Radiolabelling of Low GWP pMDI Formulations for Scintigraphy

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Introduction

Some pharmaceutical companies have stated their intention to transition to low global warming potential (GWP) propellants. Chiesi [1] announced reformulation of its pMDIs using HFC152a (GWP = 138). AstraZeneca (AZ) [2] have stated that the Breztri (Trixeo) Aerosphere® triple combination product, is expected to transition to hydrofluoro-olefin (HFO) propellant 1234ze (GWP <1).

The objective of this study was to radiolabel two model low GWP pMDI formulations, one solution and one suspension, with the same API compositions as used in HFC134a pMDIs, currently marketed by Chiesi and AZ.

The solution formulation was based on Trimbow® (Chiesi) i.e. beclometasone dipropionate (BDP), formoterol fumarate dihydrate (FF) and glycopyrronium bromide (GP) dissolved in HFC 152a/ethanol.

The suspension formulation was based on Trixeo Aerosphere® (AZ) i.e. budesonide (BD), glycopyrronium bromide (GP), and formoterol fumarate dihydrate (FF), suspended in HFO1234ze. The commercial formulation uses co-suspension delivery technology, in which micronized drug crystals are suspended with spray-dried phospholipid excipient porous particles (distearoylphosphatidylcholine (DSPC) and calcium chloride) in HFC propellant.

Methods

Tc-99m was eluted from a commercial generator (Tekcis, Curium Pharma), the saline was precipitated and the aqueous phase evaporated to yield a dried film of saline-free Tc-99m.

Model Formulation 1 (Solution pMDI in HFC152a): Pre-weighed Trimbow cans were cooled (-70°C), the valves removed and the contents transferred to new pMDI cans (Presspart). The propellant was evaporated to constant weight. The calculated amount of HFC152a (Koura) to reconstitute the formulation to its original composition was cold transferred, radiolabelled using saline-free Tc-99m, and new 63 µL metering valves were crimped on to the canisters.

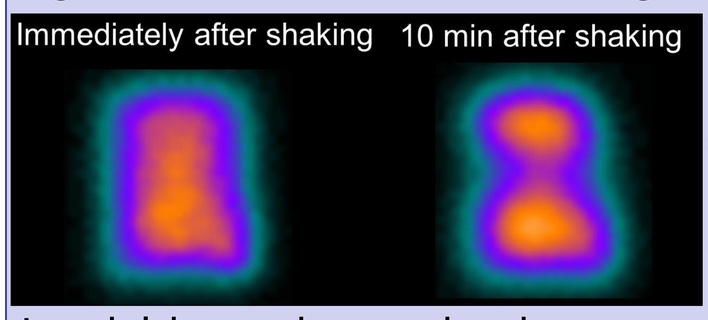
Model Formulation 2 (Suspension in HFO1234ze): Pre-weighed Trixeo cans were cooled (-70°C) and transferred to new pMDI cans (Presspart UK Ltd). The propellant was evaporated under controlled conditions. HFO1234ze (technical grade, MG Chemicals) required to reconstitute the formulation to its original composition was cold transferred. Saline-free Tc-99m was added and new metering valves (50 µL) were crimped.

All cans were mechanically shaken followed by priming in accord with the commercial product PILs prior to testing. Aerosol characteristics of active pharmaceutical ingredients (APIs) and the radiolabel Technetium-99m (Tc-99m), were determined by HPLC-UV and gamma camera respectively.

Results & Discussion

Gamma camera images of radiolabel distribution immediately post-shaking indicated that Tc-99m was homogeneously dispersed. Whilst the chemical form of Tc-99m was the same in both model systems different behavior was observed. For the solution system the radiolabel remained uniformly dispersed for the duration of the 10 min observation period. For the suspension the radiolabel distribution became less homogeneous over time (Figure 1), however it was found that gentle shaking of the canister ensured effective re-dispersion.

Figure 1: **Gamma Camera Images of Suspension pMDI Can**



The canisters were located upright in front of the gamma camera and images were acquired every 60 s for 10 min.

Inertial impaction testing however showed different deposition patterns. It is postulated that Tc-99m was dissolved in the ethanol / HFC152a phase of the solution pMDI and thus co-deposited with the dissolved APIs. In the suspension system co-deposition with the micronised API suggested that Tc-99m preferentially associated with the surface of the API/DSPC porous particles. The radiolabel and API distribution data shown in Figures 2 & 3 were analysed according to recommendations published in Devadason *et al*., [3].

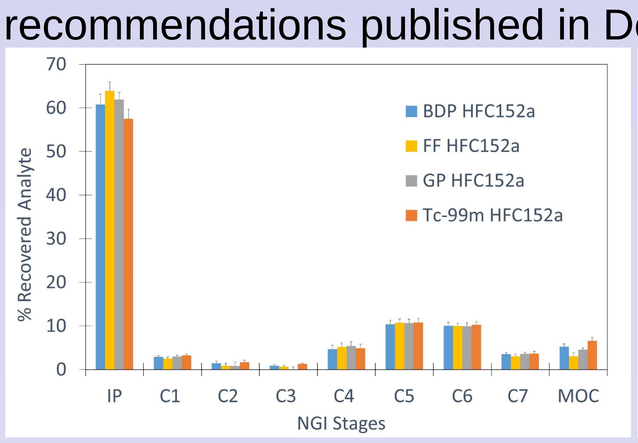


Figure 2: Analyte Recovery from Model Formulation 1 Prepared in HFC152a (Mean % ±SD, n=4) .

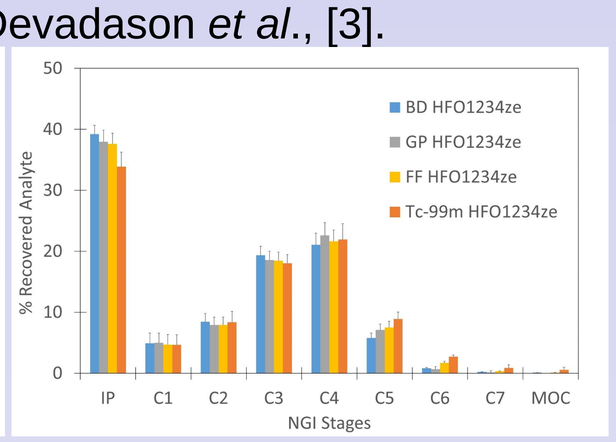


Figure 3: Analyte Recovery from Model Formulation 2 Prepared in HFO1234ze (Mean % ±SD, n=4,) .

Deposition values were pooled into 4 NGI stage groupings and compared for Tc-99m and API. Where the pooled stage deposition was >10%, the data were analysed as a Tc-99m / API ratio, with an acceptance criteria of 0.85 - 1.18. For pooled stage data <10% (indicated by * on the Tables) an absolute difference between Tc-99m and API of ±2% was used for acceptance. Data exceeding the limits are highlighted by ^ in the Tables.

Table 1: **Grouped Stage Analysis Model Formulation 1**

Grouped stages	Tc-99m/BDP	Tc-99m/FF	Tc-99m/GLY
IP+C1	0.95	0.91	0.94
C2+C3* abs diff. (Tc-99m – API)	0.61%	1.42%	2.13%^
C4+C5	1.04	0.99	0.98
C6+C7+MOC	1.09	1.28^	1.13

Table 2: **Grouped Stage Analysis Model Formulation 2**

Grouped stages	Tc-99m/FF	Tc-99m/GP	Tc-99m/BD
IP+C1	0.87	0.90	0.91
C2+C3	0.95	1.00	1.00
C4+C5	1.15	1.04	1.06
C6+C7+MOC* abs diff. (Tc-99m – API)	3.02%^	3.36%^	2.02%

Conclusions

These data demonstrate the successful radiolabelling of solution and suspension formulations in low GWP propellants. Radiolabelled formulations are used in clinical scintigraphy studies to accurately quantify lung deposition and distribution of inhaled drugs, and thus can accelerate the transition to next generation low GWP propellants.

References

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