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Title: Eliminating in-vitro drug-drug interactions in dual and triple fixed-dose combination therapies using a novel cosuspension metered dose inhaler platform

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Body: Developing fixed dose combinations requires comparison with component therapies, first over a wide range of doses, and then at a fixed dose over prolonged periods. When coupled with the need for dose ranging, the clinical development of combinations becomes very difficult when the in vitro performance of a given drug is affected by the presence of the other drug(s). We report interaction-free in vitro performance of a dual and a triple drug combination, and their component therapies, in simple metered dose inhalers (MDI) made by a novel cosuspension platform over a dose range starting from sub-microgram levels. Methods: Glycopyrrolate (GP, up to 18 µg/actuation) and formoterol fumarate (FF, fixed at 4.8 µg/actuation) MDIs, and their combination (GFF), were prepared by cosuspending drug crystals in hydrofluoroalkane with spray-dried distearoyl-phosphatidylcholine porous particles. Triple drug MDIs were made by cosuspending mometasone furoate (MF, up to 300 µg/actuation) with GFF. Dual combinations MF+GP and MF+FF were prepared as well. Aerodynamic particle size distribution (aPSD) was tested at 30 L/min, including upon storage at fixed temperatures. Results: The in vitro drug delivery and stability of each drug was unaffected by the presence of one or more drugs in dual or in triple cosuspension formulations. The aPSD was linearly dose proportional ($r2 > 0.99$) over the entire dose range evaluated. Conclusions: Pearl’s novel cosuspension platform presents an opportunity to develop dual and triple combination regardless of drug type or dose due to the in vitro drug-drug interaction free delivery from its cosuspension formulations.