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 ñExtreme Vertices Mixtureò 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 inhalable hydrogel microparticles in comparison to orally administered ViagraÈ. The results demonstrated that formulated microparticles had a mean geometric particle size between 2 and 5 µm, entrapment efficiency of >80%, and yield ranging between 47 and 66% w/w. The in-vitro drug release profiles showed a sustained drug release of sildenafil citrate for over 24 h. The statistical design showed a significant influence of the microparticulate composition on the physicochemical properties. Furthermore, selected formulations were evaluated for their aerodynamic properties. The aerodynamic properties included fine particle fraction ranging between 24 and 30%, dose recovery percent of 68ï8 5%, and average mass median aerodynamic diameter of 4.6ï4.8 µm. The in-vivo pharmacokinetic study showed that inhaled spray dried hydrogel microparticles (M6) formulation had significantly higher lung/blood Cmax, 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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