A Novel technique for determining API Solubility in Hydrofluoroalkane Propellants Using Nuclear Magnetic Resonance (NMR) Spectroscopy

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INTRODUCTION

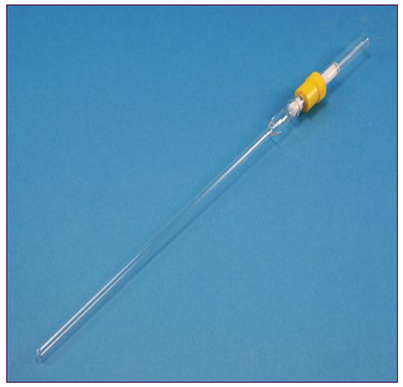
Drug solubility in propellant is a key factor in determining the formulation approach for a new active pharmaceutical ingredient (API) for use in a pressurised metered dose inhaler (pMDI). The extent to which an API is soluble in hydrofluoroalkane (HFA) propellants can dictate whether the formulator decides to develop a solution or suspension based pMDI formulation.

Determination of API solubility in propellant is problematic, the high volatility of the propellant means that measurement of API solubility in propellant must be undertaken using systems based on pressurised filtration of undissolved API from the propellant. This abstract describes a rapid new technique that has been developed to determine drug solubility in HFA using NMR spectroscopy. The Beclomethasone dipropionate - BDP generated using the method described compares favourably with data generated from pressurised filtration methods.

EXPERIMENTAL

EQUIPMENT

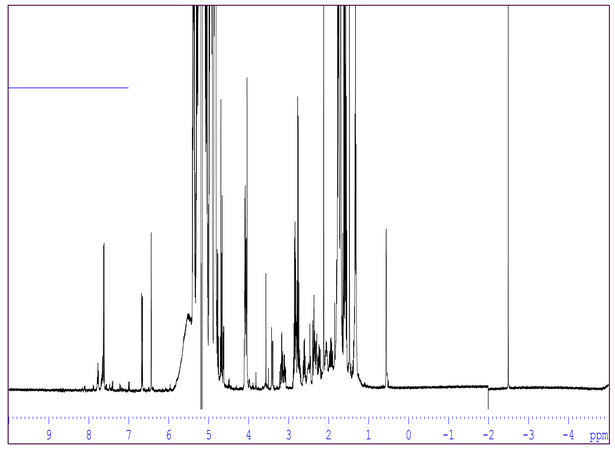
- J Young valved NMR tubes
- A Bruker Avance 500 NMR using a 5mm BBI probe.
- A standard pre-saturation pulse sequence was used to suppress the solvent signal
- an ERETIC pulse method was used for quantification
- All NMR data was recorded at 290K.
- 0.2 µm PTFE filters (ex. Sartorius, Epsom, Surrey UK)
- Bespoke leak tight housing, pressure rated to 7 bar.



- **BDP (ex. Sigma Aldrich) was transferred to a J Young tube to which HFA propellant was added by cold transfer (typical volume 1 – 2 ml).**
- **The BDP spectra was quantified by using an ERETIC pulse method (a 'standard' signal is generated electronically that is referenced externally against the normal NMR standards).**
- **The solution state NMR only detects signal from API's in solution, so the solubility of the API in a saturated suspension can be readily determined.**
- **For comparison, the solubility of BDP was determined using a pressure filtration technique.**
- **pMDIs containing four different concentrations of BDP were prepared and fitted with a constant delivery non-metered valves**
- **The samples were filtered under pressure into a receiving vessel, the HFA was then vented leaving the solubilised drug behind for re-constitution into a suitable solvent.**
- **The API content was then assayed using liquid chromatography with mass spectrometry detection.**

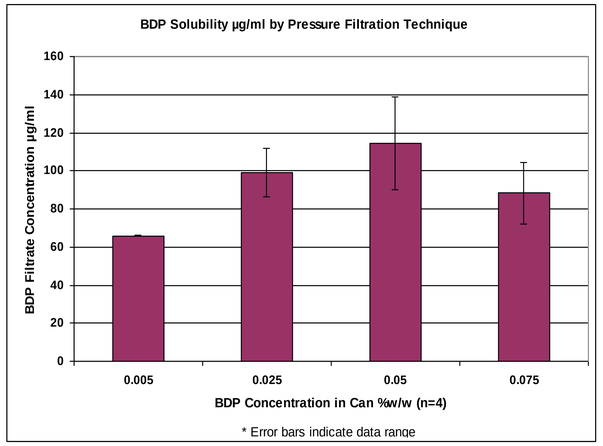
RESULTS AND DISCUSSION

BDP NMR Spectra



This spectrum shows well resolved resonances for the BDP A ring protons observed between 6 – 8 ppm, these were integrated against the calibrated ERETIC signal at –2.5 ppm. The solubility of BDP was determined to be approximately 120 µg/ml and demonstrates that the technique is sensitive enough to be applied to APIs that are sparingly soluble in HFA.

BDP Solubility by pressure filtration technique



The table summarises the results obtained by LC-MS. Maximum solubility comparable to the NMR derived value of 120 µg/ml was observed in the 0.05%w/w BDP suspension. The drop in solubility observed in the 0.075%w/w suspension (compared to 0.05%w/w) was investigated using X-ray crystallography. Differences in the diffraction patterns obtained from the 0.05% and 0.075% w/w BDP suspensions compared with the drug substance suggests that BDP-HFA solvates were being formed at higher concentrations.

CONCLUSIONS

- **Comparison of data generated by NMR and pressure filtration demonstrates that similar results were obtained using both techniques with BDP**
- **The NMR solubility method may provide a rapid alternative to pressure filtration for determination of API solubility in HFA propellants.**
- **Furthermore the method could also be used to investigate the effects of temperature, excipients, the effect of co-solvents on the solubility of API's in HFA's and might also be useful in identifying solvate formation**