Fundamental properties of propellant aerosols can guide transition to low global warming potential pMDIs: size, velocity and surface charge

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Summary

Lower global warming potential (GWP) propellants (hydrofluoroalkane, HFA, 152a and hydrofluoroolefin, HFO, 1234ze) are readily available replacements to those currently employed in life-saving medications (HFA 134a and 227a). This study aimed to investigate fundamental physical properties of aerosols emitted from pMDIs using currently employed propellants and low GWP alternatives. The net surface charges for all propellants were positive, however HFO 1234ze generated near-neutral charges of both polarities, with HFO being the least bipolar propellant. However, water content was higher for this propellant as result of storage conditions and contribution of sub-assembly components (valve, canister, and actuator). Net charge may determine relevant differences in aerosol deposition and, therefore, should drive formulation development approaches. The droplet diameter and velocity for the different propellants fell into multiple groups (for example: the two low GWP propellant droplets were larger at short distances from the actuator). This information will guide the use of excipients to achieve desirable performance of products reformulated using these propellants. Finally, the results evidenced as well the influence of valve and actuator's material components on the net-charges developed. Therefore, device sub-assembly components play an important role during pMDI re-formulation and development.

Key Message

The fundamental properties of currently used and new low GWP propellants have been characterised. Differences in aerosol droplet surface charge were observed for HFO 1234ze. Moreover, low GWP propellants droplets were larger at short distances from the actuator. These may determine relevant differences in aerosol deposition, which can be balanced by formulation composition.

Introduction

In 1987 the Montreal Protocol defined a pathway to eliminate the compounds proven to be harmful for the ozone, such as chlorofluorocarbon (CFC) employed as propellants in pressurised metered dose inhalers (pMDIs)[1]. Since the adoption of the Kyoto Protocol in 1997[2] and the Europe F-Gas regulation in 2015[3] further amendments have been proposed which aims to reduce by over 80% by 2047 the use of F-gases, known to contribute to global warming. These amendments have been foreseen to have again a great impact on the pharmaceutical industry and, particularly, on products for inhalation which contribute 2.4% of the total F-gases emissions[1]. It is therefore clear there is a real need here and now for alternatives to the current reliever pMDIs that are both affordable and exhibit a lower global warning potential (GWP)[4]. Research is on-going on the re-formulation and development of drugs for asthma and chronic obstructive pulmonary disease[5].

Differences in the physicochemical properties of high and low GWP propellants (such as vapour pressure and density) result in differences in aerosol behaviour (such as evaporation rate and surface charge) which will impact lung deposition for re-formulated products. Very little is currently known about the physicochemical fundamental properties of these low GWP propellants and their impact on pMDI aerosolisation and plume characteristics[6].

The aim of this study was to investigate fundamental physical properties of pMDI propellants currently employed in products on the market or explored as low GWP alternatives. Information on the differences in surface charge of aerosols has been collected. Such a dataset will help to guide formulation decisions.

Experimental Methods

Placebo uncoated canisters (H&T Presspart, United Kingdom) comprising an amount equal to 250 doses of four different propellants (pharmaceutical grade HFA 227a, supplied by Dehon, France; pharmaceutical grade HFA 134a and HFA 152a supplied by Koura Global, United Kingdom and industrial grade HFO 1234ze supplied by Honeywell, United Kingdom) were manually filled (P2016, DHI, United Kingdom) and crimped with a standard Aptar Pharma (France) valve (DF316, 50 µL). A standard generic actuator (OD 0.48/JL 1.5 mm) was employed to fire the placebo canisters (H&T Presspart, United Kingdom).

Table 1. Propellants investigated: density, amount filled in the placebo pMDIs manufactured and their shot weights (n = 8, mean value ± standard deviation).

Propellant	Density (g/mL)	Amount filled (g)	Shot weight (mg)
HFA 134a	1.23	15.3	63.06 ± 0.61
HFA 227a	1.41	17.6	71.91 ± 0.47
HFA 152a	0.91	11.4	46.57 ± 0.45
HFO 1234ze	1.29	14.9	59.32 ± 1.94

One dimensional Phase Doppler Anemometry (PDA) was conducted by focussing the measurement volume into a sealed windowed enclosure with a dosage unit sampling apparatus (DUSA, Copley Scientific, UK) coupled to vacuum pump to one end and the devices attached to custom made mouthpiece adaptors at the other. A constant flow rate of 30 L/min was applied through the enclosure. The device was fired into the enclosure and the velocity and droplet diameter distributions over the entire plume were recorded. Measurements were performed at a number of positions within the spray plume.

The charges generated from placebo pMDIs were measured under ambient conditions (22.2°C, 37.7% relative humidity) using a Bipolar Charge Analyser (BOLAR; Dekati, Kangasala, Finland). One pMDI of each propellant was coupled to individual actuators for the tests and shaken for at least 5 seconds before each actuation. Eight shots without priming were sampled by the BOLAR at 30 L/min. The aerodynamic cutoff diameters of the size fractions at this sampling flow rate were 0.722, 2.510, 4.787, 8.103, and 13.336 µm. The weight of each shot was determined by weighing the canisters before and after each actuation. No mass assay was conducted as the aerosols contained only propellants.

Water content in the pMDI was quantified by Karl Fisher titration (Mettler Toledo, USA). Five shots were analysed for each propellant.

Results and Discussion

The shot weight was highly consistent for all propellants, even though there was no priming (Table 1). They were also the expected shot weights for a metering volume of 50 µL when calculated with the corresponding liquid propellant density. Bipolar charges were measured on all propellants, with most charges present in the lowest size fraction (0.722 µm) because the propellants were volatile and yielded small droplets (Figure 1). The pMDIs generated more positive charges than negative ones, thus the net charges were all positive. The apparent charging propensity differed between the propellants, with HFA 152a > HFA 134a > HFA 227a > HFO 1234ze in decreasing order (Figure 1). In particular, HFO 1234ze generated near-neutral charges of both polarities.

An earlier study by Kwok et al showed that HFA 134a and HFA 227a produced net negative charges when actuated from pMDIs[7], whereas they were net positive in this study. That could be due to the difference in the materials and/or geometry of the pMDI components (e.g. metering chamber, valve stem, and actuator) as well as on the water content, high water content has been proved to invert the polarity[7]. The bipolar charging has been shown to be caused by disruption and separation of the double layer of positive and negative charges in the liquid propellant surface during aerosolisation[7].

Generally, the more polar the liquid molecules, the more easily it can become charged[7]. The charge levels measured by the BOLAR largely followed the ranking of their dipole moments and dielectric constants, which indicate the molecular polarity, except for HFO 1234ze (Table 2). HFO 1234ze charged the lowest, even though its dipole moment was higher than that of HFA 227a. However, its behaviour can be explained by the solubility of water in the propellant, as it is the lowest for HFO 1234ze (Table 2), indicating this propellant as the least bipolar. It is known that water in the propellant can affect its charging by increasing the electrical conductivity[7]. Therefore, water content in the propellants was measured (Table 2). Charging propensity and water content were correlated for HFA 152a and HFA 134a, which reported the highest values. It is important to note that sub-assembly components (valve, canister and actuator) and storage conditions (in this case two months at uncontrolled ambient conditions) influence moisture content. This could explain the higher water content observed in HFO 1234ze compared to HFA 227a.

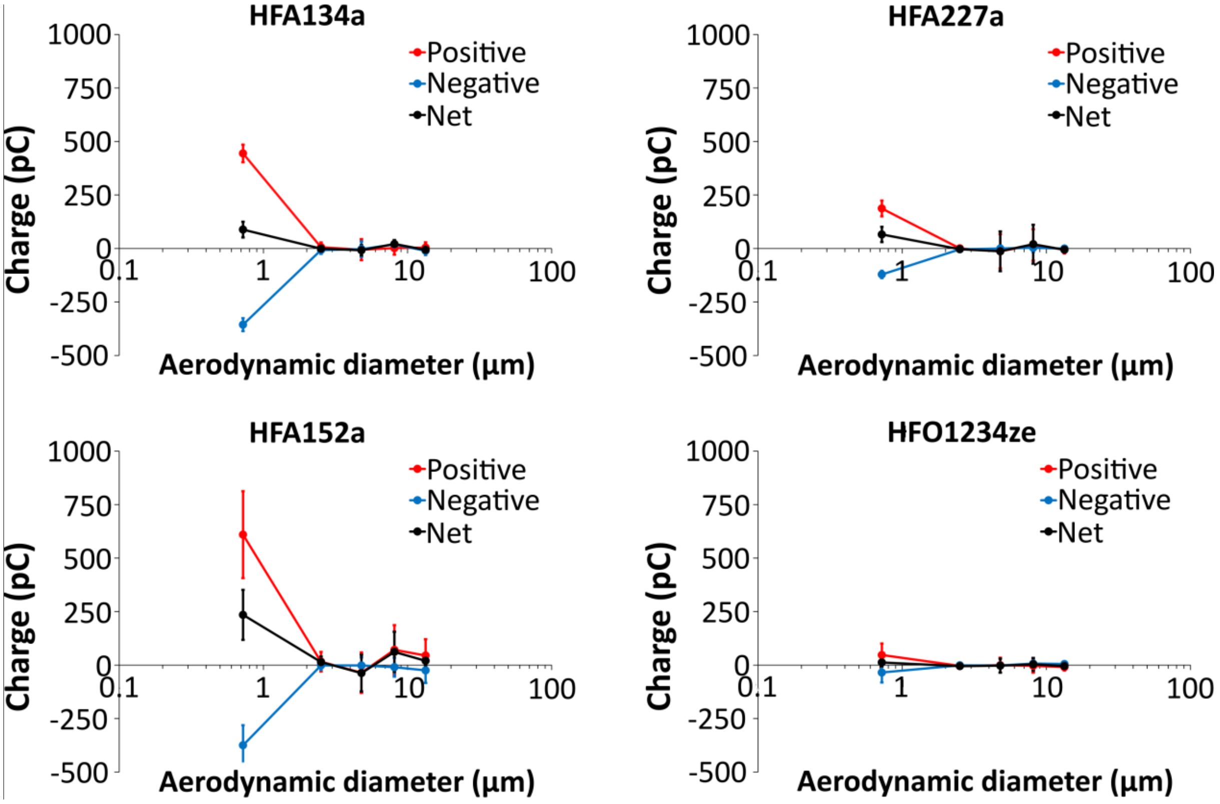

Figure 1. Bipolar charge profiles of propellant aerosols (*n*=8, mean value and bars represent standard deviation).

Table 2. Properties of propellants studied and water content of placebo pMDIs (*n*=3, mean value and residual standard deviation in parenthesis).

Propellant	Dipole moment	Dielectric constant of liquid	Solubility of water in propellant (ppm)	Water content of placebo pMDIs (ppm)
HFA 134a	2.058	9.8 (20°C)	2200	1689.9 (10.2%)
HFA 227a	0.93	4.1 (20°C)	610	167.6 (43.9%)
HFA 152a	3.69	12.52 (25°C)	2200	4052.6 (14.5%)
HFO 1234ze	1.44	NA	225	903.4 (25.8%)

The droplet diameters and velocities of emitted droplets of each of different propellant are shown in Figure 2. The solid lines refer to the means of multiple repeat measurements where the mean droplet diameter and velocity is extracted from each measurement. The droplet diameters at short distances (which are relevant to impaction in the oropharynx) fall into two groups with HFO1234ze and HFA152a falling from 1.6 µm at 20 mm from the actuator mouthpiece to around 1.0 µm at 80 mm. Droplet diameters for HFA134a and HFA 227a fall from around 1.3 µm to 1.0 µm or a little under at 80 mm. The droplet velocities separate into three groups at 20 mm with HFA227a showing the fastest droplets, HFA134a and HFO1234ze being similar and slightly lower and HFA152a giving the slowest droplet velocity. The differences in diameter become less at greater distances, but HFA227a shows a significantly greater droplet velocity at all distances measured.

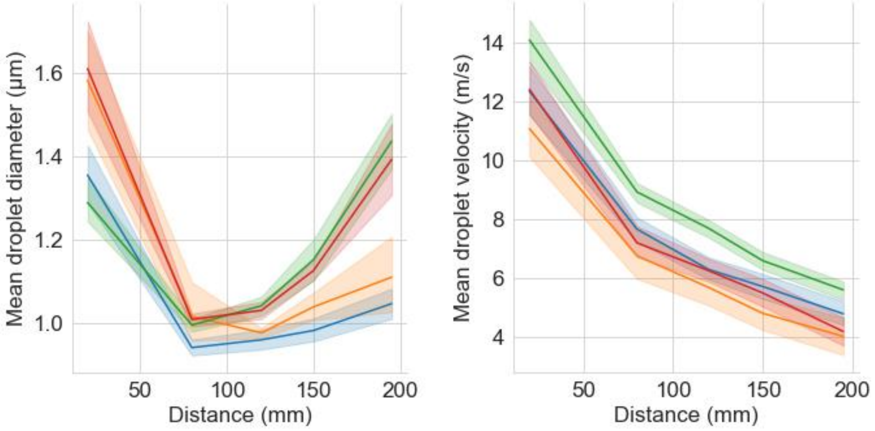

Figure 2. Mean diameter (left) and velocity (right) of emitted HFA134a (blue), HFA227a (green), HFA152a (orange) and HFO1234ze (red) at 20, 80, 150 and 195 mm from the actuator mouthpiece with a 30 L/min co-flow. Lines are means and ribbons are ranges of repeat measurements.

Conclusions

This work focused on the study of fundamental properties of propellants, present and greener ones. Even though net charges were all positive, differences have been observed with HFO 1234ze generating near-neutral charges of both polarities, in line with the water solubility value in HFO. Droplet diameter and velocity measurements showed differentiation across propellants, which point towards the use of excipients such as ethanol, for example, to modulate the evaporation rate of the droplets. This behaviour may determine relevant differences in aerosol deposition and, therefore, specific excipients should be considered during formulation development. Ultimately, the propellant droplet size distribution by number or by mass is required to properly evaluate charging propensity by calculating the number of charges per droplet or charge-to-mass ratio, respectively. However, the charge data obtained already showed interesting electrostatic behaviours of the low GWP propellants. Finally, the results evidenced as well the influence of valve, canisters and actuator's material components. Therefore, device sub-assembly components play an important role during pMDI re-formulation and development.

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