

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

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## Introduction

Cleaning validation is a critical analytical responsibility of the quality assurance system and an important activity which establishes that cross-contamination of the next batch of different pharmaceutical products is under control, in order to ensure the quality of the finished product and patient safety (Bagade S.B. et al, 2014). Cleaning validation is required by the FDA (Food and Drug Administration) and the GMP (Good Manufacturing Practice) authorities in the pharmaceutical industry (Eudralex, 2015; FDA, 2014; ICH Q7, 2000). The cleaning procedures used must be supported by documented evidence with high degree of assurance that the cleaning procedure effectively removes chemical or microbial residues from the manufacturing equipment and facilities, below the scientifically predetermined maximum allowable carry-over levels (MACO) (Bagade and Krishna, 2014; LeBlanc, 2000; Geremia, 2019).

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. In reproductive toxicity studies in animals no teratogenic effects were observed, but prolonged parturition and reduced viability of offspring were observed in rats at plasma levels 10 times higher than those achieved with clinical doses (FDA, Pharmacological Review, 2011; FDA, Pharmacological Review, 2000).

The lowest value for permitted daily exposure (EMA, 2014; Geremia, 2019) calculated from repeated dose toxicity study in rats (NOAEL 8 mg/kg) was estimated to

be 0.16 mg/day or 16 0µg/day. This value, when compared with 1/1000<sup>th</sup> part of Loratadine minimal daily dose (5 µg), is more than thirty times bigger (FDA, Pharmacological Review, 2011; FDA, Pharmacological Review, 2000). Therefore, the MACO calculation was estimated by dosage criteria, i.e. the carryover of product residues should not be more than 0.1% (1/1000<sup>th</sup>) of minimal therapeutic dose of the API of previous product in the maximal daily dose of the subsequent product (LeBlanc, 2000). The obtained results were: MACO 0.15 ppm, the limit per surface area of manufacturing equipment 1.04 µg/cm<sup>2</sup> and limit in analyzed sample 1.3 ppm.

The aim of our work was to develop 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*

Chromatography was carried out using UPLC Shimadzu Nexera XR system with LPG quaternary pump with degasser, autosempler, controller and PDA detector and column oven, controlled by Lab Solutions software. Analytical balance Mettler Toledo AG285, Ultrasonic bath TP690/H, IKA orbital shaker KS 260 basic and pH/Conductivity meter Mettler Toledo S213 were used. The demineralized water was prepared by Simplicity UV System. The syringe filters RC (regenerated cellulose) 0,45 µm, were purchased from Agilent Technologies (USA).

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### Chemical and Reagents

The reagents that have been used are potassium dihydrogen phosphate, methanol and acetonitrile purchased from Carlo Erba, and 85% o-phosphoric acid from Sigma Aldrich. Reference standards Loratadine CRM, was supplied by the European Directorate for the Quality of Medicines (EDQM). Textwipes 714 A Swabs (Large Alpha Swab) were used for direct sampling.

### Chromatographic conditions

Separation was performed on LiChrospher RP Select B 125 mm × 4.0 mm, 5 µm column. The column temperature was maintained at 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. Methanol was used as diluent.

### 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 (ICH Q2 (R1), 2005). During selectivity testing, no interference from the blank swab sample at the retention time of Loratadine was observed. In order to demonstrate that the direct sampling procedure is suitable for determination of Loratadine residues on equipment surface, recovery or spiking studies were performed. The determination of the swab recovery for direct sampling method from manufacturing surface was performed on the stainless steel plate by spiking standard solutions of Loratadine at three concentration levels: 2 µg/mL, 1 µg/mL and 0.2 µg/mL, in duplicate for each level. 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.

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. 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%.

### 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.

### References

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