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Pharmaceutical analysis and in-vitro aerodynamic characterisation of inhaled theophylline formulations containing drug particles prepared by supercritical fluid processing. Chromatographic, spectroscopic, and thermal analysis of micron-sized theophylline particles prepared by supercritical fluid technology and in-vitro evaluation of their performance as inhaled dry powder formulations.

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Pharmaceutical analysis and in-vitro aerodynamic characterisation of inhaled theophylline formulations containing drug particles prepared by supercritical fluid processing

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Keywords: Methylxanthines, theophylline, HPLC, monolith column, SEDS, characterisation, particle size, aerodynamic performance

Abstract:

The aim of this work is to study the *in-vitro* aerodynamic performance of a new inhaled theophylline formulation prepared by supercritical fluids technique.

For the analysis of the output from the *in-vitro* tests (and further *in-vivo* tests) a new, fast, sensitive high performance liquid chromatographic (HPLC) method was developed and validated for the determination of theophylline and other related derivatives in aqueous and urine samples using new packing materials (monolithic columns). These columns achieve efficient separation under lower backpressure and shorter time comparing to other traditionally or newly introduced C18 columns.

Solution enhanced dispersion by supercritical fluid (SEDS) process has been applied for the production of anhydrous theophylline as pure crystals in the range 2-5 μm to be used as new inhaled dry powder formulation for asthma. Fifteen theophylline samples have been prepared under different experimental conditions.

The drug produced by this method has been subject to a number of solid-phase analytical procedures designed to establish the crystal structure [X-ray powder diffraction (XRPD)], the structure and conformation [(FTIR), Fourier-transform Raman spectroscopy (FT-Raman)], and the morphology and particle size [scanning electron microscope (SEM)]. While, thermal gravimetric analysis (TGA), and differential scanning calorimetry (DSC) have been used to monitor any phase transition or polymorphic changes after processing. All these analytical techniques gave a satisfactory indication of the solid-state chemistry of the processed particles and assess the development of new inhalation product.

The performance of inhaled SEDS theophylline with or without a carrier was evaluated using the developed HPLC method. Three samples having different particle sizes were selected out of the prepared powders by SEDS technique to be tested. The dose sampling unit and the Anderson Cascade Impactor were used to determine the *in-vitro* emitted dose and the deposition profiles of SEDS samples, respectively. The effect of different inhalation flows was studied using two different flows 28.3, and 60 L min^{-1} with 4 L inhalation volume. Different DPI devices were investigated in this study; Easyhaler[®] and Spinhaler[®]. The particle size has an important effect on the aerodynamic behaviour and deposition profile of inhaled drug, the smaller the particles the greater the total lung deposition. The presence of a carrier improves the respirable fraction for all the tested formulations.

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