

Formulating HFO-1234ze(E) pMDIs with Ethanol: Flammability Considerations



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Introduction

To meet sustainability targets, the pMDI industry is currently transitioning from high global warming potential (GWP) hydrofluoroalkane (HFA) propellants HFA-134a and HFA-227ea to low GWP propellants HFA-152a or hydrofluoroolefin (HFO)-1234ze(E). [1-5] While standard flammability tests [6] classify HFA-152a as flammable and HFO-1234ze(E) as non-flammable, and a recent manufacturing risk assessment [7] found that HFO-1234ze(E) could be handled like non-flammable HFA-134a, the industry is assessing the handling of HFO-1234ze(E) in bulk manufacturing processes [8,9] when including flammable cosolvents like ethanol.

Objective

Test pMDI devices containing mixtures of HFO-1234ze(E) with ethanol by the UN GHS standard ignition distance test and an incandescing copper wire test. Compare to HFA-152a and HFA-134a and ethanol mixtures to help inform handling considerations for HFO-1234ze(E) at point of use and in pharmaceutical manufacturing environments.

Methods

Ethanol was weighed into a clean, PTFE-lined canister and capped with a crimped 50 μ L valve. HFO-1234ze(E), HFA-134a, or HFA-152a propellant was pressure-filled through the valve to a final weight of 10 g and the canister was placed into an actuator with a 0.22mm orifice.

Ignition distance testing was performed according to the UN Globally Harmonized System (GHS) method [6] with inhalers held a specified distance from, and actuated toward, an open flame (Figure 1) with two modifications: i) spray time was reduced from 5 seconds to one actuation due to the practical limitations of the metered dose device, and ii) test distances below the standard minimum 6 inches were tested due to no flame events observed for any mixtures at 6 inches.

Incandescing copper wire testing took place within a custom designed enclosed chamber (Figure 2) which accommodated the introduction of vapors of propane or test mixtures onto copper wire coils powered by a variable DC supply. Temperatures were controlled by an electric heater to 31 ± 3 $^{\circ}$ C and humidity set to the maximally attainable (>80% relative humidity). For each test, a quiescent and non-quiescent test was examined, with the latter achieved using a computer cooling fan. As shown in Figure 3, once the wire coils were incandescing (A), propane vapors were introduced as a control to verify the incandescing wire's capacity to produce a positive flame event (B). Once verified, propellant and ethanol mixture vapors were introduced to the same coil (C). Propane added after the test confirmed that the state of copper wire incandescence remained largely unchanged throughout testing (D), all recorded by digital camera. Propane and propellant/ethanol introductions were via ca. 2-second discharges from a 300 mL feed cylinder.

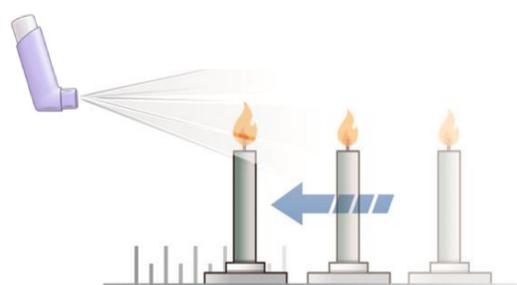


Figure 1. Representation of the ignition distance test set-up for MDI devices

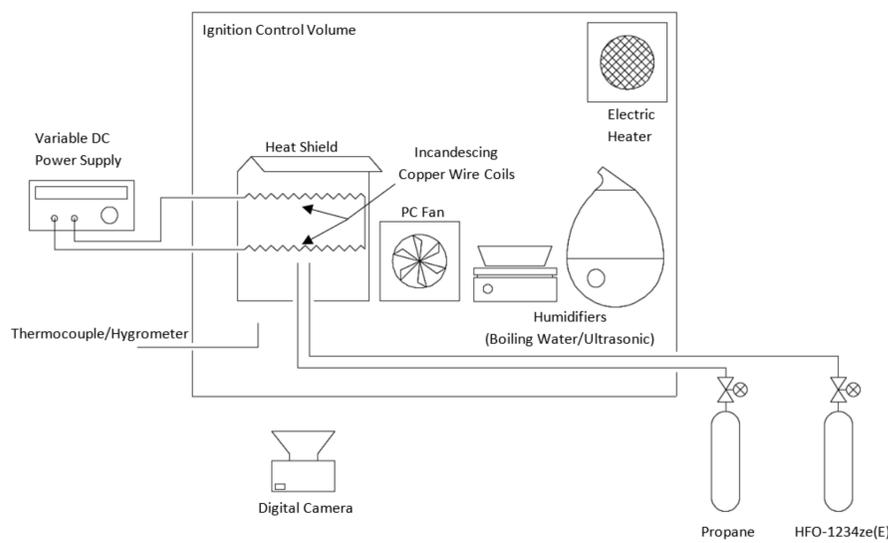


Figure 2. Schematic diagram of the incandescing copper wire (ICW) experimental set-up

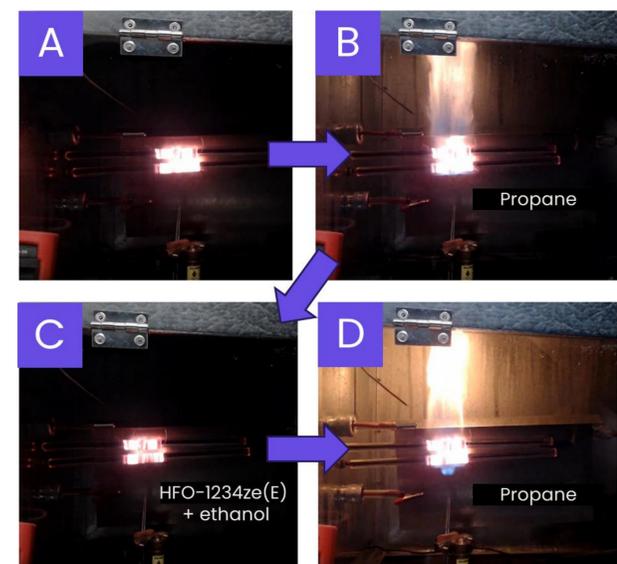


Figure 3. Frame stills showing ICW test

Results – Ignition Distance Testing

Table 1. Flame propagation results from the ignition distance test modified for pMDI assessment

Test mixture	pMDI distance from flame		
	6 in	3 in	2 in
HFA-152a	NO	YES	YES
HFA-134a with 15 wt% ethanol	NO	NO	NO
HFO-1234ze(E) with 5 wt% ethanol	NO	NO	NO
HFO-1234ze(E) with 10 wt% ethanol	NO	NO	NO
HFO-1234ze(E) with 15 wt% ethanol	NO	NO	NO

While all five test mixtures were found to be non-flammable at 6 inches, the 3-inch and 2-inch test results show a distinction between the HFA-152a, which propagated the flame, and the HFA-134a with ethanol and HFO-1234ze(E) with ethanol mixtures, which did not propagate the flame.

Results – Incandescing Copper Wire Testing

Table 2. Results from the incandescing copper wire testing at 31 ± 3 $^{\circ}$ C and >80% relative humidity

Test Mixture	Fan (ON/OFF)	Flame Event? (YES/NO)
HFA-152a	OFF	YES
	ON	YES
HFA-134a with 2.5 wt% ethanol	OFF	NO
	ON	NO
HFA-134a with 15 wt% ethanol	OFF	NO
	ON	NO
HFO-1234ze(E)	OFF	NO
	ON	NO
HFO-1234ze(E) with 2.5 wt% ethanol	OFF	NO
	ON	NO
HFO-1234ze(E) with 15 wt% ethanol	OFF	NO
	ON	NO

Each test condition was tested at least three times. All HFA-152a tests generated a flame event. For all HFA-134a and HFO-1234ze(E) tests, alone or with ethanol, no flame events were observed.

Conclusions

- The ignition distance testing shows that with respect to flammability at the point of pMDI use, the behaviour of the HFO-1234ze(E) and ethanol mixtures matches that of the HFA-134a and ethanol mixtures.
- The energy of an incandescing copper wire was not sufficient to generate a flame event when vapor phase mixtures of HFO-1234ze(E) with 2.5 wt% ethanol or 15 wt% ethanol were introduced at any test condition. This matched the behaviour of similar mixtures of HFA-134a with ethanol.
- These studies support the handling of HFO-1234ze(E) with ethanol like HFA-134a with ethanol is handled today – with modest mitigation measures such as temperature, humidity and ventilation controls which are already common in pharmaceutical manufacturing environments.**

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