

# Design and evaluation of novel inhalable sildenafil citrate spray-dried microparticles for pulmonary arterial hypertension

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## Abstract

Pulmonary delivery of vasodilators is a promising alternative for the intravenous and oral treatment of pulmonary arterial hypertension (PAH). The aim of this study was to design and evaluate hydrogel microparticles as a carrier for sustained pulmonary delivery of sildenafil citrate. Spray dried hydrogel microparticles containing biodegradable sodium carboxymethyl cellulose, sodium alginate, and sodium hyaluronate polymers at variable concentrations were prepared. A design of experiment using the "Extreme Vertices Mixture" design was executed. The design was used to study the influence of polymer concentration and their interactions on the physicochemical properties of the formulations in terms of particle size, particle size distribution, product yield, entrapment efficiency, and in-vitro drug release. Selected formulations were also evaluated for swelling, biodegradation, moisture content, in-vitro aerodynamic performance, and cytotoxicity. In addition, a lung deposition and pharmacokinetic study was conducted in rats to study drug accumulation in lungs and blood after intratracheal administration of the spray dried microparticles. The results demonstrated that formulated microparticles had a mean geometric diameter of 4.7  $\mu$ m, entrapment efficiency of >80%, and yield ranging between 47 and 66% w/w. The in-vitro drug release profiles showed a sustained release of 80% over 24 h. The in-vivo pharmacokinetic study showed that inhaled spray dried hydrogel microparticles (M6) formulation had significantly higher lung/blood C<sub>max</sub>, AUC, extended half-life, and mean residence time in comparison to orally administered sildenafil citrate of the same dose. In conclusion, the formulated drug-loaded spray dried hydrogel microparticles showed promising in-vitro and in-vivo results for the pulmonary delivery of sildenafil citrate. The spray dried hydrogel microparticles formulation can be considered as a potential alternative of oral sildenafil citrate for treatment of PAH.

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