Determination of loratadine residues from manufacturing equipment surfaces and setting acceptance limits for cleaning validation

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Introduction

Loratadine is a tricyclic antihistamine with selective, peripheral H1-receptor activity. Preclinical and clinical safety data for Loratadine reveal no special hazard for humans based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

The lowest value for permitted daily exposure calculated from repeated dose toxicity study in rats (NOAEL 8 mg/kg) was estimated to be 0.16 mg/day or 160µg/day. This value, when compared with 1/1000th part of Loratadine minimal daily dose (5 µg), is more than thirty times bigger (Figure 1.).

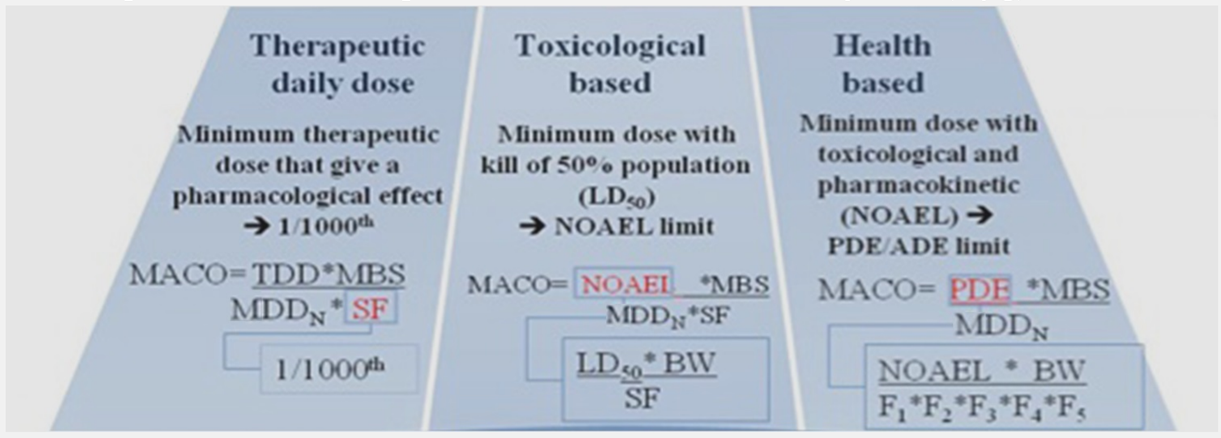

Figure 1. MACO calculations in Cleaning Validation

Limit per Surface Area / L_2 (µg/cm^2)

$$L_2 = \frac{\text{MACO x batch size of next product (kg)}}{\text{shared equipment surface area (cm}^2\text{)}} \times 1000$$

Limits in Samples to be Analysed / L_3 (µg/mL - ppm)

$$L_3 = \frac{L_2 \text{ x swabbed surface area (cm}^2\text{)}}{\text{Volume of desorption solvent}}$$

Figure 2. Setting a limit per Surface Area and Samples to be Analysed

Therefore, the MACO calculation was estimated by dosage criteria, i.e. the carryover of product residues should not be more than 0.1% (1/1000th) of minimal therapeutic dose of the API of previous product in the maximal daily dose of the subsequent product.

The obtained results were: MACO 0.15 ppm, the limit per surface area of manufacturing equipment 1.04 µg/cm^2 and limit in analyzed sample 1.3 ppm (Figure 2.).

Purpose

Develope and validate sensitive analytical method using reversed-phase high performance liquid chromatography (RP-HPLC) for determination of Loratadine residues in swab samples in cleaning validation procedure.

Materials and Methods

Instrumentation and equipment: Chromatographic system: UPLC Shimadzu Nexera XR system with LPG quaternary pump with degasser, autosempler, controller and PDA detector and column oven, controlled by Lab Solutions software.

Chromatographic conditions: Separation was performed on LiChrospher RP Select B 125 mm × 4.0 mm, 5 µm column, at column temperature 30°C. An isocratic elution was used, with flow rate 1.1 ml/min. The injection volume was 20 µL and detection wavelength was 242 nm. A mixture of 20 volumes of methanol, 47 volumes of acetonitrile and 33 volumes of 15 mM potassium dihydrogen phosphate, (pH adjusted to 2.5 with phosphoric acid) was used as mobile phase.

Preparation of test solutions using the swabbing technique:

Using of AlphaTM Swab Texwipe 714A, previously rinsed with methanol the predefined 25 cm² surface area of the plates was wiped first in a horizontal and then in a vertical way, starting from the outside towards the center. The head of the swabs was cut and introduced into a flask, 20 ml of methanol added in flask, placed in an ultrasonic bath for 15 minutes.

Results and Discussion

HPLC method was validated according to the propositions recommended in International Conference on Harmonization (ICH) Q2 (R1) guideline for validation of analytical procedures. During selectivity testing, no interference from the blank swab sample at the retention time of Loratadine was observed. (Figure 3.).

Swabbing procedure was optimized in order to obtain a suitable recovery of loratadine and the obtained swab recovery factor was 0.79 (79%). The achieved swab recovery factor confirmed the suitability of the cleaning method, and was taken into account in the results for cleaning validation, as a correction factor (Figure 4.).

The linearity of the method was proved through five concentrations, in the range from 0.05 µg/mL to 2 µg/mL. The correlation coefficient value (R^2) was 0.9999 (Figure 5.).

The limit of detection (LOD) and limit of quantification (LOQ) were established by using series of linearity solutions and were found to be 0.0199 µg/mL and 0.066 µg/mL, respectively. The precision of the system was also evaluated at the LOQ level and the obtained RSD value was less than 5 % (Figure 6.).

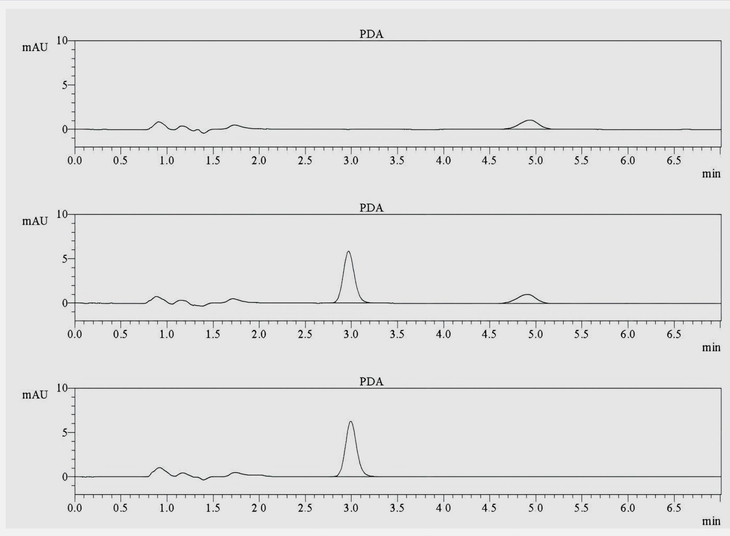

Figure 3. Selectivity of Loratadine

Injection	Concentration Level (%)	Added µg cm^{-2}	Peak Area	Found µg cm^{-2}	Recovery (%)
1	50,60	2,02	70453	1,58	78,20
2	50,60	2,02	70266	1,58	78,00
1	25,30	1,01	35158	0,78	76,67
2	25,30	1,01	37559	0,83	81,90
1	5,06	0,20	7601	0,17	81,65
2	5,06	0,20	7156	0,16	76,87
				Mean value	78,88
				Standard deviation	2,32
				Coefficient of variation	2,95
				Confidence limits (P= 95%)	0,64

Figure 4. Recovery results for stainless steel material using the swabbing technique

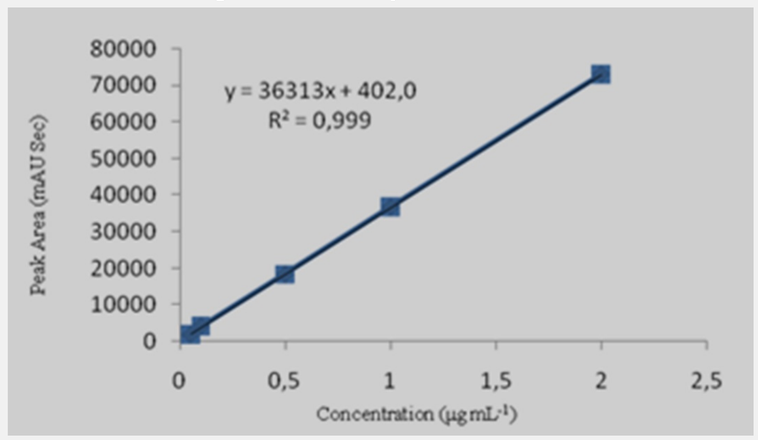

Figure 5. Linearity of Loratadine

LOD (µg mL^{-1})	LOQ (µg mL^{-1})	Regression equation (y)		Correlation coefficient	System precision (RSD, %)
		Slope (b)	Intercept (a)		
0.0199	0,066	36313,5	402,03	0.9999	0,29

Figure 6. LOD, LOQ, Regression and Precision results

Conclusion

The limits established on all the above-mentioned criteria demonstrate logical, practical, achievable and verifiable values that ensure product quality and patient safety. According to the validation results, the HPLC method is suitable for determination of loratadine residues in swabbing samples obtained from the manufacturing equipment surface. The validation parameters of HPLC method met the acceptance criteria and the proposed acceptance limits can be applied for the intended routine cleaning validation procedures.

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