INTERACTION BETWEEN DRUG AND MATERIALS COMPOSING VALVED HOLDING CHAMBERS

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INTRODUCTION

- The objective of this study was to evaluate the possible interactions between drug and materials of different valved holding chambers.

METHODS

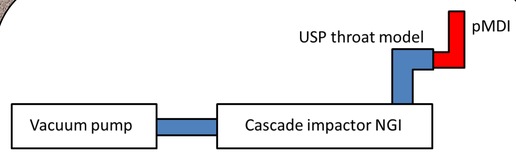
- In this study, HFA pMDI (Becotide®, 250 µg/puff, GlaxoSmithKline, France) was used with or without a VHC (pMDI+VHC). We tested two VHCs with Becotide: a VHC1 (Itinhaler® or Tipshaler® Silicone, Protec'Som Laboratory, Valognes, France) made in silicone and a VHC2 (Tipshaler®, Protec'Som Laboratory, Valognes, France) made in plastic.


pMDI+VHC1


pMDI


pMDI+VHC2

- A pMDI (beclomethasone dipropionate [BDP], GlaxoSmithKline, France) was connected to the NGI impactor.
- 10 doses were actuated into the NGI. All samples deposited in model throat and in each stage were collected by the addition of 1 ml of deuterochloroform and mixed. Then, these samples were analyzed by proton nuclear magnetic resonance (1H NMR) spectroscopy.



This method, according to the European Pharmacopoeia, used a constant flow rate (30 L/min).

The ^{1}H NMR spectra were performed on a Bruker DRX-500 spectrometer (Bruker SADIS, Wissembourg, France), operating at 11.7 T, with a Broad Band Inverse (BBI) probehead equipped with Z gradient coil. NMR measurements were done at 298K. Conventional ^{1}H NMR spectra were recorded with 90° pulse (p1=7.3µs, pl=0dB) using a pulse-and-acquire sequence. 1H spectra were collected with 128 transients in 64K data points with a spectral width of 7500 Hz (15ppm), a recycling time of 5s.

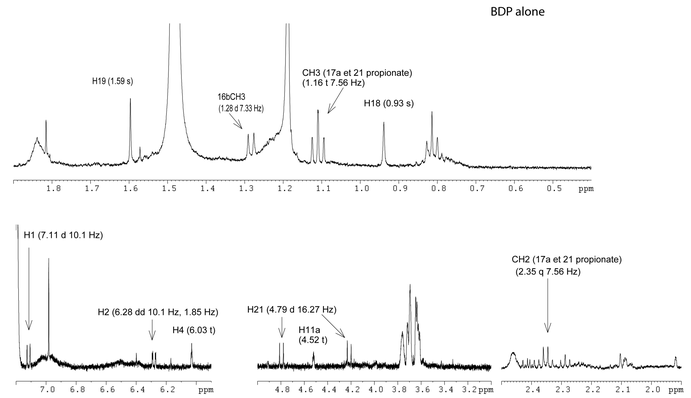
Spectra were processed using WinNMR version 3.5 software (Bruker Daltonik, Karlsruhe, Germany). Prior to Fourier transformation (FT), the FIDs were zero-filled to 64K data points which provided sufficient data points for each resonance and a line broadening factor of 0.3Hz was applied. All spectra were autocorrected for phase distortion and baseline using WinNMR software.

Each spectrum was integrated using WinNMR software automated integral function.

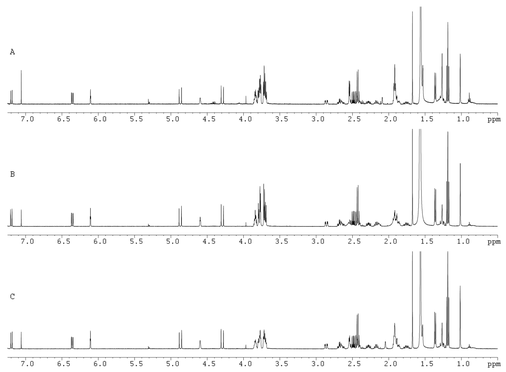
RESULTS

A) ^{1}H NMR spectra of BDP alone (scale range from 0 ppm to 7.2 ppm) identifies ^{1}H signals from BDP molecule.

- The arrows and annotated peaks show the different ^{1}H of interest present in the BDP molecule (glycerol, water and methanol belong to the formulation of the pMDI Becotide®) observed in the ^{1}H NMR spectrum.



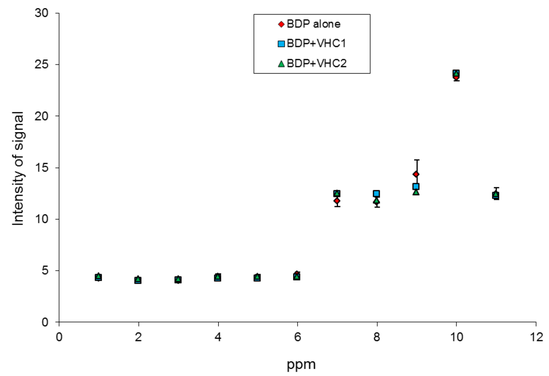
B) ^{1}H NMR spectra (scale range from 0 ppm to 7.2 ppm) of BDP alone (A), of BDP with VHC1 (B) and BDP with VHC2 (C).



- The figure B shows that there is no difference in the NMR signals coming from the ^{1}H of interest present in the BDP molecule between these three spectra whatever the experimental conditions. The spectra are perfectly superimposable.

C) ^{1}H NMR signal intensities of the different moieties coming from the BDP molecule alone or BDP with VHC1 and VHC2. The intensities are the same between the three experimental conditions, meaning that there are no complexes or interactions between BDP and materials.

- The ^{1}H NMR integration of BDP molecule moieties are the same between the three experimental conditions (three replicates, n=3) (Figure C). Thus, the signals corresponding to the excipients (glycerol: 3,6-3,9 ppm), water (1,20 ppm) and methanol (1,48 ppm) were excluded.



- ^{1}H NMR signal intensities of the different moieties coming from the BDP molecule alone or BDP with VHC1 and VHC2. The intensities are the same between the three experimental conditions, meaning that there are no complexes or interactions between BDP and materials.

CONCLUSION

- There are no interactions between BDP and soft silicone composing VHC1.
- There are no interactions between BDP and plastic composing VHC2. These results will be confirmed by Raman spectroscopy.