

Determination of betamethasone residues on manufacturing equipment surfaces and PDE calculation in cleaning validation processes

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Introduction

Determination of Permitted Daily Exposure (PDE) implies reviewing all relevant data available, identification of the pharmacological and toxicological effects and the therapeutic dose that can cause specific and serious adverse effect and understanding and applying several adjustment factors to account for various uncertainties (Bagade and Krishna, 2014; EMA, 2014; Geremia, 2019; LeBlanc, 2000). Topical formulations are generally considered to be safe and less potent than oral or parenteral formulations (Aung and Aung, 2021; FDA, 2008). The minimum and maximum daily dose of topical formulations can be calculated based on the criteria of finger-tip unit (FTU) set by Long and Finely (1991) (Ovais and Lian, 2008).

The resorption of Betamethasone during topical administration is low and it is unreliable to result in toxicological systemic side effects (Aung and Aung, 2021; EMA, 1999; FDA, 2008; Mahalingam et al., 2008). There are no evident long-term studied to assess the potential carcinogenicity and mutagenicity of topical corticosteroids (FDA, 2008). However, the literature data proved some teratogenic effects in animal studies after systemic administration (EMA, 1999; FDA, 2008). According to data obtained from animal studies on rabbits the minimal obtained PDE value, extrapolated on topical administration, is 33 µg/day and the calculated MACO value is 0.82 ppm, or 80.67 mg carryover in subsequent product (EMA, 1999; FDA, 2008).

Betamethasone dipropionate is the 17,21-dipropionate ester of Betamethasone, a synthetic

corticosteroid with dominant glucocorticoid effect (EMA, 1999; Manassra et al., 2010). Betamethasone is extensively used for topical application in the treatment of various skin disorders and is available in several semi-solid pharmaceutical dosage forms with strength of 0.05% (Aung and Aung, 2021; Manassra et al., 2010; Sweetman, 2011).

The aim of this study was to develop and validate sensitive reversed-phase high performance liquid chromatography (RP-HPLC) method for quantification of Betamethasone residues from manufacturing equipment surface in cleaning validation processes.

Materials and Methods

The determination of Betamethasone was performed on UPLC chromatographic system Shimadzu Nexera with DGU-20A5R degassing unit, SIL-20AC autosampler, LC-20AD pump, CTO-20AC prominence column oven, CMB-20A system controller and SPD-M20A diode array detector. Lichrospher RP-18 chromatographic column (125 x 4 mm with 5 µm particles) was used.

Acetonitrile was purchased from Carlo Erba and demineralized water was in-house product with conductivity approximately 0,05 µS/cm (prepared by Simplicity UV). Betamethasone dipropionate CRM standard was used. Textwipe 714 A Swabs (Large Alpha Swab) are used for direct sampling.

Results and discussion

The optimized chromatographic method uses mobile phase consisted of 40 % (v/v) H₂O and 60 % ACN. The separation is performed on Lichrospher RP-18 chromatographic column (125 x 4 mm with 5 µm particles) with UV detection at 240 nm. The column temperature was maintained at 30°C. Volume of injection used is 20 µL, with mobile phase flow rate of 1.1 mL/min.

The method was validated according to ICH Q2 (R1) guideline for validation of analytical procedures (ICH, 2005; FDA, 2014). The method proved to be selective, with no interference from the blank swab sample. The linearity was estimated at seven concentration levels, in the range from 0.06 µg/mL to 4.6 µg/mL with correlation factor of 1,0000. The LOD and LOQ concentrations were calculated based on the residual standard deviation from the regression analysis in the concentration range from 0.06 µg/mL to 2.5 µg/mL. The values obtained were 0,02 µg/mL for LOD, which is 0.6 % of acceptance limit in analyzed sample (3.2 µg/mL), and 0.06 µg/mL for LOQ, which is 1.9 % of acceptance limit. Swab recovery study was performed on predefined stainless-steel plate (25 cm²) by spiking standard solutions at three concentration levels: 1.8 µg/cm², 3 µg/cm², 3.6 µg/cm², duplicate for each level. Swabbing procedure was optimized in order to obtain a suitable recovery of Betamethasone and the obtained swab recovery factor was 0.75 (75%), which is used as correction factor in analytical calculations. The obtained relative standard deviation of response from five subsequent injections at LOQ level was less than 5%, and at concentration level 3 µg/mL, which is approximately to acceptance limit in analyzed sample, less than 1%, which proved the method reproducibility.

Conclusion

PDE for Betamethasone is determined, based on the available data from pharmacological and toxicological studies, and extrapolated for topical administration of the pharmaceutical dosage form. The method developed is fast, simple, precise, selective, linear in the concentration range studied and sufficiently sensitive to detect the established acceptance limits for carryover in the subsequent product manufactured. The developed method can be used for quantitative determination of Betamethasone residues on manufacturing equipment surface area.

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