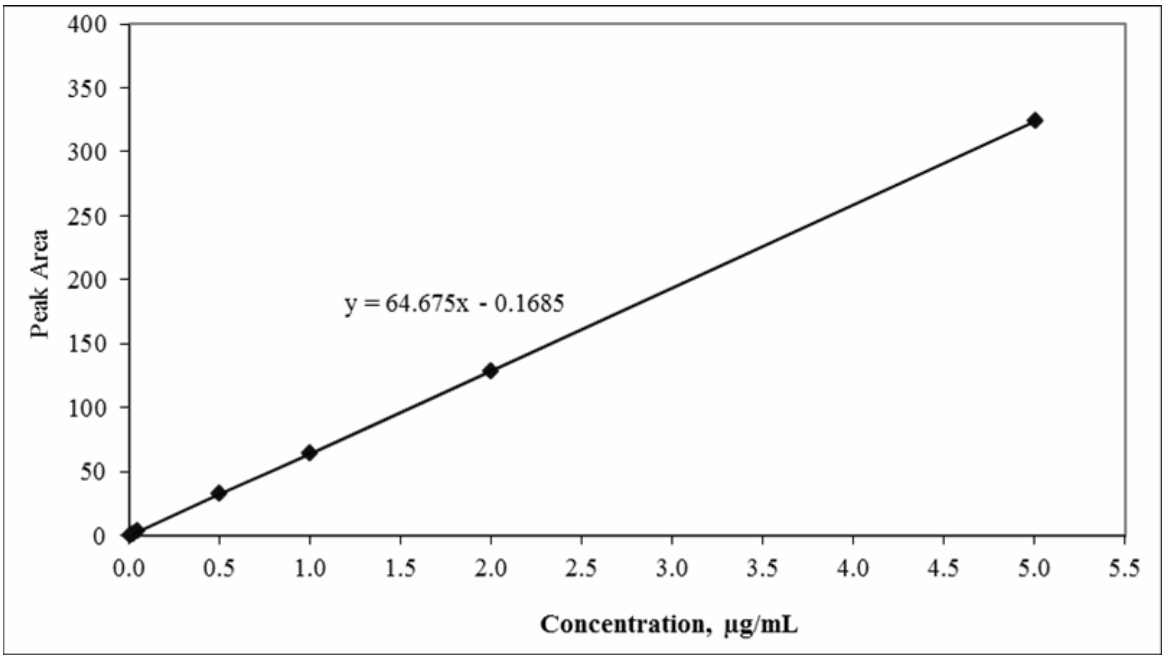

Fig. 6 – The linear response function for vincamine.

Table 1

The linear regression data

Level	Concentration, µg/mL	Average peak area	RSD of peak areas, % (n = 6)
I	5.007	323.97	0.292
II	2.003	128.80	0.083
III	1.001	63.95	0.052
IV	0.501	32.66	0.150
V	0.050	3.20	1.390
VI	0.025	1.62	3.818
VII	0.005	0.31	17.352
Correlation coefficient (r)		0.999	
Square of correlation coefficient (r^2)		0.999	

Table 2

The LOQ and LOD of method

Parameter	Value
LOQ, µg /mL	0.025
LOD, µg /mL	0.005
RSD of peak areas, % for LOQ (n=6)	3.262
RSD of peak areas, % for LOD (n=6)	17.352

Table 3

The system suitability parameters results

Inj. #	Peak area	Retention Time, min	Number of theoretical plates	Tailing factor
1	319.57	3.520	2296	1.31
2	319.54	3.522	2308	1.32
3	320.08	3.522	2312	1.33
4	319.71	3.521	2309	1.31
5	319.44	3.520	2311	1.31
6	320.19	3.522	2317	1.30
Average	319.75	3.521	2309	1.31
RSD, %	319.57	3.520	0.304	0.786

Table 4

The accuracy results

Theoretical concentration of the spiked sample solution, μg/mL	Concentration, mg/mL		Peak area	Recovery, %	Mean recovery, %	RSD, % for recovery values (n=3)
	Amount added	Amount recovered				
		4.8	301.96	93.91		
5	5.08	4.7	294.41	91.56	92.23	1.584
		4.6	293.35	91.23		
		0.9	13.20	89.21		
1	1.02	0.9	13.12	88.62	89.61	1.389
		0.9	13.47	91.01		
		0.45	2.82	87.98		
0.5	0.51	0.45	2.82	88.01	87.54	0.900
		0.44	2.77	86.63		

System suitability parameters

The system suitability parameters were measured to verify the chromatographic system performance. System suitability was checked by six replicate injections (n = 6) of the standard solution. The main parameters include: the RSD, % of peak area values (acceptance criteria: <2.0 %), the RSD, % of the retention time values (acceptance criteria: <1.0 %), the peak tailing factor (the USP coefficient of the peak symmetry $S = W_{0.05}/2f$) (acceptance criteria: 0.8–1.2), the number of theoretical plates (acceptance criteria: >2 000) were measured. The results are summarized in Table 3.

Accuracy

The accuracy of the method was assessed by comparing the analyte amount determined *versus* the known amount spiked at three different concentration levels (5, 1, 0.5 μg/mL) with three replicates (n = 3). The accuracy is expressed as percentage of standard compound recovered from a spiked solution (placebo + standard) with a corresponding RSD, %. The average recovery should be within 85.0 – 115.0% and the RSD, % of percentage recovery should be < 5.0% for each concentration level of spiked sample solution (acceptance criteria). The recovery for each concentration level of spiked solution was calculated by the following formula: Rec, $\% = A_{rec} \times 100/A_{sp}$, where A_{rec} is peak area of vincamine obtained from swab sample solution (recovered amount); A_{sp} is peak area of vincamine obtained from spiked solution (amount added). The recovery results are shown in Table 4. The resulting recoveries were 92.23%, 89.61% and 87.54% while the corresponding RSD, % values were 1.584%, 1.389 % and 0.900 %, which is well within the usually accepted limits indicating the accuracy of the method.

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 (intra-day precision) and time-dependent intermediate precision (inter-day) on six replicate injections of a standard solution and on six individual determinations of vincamine in sample solution at the same concentration (5 μg/mL). The validation parameter was studied during the determination of the recovery rate of swab sampling. Swab sample solutions were prepared in the way in the Experimental section (recovery rate of swab sampling from stainless steel surfaces). The intermediate precision (inter-day) was carried out on a different day. The intra-day precision was checked by the RSD, % of determined concentrations (μg/mL) for six individual determinations of vincamine which should not be more than 4.0 %. The intermediate precision was checked by the RSD, % of twelve individual determinations (totally inter-day and intra-day determinations) of vincamine which should not be more than 5.0 % (acceptance criteria) and F-test which should not be more than 5.05. The results obtained for precision study are given in Tables 5, 6. The RSD, % of determined concentrations (μg/mL) for six individual determinations and for twelve individual determinations of vincamine, also, F-test were within the acceptance criteria which indicates that this method has a good precision.

Table 5

The precision results for standard solution

Standard solution		
The number of injection	Precision repeatability (intra-day) Peak area	Intermediate precision (inter-day) Peak area
1	319.57	319.04
2	319.54	319.32
3	320.08	318.89
4	319.71	319.26
5	319.44	319.44
6	320.19	319.56
Average	319.75	319.25
RSD	0.097	0.078

Table 6

The precision results for sample solution

Sample solution				
Solution #	Precision repeatability (intra-day)		Intermediate precision (inter-day)	
	Peak area	Concentration, µg/mL	Peak area	Concentration, µg/mL
1	303.16	4.75	290.22	4.80
2	275.44	4.31	310.41	4.81
3	281.00	4.40	308.64	4.78
4	301.26	4.72	301.54	4.68
5	288.65	4.52	295.37	4.68
6	289.78	4.54	289.78	4.60
Average	289.88	4.54	299.33	4.49
RSD (n=6)	3.761	3.761	3.004	2.741
RSD (n=12)		3.994		
Variance		0.030		0.007
F-test		4.29		

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 bias between peak areas of standard solutions stored at room temperature and freshly prepared which should not be more than 3.0 % (acceptance criteria). The bias in terms of peak area between two standard solutions should be within 0.98-1.02 (acceptance criteria). The percentage biases between peak areas in standard solutions stored at room temperature for 6, 24 and 48 hours and freshly prepared ones are 0.20, 0.88 and 0.91 %, respectively. This gives the confidence that API residues are stable and the residues concentration does not change in sample solutions during cleaning validation analysis.

Filter compatibility test

The PVDF membrane filter compatibility was evaluated using standard solution and by calculating the percentage difference between peak areas of standard solutions filtered and non-filtered which should not be more than 0.5% (acceptance criteria). The result is 0.038% which gives the confidence that adsorption of analyte does not occur on the used filter.

The compatibility of swab material

To estimate the compatibility of used swab material – polyester (ITW Texwipe swab, USA) the standard solution and extracted swab solution added standard of the same concentration were prepared and injected. This test confirms the existence of desorption of vincamine residues from the swab material. The compatibility of swab material 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). The calculated percentage difference is 1.0%. Hence, the vincamine residues desorb from

the swab and the swab material does not have effect on the determination of API's residues.

Estimation of vincamine in swab and rinse samples

After manufacturing of three consecutive batches of Glatan 30 mg uncoated tablets and equipment cleaning samples were collected from different sampling points. The equipment surfaces were rinsed with deionized water for several times in order to remove extraction solution – diluent (methanol) and the last rinsing portions were checked for the existence of the diluent (methanol) using gas chromatography. Swab and rinse samples were tested immediately for estimation of vincamine residues using the developed and validated HPLC method. The results are shown in Table 7. Figure 7 shows a typical chromatogram obtained from a swab sample solution.

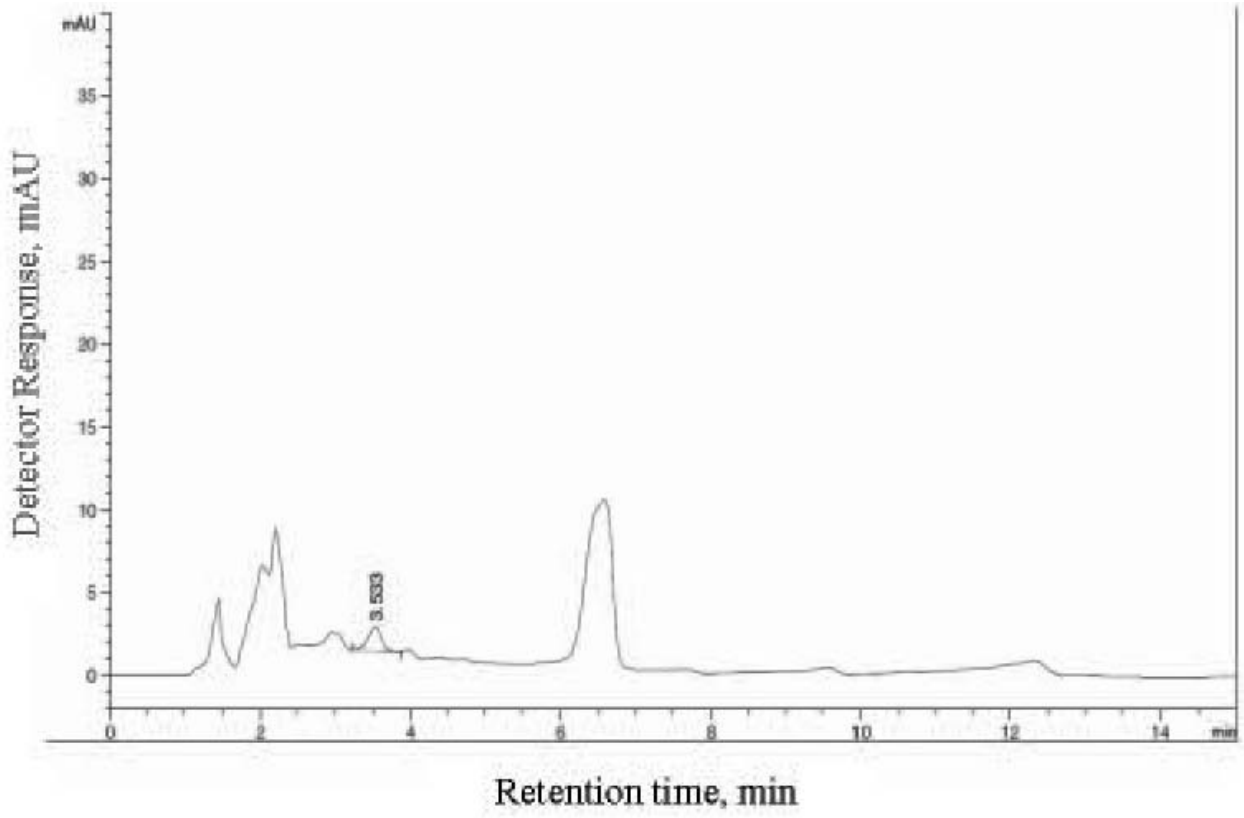

Fig. 7 – Chromatogram of swab sample solution.

Table 7

The results of vincamine residues analysis

Sampling method	Sampling point #	Concentration of vincamine residues, µg/mL		
		Batch 01	Batch 02	Batch 03
Swabbing	1	0.2002	0.0069	0.0542
	2	0.2754	0.0578	0.0120
	3	0.0898	0.0077	0.3542
	4	11.5982	0.7875	0.0650
Average		3.0409	0.2150	0.1214
Rinsing	1	0.3541	0.1444	0.0765
	2	0.0957	0.0798	0.1770
Average		0.2249	0.1121	0.1271

The determined concentration of residues of vincamine varies from 0.0069 to 11.5982 µg/mL which is well below the calculated limits for cross-contamination. Despite the fact that the

pharmaceutical formulation Glatan 30 mg uncoated tablet contains an insoluble active pharmaceutical ingredient, the standard operation procedure established for cleaning equipment provides enough efficacy in order to remove vincamine from the cleaned surfaces and excludes the risk of cross-contamination of the next finished product.

CONCLUSION

An analytical procedure was developed and validated for the assay of vincamine residues on surfaces of equipment used during the manufacture of Glatan 30 mg uncoated tablets to demonstrate cleaning validation. Both swab wipe and rinse procedures were found to be selective, accurate, and precise. No interferences from swab/blank solutions were observed and samples were stable during analysis for residues estimation. Hence, the obtained results confirm that the cleaning procedures in use are adequate for removing residues from equipment surfaces well below the calculated limit of cross- contamination. Sampling and HPLC validated protocols may be successfully used by other pharmaceutical quality control laboratories to sustain cleaning validation procedures for vincamine residues after manufacturing of uncoated tablets.

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