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Short communication

Setting cleaning validation acceptance limits and developing an HPLC method for the determination of Risperidone residues on manufacturing equipment

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Introduction

Risperidone is a member of the class of pyridopyrimidines and has a role as an atypical psychotropic agent. It is most often used to treat delusional psychosis (including schizophrenia), some forms of bipolar disorder, psychotic depression and Tourette syndrome (PubChem, 2026). Risperidone's mechanism of action involves antagonism of serotonin and dopamine receptors. Which helps to reduce both positive and negative syndromes of schizophrenia (Schotte et al., 1993).

Risperidone is a potent antipsychotic medication, making strict cleaning validation and cross-contamination limits essential. The Maximum Allowable Carryover (MACO) was calculated using the Permitted Daily Exposure (PDE) approach to demonstrate that residual drug levels remaining after cleaning are not toxicologically significant for patients exposed to the next product. For setting the maximum allowable carryover (MACO) limit for risperidone residues on manufacturing equipment, as a next product was selected the product with the highest maximum daily dose as the worst-case scenario.

The obtained MACO value of 29.83 mg or 0.686 ppm, ensure the safe value. Furthermore, the limit per surface area of manufacturing equipment and in the analyzed sample were calculated, with the obtained values 1.1 μg/cm^2 and 2.77 ppm, respectively (LeBlanc, 2000).

The goal of this study was to develop a sensitive reversed-phase high-performance liquid chromatography (RP-HPLC) analytical method, validated for quantitative determination of Risperidone in swab samples from manufacturing equipment after the cleaning process.

Materials and methods

Instrumentation and equipment

The separation was carried out on Shimadzu Nexera XR UPLC system equipped with a quaternary low-pressure gradient (LPG) pump, with degasser, autosampler, column oven, controller and a photodiode array (PDA) detector, controlled by Lab Solutions software.

The additional equipment used included a Mettler Toledo XRP10 semi-micro analytical balance, a TP690/H ultrasonic bath, and a Mettler Toledo S213 pH/conductivity meter. Ultrapure water was prepared using a Simplicity UV water purification system. Filtration was performed using 0.45 μm regenerated cellulose syringe filters purchased from Agilent Technologies (USA).

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Chemical and reagents

The reagents that have been used are: acetonitrile, methanol, o-phosphoric acid (H_3PO_4) and potassium dihydrogen phosphate purchased from Thermo Fisher Scientific and VWR Chemicals. The reference standard Risperidone CRM was purchased from Sigma Aldrich. Textwipe 714 A Swabs (Large Alpha Swab) were used for direct sampling.

Chromatographic conditions

Separation was achieved on a LiChrospher RP Select B 125 mm, 4.0 mm, 5 µm column, using isocratic elution, with a flow rate of 1.0 mL/min, at 35°C. The detection wavelength was 235 nm, and the injection volume was 50 µL. The mobile phase consisted of a mixture of 34 volumes of acetonitrile and 66 volumes of 0.25 % potassium dihydrogen phosphate with the pH adjusted to 3.0 using phosphoric acid. A 7:3 (*v/v*) mixture of Methanol and 0.08% phosphoric acid was used as diluent.

Results and discussion

The RP-HPLC method was validated in accordance with the requirements obtained in the International Conference on Harmonisation (ICH) guideline for validation of analytical procedures (International Conference on Harmonisation, 2005). Selectivity assessment demonstrated that the blank swab sample did not produce any interfering peaks at the retention time corresponding to Risperidone. Recovery and spiking tests were carried out on a stainless-steel plate in order to confirm the suitability of the direct sampling procedure used to determine Risperidone residues on the equipment surfaces. This was achieved through spiking the plate with standard solutions at three concentration levels: 0.12 µg/mL, 3.0 µg/mL, and 3.6 µg/mL. The attained swab recovery factor of 0.751 (75.11 %) was used as a correction factor in the results for the cleaning validation.

The linearity of the method was demonstrated through seven concentrations, from 3.6 µg/mL to 0.12 µg/mL whose correlation coefficient value (R^2) was 0.9990. The limit of quantification (LOQ) was determined by using a series of linearity solutions and was calculated to be 0.12 µg/mL. The precision of the system was also evaluated at the LOQ level, and the obtained RSD value was less than 5 %.

Conclusion

The HPLC method was developed and validated for the quantification of Risperidone residuals after equipment cleaning. The method provides acceptable sensitivity, linearity, and selectivity throughout this validation. Calculated acceptance limits were shown to be realistic and attainable, providing assurance of product quality and proving to be an effective prevention of cross-contamination. The validation process confirmed that the method is suitable for monitoring Risperidone in swab samples collected from manufacturing equipment surfaces and the proposed limits can be routinely used as part of cleaning validation procedures.

References

International Conference on Harmonisation, 2005. Validation of Analytical Procedures: Text and Methodology Q2(R1). ICH, Geneva, Switzerland. https://database.ich.org/sites/default/files/Q2_R1__Guideline.pdf

LeBlanc, D.A., 2000. Validated Cleaning Technologies for Pharmaceutical manufacturing. Interpharm Press, Denver, Colorado, US.

PubChem, 2026. PubChem Compound Summary for CID 5073, Risperidone. National Center for Biotechnology Information, National Library of Medicine, Bethesda, MD. https://pubchem.ncbi.nlm.nih.gov/compound/Risperidone (accessed 9 May 2026).

Schotte, A. et al., 1993. Occupancy of central neurotransmitter receptors by risperidone, clozapine and haloperidol, measured ex vivo by quantitative autoradiography. Brain Res.. 631, 191–202. https://doi.org/10.1016/0006-8993(93)91535-Z