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Novel hydrofluoroalkane suspension formulations for respiratory drug delivery

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Due to the poor solvent properties of hydrofluoroalkanes, suspension is often the only formulation option for respiratory drug delivery. Research in this area has focussed mainly on two main themes over the past 5 years: new design of stabilisers and particle engineering. Among the most important advances, the introduction of secondary particulate systems and the establishment of porous particles as a viable delivery system must be mentioned. Other noteworthy developments include new classes of stabilisers and surface tailoring approaches. Work has been underpinned by new theoretical insights, via the introduction of atomic force microscopy to measure particle interactions, and the development of the surface tension component approach to predict them. Future areas of development include the formulation of nanoparticles and of non-inhalation therapies in non-pressurised hydrofluoroalkanes. All these aspects are reviewed in this article.

Keywords: drug delivery to the lung, formulations, HFA, inhalation, non-aqueous, pMDI, suspension

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1. Introduction

Over the past 5 years, the formulation of hydrofluoroalkane (HFA) drug delivery products has come a long way from the empirical approach that prevailed when they were introduced into the field of pressure metered dose inhaler (pMDIs). The move from chlorofluorocarbons (CFCs) to HFAs was nothing short of a technological revolution. It is often out of necessity that the best inventions stem. It is, therefore, of no surprise that it is thanks to the particularly difficult properties of HFAs that ingenious technological developments have come to light. Particle engineering (e.g., porous particle formation and surface modification) and excipient design are just two examples that ought to be mentioned.

Novel HFA suspension formulations have attempted to remedy some of the known problems of HFA suspensions; these include fast phase separation time (sedimentation and creaming), aggregation and particle growth, aerosolisation properties and drug losses via device adhesion.

In addition to practical developments, the theory of HFA formulation has been refined, albeit at a different pace. Because of the nature of the driving force behind these developments (i.e., product development and the need to have products on the market), theoretical understanding has often been neglected at the expense of faster and more daring inventions. Theoretical explanations are borrowed from the field of colloid and surface science but are often not sufficiently developed to include the specificities of HFA systems, namely the properties of fluorine atoms.

HFA inhalation suspension formulations are usually based on two liquids, namely propellants HFA 227 and HFA 134a (these are gases at room temperature and pressure, and are maintained in the liquid state by pressurised storage). Pittroff *et al.* [1] recently identified 21 inhalation products that use HFAs, six of which are formulated with HFA 227 and 15 with HFA 134a. Of these, 10 are solution formulations

and 11 are suspensions. Most of the solution formulations comprise ethanol, whereas suspension formulations are more inventive. There is little difference in the delivery performance between optimised formulations based on either HFA 227 or HFA 134a [2], although some differences had been observed with the selection of CFC propellants [3]. In addition, there is no therapeutic efficacy difference between formulations based on the two propellants, or even between solutions and suspensions [4]. Both propellants have pros and cons that can be remedied. HFA 227 has the lower vapour pressure and can lead to a marginally larger droplet size distribution, which can subsequently lead to a bigger mass median aerodynamic diameter. Particle diameters can be reduced for HFA 134a due to its higher vapour pressure; however, the downside is higher oropharyngeal deposition by impact due to the higher velocity of the particles. Both effects tend to lower the fine particle fraction (FPF), and are comparable in their adverse influence.

One of the criticisms levied against suspension formulations is the dose upper limit they can deliver. Weers *et al.* made this point in a recent publication [5]. Assuming a 100 µl valve for a 5% weight-in-weight (w/w) suspension concentration, and with an overall delivery efficiency of 10%, the maximum theoretical dose that could be delivered by a pMDI would be 500 µg/dose. Experimental tests on the upper limit of delivery of pMDIs were published by Kotsokechagia *et al.* [6] and Hartman *et al.* [7,8]. In both cases, a maximum dose delivered seemed to be reached regardless of bulk concentration. A fine particle dose of 600 µg was reached in the case of a micronised drug suspended in either HFA, and 300 µg for Pulmospheres™ particles (porous particles) in HFA 134a. The reason for reaching an apparent plateau (at least over the concentration range studied) is unclear. It may be due to primary particles aggregation (as suggested by Gonda [9]), modification of aerosol properties as a function of drug content leading to low velocity of the sprays and high deposition in the throat, or some other reason that remains to be elucidated. These limits, if real, could be increased by the use of larger metering valves but they will, in turn, modify the flow properties of the HFA propellants, and may require substantial design modifications to retain their performance (FPF and dose uniformity).

Another way to improve the delivery of pMDIs and increase the dose delivered is by reducing losses (i.e., increasing the fine particle dose by refining the targeting of relevant delivery sites), or reducing device losses. This has been achieved to an extent by the use of porous particles, such as those developed by Alkermes [10] and Nektar [11]. FPFs as high as 70% have been reached, and there are no reasons why higher levels cannot be attained.

This review will cover all HFA formulations: with or without excipients, those that make use of tailored particles and those that do not. After a brief reminder of the state of the art non-aqueous colloid theories applicable to HFA suspensions, the latest advances in the formulations of micronised HFA suspensions will be reviewed; in particular, the design of new excipients and secondary particulate systems. Particle tailoring to improve HFA suspension characteristics will then be studied. Finally, the cases of microemulsions and nanoparticle formulations will be examined. The surface treatment of devices will not be covered in this review, even though they help improve delivery and prevent particulate adhesion.

So far, HFA respiratory drug delivery has been understood as HFA aerosols, (i.e., pMDIs). In fact, drug delivery with HFAs has a broader meaning. HFAs are hydrofluoroalkanes; therefore, this category of liquids includes non-pressurised liquids such as perfluorooctyl bromide (PFOB) and perfluorodecalin (PFD). These have been used extensively for pulmonary liquid ventilations [12], and more recently have been reviewed as delivery vehicles for systemic treatments via the lungs [13]. Most of the drug compounds that have been delivered via PFD and PFOB have been formulated as microemulsions or suspensions. Much can be learned from these formulations, mostly because they are non-pressurised and can be easily studied by conventional investigation tools.

2. Non-aqueous suspensions: the latest theories

The best summary of interaction theories in HFAs is given by Johnson [14]. It is a review for non-specialists of interactions in inhalation products. In short, particle interactions in HFAs are governed by attractive van der Waals forces. These can be overcome by repulsive forces such as electrostatic forces or steric forces and lead to stable suspensions. Expressions for van der Waals forces, are well known and can be found in most colloid textbooks [15].

The relevance of electrostatic forces in non-aqueous liquids, or in liquids with low dielectric constants and low conductivity, is still a controversial point. Non-aqueous formulations are known to be able to carry charges. Charges can stem from the dissociation of surface groups on particles surfaces, or can result from the adsorption of charged species on the particle surface. Charges on the surface of inhalation drugs have been measured by Washington [16] and Vincent [17] in CFCs. Measurements were reproducible, and corresponding zeta potentials were much higher than in aqueous systems (e.g., lactose in trichlorotrifluoroethane was -33 mV, and salbutamol sulfate in dry chloroform was 55). Fowkes *et al.* [18] suggested that large zeta potentials (e.g., > 50 mV) could yield stable systems, and established that stability ratios of $\geq 10^8$ associated with energy barriers > 25 kT were common in non-aqueous systems. However, the relationship with suspension properties is not clear. The author's measurements [19,20] on a series of inhalation drugs in HFAs yielded equally high potentials (33 mV for salbutamol sulfate in model propellant 2H, 3H decafluoropentane [HPFP] [21], 75 mV for formoterol fumarate dihydrate [FFD] in HPFP and 20 – 40 mV for FFD in dry HFA 227), yet did not necessarily lead to suspensions with improved stability. Therefore, the relevance of these high

potentials is questionable. Furthermore, experimental evidence from AFM measurements [28] between micronised drugs in HPFP failed to highlight any form of long-range electrostatic repulsion. Often, the reason put forward for this is that the very long and overlapping electrical double layers in low dielectric constant liquids leads to very weak electrostatic repulsions. More recent data from Jones *et al.* [22] yielded high zeta potentials for micronised steroid particles in methyl trifluoroacetate, perfluoropentane and dichloromethane from 40 to 100 mV. These potentials could be modulated by the presence of polymers on the particle surface, and even inverted (neither the nature of the polymers nor the particle nature were stated in the publication). They failed to find a tangible link between zeta potentials and stability. There could be several reasons for this, other than the theoretical one previously given. Measuring zeta potentials in non-aqueous liquids is a difficult task; commercial instruments assume that the zeta potential theory developed for aqueous solution is valid for non-aqueous solutions. Furthermore, the purity of the non-aqueous liquids is often overlooked. There is no mention of it in any of the publications referenced so far. Traces of impurities can have a dramatic effect on surface potentials, and can lead to wide variations between measurements. To add to the complications, it is difficult to calculate the extent of the electric double layer in non-aqueous liquids; hence, the application of zeta potentials as predictive tools for stability is subjective. The origin of surface charges in HFAs is yet to be elucidated. Current theories indicate that surface charges would stem from the dissociation of surface groups, or from the absorption of charged species on the particle surface. For surface groups to be expressed, the corresponding chemical entities must be soluble in the suspending medium. Ionic functions are rarely soluble in HFAs; therefore, charges may not be expressed. Surface adsorption may be possible but this would again require that the ionic species be soluble (even in very low quantities) in the HFAs. Solubility measurements on a series of molecules have shown that solubility in HFAs can be measured [23,24] and may be very low (ppm level). So far, no investigation has looked at the relationship between very low solubilities and zeta potentials in HFAs, although this could be the key to understanding their genesis. The relationship between bulk zeta potentials and aerosol charging is even more difficult to understand. No link has been found between suspension bulk properties (such as zeta potentials) and aerosol charge, despite the interesting results published by Chan [25,26] and Peart [27].

The last, and probably most important force, is steric repulsion. This is traditionally understood to come from the exclusion volume effect (entropic in nature) between polymer chains absorbed on particles surfaces, which has been evidenced with non-ionic polymer chains in HPFP [28]. The attraction between micronised particles can be substantially reduced by the addition of polymers.

Water is well known to influence the forces of interactions. Its mode of uptake has been well documented by Miller [29]. Its influence on dose delivery (i.e., dose reduction) has been thought to be due to Ostwald ripening. There is some evidence to support such a hypothesis in the paper by Miller, and in a recent publication by Berry *et al.* [30]; however, for drugs insoluble in water, it is unlikely to be the main reason. It is interesting to note that adding water addition to non-aqueous suspensions does not systematically lead to destabilisation. Indeed, as in the work of Malbrel and Somasundaran [31], who studied alumina suspended in cyclohexane with aerosol OT (dioctyl sodium sulfosuccinate), water first increased the stability of the suspension (by reducing its settling rate), before destabilising the suspension and restabilising it at higher water content. A similarly odd behaviour has been observed for the zeta potential of a micronised FFD suspension in HFA 227 with water content between 11 and 20 ppm, for which the zeta potential increased from 20 to 75 mV as water content increased [19]. This is contrary to the knowledge that HFA suspensions are destabilised by water; however, data to determine if this zeta potential increase led to increase stability was not reported. Recent work by Paul *et al.* [32] has shown how water can separate out silica particles suspended in HPFP with polymers. This work seems to indicate that the destabilisation mechanism is due to some specific polymer–water phase behaviour. Depending on the drug solubility, the presence or not of stabilisers, water may express charges on particle surfaces and enhance repulsive forces, or act as a flocculation bridge, a protective layer, or even form separate phases with polymers. In summary, there is no unique mode of action for water in HFAs; it is formulation dependent and may not systematically lead to destabilisation. As a matter of fact, it is possible to find formulations that use water as a stabiliser, as claimed in recent patents [201-203].

The forces present between drug particles are of course the same between particles and device components, such as can wall, metering chamber and valve components. They can be modulated in a similar way by the addition of polymers or surface modification treatments.

When theory fails, the recourse to experiments is essential. Atomic force microscopy (AFM) is the technique of choice in this case. With AFM, interactions between particles can be measured directly. The application of AFM to measure interaction forces in HFA pMDIs is probably the major advance of the past 5 years. Although much remains to be done to understand the nature of interaction forces between particles and the factors influencing them [33]. So far, AFM measurements have shown the lack of long-range electrostatic repulsion [28], been able to discriminate between successful particle processing techniques [34], select device components [35], discriminate between polymeric stabilisers [36], understand the surface energy interaction relationship [37], and develop an alternative interaction theory to the Derjaguin-Landau-Verwey-Overbeck (DLVO) theory [38]. AFM is rapidly developing as the preformulation technique of choice for HFA pMDIs.

Stemming from a seminal idea from Cline [39], AFM measurements have been found to correlate well with the surface

properties of micronised particles. In his work, Cline suggested a correlation between particle surface properties (as measured by inverted gas chromatography [IGC]); drugs were albuterol and ipratropium bromide; work also included a range of non-active carriers such as lactose and mannitol and the delivery efficiency of DPIs (i.e., the higher the surface energy, the higher the cohesion of the dry particle powders, the higher the mass median aerodynamic diameter and the lower the FPF); the basis of which is interesting, and has been taken on in a recent research endeavour by Traini *et al.* [38]. Instead of relating surface properties to delivery efficiency, they are seeking to find a correlation between surface properties and direct interaction forces as measured by AFM. This removes the difficulty and idiosyncrasies associated with aerosol testing and device efficiency. It has thus been found that it is possible to relate surface properties and interactions. This can be done via the surface tension components of the solid surface as measured by contact angle and not IGC. The model must include polar surface components and not solely dispersive ones. This surface component approach theory of interparticle forces could prove to be a powerful theory to predict interparticle interactions, and remove the need for delicate AFM measurements or the use of the DLVO theory.

3. Formulating micronised particles

3.1 Pure hydrofluoroalkane suspensions

Micronised drug suspended in pure HFA is the simplest form of pMDI formulation. It is also the one that affords the least intellectual property protection, as the use of HFAs for inhalation is fairly generic. It may be the preferred option from a safety point of view, as it does not require any excipients to be tested. Typically, drug concentrations up to 1% w/w have been prepared depending on the potency and dose of the active ingredient. The maximum limit a pMDI can deliver was previously discussed, and the upper limit depends largely on the performance of the device. The development of pure HFA suspensions is, however, fraught with difficulties.

First the drug to be formulated must be fully insoluble in the HFAs, with a suggested limit of < 0.1 ppm. Partial solubility (i.e., less than the dose intended to be delivered) may lead to crystal growth through Ostwald ripening as shown by Phillips *et al.* [40,41]. Their work was performed in CFCs, which have a much higher solvency than HFAs, but this phenomenon could still occur in HFAs. Knowledge of the drug solubility in HFAs is required before attempting to formulate a suspension formulation. Some compounds have been shown to be soluble in HFAs, as shown in **Table 1**. Drug compounds with solubilities as high as 300 ppm (as is the case with beclomethasone dipropionate in HFA 134a) would require care when formulating as a suspension. An Ostwald ripening inhibitor should be used in this case. Partial solubility could also mean a potential for chemical degradation.

Direct measurements of interactions between particles in pressurised HFAs have never been performed. Some measurements have been performed in HPFP. The forces in HPFP are predominantly attractive and dominated by van der Waals forces. FFD–FFD interactions in HPFP are typically -30 nN, whereas for salbutamol sulfate they are 1.1 nN [20,28,36]. There is, therefore, a range of strength of interactions that are compound dependent. This goes some way to explain the differences observed in the stabilising of drug suspensions. The measurement of interparticle forces is particularly difficult with micronised particles as these do not have a defined geometry nor surface composition; therefore, it is not surprising to find a range of force values.

These interactions can be modulated by modifying the liquid properties, through the addition of excipients for instance. Interestingly, it was shown that the attraction between micronised FFD particles could be reduced by using non-fluorinated liquids [45]. AFM experiments were performed with micronised FFD in a series of linear octanes with increasing degrees of fluorine substitution, from octane to perfluorooctane. The attractive force increased from 0.2 nN for octane to 1.5 nN for perfluorooctane. This was in broad agreement with theoretical calculations of the Hamaker constant.

Interactions between drug particles and pMDI device components are equally strong and often attractive. The interaction between micronised FFD and bare aluminium in HPFP is attractive at -13 nN, whereas the attraction with nitrile is very weak (below detection limits), and the force becomes repulsive with chloroprene [28,35]. Hooton *et al.* report the salbutamol sulfate–pyrolitic graphite interaction at -14.1 nN in HPFP [34]. Other studies have been published on the interactions in pure HFA (i.e., HPFP as no pressure cell is yet available), notably from Traini *et al.* [46,47], who have started to develop theoretical models to relate surface properties with interactions.

As well as comparing forces, it is interesting to study interaction energies, as these can be compared with the thermal energy (3/2 k T), and the kinetic energy due to density differences (i.e., gravity);

$$E = \frac{1}{2}mv^2$$

$$v = \frac{2}{9}\frac{(\rho_s - \rho_1)gr^2}{\eta}$$

where m is the weight of the particle, v its settling velocity, ρ_s is the particle density, ρ_l the density of the dispersing medium, g is gravity, η the viscosity of the dispersing medium and r is the diameter of the particle). A solid particle of density 1.35 g/cm^3 and diameter 2 µm, dispersed in HFA 227 (d = 1.58 g/cm^3 and η = 0.537 mPA at 20°C) will have a kinetic energy of 3.38×10^{-19} J, whereas its Brownian energy will be 6.07×10^{-21} J. Typical attractive energies measured by AFM are in the range of $10 - 100 \times 10^{-18}$ J at

Table 1. Drug solubilities in hydrofluoroalkanes in ppm or µg/g.

Drug	HFA 227	HFA 134a	T (°C)	Ref.
Beclomethasone dipropionate	100	300	20	[42,43]
Albuterol sulfate	0.18	0.4	20	[43]
Pirabuterol acetate	0.055	0.07	20	[43]
Prednisone	20	20	25	[24]
Hydrocortisone	10	13	25	[24]
Dexamethasone	15	13	25	[24]
Hydrocortisone 21 acetate	40	35	25	[24]
Betamethasone 17 valerate	40	30	25	[24]
Danazol	100	130	25	[24]
Salbutamol	< 4	< 2	22 – 25	[24]
Insulin	NA	0.0013	Room temperature	[44]

HFA: Hydrofluoroalkanes; NA: Not applicable; T: Temperature.

room temperature; therefore, pure HFA suspensions will always be driven to aggregation at room temperature and are inherently instable. The other source of instability comes from the influence of gravity; particles will always have a tendency to phase separately; the larger, the more pronounced that effect. Reducing the size of the particles in the nanometer range can increase the stability by reducing the gravitational component, as can density matching. Williams *et al.* [48] have studied the possibility of matching the density of propellant blends with that of micronised triamcinolone acetonide, and found a favourable correlation with regards to pMDI delivery efficiency. Density matching could also be achieved by modifying the particle density as explained in Section 4.1. The performance of pure suspensions can also be improved by modifying the propellant. Use of propellant mixtures (HFA 134a with HFA 227) [48], and the addition of CO_2 [204,205] or N_2O [206], is known to improve drug delivery. The most dramatic results are found in systems containing CO_2, for which FPFs of ≤ 70% are reported. The improvements for propellant mixtures are not so startling, although notable suspension stability is achieved thanks to density matching of the micronised powder with the dispersing medium.

The results referenced above show that pure HFA suspensions are almost universally unstable due to the attraction between drug particles, and between drug particles and device surfaces. Because of the difficulties with effective electrostatic stabilisation, there is only one way to improve the stability of the suspension: by the addition of stabilising polymers.

3.2 Suspensions with additives

The formulation examples highlighted in previous sections are excipient free: suspensions of solid particles in pure HFAs. It has been shown that suspensions that are not well stabilised lead to poor delivery performance and manufacturing difficulties [49,50]. Recent work published by Govind *et al.* [51] has confirmed these findings. In their work on shake-pause-fire experiments on a series of stabilised and unstabilised HFA 227 suspensions, they demonstrated the necessity to formulate stable suspensions. A further example is provided by the work published by Nagel *et al.* [2] who studied the delivery performance of Seretide™ pMDI. Seretide is a pure HFA suspension (in HFA 134a) with no additives. Its average FPF is 40% [2], which is lower than expected for stabilised suspension, which is typically in excess of 55% for non-optimised formulations [52]. Seretide is known to aggregate [53,54] as evidenced by Raman microscopy studies. This is a direct consequence of poor stabilisation leading to the loss of delivery efficiency. It is, therefore, necessary to stabilise pMDI suspensions to reduce particle interactions so as to improve their delivery characteristics. This can be achieved by the addition of soluble polymeric excipients or surfactants [28,36,55,56]. The range of recipients that are alleged to be helpful can be found in many formulation patents. Oleic acid, sorbitan trioleate, cetyl pyridinium chloride, soya lecithin, polyoxyethylene, polyoxyethyleneglycol and their copolymers and many fatty acid are often mentioned; however, most of these are not adequate on their own, as their natural solubilities are below any useful concentration range. Efficient excipient concentration ranges are structure dependent, but typically between 0.1 and 1% w/w. When > 1% w/w, attention must be paid to the influence of the additive on the aerosolisation process. The stabilising power of polymers and excipients is not the same for all polymers [28,36].

For stabilisers to be efficient they need to be in solution. Only a few papers report solubility values [42,57-59]. Attempts to understand the relationship between solubility and chemical structure have been sparse. Current knowledge can be summarised thus: no correlation has been found between solubility values and hydrophilic–lipophilic balance parameters [57], Fedors' solubility parameters have proved unsuccessful [59,60], so did Hansen's [58]. The best prediction so far has come from the comparison of octanol/water partition coefficient values with solubility by Dickinson *et al.* [59]. Thus, solubility in HFAs remains a mystery and hinders further testing and development of stabilisers. Any attempt at understanding structure versus solubility would need to include molecular configuration considerations with respect to the fluorinated atoms. HFAs are polar molecules by virtue of the highly electronegative fluorine atoms, as discussed by Byron *et al.* [58]. Therefore, orientation of the dipole ($-CF_2-H$) vis-à-vis the solute is important. Most of the surfactants that have a measurable solubility in HFAs tend to be oxygen rich. It has been suggested [56] that the solubilisation mechanism in HFAs is

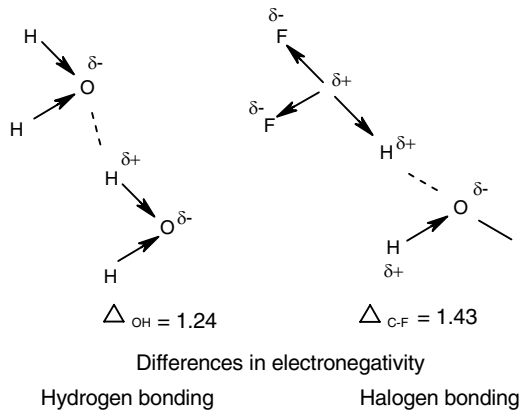

Figure 1. Halogen bonding: a similar interaction to hydrogen bonding. This theory is suggested to explain the high solubility of oxygen-rich molecules in hydrofluoroalkanes, such as tweens, polyetehylene glycol, pluronics and ethanol.

driven by a non-covalent interaction similar to hydrogen bonding, dubbed halogen bonding, by reference to the work done of Metrangolo *et al.* on the aggregation of fluorinated and non-fluorinated alkanes [61]. According to this theory, the hydrogen atoms on the HFA backbone act as electron acceptors from the oxygen atoms in the solute as shown on **Figure 1**.

In this context, identifying excipients that might be used as stabilisers is difficult, in addition to the issue about their potential toxicity, or compatibility with the compounds formulated. Nevertheless, some discoveries have been made. Oligo lactic acids, acyl amide acids and monofunctionalised PEGs (**Figure 2**) have recently been identified as suitable excipients [62]. They help to achieve a uniform dose delivery through can life thanks to a stable suspension. The tailored-design route for new excipients is gaining popularity and more classes of surfactants have been identified for HFA formulations as shown in **Figure 2**. These surfactants are best described as oxygen-rich alkanes, with some degree of fluorinated substitution when required. Other excipients that have been designed for microemulsion preparation (see Section 6) include fluorinated polyols and phosphates [63]. These molecules have never been tested in suspensions, mostly because they are not available commercially. Much could be done in this area as their *in vivo* use does not seem to indicate any adverse events [64].

HFA suspension formulations can use more widely accepted excipients such as oleic acid, cyclodextrins and pegylated phospholipids, but these need the addition of a co-solvent. Ethanol is most often used [65,66]. PEG is also known to be used [207], and fluorinated alcohols and ethers have also been employed successfully [208]. Because of the novelty of these formulations, little data are available on their dose delivery performance. The stability of the suspension is the only assessment performed, which is invariably improved.

Knowledge of the phase behaviour of the excipients in the HFAs is essential, as some excipients have been found to exhibit phase separation phenomenon normally seen in aqueous systems. Tween 80, for instance, shows a lower consolute boundary between 0.1 and 0.15% w/w in HFA 134a at room temperature [67]. This has also been seen for Tween 20 and PEG 600 and 1000 in both HFAs [57,68]. A study of this phase separation phenomenon should provide essential understanding on the interactions between solvent and solute in HFAs, and yield further insights on solubility rules.

The addition of excipients to the formulations has a range of effect on the aerosol performance [69-71]. It mainly leads to size increase of the aerosol droplets and reduction of the FPF. This effect may not be detectable below certain concentrations (1 – 5% w/w). The reason for the aerosol modifications has been attributed to a vapour pressure drop. Other reasons put forward include the modification of the dynamic surface tension of the HFAs by the kinetics of absorption of the excipients [71]. This seems to be a more plausible effect and would account for their chemical dependence.

Some publications have made references to the stabilising power of insoluble surfactants [72,73]; however, their mode of action is more akin to secondary particulate systems and solid surface modifiers than solubilised stabilisers. Surface modification and secondary particulate systems will be discussed in Sections 3.3 and 4.3.

3.3 Secondary particulate systems

Secondary particulate systems have recently appeared in HFA formulations. These systems have been well known in colloid science for many years [74,75]. They consist of a suspension of heterogeneous particles (i.e., a suspension composed of at least two particle populations of different average size). This is often referred to as heterocoagulation or aggregation, and results from a form of bridging flocculation. The aggregates formed are composed of a core large particle surrounded by a shell of adsorbed small particles; they have been dubbed 'raspberry-like' particles. These aggregates are known to form even in systems containing particles of the same surface charge, and are reminiscent of carrier systems used in DPIs.

The idea of heteroaggregation has been successfully translated to HFA suspensions with L-leucine [76,77], cromolycate salts, nedocromil [78,211] and metal stearate or palmitate [212]. The quantities used are usually between 0.1 and 5% w/w. The particle size of the additive can be in the nanometer range, in which case the active ingredient is stabilised by the small particles, or larger than the active particles (i.e., > 5 mm), and act as a carrier for the active compound.

L-Leucine has been formulated as the large particle (with diameters ranging from 38 to 125 µm) with micronised salbutamol sulfate or fluticasone propionate. The corresponding pMDIs were prepared using HFA 134a. Delivery efficiency (FPF) was typically between 10 and 40% depending on the particulate ratios. The combination product formoterol fumarate dihydrate with fluticasone was formulated

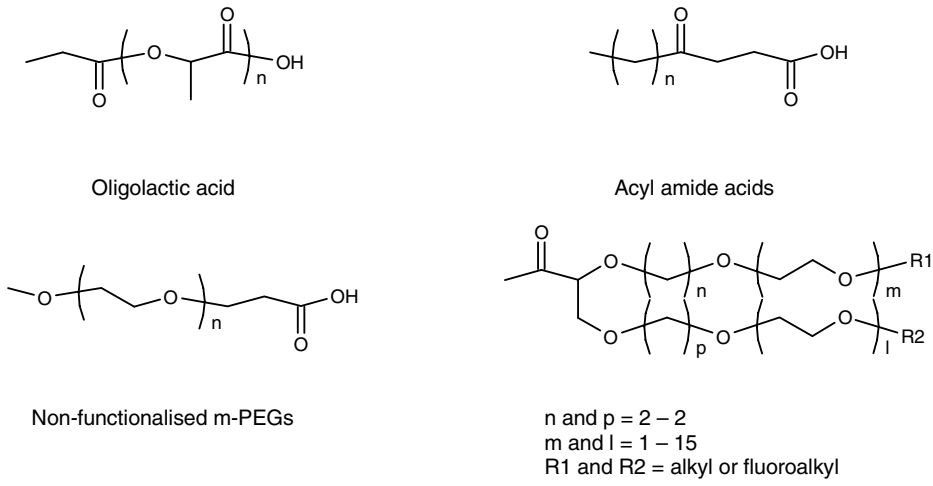

Figure 2. Examples of new classes of surfactants developed for hydrofluoroalkane formulations [62,209,210].
PEG: Polyethylene glycol.

with micronised cromolyn sodium. The pMDI was prepared in HFA 227, and yielded a FPF of 50%. The cromolyn is said to be acting as a dose reproducibility aid and/or water scavenger [213-215]. Secondary particulate systems can be prepared *in situ* as in a recent work published by Steckel and Wehle [79], who precipitated hydroxylpropyl cyclodextrins in a budesonide/ethanol/PEG 300 mixture by adding HFA 227. The very stable suspension formed is thought to be stabilised by a secondary particulate system mechanism thanks to the solid cyclodextrins.

It is debatable if bulking agents belong to the category of secondary particulate system. Nanometer-sized particles of lactose and other sugars have been known to improve suspension properties and pMDI delivery [216]. The particles would then act as stabiliser for the micron-sized inhalation particles. This is reminiscent of secondary particulate systems, and until it can be proven otherwise, it is probably safe to describe them as such.

Finally, combination products can provide the ultimate opportunity for secondary particle stabilisation, as shown in a patent application [217] concerning formoterol and fluticasone propionate. This patent claims a bimodal particle size distribution, 5 – 6 µm for formoterol fumarate and 2 – 3 µm for fluticasone propionate. Although the ultimate claim is about the site of deposition of the drugs and clinical effect, the suspension quality benefits from this size complementarity.

4. Tailoring particles for hydrofluoroalkane suspensions

4.1 Density matching

Density matching is the easiest way to improve suspension properties. Although density matching can really only be effective at one temperature, it has been shown to improve the delivery performance of pMDIs, and slow down phase separation; however, density matching may not reduce particle–device interactions, nor will it prevent particle agglomeration if interparticle attraction is strong.

HFA 227 has a density of 1.42 g/cm^3, and HFA 134a has a density of 1.21 g/cm^3 at 20°C. Williams *et al.* have shown that propellant mixtures behave as ideal mixtures [48], and, hence, their densities can be calculated with a simple proportionality relationship between density and composition. Matching the density of suspended particles to that of the propellant is merely a question of changing the propellant composition as mentioned in Section 3.1, or modifying the composition of the particles by processing the active ingredient with an excipient to adjust its density. This can be done by a range of particle processing techniques, such as spray drying or processing with supercritical fluids. Williams *et al.* [80] have matched the density of chitosan particles with that of HFA 134a by crosslinking with pentasodium tripolyphosphate and glutaraldehyde, and adding aluminium hydroxide. The densities of the micronised particles ranged from 1.42 to 1.62 g/cm^3. Similarly, a patent application has claimed an HFA insulin formulation where the particle density (with added PEG and poly-*N*-vinylpyrrolidone [PVP]) is matched with that of the propellant, and the ratio of densities (microparticles over propellant) is chosen preferably in the range 0.5 – 3 [218].

4.2 Particles with modified surface properties

Modification of the surface properties of suspended particles is a way of tuning the forces of interactions and improving suspension properties. This can be achieved by the addition of surfactants in solution, as seen in Section 3.2, or by processing particles so they have new surface properties. It was explained in Section 2 that new theories are being developed to relate surface properties and interactions. Although these theoretical advances are in development, formulations that make use of these ideas have already been tested. Surface modifications can

be of several types; the surface geometry of the particles can be tailored, as well as the chemical composition.

Coating with lipids and alkyl polyglycosides has been reported [8,81]. Both led to much improved suspension properties and dose delivered. Unfortunately, surface energetics measurements are not always available; therefore, it is not yet possible to map the chemical entities likely to yield low interactions. Preliminary work by Traini *et al.* [46] seems to have found a correlation; the higher the surface energy (from the surface component approach inclusive of polar contributions), the stronger the attraction. Therefore, excipients to be chosen for surface modifications must have very low surface energy.

Micronised particles are naturally uneven; therefore, surface modification consists of smoothing out rugosity (by spray drying for instance or spherical crystallisation) to remove the possibility of mechanical interlocking. Another approach consists of precisely the opposite by creating small dimples on the particle surface or increasing the surface heterogeneity (such as with a solution enhanced dispersion of supercritical fluids [SEDS] process). SEDS particles have been shown to improve delivery efficiency of HFA pMDIs and their suspension properties [82], and so have particles with dimples or 'whiffle balls' [8]. It is difficult to fully understand what presides over this interaction reduction; a possibility may be chemical composition associated with geometric factors, such as crystal planes orientation.

4.3 Porous particles

Ever since the late 1990s, and thanks to the pioneering work of Langer and Edwards [83], porous particles have been heralded as the panacea for HFA pMDI shortcomings. It must be said that their performance has improved.

Porous particles are usually large particles (5 – 10 µm) prepared from a mixture of excipients and active ingredients to form a hollow chemical network. Because of their hollow nature, the tapped density of the particles is reduced to < 0.4 g/cm^3, and their aerodynamic properties are similar to those of smaller micronised particles. They were originally designed to prevent phagocytosis in the lung by macrophages to enable drug release over a long period of time. Their aerosol properties were then discovered, and the stability of the suspensions formed from them.

Although the information on pMDI delivery from porous particle suspensions is readily available [10,11,84,85], there is not much information on the reasons for their good suspension stability. No interaction measurements are publicly available, nor are reliable surface component measurements. The only attempt to understand these suspensions has been made by Dellamary *et al.* [11]. They claim that the effective stabilisation is due to two factors; first, density matching with the propellant, and second, minimisation of the van der Waals forces via refractive index matching between the porous HFA-filled particles and the HFA. Of the two suggestions, the first one seems to be the most plausible. This is because the outer shell of the particles is still constituted mostly of solid; therefore, van der Waals forces may be reduced to a large extent. There is a third possibility that could play a role: it is the chemical composition, which, as for particles with modified surface properties, may reduce the attraction. However, density matching, and also the apparent drag coefficient of the particles in the HFAs, are more likely to become the reason for the improved suspension stability.

Regardless of the stability mechanism, HFA suspensions of porous particles cream or sediment are much slower than their solid micronised counterparts, and have enabled the delivery of high does > 400 µg, with a high FPF (> 70%) [11], with good dose stability and no Cyr effect (i.e., dose variability on storage).

5. The case of nanoparticle suspensions

The use of nanoparticles in suspensions has already been discussed in Section 3.3. Nanosuspensions with uniform size distribution can also be prepared. Their benefits for drug delivery have been reviewed elsewhere [86].

No pressurised HFA nanosuspension is on the market so far, although one patent claims a specific nanoparticle size range [219], and some drug delivery companies have made claims over a possible nanoformulation [87]. Nanoparticles for gene delivery to the pulmonary epithelium have been evaluated but these suspensions were prepared in water and studied *in vitro* [88]. It is possible, however, to imagine that these polylactic glycolic acid–polyethylene imine composites could be delivered with HFAs through artificial ventilation or with a pMDI. Many more applications could be found for nanoparticle suspensions in HFAs, particularly for parenteral delivery and systemic delivery, thanks to the good dissolution properties of the nanoparticles *in vivo*. The aerosols produced by pMDIs are known to contain a certain amount of nanodroplets [89]. These could mediate the delivery of nanoparticles to the deep lungs.

There are several problems associated with nanoparticle suspensions in HFAs that would need to be resolved before these formulations could become accepted. Following Gonda's work on aggregation in aerosols [9], as the concentration of nanoparticles increase in the suspension so will their tendency to form aggregates in the HFA aerosolised droplets. Although the validity of Gonda's theory remains to be tested for pressurised aerosols, it is a likely scenario that would defeat the point of preparing a nanosuspension. The difficulties in preparing the nanoparticles themselves now need to be resolved. Most preparation methods are based on the processing of a slurry, and size reduction by mechanical means, milling or high energy micronisation. Subsequently, budesonide nanopartilces were prepared by Jacobs and Muller [90]. The difficulty with these preparations is that they require the addition of stabilisers that may not be suitable for drug delivery, and that separation of the dry particles may not be possible. Direct crystallisation of nanoparticles or supercritical fluid processing may provide an answer. Direct processing in HFA

liquids has so far proved unsuccessful partly due to their volatility and inability to solubilise suitable stabilisers. Finally, the toxicity of nanoparticles in the body is the object of much debate, although the odds are in their favour [91,92].

The stability of nanoparticle suspensions in non-aqueous liquids has not been widely studied. The electrostatic stabilisation mechanism found in aqueous solutions will not be present; therefore, other methods of stabilisation will have to be relied on: mainly steric stabilisation. However, because of their size, the contribution of Brownian motion may become of the same order of magnitude as the van der Waals attraction, and the influence of gravity will be reduced; therefore, stability (at least vis-à-vis creaming or sedimentation) will be improved. Because of the increased surface area of the particles, the concentrations of stabilising excipients will need to be adjusted, and probably increased. Finally, solubilisation of the particles will be more pronounced because of their size, and this may lead to enhanced problems with Ostwald ripening. The reduction of the particle size close to molecular dimensions will, therefore, open exciting investigation opportunities.

6. Microemulsions

No microemulsion-based pMDI HFA formulations are available on the market or in development. However, a few formulation ideas have been patented or divulged in the literature [93,220]. Non-pressurised HFA microemulsions are already available as blood substitutes or lung fluid replacement [64,94,95]. These are reverse water-in-HFA microemulsions dispersed with surfactants. A range of surfactants have been used, from fluorinated ones, such as fluorinated AOT, fluorinated ethylene oxides or perfluoroheptanoic acid, to phospholipids. These are often tailor made with no known toxicological profiles [93,96,97].

Unfortunately, no data on the delivery efficiency of pMDI HFA microemulsions are available so far. Some tests on caffeine delivery have hinted to their robustness [98], but the tests performed were not standard and did not make reference to the hardware used; therefore, it is difficult to assess their potential. The only evidence of the suitability of microemulsions for pMDI delivery has been provided for water-in-dimethyl ether or propane microemulsions [99]. It was considered for some time as a replacement for CFCs before HFAs were favoured but it was subsequently realised that its compatibility with device components was not optimal). These microemulsions are prepared with lecithins, and FPFs of $\leq 59\%$ have been achieved. They have been suggested for lung delivery of water-soluble molecules.

7. Non-aerosol formulations

HFAs are not used exclusively in pMDIs. They are found in the electronics industry, where they are used as solvents, and in fire extinguishers. Much could be learned on their properties by reviewing these applications.

As for drug delivery, HFAs have been formulated successfully as blood substitutes and lung fluid therapies. Future applications include gels for topical or intra-articular delivery, and drug suspensions for systemic delivery via the lungs during artificial ventilation. Reviews on these topics have been written by Riess and Krafft [63,64,100], Lehmer *et al.* [12] and Courrier *et al.* [13].

Almost exclusively, non-pressurised HFA formulations use one of three molecules: perfluorooctane (FC3280), perfluorodecalin and perfluorooctyl bromide. These HFAs are known to be biologically inert, physically stable and can provide a mean to shield active molecules from degradation (such as oxidation). There are, however, very few formulation types based on them. Suspensions have been mentioned but no literature searches have unveiled any published work. The only formulation details available concern microemulsions for blood transfusions. These are water-in-fluoroliquid microemulsions stabilised with egg phospholipids. The water phase is often a saline phosphate buffer, and the fluorinated phase (perfluorooctyl bromide or perfluorodecalin in most cases) can be further stabilised by the addition of aliquots of a higher molecular weight lipophilic fluorocarbon, such as perfluorooctyldecyl. Series of partially fluorinated surfactants can also be added, a list of which can be found in the review by Riess and Krafft [100].

The synthesis and use of fluorinated and partially fluorinated surfactants is better documented. There is a wealth of chemical structures that have been developed for effective formulations, micellar systems and lipidic reservoir systems. Their development is, however, hindered by several factors: first, the synthesis of the materials is costly and small scale; second, purity of the molecules is a matter of concern; and third, their toxicology profiles are not known, although some preliminary tests by Krafft on their fate *in vivo* are very encouraging [64].

8. Conclusions

Most current HFA suspension formulations fall into two categories: suspensions with additives, polymers or secondary particulate systems, or particle tailoring. Advances have been made in designing new additives (in particular non ionic copolymers) to improve suspension stability and pMDI delivery, although a lot remains to be done to understand the relationship between chemical structure and solubility in HFAs. Particle tailoring has been more successful, thanks largely to new processing technique and the advent of porous particles. Other formulation opportunities are available, whose potentials remain to be fully explored: microemulsions and nanosuspension formulations. Finally, non-pressurised HFA formulations could provide the answers to many of the issues raised by the formulation of HFA pMDIs.

The data presented in this paper shows the wealth of formulation options available to develop HFA suspensions. A

recent survey of the patent literature over the past 5 years, based on a search for HFA suspension formulations, with particular emphasis on HFA pMDIs, revealed that of the 63 patents found, 17 described solution formulations, whereas 46 were devoted to suspensions. The solution patents invariably had recourse to a cosolvent with a predominance of ethanol as the solvent of choice. The suspension patents were far more inventive; their number is bound to increase as product developers attempt to claim intellectual property to protect their products. Inventions have come from the different fields of formulation science and drug delivery, but also from the surfactant industry for instance. Many more inventions are likely to come from related sciences, and in particular from non-pressurised suspension formulations.

However, successful, the advances made have been empirical, and the fundamental science required to go beyond the current state of the art is still sparse. Much more work needs to be carried out to understand the relationship between chemical structure and HFA solubility or even the stability mechanisms in HFAs (i.e., is the DLVO theory valid in non-aqueous liquids and if not, what should replace it?).

The delivery efficiency of many of these formulations is not well documented. Whenever possible, it has been quoted but the paucity of data in the literature has made this task result in a very patchy collection of records. It is difficult to access poor delivery data, for instance, as this is never published. Hence, the opportunity to understand why a particular formulation may not work is not afforded.

9. Expert opinion

The most striking feature of the development of HFA suspensions is the fact that most of them rely on a very small number of excipients. Bearing in mind the nature of pharmaceutical development, it may not be surprising, but there is a world of opportunities that remains untapped and could provide better delivery vehicles with more robust intellectual property protection. Academia has designed and studied many molecules that have not been transferred into technological progress; this is a great shame. Whoever will be bold enough to take through some of these new excipients will be richly rewarded because the current options are good but not the best. The situation with particle tailoring is more hopeful, with the advent of the surface component approach as a welcome theoretical understanding.

However, there remains a need to better understand the relationship between chemical structure and solubility, as well as particulate properties and stability. The tools exist, and need to be applied more generally. Those who will use them will be leading the industry.

Specifically for HFA pMDIs, the choice between a solution or a suspension is one that rests with the chemistry of the drug and its compatibility with the propellants. Byron [101] made a good attempt to guide this choice, although his work would need to be updated with the information and knowledge gained over the past 10 years. Formulations are only one part of the drug delivery space; devices also play a very important role. It is disappointing that 50 years after the introduction of the first pMDI, no substantially new valves have been designed. Stepwise improvements have taken place, such as change of the valve material and change of crimping mechanism, but what is needed is a fundamental redesign of the metering valves. Where are the daring valve suppliers, eager to capture a market in need?

The future of HFA suspensions is bright. Because of the multiple uses of fluorinated liquids as a delivery medium, they are likely to remain at the forefront of pharmaceutical sciences for a long time. HFA pMDIs are only a small portion of that field. Quantum leaps in their formulations will only happen when full and complete cross-fertilisation between the different teams working with HFA formulations occurs.

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