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Preparation and Evaluation of Nanosuspension-based Sildenafil Pressurized Metered-dose Inhalers for Treatment of Pulmonary Arterial Hypertension Using Poloxamer 188 as a Stabilizer

Sildenafil is a phosphodiesterase-5 (PDE5) inhibitor approved for the treatment of pulmonary arterial hypertension; commercially available in oral and intravenous forms. The major obstacles in developing a new dosage form of sildenafil are its limited solubility and stability. To develop an alternative, pulmonary dosage form, these problems must be overcome. The objectives of this study are to formulate the nanosuspension-based sildenafil pressurized metered-dose inhalers using poloxamer 188 (P188) as a stabilizer and to evaluate their physical and chemical stability, delivered dose uniformity, in vitro aerosol performance, hydrodynamic particle size, and cytotoxicity. Twelve formulations of nanosuspension-based sildenafil pMDIs were prepared by the bottom-up process and pressure filling method. The formulations consisted of nano spray-dried sildenafil citrate, P188, sorbitan monooleate, ethanol, and HFA134a. Sildenafil content and delivered dose uniformity were evaluated using in-house sampling technique and high-performance liquid chromatography. In vitro aerosol performance was evaluated using a Next Generation Impactor. The dose uniformity of sildenafil content in formulation #5-12 was displayed throughout their lifespan (82.21-95.07 %). The results of aerosol performance including, emitted dose (ED), fine particle fraction (FPF), and mass median aerodynamic diameter (MMAD) of formulation #5-12 varied from 77.49-87.55 %, 51.55-62.61 %, and 1.26-1.81 µm, respectively, and the geometric standard deviation (GSD) of the results were approximately 2, which indicates a good distribution of data. Formulation #7 was selected by MODDE software as an optimal formulation based on specified criteria. The analysis of the aerosol parameters displayed the effect of ethanol content on ED and FPF, and P188 content on MMAD. The selected formulation was chemically and physically stable throughout 6 months. The hydrodynamic particle sizes of selected formulation in dichloromethane and milli-Q water obtained at month 1 were 243.8 ± 13.5 nm and 466.6 ± 138.0 nm, respectively, and the results obtained at month 6 were 255.6 ± 16.5 nm and 481.0 ± 97.6 nm, respectively, with the polydispersity indices (PDI) less than 1. The zeta potentials of the selected formulation obtained at month 1 and month 6 were -44.6 ± 2.5 and -43.4 ± 0.4 mV, respectively, which indicated a good stability. No cytotoxicity was found. This study has successfully formulated stable nanosuspension-based sildenafil pMDI using P188 as a stabilizer. The delivered dose uniformity and aerosol parameters were within the appropriate ranges; thus, P188 displayed a promising use in the pulmonary delivery system.

Primary author: Mr CHUNHACHAICHANA, Charisopon (DDSEC, Faculty of Pharmaceutical Sciences, Prince of Songkla University)

Presenter: Mr CHUNHACHAICHANA, Charisopon (DDSEC, Faculty of Pharmaceutical Sciences, Prince of Songkla University)

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