MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY®
Vol. 29, No. 1, pp. 39–49, 2003

RESEARCH PAPER

HPFP, a Model Propellant for pMDIs

Philippe G. A. Rogueda*

Pharmaceutical and Analytical Research & Development,
AstraZeneca R&D Charnwood, Loughborough, UK

ABSTRACT

A novel model propellant for the study of the properties of pMDIs (pressurized metered-dose inhalers) at atmospheric pressure is proposed and extensively characterized. The reasons for the choice of this liquid, with its advantages and drawbacks, are explained and justified. Comparison with existing fluorinated propellants is also documented.

Key Words: pMDI; HFA; Model; Propellant; HPFP; 2H,3H perfluoropentane.

FOREWORD

Pressurized metered-dose inhalers (pMDIs) are used extensively in inhalation drug delivery. They consist of drug particles (although solution pMDIs can also be found) suspended in a liquefied gas stabilized by excipients. Because they are formulated with pressurized liquids, the study of their properties is made more difficult than for nonpressurized systems. Although the vapor pressure of these propellants is relatively low, typically 5 bars, it is a hindrance when wanting to fully characterize the physicochemical characteristics of these formulations. Most techniques such as surface tension, contact angle, particle sizing, Zetametry, or microcalorimetry are not commercially available for work in the pressure regime. When they are, and AstraZeneca R&D Charnwood has done substantial work to develop technical solutions to study pMDI formulations in situ, these are not as convenient to use as nonpressurized ones. Therefore, there is a need to find a model propellant, a nonvolatile liquid under normal temperature and pressure conditions, that will be a reference in which to investigate formulation properties and predict their behavior in propellants.

INTRODUCTION

The Study of pMDIs

pMDIs systems[1] consist most of the time of a drug suspension stabilized by a range of additives,

---

*Correspondence: Philippe G. A. Rogueda, Pharmaceutical and Analytical Research & Development, AstraZeneca R&D Charnwood, Bakewell Road, Loughborough LE11 2HD, UK; E-mail: philippe.rogueda@astrazeneca.com.

DOI: 10.1081/DDC-120016682
0363-9045 (Print); 1520-5762 (Online)
www.dekker.com

including surfactants and polymers, in a propellant or mixture of propellants. The system can contain further elements, such as taste-masking agents or cosolvents. The terms additive and excipient will be used indifferently in the context of this communication. The drug suspension is made up of micronized drug particles with a size range between 1 and 30 μm. The quality of the suspension is what formulators have to assess, and for which so few tools are available. Suspension quality can be characterized by a set of properties. Creaming or sedimenting speeds are common ones to look at for instance, but so are the extent and the rate of flocculation of the micronized particles, or the strength of the attractive or repulsive forces between individual particles.

The propellants currently used in the pharmaceutical industry to formulate pMDIs are HFA 227 and HFA 134a. Both are fluorinated short-chain alkanes (see their properties in Table 1, and Fig. 1 for their molecular structure). Their most important characteristics are their boiling point, vapor pressure, and chemical structure, which confer them unique properties. Both propellants can be described as perfluoro alkanes with a low degree of hydrogen substitution. The presence of the hydrogen atoms is important since the C–F bonds are very polarized, and therefore, the introduction of a less-electronegative atom will lead to a substantial modification of the molecule polarization and physical properties. The degree of hydrogen substitution and the location of the substituted atoms are paramount to the characteristics of the propellant. This will have to be taken into account when choosing a suitable model molecule.

HFA stands for Hydro Fluoro Alkane. The nomenclature of HFA propellants follows a simple rule[2]: the first number is the number of carbon atoms in the chain minus one, the second digit corresponds to the number of hydrogen atoms plus one, the third and last digit corresponds to the real number of fluorine atoms. Therefore, HFA 227 has the molecular formula C_3F_7H. A letter, to indicate positional isomers, when they exist, can sometimes follow the numbers, as in HFA 134a. The most symmetrical molecules are referenced with an "a," and suffixes increase through the alphabet with decreasing symmetry.

Before HFAs were introduced, i.e. before the Montreal protocol on substances that deplete the Ozone layer,[3] CFC (Chloro Fluoro Carbon) propellants were used in pMDIs. When pMDIs suspensions could not be studied in situ, a model propellant was used.[4,5] At the time the most suitable molecule used was P113, also known as Arklone 113 or 1,1,2-trichlorotrifluoroethane. This was not the only choice, and a few research groups preferred chloroform.[6] Both systems had the same advantages. They were well characterized, cheap, and acted as standards to describe the properties of pressurized systems. Chloroform can still be used as a model propellant, but because of its chlorine atoms, its properties are going to be substantially different from a fluorinated molecule. A new model liquid for HFAs is therefore needed.

HFA 227 HFA 134a

Figure 1. Molecular formulae of propellants HFA 227 and HFA 134a.

Table 1. Physical characteristics of propellants HFA 227 and HFA 134a.[19]

	HFA 227				HFA 134a			
Temp (°C)	Vapour pressure (bar)	Density of liquid (g/cm³)	Dynamic viscosity (mPa s)	Surface tension (mN/m)	Vapour pressure (bar)	Density of liquid (g/cm³)	Dynamic viscosity (mPa s)	Surface tension (mN/m)
10	2.80	1.446	0.324	8.22	4.15	1.262	0.239	10.07
15	3.32	1.428	0.302	7.64	4.89	1.245	0.225	9.38
20	3.90	1.408	0.267	6.96	5.72	1.226	0.2107	8.69
25	4.56	1.388	0.259	6.47	6.65	1.208	0.1974	8.02
30	5.29	1.367	0.237	5.88	7.70	1.189	0.1849	7.36
35	6.11	1.345	0.216	5.30	8.87	1.169	0.1731	6.70

There have only been a few attempts to put forward a suitable model HFA. To our knowledge there exists only one paper that made an attempt in defining a new system.[7] Dickinson et al. selected model liquids primarily on comparing excipients solubility in propellants and in model systems. Most excipients or drugs are well known to be insoluble in fluorinated liquids. Recent publications by Byron et al.[8,9] have set it in print: with the exception of a few ethoxylated and ethylene glycol compounds and their derivatives, hardly any compounds are soluble in HFAs. One can therefore legitimately ask if a selection based on solubility values is the most judicious.

Selecting a Model Propellant

The selection of a model propellant needs to be based on a scrutiny of a range of properties. This raises the question of which criteria to invoke for such a choice. If one were to measure creaming rates for instance, one would choose a fluorinated molecule with a density matched to the one of the propellant. When measuring zeta potentials, one could prefer to concentrate on dielectric constants or viscosity. For each property, a new model system would need to be called upon, and for each propellant a new substitute molecule. Although one property might be matched, another will be distorted. Densities might be matched, but the chemical structure of the model molecule might be such that it could become a suitable solvent for charged chemical groups on the drug surface to be expressed, thus triggering electrostatic forces and enhancing the suspension stability. The choice of the model propellant will need to reach a compromise, and ways to achieve it are explained below.

In their paper, Dickinson et al.[7] suggested three model systems: perfluorohexane, 1H perfluorohexane, and 2,2,2 trifluoroethanol. All of them are suitable, but can lead to errors. The choice of a perfluorinated molecule, for example, should be proscribed. Perfluorinated molecules are very different from molecules with some degree of hydrogen substitution. Their surface tension against air and water, for instance, clearly shows a strong deviation from hydrogen-substituted ones,[10] thus pointing at very different cohesion forces within the liquid, and different Hamacker constants. This would lead ultimately to unique interaction forces between particles in their midst. Molecules with some degree of oxygen substitution should also be disregarded, because, like alcohols, they are likely to have a much higher dielectric constant and may lead to surface potentials high enough to magnify electrostatic stabilization and modify substantially the characteristics of the pMDI suspension. Fluorinated alcohols should not be selected either as they will increase the solubility of the excipients.

This is why it is preferable to select a partially fluorinated alkane as a model propellant. These can also be described as perfluorinated molecules with a low degree of hydrogen substitution. In this case, the location and number of hydrogen atoms must be considered carefully. The chemical structure of the carbon chain will influence the geometry of the molecule and its ability for intermolecular bonding. This is why a perfluorinated molecule with a solitary-end hydrogen atom would not be the first recommendation. A hydrogen atom at an end position would be too accessible to external molecules, and much unlike HFA 227, with no end hydrogen atom. It would also be appropriate to keep the length of the carbon chain to a minimum to copy some of the rigidity of short HFA propellant chains. However, the chain must be long enough for the boiling point of the model propellant to be in a suitable range (ideally above 50°C to avoid rapid evaporation).

To summarize, the selection of a model propellant should follow the path below (not withstanding the need for a cheap, pure, and commercially available compound):

(i) Look for structural similarities, preferably a straight carbon chain. This rules out molecules such as perfluorodecalin and other cyclic compounds.
(ii) Select molecules with a low degree of H-substitution in the middle of the carbon chain.
(iii) Choose a short carbon chain. The molecule should have a carbon chain long enough for its boiling point to be within a workable range, but short enough to be sufficiently similar to the propellants.
(iv) Try to match the dielectric and optical properties. This, unfortunately, would remove most alcohols or carboxylic acids. The polar properties of the molecule will in turn influence the strength of the colloidal forces.
(v) Try to match the density of the propellant; hence, the need to avoid fully perfluorinated molecules.

Regardless of which molecule might be chosen, its application will be limited. A good model system for HFA 227 may not be suitable for HFA 134a. One should therefore continue to strive to develop in situ methods and adapt existing colloidal techniques to the pressure regime.

2H,3H Perfluoropentane, a Model System

A range of molecules were considered, amongst which was 1H perfluoroheptane, already described by Dickinson et al.[7] For the reasons mentioned previously, fluorinated alcohols, acids, ethers, and molecules containing oxygen atoms were not selected. The choice was therefore limited to straight alkyl chains. The best model commercially available was found to be 2H,3H perfluoropentane, abbreviated as HPFP (whose structure can be seen in Fig. 2). Its boiling point is 53°C, which makes it suitable for use under standard laboratory conditions. A summary of some common properties of propellants and model propellant has been drawn in Table 2.

HPFP is closer to HFA 227 than to HFA 134a, as can be seen from its chemical structure. A little imagination will therefore be necessary to extrapolate conclusions drawn in HPFP to that in HFA 134a. The major difference lies in the density values, since HFA 134a is lighter than both HFA 227 and the model system.

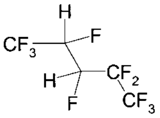

Figure 2. Molecular formula of model propellant HPFP (2H,3H-perfluoropentane).

In the following sections, a range of physical properties of HPFP have been measured and compared with those of HFA 227 and HFA 134a. These are: UV spectra, density, refractive indices, dielectric constants, surface and interfacial tensions, solubility of water, and solubility of selected excipients.

N.B.: Results on some of the studies using the model propellant have already been published at conferences.[11,12]

EXPERIMENTAL

Materials

2H,3H perfluoropentane, or HPFP (MW 252.05 $\mathrm{g\,mol^{-1}}$), was purchased from Apollo Chemicals (UK) at a purity in excess of 99.9%. Residual assay was evaluated at 99.98%, with a moisture content of 35 ppm. HPFP is stable for at least three years and is essentially nonhazardous. Supplier literature gives the following constants: m.p. −80°C, b.p. 53.6°C, $d^{25} = 1.58\ \mathrm{g\,cm^{-3}}$.

Alumina and aluminium oxide, basic and acidic, were purchased from Fluka (UK) and were of chromatographic grade.

Millipore water was used for all operations throughout this work, including all cleaning procedures.

For the solubility tests, PEG (Poly Ethylene Glycol) 600, PEG 1000, PVP K25 (Poly Vinyl Pyrrolidone), and PVP K30 were used. These are nonionic homopolymers often used in pharmaceutical formulations. The numbers 600 and 1000 refer to the

Table 2. Comparative table of some properties of propellants HFA 227 and 134a with HPFP (values for both propellants are from Solvay, Germany, while those for HPFP have been determined in this work).

	HPFP	HFA 227	HFA 134a
MW ($\mathrm{g\,mol^{-1}}$)	252.051	170.03	102.03
n_d	$^{25}1.26089 \pm 0.00008$	1.2207	1.1846
d ($\mathrm{g\,cm^{-3}}$)	$^{20}1.583$	$^{25}1.388$	$^{25}1.208$
b.p. (°C)	53.6	−16.5	−26.3
m.p. (°C)	−80	−131	−101
ε	$^{25}15.05$ at 18.66 kHz	$^{20}4.071_{(3.9\ \mathrm{bar})}$	$^{24}9.46_{(4.5\ \mathrm{bar})}$
γ($\mathrm{mN\,m^{-1}}$)	$^{20}13.59$	$^{20}7.55$	$^{20}8.69$
η (mPa s)	$^{20}0.537$	$^{20}0.266$	$^{20}0.211$
Water solubility	$^{23}390_{\pm 40}$ ppm	$^{25}610$ ppm	$^{25}2200$ ppm

molecular weights of the molecule (600 is for 570 to 613 g mol^{-1}, and 1000 is for 950 to 1050 g mol^{-1}), while K25 and K30 refer to viscosity and indirectly reflect the bi-nodal molecular weight distributions (PVP K25: 28,000 to 34,000 g mol^{-1}, PVP K30: 44,000 to 54,000 g mol^{-1}). The polymers were of industrial grade suitable for pharmaceutical applications.

TECHNIQUES

UV Spectroscopy

A Lambda II UV-vis spectrometer from Perkin Elmer (UK) was used to record the UV spectra of the propellants and model propellant. The spectrometer was kept in a temperature-controlled room at 22°C. The spectrometer was calibrated before use for both wavelength accuracy and absorbance. One-centimeter quartz cells were used for the model propellant. These were cleaned as for surface-tension measurements. The liquid was poured in the cells with no further filtration. An empty cell was placed in the reference beam.

UV-vis spectrum of HFA 227 and HFA 134a were taken in purpose-made pressure cells. These were made out of black acetal with 3-mm thick quartz windows. The path length of the cell was calibrated with ethanol. The same cell was used as a reference and for the propellants. The cell contribution was then subtracted from the propellant spectrum. The propellants were transferred under pressure.

Density

Density measurements were performed on a DA-100M from Mettler Toledo, with which the density is measured with an accuracy of 0.001 g cm^{-3}. The DA-100M relies on crystal vibration to measure the density of liquids. It was calibrated with both air and water at 20°C. The temperature was controlled with a Peltier. The model propellant and densitimeter were located in a temperature-controlled incubator and the model propellant was left to equilibrate at the required temperatures for at least 30 min before measurements were taken. The experiments were repeated at least twice for each temperature.

Refractive Index

Refractive index measurements were performed on an Abbe 60/LR refractometer (UK) fitted with a Grant water bath. The light source was a sodium lamp at 589.6 nm. The instrument was calibrated with water after a 30-min stabilization time. Measurements at each temperature were performed five times on reapplication of the sample and averaged. The refractive index accuracy was down to the fifth decimal place.

Dielectric Constant

Dielectric-constant investigations were performed over a frequency range of 106 to 10^{-2} Hz using a BDC-N broad-band dielectric converter (Novocontrol GmbH, Germany) and a SI 1255 Frequency Response Analyzer (Solartron-Schlumberger, Germany) linked to a Quatro temperature-control system (Novocontrol GmbH, Germany). A parallel plate sample cell with stainless-steel electrodes of area 254.5 mm^2 and separation distance 1.5 mm was used for all measurements. The applied voltage was 0.5 V r.m.s. Sample temperature was controlled to ±0.1°C. Following temperature equilibration, measurements were made at 5°C, 15°C, 25°C, 35°C, and 45°C as the temperature was decreased. The sample temperature was reduced at a rate of 2°C/min between measurement temperatures. Temperature calibration of the cryostat was performed electronically. Excellent reproducibility was found between repeat spectra.

Surface and Interfacial Tension

Surface-tension measurements were performed on the Tracker from ITconcept (France). It is akin to an asymmetric drop-analysis system.[13] The temperature was controlled by a water bath (Grant LTD 6 G), and measured directly in the measuring chamber. The whole equipment was itself in a temperature controlled room. The temperature was found to be stable at 20.00 ± 0.01°C. Temperature equilibrium times of at least 30 min were respected. Experiments were carried out typically over 15 min, and the tension values were then averaged over the whole time span. The water used in the interfacial experiments was fresh millipore water. Glassware was cleaned by successive ultrasonic cleaning in hot Decon 90 solutions and diluted nitric acid solutions, followed by thorough rinsing with millipore water, and dried either with N_2 or by heating. To avoid evaporation, the experiments were carried out with water in the upper phase, and dropping bubbles were observed. The surface-tension values could then be recorded with an accuracy of ±0.05 mN/m.

Solubility of Water

Water content was measured by coulometric Karl Fisher titrimetry method with a Mitsubishi CA06. Karl Fisher titrimetry is an accurate moisture measurement utilizing the quantitative reaction of water with iodine. Measurements were performed on three aliquots of model propellant at room temperature (22°C). Equilibration times of 15 min were observed.

Solubility Tests of Selected Excipients

The solubility of the polymers in the propellants and the model propellant were evaluated by visual observations and UV spectroscopy.

The visual method was based on the preparation of known sample concentrations in clear vials. These were glass vials with screw-on caps for the model propellant and clear plastic vials (PET vials from Createchnic, Germany) with crimped continuous valves for the propellants. The samples were left to equilibrate for a couple of days before observations were recorded. This method was useful for solubilities of the order of a few % w/w, and for the PEG polymers in particular.

The solubility of the compounds could be determined with higher accuracy in the model propellant by UV detection. This method could only be applied to PVP polymers, which have a chromophore. Vials of known concentrations of the polymers were prepared by weighing. Saturated samples were also prepared. After a couple of days of equilibration, the solutions and suspensions were filtered with a 2 μm PTFE filter. The solutions thus obtained were analyzed at 212 nm. The solubility point was measured at the break in the Absorbance-vs.-concentration curve.

The solubilities were determined at room temperature, $T = 22^\circ$C.

RESULTS

Purity of HPFP

The purity level of commercial HPFP may be limiting in certain situations, particularly when engaging in surface tension or contact-angle studies. Further purification can be achieved with aluminium oxide powders, in particular, acidic aluminium oxide. A good purification method is the one devised by Goebel and Lunkenheimer.[14] Known quantities of HPFP are dispensed in clean glass vials. The oxide powder is then added to the liquid (up to 50% volume). The system is sealed, and left to be agitated for at least 45 min at room temperature. The vials are then left to stand for the oxide to sediment. The supernatant phase is subsequently sampled and any remaining oxide powder removed by filtration over a 0.2 μm PTFE filter. In this work, a disposable syringe filter unit was used (Autovial from Whatman, UK). This cleaning method proved very effective and is best evidenced from dynamic interfacial-tension measurements against water. When impurities are present in an organic liquid, they migrate quickly to the water-liquid interface to modify the value of interfacial tension over a short period of time. A pure liquid, however, will have a stable interfacial tension with time.

Figure 3 shows the dynamic surface-tension profiles of commercial and cleaned HPFP. Dynamic interfacial-tension measurements were performed against fresh millipore water on the Tracker. Commercial HPFP shows a characteristic interfacial-tension decrease with time due to the presence of impurities whereas cleaned HPFP has a flat interfacial-tension curve. The impurities could be unreacted organic compounds from the preparation of the HPFP, or more probably isomers of HPFP. These impurities have a very low concentration and may not be an issue for most experiments.

UV Spectroscopy

The UV-vis spectrum for HPFP can be found in Fig. 4, alongside those of HFA 227 and HFA 134a. The absorbance on the HFAs spectra have been normalized to a 1 cm cell.

The three spectrum were rather similar with no features above 300 nm. Below 300 nm, 134a is the only one with a notable peak at 262 nm. The flat

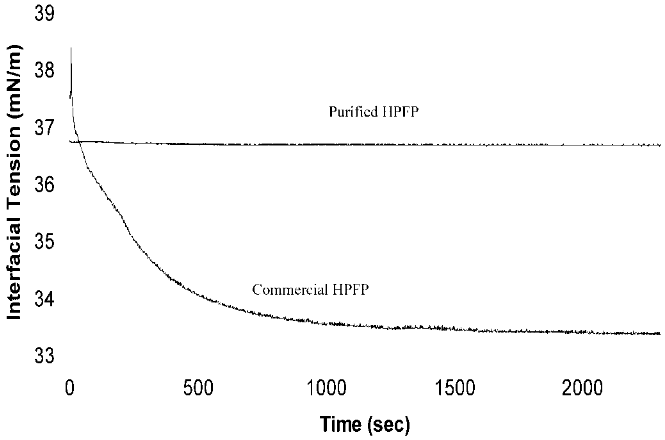

Figure 3. Interfacial tension of commercial and purified HPFP against water at $T = 20^\circ$C.

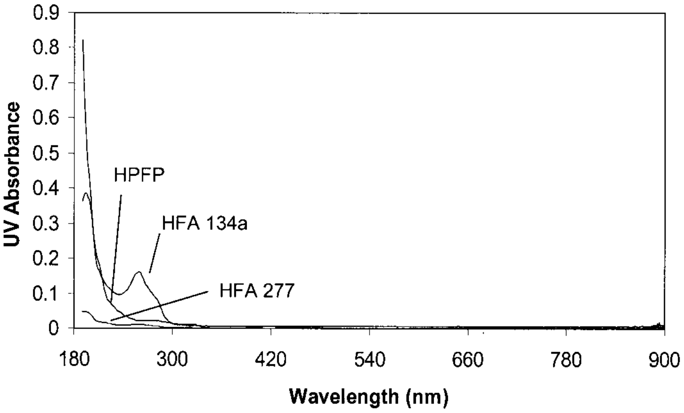

Figure 4. UV spectra of HPFP, HFA 227, and HFA 134a in a 1-cm quartz cell at room temperature.

UV-vis traces make the three compounds highly suitable for spectroscopic studies of drug materials, which typically have spectroscopic features above 300 nm. More importantly, HPFP is very similar to the propellants.

Density of HPFP

The density of the model propellant was measured over a range of temperatures. The density values are commensurate with those usually given for fluorinated systems. They span from 1.556 g cm^{-3} to 1.609 g cm^{-3} as shown in Table 3. These values are higher than for HFA 227 and HFA 134a. The density decreases with increasing temperature and can be modelled by the following linear relationship:

Table 3. Density of the model propellant compared with propellants as a function of temperature (units: g cm^{-3}).

Temp (°C)	HPFP	HFA 227	HFA 134a
15	1.609	1.428	1.245
20	1.598	1.408	1.226
25	1.583	1.388	1.208
30	1.570	1.367	1.189
35	1.556	1.345	1.169

$$d = -0.0027T + 1.65$$

where d is the density in g cm^{-3} and T the temperature in Celsius. For HFA 227, the gradient is -0.0041, while for HFA 134a, it is -0.0038. Both are steeper than HPFP, but not so different. Knowing the density values, it is possible to use the model propellant as a substitute for true propellants in phase-separation experiments and correct for any discrepancies arising from the difference.

Surface Tension

Surface and interfacial tensions against water were measured for a selection of temperatures with the Tracker from ITConcept. The measurements were performed between 10°C and 35°C (see Table 4). These can be compared with literature values for both propellants, as listed in Table 1.

Before testing, HPFP was purified with acidic alumina, as described in the purity section previously. To check for trace impurities, measurements were performed in the dynamic mode over at least 15 min. HPFP was considered cleaned when the surface-tension curve showed no variation with time.

The surface-tension values for HPFP are higher than for both propellants. HPFP is therefore more cohesive a liquid than HFA 227 and HFA 134a. However, this does not affect substantially its ability to wet surfaces. It still has very good wetting properties akin to those of the propellants. It is generally accepted in surface-tension science that below 15/20 mN/m, any surface-tension reduction has little effect on macroscopic properties such as wetting or ability to form emulsions. Therefore, the model propellant is a good substitute for the propellants as far as surface tension is concerned.

The interfacial tensions against water cannot be compared with literature values since these are not available yet. They point to strong interaction between water and the fluorinated liquid, akin to a form of hydrogen bonding, due to the polarization of the C–F bond. These interfacial tensions cannot be modelled by traditional alkane-based theories.[15,16] This is further evidence of the influence of fluorine atoms on the polarity of fluorinated molecules, and their interactions with other molecules.

Table 4. Surface tension and interfacial tension vs. water for HPFP as a function of temperature.

Temp (°C)	Surface tension γ (mN/m)	Interfacial tension γ_i, (mN/m)
10	14.20	36.18
15	13.90	35.94
20	13.59	35.70
25	13.32	35.47
30	13.02	35.29
35	12.08	35.12

Solubility of Water

Water is only sparingly soluble in fluorinated liquids. Pure HPFP has a very low water content, of the order of a few ppm. The saturation level for water is slightly higher than that. To assess it, HPFP/water mix solutions were prepared and agitated at room temperature for a couple of days. The water content was then measured by the Karl Fisher method with the Mitsubishi CA06. The maximum solubility was found to be 390 ± 40 ppm. Literature values for water content of the propellants give HFA 227, 610 ppm at 25°C, and HFA 134a, 2220 ppm at 25°C.

The model propellant is drier than the propellants themselves. This, of course, will have some effect on the properties of drug suspensions since water is known to destabilize pMDIs suspensions.[17]

Refractive Index

The refractive index variation with temperature can be found in Table 5. The corresponding linear regression is

$$n_D = 1.272_{708} - 4.7_{32} \times 10^{-4} T$$

where T is the measuring temperature in °C and n_D is the refractive index at 589.6 nm. The relationship is valid for the temperature range studied, i.e., $20.0°\mathrm{C} \leq T \leq 40.0°\mathrm{C}$.

Table 5. Refractive index variation of HPFP as a function of temperature.

Temperature (°C)	Refractive index n_D
20.0	1.26325 ± 0.00007
25.0	1.26089 ± 0.00008
30.0	1.25848 ± 0.00005
35.0	1.25615 ± 0.00005
40.0	1.25379 ± 0.00009

The refractive index of the propellants are not known with accuracy. The refractive index for HFA 227 has been measured by Solvay Fluor GmBH as $n_D = 1.2207$ and the one for HFA 134a estimated as $n_D = 1.1846$. The refractive index of the model propellant is therefore in the expected range for fluorinated liquids, close enough to the one of HFA 227. These values are useful for optical studies, and sizing by laser diffraction in particular. Knowledge of the value for the model system and its deviation from the propellants is useful for study comparison.

Dielectric Constant

The dielectric constant of the model propellant was measured for a range of temperatures. Values can be found in Table 6. There was no evidence of electrode polarization and responses corresponded very well to an ideal resistor-capacitor system whereby both dielectric constant and conductance were frequency independent. This constant response is a good omen for zeta potential measurements, and a clear indication that the variation of an electric field (as in zeta potential measurements) will not modify the liquid properties. The dielectric constants are found to decrease with increasing temperature and to increase slightly as the frequency decreases.

The dielectric constant of the model propellant is higher than that of both HFA 227 ($\varepsilon^{20} = 4.071$) and HFA 134a ($\varepsilon^{20} = 9.46$). This will have an influence on the electrostatic stabilization of drug suspension and will modify accordingly the value of the measured zeta potentials. However, the ability of a solvent to express charged-surface groups is not directly linked to its dielectric constants. Measurements of zeta potentials of suspended drug particles in model propellant and propellants have indicated that mobilities are not affected by these changes (internal AZ work yet unpublished).

Solubility of Selected Compounds

The solubilities of the homopolymers have been summarized in Table 7 for four polymers in the propellants (HFAs 227 and 134a) and in the model propellant. The polymers were PEG 600, PEG 1000, PVP K25, and PVP K30.

The PEG 600 has a fairly high solubility in HFA 227, above 44% w/w. Its solubility is more restricted in HFA 134a, in which the limit was found to be between 4.49% w/w and 4.6% w/w. In the model propellant, its solubility is between 47.6% w/w and 51.6% w/w. This value is much closer to the one found in HFA 227 than in HFA 134a. It is to be noted that above the solubility limit quoted, PEG

Table 6. Dielectric constant variations of HPFP as a function temperature and frequency.

	Temperature (°C)				
Frequency (kHz)	5	15	25	35	45
100.00	16.14	15.51	14.90	14.37	13.86
57.14	16.15	15.54	14.92	14.41	13.92
32.65	16.21	15.58	14.97	14.47	13.98
18.66	16.37	15.64	15.05	14.52	14.08
10.66	16.37	15.72	15.14	14.64	14.16
3.48	16.56	15.90	15.32	14.80	14.29
1.00	16.92	16.43	15.69	15.17	14.30

Table 7. Solubility of selected pharmaceutical excipients in propellants and HPFP at 22°C.

	PEG 600	PEG 1000	PVP K25	PVP K30
HFA 227	44 < < 46% w/w	13.43 < < 14.19% w/w	< 0.05% w/w	< 0.05% w/w
HFA 134a	4.485 < < 4.599% w/w	4.519 < < 4.641% w/w	< 0.05% w/w	< 0.05% w/w
HPFP	47.55 < < 51.59% w/w	1.28 ± 0.11% w/w	113 ± 6 ppm	2700 ± 700 ppm

600 forms an oily phase, i.e., the solubility limit is more akin to a consolute boundary usually found with short-chains PEO than a true solubility limit.[18] It is more accurate to describe it as a phase boundary. Below this limit the system is monophasic, above it, it is biphasic, made of a diluted PEG solution and a more concentrated one in equilibrium.

The PEG 1000 has a more limited solubility range than PEG 600. The solubility limit is detected here by the presence of swollen PEG 1000 particles in the propellant. The phase separation observed for PEG 600 is not present. In HFA 227, its solubility is between 13.43% w/w and 14.19% w/w. In HFA 134a, it lies between 4.519% w/w and 4.641% w/w. Finally, in HPFP it was evaluated at 1.28 ± 0.11% w/w. Therefore, PEG 1000 is less soluble in the propellants than PEG 600, and this difference is even more accentuated in HPFP.

The PVP K25 has a low, but defined solubility in both HFA 227 and HFA 134a. The solubility was noted to be less than 500 ppm. In HPFP, its solubility was 113 ± 6 ppm. This is commensurate with the propellant results.

Similarly, PVP K30 has a low, but defined solubility in both propellants and its solubility is less than 500 ppm. Its solubility in HPFP, however, is higher than for PVP K25, at 2700 ± 700 ppm.

This succinct solubility study, of some important pharmaceutical excipients, shows that HPFP is a good model for the propellants. Although not identical, solubilities are close enough for HPFP to be considered a suitable model system.

CONCLUSIONS

The properties of the model propellant discussed in this paper are very similar to the ones of the propellants. They have been extensively characterized and therefore make HPFP a useful model system to study pMDIs properties when characterization methods cannot be adapted to the pressure regime. HPFP is not only suitable for its structure but also because it is now very well characterized, and suspension properties can be fully investigated and interpreted.

As a short linear partially fluorinated liquid, it is a very good model for HFA 227. It can also be used to replace HFA 134a for study purposes, although its properties are somewhat different. The property differences are known, therefore extrapolation to HFA 134a systems is made easier than for model systems with unknown properties.

HPFP is a highly suitable model propellant to be used in the study of medicinal pMDIs. As demonstrated, it is not the only one that could have been chosen, but it is a very good compromise while pressure techniques are being developed to study drug suspensions in situ.

REFERENCES

1. Ganderton, D.; Jones, T. *Drug Delivery to the Respiratory Tract*; Ellis Horwood Series in Biomedicine1, 1987.
2. Banks, R.E.; Tatlow, J.C. Organofluorine chemistry: nomenclature and historical landmarks. In *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R.E., Tatlow, J.C., Smart, B.E., Eds.; Plenum Press: London, 1994.
3. Montreal protocol on substances that deplete the ozone layer. *1998 Report of the Aerosols, Sterilants, Miscellaneous Uses and Carbon Tetrachloride Technical Options Committee*; UNEP: New York, 1999.
4. Bower, C.; Washington, C.; Purewal, T.S. Characterisation of surfactant effect on aggregates in model aerosol propellant suspensions. J. Pharm. Pharmacol. **1996**, *48*, 337–341.
5. Clarke, J.G.; Wicks, S.R.; Farr, S.J. Surfactant mediated effects in pressurized metered dose inhalers formulated as suspensions. I. Drug/surfactant interactions in a model propellant system. Int. J. Pharm. **1993**, *93*, 221–231.
6. Sidhu, B.K.; Washington, C.; Davis, S.S.; Purewal, T.S. Rheology of model aerosol suspensions. J. Pharm. Pharmacol. **1993**, *45*, 597–600.
7. Dickinson, P.A.; Seville, P.C.; McHale, H.; Perkins, N.C.; Taylor, G. An investigation of the solubility of various compounds in the hydrofluoroalkane propellants and possible model liquid propellants. J. Aerosol Med. **2000**, *13* (3), 179–186.
8. Blondino, F.E.; Byron, P.R. Surfactant dissolution and water solubilization in chlorine-free liquefied gas propellants. Drug Dev. Ind. Pharm. **1998**, *24* (10), 935–945.
9. Vervaet, C.; Byron, P.R. Drug-surfactant-propellant interactions in HFA-formulations. Int. J. Pharm. **1999**, *186*, 13–30.

10. Jasper, J.J. The surface tension of pure liquid compounds. J. Phys. Chem. Reference Data **1972**, *1* (4), 841–1010.
11. Boswell, S.; Esan, L.; Rogueda, Ph. Phase separation of non-aqueous solid dispersion. *Drug Delivery to the Lungs*; London, 1998.
12. Rogueda, Ph. The water fluoroalkane interface. *Euresco*, European Science Foundation Conference, Aghia Pelaghia, 1999.
13. Benjamins, J.; Cagna, A.; Lucassen-Reynders, E.H. Viscoelastic properties of triacylglycerol/water interfaces covered by proteins. Colloids and Surfaces A **1996**, *114*, 245–254.
14. Goebel, A.; Lunkenheimer, K. Interfacial tension of the water/*n*-alkane interface. Langmuir **1997**, *13*, 369–372.
15. van Oss, C.J.; Good, R.J.; Chaudhury, M.K. The role of van der Waals forces and hydrogen bonds in hydrophobic interactions between biopolymers and low energy surfaces. J. Col. Int. Sci. **1986**, *111*, 2.
16. Fowkes, F.M. Attractive forces at interfaces. Industrial and Engineering Chemistry **1964**, *56*, 12.
17. Sciarra, J.J.; Cutie, A.J. The theory and practice of industrial pharmacy. In *Pharmaceutical Aerosol*; Lachman, L., Lieberman, H.A., Kanig, J.L., Eds.; Lea & Febiger: Philadelphia, 1986; p. 603.
18. van Os, N.M.; Haak, J.R.; Rupert, L.A.M. *Physico-chemical Properties of Selected Anionic*, *Cationic and Non-Ionic Surfactants*; Elsevier: London, 1993.
19. Solkane refrigerants characteristics. version 2.009.99. CD ROM available from Solvay Fluor und Derivative GmbH, Technical service, PO Box 220 30002, Hanover, Germany.