

An Investigation into the Physical Interactions of a Model Clathrate in a Suspension Metered Dose Inhaler Formulation

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Summary:

Clathrates are crystalline compounds consisting of a lattice of one type of molecule which hosts a second type of guest molecule within its structure. The guest molecules prevent the collapse of the open framework structure and render it more thermodynamically stable. The aim of this study is to investigate the physico-chemical properties of the known clathrate of beclomethasone dipropionate (BDP), crystallised from trichloromonofluoromethane (CFC-11), and to determine its physical interactions in a model suspension pMDI system. BDP-CFC-11 clathrate is a stable entity and thus suitable as a model for our initial investigations. The crystals investigated in this study were grown in 0.1%-3% w/w BDP in CFC-11 at ambient room temperature. The structure of the BDP CFC-11 clathrate was determined using direct methods such as XPS and X-ray powder diffraction. Atomic force microscopy was employed for the determination of the dispersive surface free energy (SE) and force of adhesion (Fadh) measurements of the BDP CFC-11 clathrate with different pMDI components in model propellant (decafluoropentane). The results obtained using different techniques show an efficient growth of the clathrate. The formation of BDP CFC-11 clathrate is favourable when compared to the anhydrous form, in terms of its potential interactions within a suspension MDI formulation due to the lower adhesion with different pMDI components. This could therefore have significant implications for the future development of HFA formulations with APIs which are prone to the formation of propellant clathrates.

Introduction:

Clathrates are crystalline compounds consisting of a lattice of one type of molecule which hosts a second type of guest molecule within its structure. Guest molecules in clathrates are packed (in channels and cages) in coordination compound frameworks. When removed from the stabilising medium, clathrates become thermodynamically unstable and generally tend to dissociate rapidly due to the presence of large empty cavities at the core of the structure. The guest molecules prevent the collapse of the open framework structure and render it more thermodynamically stable. The aim of this study is to investigate and characterize the physico-chemical properties of the beclomethasone dipropionate (BDP) clathrate crystallised from trichloromonofluoromethane (CFC-11) and determine its physical interactions in a model suspension pMDI system. Although CFC-11 will shortly be phased out of use, the BDP-CFC-11 clathrate is a stable entity and thus suitable as a model for our initial investigations (C. Vervaeet et al (1999)). In addition, although propellant clathrates have been known for sometime, as far as the authors are aware, the surface energies and adhesive interactions have not been reported.

Method:

Since the solid state chemistry can significantly alter the physical interactions within a suspension formulation, it is crucial to determine the most stable crystalline form in the presence of the propellant. In this work, crystal growth of anhydrous BDP in CFC-11 is examined. Anhydrous BDP was suspended in CFC-11 in a pressure resistant vial, shaken for 2 hrs and then placed in the fridge for 24 hrs prior to filtration. The crystals investigated in this study are grown in concentration levels varying from 0.1% to 3% w/w BDP in CFC-11. BDP crystallizes with a channel structure which allows the insertion of CFC-11 molecules. The structure is held together through hydrogen bonding (P.J. Kuehl *et al* (2003)). Furthermore, 3M Drug Delivery Systems supplied an isopropyl alcohol clathrate of BDP for additional investigation.

Spontaneous crystal growth occurs rapidly when anhydrous BDP is dispersed in CFC-11 with the formation of BDP CFC-11 clathrate. The structure of the clathrate was determined using the direct methods of scanning electron microscopy (SEM), X-ray photoelectron spectroscopy (XPS) and X-ray powder diffraction (XRPD). In addition, the use of atomic force microscopy (AFM) was employed for the determination of the dispersive surface free energy (SE) and the force of adhesion (Fadh) measurements of the BDP CFC-11 clathrate with different pMDI components in model propellant (decafluoropentane).

Results and discussion:

Anhydrous BDP, when suspended in CFC-11, forms perfect geometric crystals with a well defined hexagonal structure of about 30-70 μm in diameter (Fig. 1). This clathrate formation is spontaneous and quite rapid. Both anhydrous BDP and BDP CFC-11 clathrate were analysed using XPS in order to determine the difference in their surface chemical structure. The main peaks shown on the different scans corresponded to

the three atoms oxygen, carbon, and chlorine respectively. These elements constitute the backbone structure of BDP. The scan obtained for BDP CFC-11 clathrate exhibits an additional small peak at 685 eV position which was assigned to the fluorine and hence confirms the formation of the clathrate. ATR-IR spectroscopy was performed on the BDP CFC-11 clathrates. In order to show the presence of fluorine on the crystal obtained (results not shown). The spectra obtained showed a very noticeable peak at a wavenumber of around 1000 cm^{-1} . This peak was ascribed to CFC-11 as it has exactly the same number of peaks and occurs at the same wavenumber [Integrated Spectral Database System of Organic Compounds (SBDS)]. The results obtained from XPS were used to calculate the atomic percentage (atomic %) of each element and comparisons were made to the theoretical atomic % (table 1). The atomic percentage at the surface of the BDP CFC-11 clathrates obtained appears to be quite different from the theoretical atomic percentage calculated for the 1:1 molar ratio of CFC-11 to BDP. It showed a 0.4:1 molar ratio of CFC-11 to BDP.

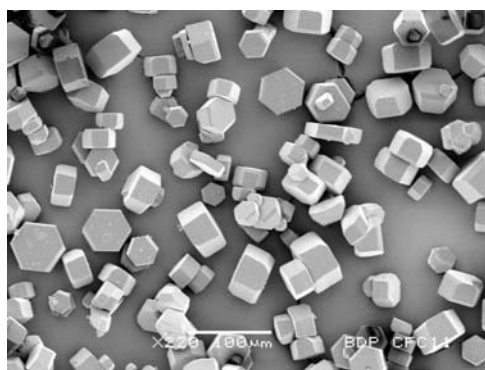


Figure 1: Scanning electron microscopic (SEM) image of BDP CFC-11 clathrate.

Atomic %	Anhydrous BDP		BDP CFC-11 clathrate	
	Theoretical	Measured	Theoretical	Measured
C 1s	77.77	81.07	70.73	75.1
O 1s	19.44	17.01	17.07	18.54
Cl 2p	2.78	1.914	9.75	5.43
F 1s	0	0	2.44	0.92

Table 1: Theoretical and measured atomic percentage of the surface analysis of anhydrous BDP and BDP CFC-11 (0.5 % w/w).

The DSC and TGA results for 1.67% w/w BDP in CFC-11 clathrates are represented in Fig. 2 and 3 respectively. Anhydrous BDP melts at 212°C which corresponds to the literature values. The magnitude of the endothermic transition seen at about 100°C can be slightly variable and is thought to be due to the release of CFC-11 from the tunnels of the clathrate structure. However, a small exothermic peak can be observed just before the endothermic peak at about 99°C which can be speculatively assigned to a solid state rearrangement of the BDP CFC-11 clathrate structure, prior to desolvation (removal of solvent/propellant from the structure). The structural rearrangement of the clathrate may lead to the opening of channels, which could allow easier desolvation of the CFC-11. The complex thermal events around the melting point observed in the DSC curves for the different samples indicate that BDP undergoes significant degradation during melting. The loss of CFC-11 from the clathrate structure is confirmed by the TGA results (Fig. 3) expressed by 14.5% weight loss which corresponds to 0.6:1 molar ratio of CFC-11 to BDP. It was found that CFC-11 was incorporated into the crystal structures obtained at different concentrations of BDP. However, the stoichiometric relationship of the clathrate is not clear. An increased molar ratio of CFC-11 to BDP is observed with an increasing concentration ratio of BDP to CFC-11 during the crystallisation stage.

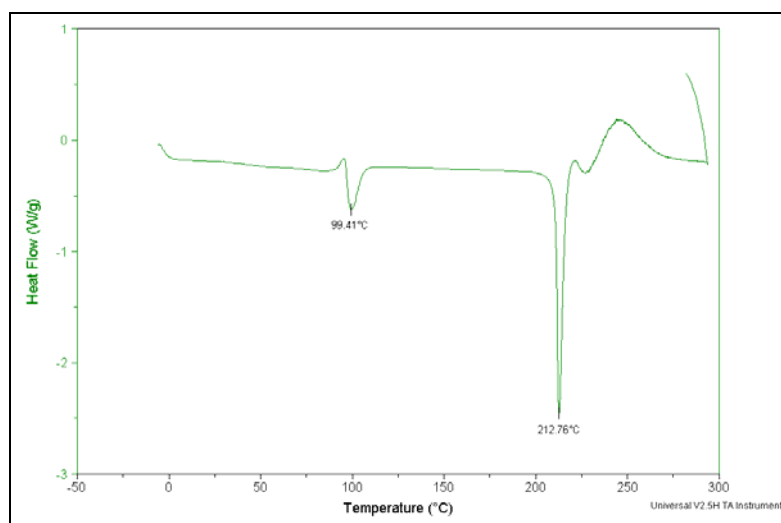


Figure 2: Differential scanning calorimetry (DSC) thermogram of BDP CFC-11 clathrate (1.67% w/w). The endotherm at 99.41°C is due to the loss of CFC 11. The drug's melting point is at 212.76°C .

This reaches a maximum at a molar ratio of 0.6:1 of CFC-11 to BDP and then decreases as the concentration increases (Fig. 4). It is not clear why this is the case, but it appears to be reproducible.

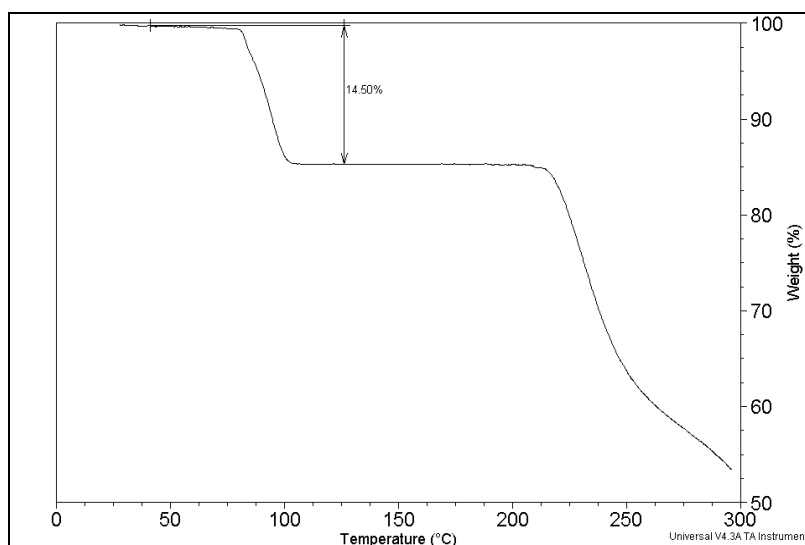


Figure 3: Thermogravimetric analysis (TGA) thermogram of BDP CFC-11 clathrate (1.67% w/w). The total loss of CFC-11 corresponds to the first endothermic peak show on Fig.1 at 99.41°C.

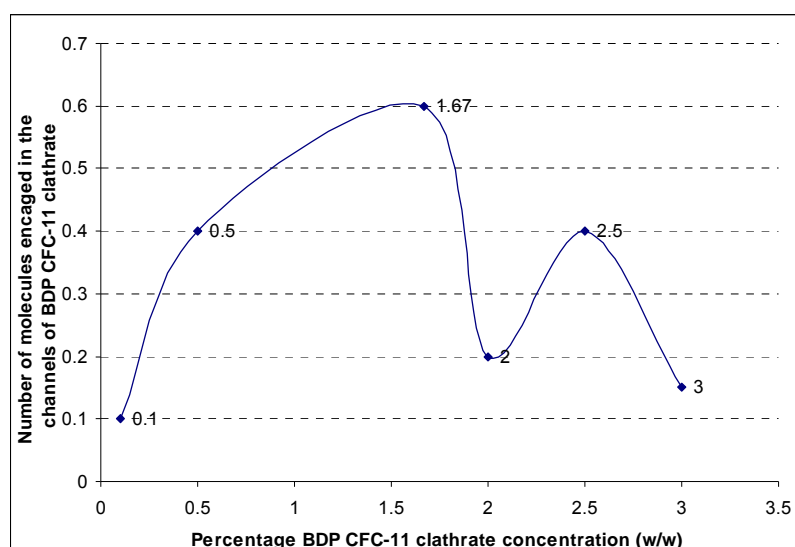


Figure 4: Stoichiometric relationship of BDP CFC-11 clathrate using the calculation of the molar ratio of CFC-11 to BDP, using results obtained from TGA.

The measured XR-PD results matched well with the calculated pattern for the BDP CFC-11 clathrate (Fig. 5) and confirmed that the majority of the BDP and CFC-11 had been crystallized into the BDP CFC-11 clathrate. However, very broad peaks can be observed starting from a 2θ value of 18.5° . This corresponds to the CFC-11 molecules present in the structure. In the calculated pattern, the software emits the presence of any molecule inside the channels. Characteristic diffraction peaks can be observed at 2θ values of $7.2, 8.5, 9.6, 11.2, 13.8, 16.8, 18.5^\circ$ for BDP CFC-11 clathrate. These peaks can be used to differentiate this clathrate form from other BDP polymorphs.

The dispersive surface free energies for anhydrous BDP (micronised) and the CFC-11 clathrate are $47.5 \pm 4.9 \text{ mJm}^{-2}$ and $11.27 \pm 4.05 \text{ mJm}^{-2}$ respectively. Investigations are currently underway to study the effect of particle size reduction on the stoichiometry of the clathrate and its surface energy. Force of adhesion results show that BDP CFC-11 clathrates have a lower F_{adh} compared to anhydrous BDP with different pMDI components (Fig. 6). The formation of the CFC-11 clathrate appears to be favourable when compared to the anhydrous form, in terms of its potential interactions within a suspension pMDI formulation. Conversely, the IPA clathrate was found to have similar or higher F_{adh} interactions than anhydrous BDP with most of the components. This could therefore have significant implications for the future development of HFA formulations with APIs that are prone to the formation of HFA-134 propellant clathrates (J.A. Harris *et al*

(2003)). The formation of a HFA clathrate may be favourable for one API but not for another. Careful choice of propellant may be prudent for such APIs. However, isolation and full characterisation of such HFA clathrates remains challenging.

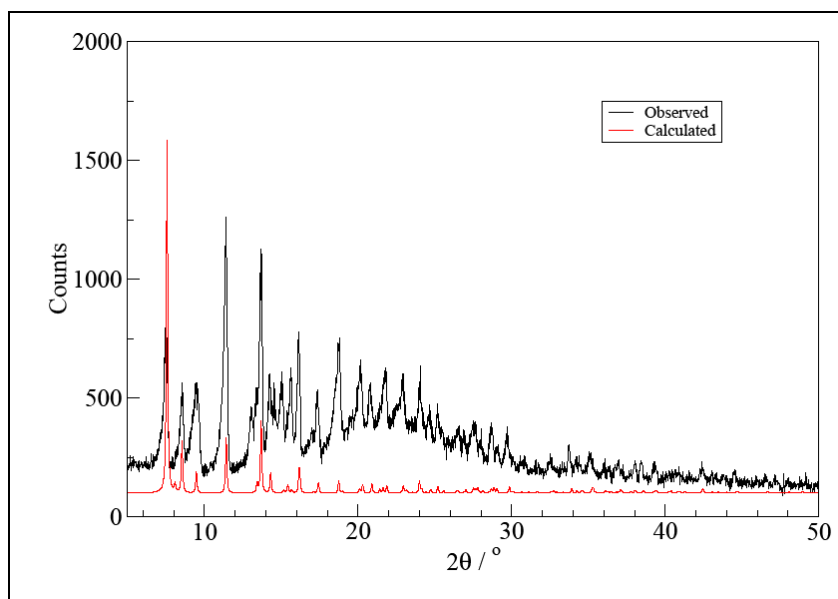


Figure 5: Superimposition of experimental BDP CFC-11 clathrate XRPD patterns with that of the calculated BDP EtOH solvate pattern without the EtOH.

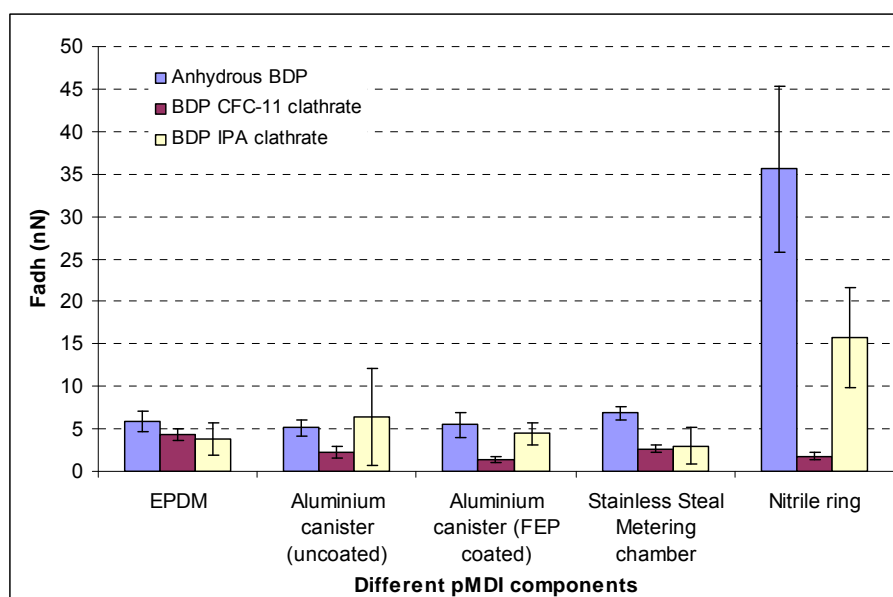


Figure 6: Fadh of BDP CFC-11 clathrate, anhydrous BDP and BDP IPA solvate with different pMDIs components, determined by AFM (*metering chamber material needs adding*).

Conclusion:

To the authors' knowledge, this is the first time that a propellant clathrate has been proven to be beneficial in terms a reduction in the Fadh with pMDI components. This could have implications for future HFA formulation development with APIs which are prone to the formation of propellant clathrates.

References:

- Vervaet, C. et al (1999), Int. J. Pharm., 186, 13-30
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