RESEARCH PAPER

Surfactant Dissolution and Water Solubilization in Chlorine-Free Liquified Gas Propellants

Frank E. Blondino[1,*] and Peter R. Byron[2]

[1]*Inhalation Product Development*
Baker Norton Pharmaceuticals Inc.
Miami, Florida 33137
[2]*Aerosol Research Group*
Department of Pharmacy and Pharmaceutics
Medical College of Virginia/Virginia Commonwealth University
Richmond, Virginia 23298

ABSTRACT

The initial water content of a group of 15 pharmaceutically and toxicologically acceptable surfactants showed a tendency to increase with the surfactant hydrophilic–lipophilic balance (HLB) value. Surfactant solubility was determined in chlorine-free "alternative propellants" (n-butane, propane, dimethyl ether [DME], 1,1,1,2-tetrafluoroethane (HFA-134a), and 1,1,1,2,3,3,3-heptafluoropropane [HFA-227ea], and trichloromonofluoromethane [CFC-11] in the absence of cosolvents such as ethanol. Water-soluble surfactants such as Carbowax®, Sentry®, PEG 300, Tween® 20, and Brij® 30, with high HLB values showed appreciable solubility in HFA-134a and HFA-227ea. In systems containing ≥ 80% propellant by weight, each single-phase propellant–surfactant blend was screened for its ability to solubilize iodine and dissolve or solubilize water with increasing surfactant concentration. This screening was performed to investigate the possibility of formulating high-volatility, single-phase systems with increased polarity and solvency from these conventional excipients and vehicles. Ternary-phase diagrams show the regions of apparent single and multiple phase behavior in each system. Despite the increased polarity of the hydrofluoroalkanes (HFAs), appreciable water solubility was seen only with these surfactants in DME and in the hydrocarbons (HCs) n-butane and propane.

* To whom correspondence should be addressed.

INTRODUCTION

With enforcement of the Montreal Protocol (1), pharmaceutical manufacturers of pressurized aerosol formulations must replace chlorofluorocarbons (CFCs) with chlorine-free alternatives. The most likely replacements for inhalation (2,3) are the hydrofluoroalkanes (HFAs) 1,1,1,2-tetrafluoroethane and 1,1,1,2,3,3,3-heptafluoropropane (HFA-134a and HFA-227ea, respectively). Other liquified gas alternatives that appear toxicologically acceptable for topical and/or inhalation, use (4) include propane, butane, and dimethyl ether (DME). Surfactants must be dissolved in these propellants to assist with the dispersion or dissolution of medicaments and with lubrication of the valves atop canisters. It is unfortunate, especially for inhalation purposes, that oleic acid, sorbitan trioleate, and lecithin, three surfactants that are widely used to disperse micronized drugs in pressurized metered dose inhalers (MDIs), are effectively insoluble in the alternative propellants HFA-134a and HFA-227ea (5) unless a cosolvent such as ethanol is added to the system (6). The addition of ethanol may be undesirable in MDIs because of its tendency to reduce the respirable fraction of the emitted cloud (7) and, in suspension MDIs, to increase drug solubility and induce crystal growth (8). One purpose of this article is therefore to review the solubility of different surfactants in each of the five propellants n-butane, propane, DME, HFA-134a, and HFA-227ea (Fig. 1). Several surfactants were chosen by virtue of their inclusion in one or more parenteral products marketed in the United States (9). Thus, they were believed to be toxicologically permissable systemically, and could be expected to be acceptable following administration via alternative routes. In cases in which surfactants were found to be soluble, they clearly had potential as dispersing agents. However, the phase behavior of propellant-rich systems was also studied in the presence of water at different concentrations. Microemulsion systems, containing hydrophilic drugs and water in reverse micelles (which appear like clear solutions to the naked eye), have been prepared in CFCs, and have been shown to have potential use for inhalation (10). Similar systems have been advocated to enable the dissolution and pulmonary aerosol delivery of peptide and protein products (11); aqueous micellar interiors may screen these hydrophilic compounds from the hydrophobic propellants. In this article we further review the formulation possibilities for dissolution and/or solubilization of water in a selection of alternative propellants and surfactants, and discuss the results as they relate to the reformulation of both solution and suspension aerosol products.

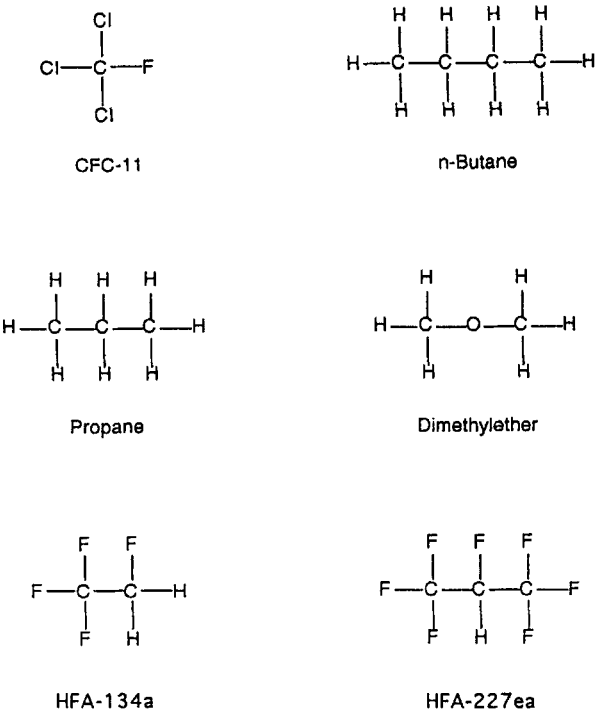

Figure 1. Chemical structures of chlorine-free alternative propellants and trichloromonofluoromethane (CFC-11).

MATERIALS AND METHODS

Materials

Surfactant names and sources are described in Table 1. DME, HFA-134a, and CFC-11 were purchased from DuPont (Wilmington, DE). HFA-227ea was supplied by Hoechst (Somerville, NJ). The hydrocarbons (HCs) n-butane (pure grade) and propane (CP grade) were purchased from Phillips 66 Company (Borger, TX) and Airco (Richmond, VA), respectively. Absolute ethanol, USP, was obtained from Pharmco (Bayonne, NJ) or AAPER Alcohol and Chemical Company (Shelbyville, KY). Aquamicron AS was purchased from COSA Instrument Company (Norwood, NJ). Hexane and tetrahydrofuran (THF) were of HPLC grade and were purchased from Fisher Scientific (Raleigh, NC). The water used in preparing study formulations was reverse-osmosis purified. All surfactants, propellants, and solvents were used as received.

Water Content of Surfactants

The initial water content of each surfactant (Table 1) was determined by conductiometric Karl Fischer titra-

Table 1

Surfactants, Sources, HLB Values, and Water Content, (in Order of Increasing HLB)

Trade Name	Chemical Name	Supplier	HLB	Water Content (% w/w)[a]
Oleic acid	Oleic acid	Fluka AG	1.0	0.23 ± 0.01
Span 85	Sorbitan trioleate	ICI Americas Inc.	1.8	0.24 ± 0.03
Antarox 31R1	Propoxylated polyethylene glycol	Rhône-Poulenc Surfactants and Specialties	4.0	0.29 ± 0.02
Glycomul SOC	Sorbitan sesquioleate	Lonza Inc.	4.0	0.33 ± 0.04
Glycomul O	Sorbitan monooleate	Lonza Inc.	4.3	0.28 ± 0.03
Arlacel 60	Sorbitan monostearate	ICI Americas Inc.	4.7	1.36 ± 0.23
Macol SA 2	Polyoxyethylene (2) stearyl ester	PPG Industries Inc.	4.9	1.40 ± 0.05
Centrolex P	Granular lecithin	Central Soya	7.0	2.47 ± 0.08
Transcutol	Purified diethylene glycol monoethyl ether	Gattefossé	8.7[b]	0.15 ± 0.02
Brij 30	Polyoxyethylene (4) lauryl ether	ICI Americas Inc.	9.7	0.71 ± 0.03
Tween 80	Polyoxyethylene (20) sorbitan monooleate	ICI Americas Inc.	15.0	2.84 ± 0.02
Tween 20	Polyoxyethylene (20) sorbitan monolaurate	ICI Americas Inc.	16.7	2.58 ± 0.03
Carbowax Sentry PEG 300	Polyethylene gycol 300	Union Carbide Chemicals and Plastics Co. Inc.	20	0.27 ± 0.02
Carbowax Sentry PEG 8000	Polyethylene glycol 8000	Union Carbide Chemicals and Plastics Co. Inc.	20	0.21 ± 0.07
Aerosol OT	Sodium dioctyl sulfosuccinate	Cytec (American Cyanamid Co.)	42.0[b,c]	1.74 ± 0.03

[a] Water content expressed as mean ± SD (N = 5).
[b] Calculated values (27).
[c] This is the only ionic surfactant in the table.

tion. Approximately 5% by weight of surfactant was dissolved in absolute ethanol, Aquamicron AS, or THF. Replicate injections of 0.5 ml of pure solvent (N = 5) or solvent containing surfactant (N = 5) were titrated in an MCI Moisture Meter (Model CA-05; COSA Instrument Co.). The mean water content in the solvent was subtracted from that in the sample containing surfactant, and the initial water content of each surfactant was expressed as a percent by weight in surfactant.

Surfactant Dissolution in Propellants

The apparent surfactant dissolution in each propellant was studied at ambient temperature (19.5–25.0°C) by adding a known quantity of surfactant to a plastic-coated, pressure-resistant, clear glass aerosol bottle (Wheaton Glass, Mays Landing, NY). A continuous flow valve (Bespak 356, modified to continuous; Tenax-Bespak, Cary, NC) was then crimped onto the bottle (Pamasol Model P 2005/2; Willi Mäder AG). Propellant was added incrementally by weight via a pressure buret (Aerosol Equipment Corp., Walton, NY), which was over pressurized with nitrogen gas at 100–180 psig. After each addition, the contents were sonicated (Model 5200; Branson Ultrasonic Corp., Danbury, CT) for 30 sec and viewed with the naked eye for miscibility or dissolution. Surfactant dissolution in CFC-11 (liquid at room temperature) was determined similarly, although media bottles (Fisher Scientific; Raleigh, NC) equipped with polytetrafluoroethylene (PTFE)-faced silicon liners in screw-thread caps were used in place of the pressure-resistant bottles and valves. CFC-11 was added by weight, using a Pasteur pipet.

Iodine Solubilization

A modified iodine solubilization method (12,13) was used to determine the potential of each dissolved surfactant to micellize in propellant. Surfactant was weighed into pressure-resistant, clear glass aerosol bottles as before. A constant 0.5 ml volume of 10^{-2} M iodine solution in hexane, which was soluble in all propellants investi-

gated, was added, and a continuous valve was crimped onto the bottle. The weight equivalent of 50 ml of propellant was added via a pressure buret to yield a constant final iodine concentration of 10^{-4} M. Solutions were shaken for 4 hr on a wrist-action shaker (Model 75, Burrell Corp., Pittsburgh, PA). Because of the difficulty of measuring absorbance at 360 nm (12) in liquified propellants, a series of 10^{-4} M iodine solutions in hexane were also prepared, containing different concentrations of surfactants (Oleic acid, Span® 85, Antarox® 31R1, Glycomul® SOC, Glycomul® O, Centrolex® P, Transcutol®, Brij® 30, and Aerosol® OT); several surfactants solubilized iodine in hexane, causing a purple to yellow color conversion whose intensity increased with surfactant concentration. Measurements of absorbance at 360 nm in these low-volatility hexane solutions enabled approximate quantification of the absorbance in pressurized systems by simple visual comparison. A positive result for iodine solubilization was defined as a 360-nm absorbance >0.2 at $\geq 2\%$ w/w surfactant concentration in propellant.

Water Solubilization

When possible, ternary-phase diagrams were constructed for each propellant–surfactant–water combination. The intention was to assess the system's ability to solubilize water, especially in the high-propellant-concentration regions, where formulations were most likely to be useful for inhalational purposes (14). Surfactant and water were weighed in different ratios of surfactant to water by weight (100:0, 75:25, 50:50, 25:75, and 0:100), not accounting for initial water content of the surfactant, into clear-glass aerosol bottles that were crimped with continuous valves as before. After initial addition of propellant to >80% by weight, further propellant was added in increments via a pressure buret to >98% by weight. After each addition, the bottle was weighed and its contents were sonicated for 30 sec and viewed with the naked eye to detect the presence of single or multiple phases and the clarity of each phase. The percent by weight of each component was calculated and plotted on the phase diagram after each addition.

RESULTS AND DISCUSSION

Water Content of Surfactants

The water content of individual surfactants is shown in Table 1. The water content of those surfactants listed in the USP-NF (Span 85, Glycomul SOC, Glycomul O, Arlacel 60, Tween 80, and Aerosol OT) was within compendial specifications (15). Other surfactants contained water within the specifications of their suppliers. Water contents showed a tendency to increase with increasing hydrophilic–lipophilic balance (HLB) values. Although it has been reported that small amounts of water are needed to induce micellization in nonpolar media (16), the amounts of water determined in the surfactants investigated in the present study may or may not be sufficient to induce micellization in propellants.

Surfactant Dissolution in Propellants

Table 2 shows the apparent solubility of each surfactant in the pure propellants. Surfactants were considered to be soluble, as is the case in practice, if one clear phase was formed in the admixture. There is no attempt in Table 2 to discriminate between monomer dissolution and molecular aggregates or micelles. Solubilities are expressed in Table 2 as percent by weight, not accounting for surfactant water content (Table 1).

Aerosol OT, the only ionic surfactant studied, dissolved well in all propellants except the HFAs. In fact, only one surfactant with a low HLB value (Antarox 31R1) dissolved appreciably in the HFAs. Surfactants with high HLB values were more soluble in HFA-227ea than in HFA-134a or CFC-11, which showed similar dissolution values in several cases. The surfactants with low HLB values were quite soluble in the HCs; whereas, surfactants with high HLB values were not. DME, an extremely good solvent, had the ability to dissolve almost the entire set of surfactants investigated.

The prediction of surfactant dissolution in propellants cannot easily be made by simply comparing the physical properties of the propellants of interest (Table 3) or comparing the propellants' molecular structures (Fig. 1). However, the dipole moment and dielectric constant for the HFAs are known to be greater than those of the CFCs [Table 3 (17,18)], indicating their greater polarity. The hydrogen substituents in the HFAs (Fig. 1) allow for considerable charge separation in the propellant molecules, owing to the electronegativity of the fluorine atoms. This leads to the possibility of hydrogen bonding of the propellant hydrogen (19), and probably explains the dissolution of surfactants with relatively high HLB values (Tween 20, Tween 80, and Carbowax® Sentry® PEG 300), which have more potential for hydrogen bonding in the HFAs than do low HLB surfactants, whereas the same propellants were poor solvents for oleic acid, Span 85, and Centrolex P. The dissolution of low HLB surfactants by the HCs was anticipated on the basis of consider-

Table 2

Apparent Solubility of Surfactants in Propellants, in Order of Increasing Surfactant HLB[a]

	Solubility (% w/w) in					
Surfactant	CFC-11	n-Butane	Propane	DME	HFA-134a	HFA-227ea
Oleic acid	∞	∞	7.9–10.2	∞	<0.02	<0.02
Span 85	∞	∞	≈43.9	∞	<0.02	<0.01
Antarox 31R1	∞	≈1.8	≈0.07	≈29.3	≈3.6	1.5–15.3[b]; 32.0–60.3[b]
Glycomul SOC	≈12.2	≈24.7	≈38.5	≈0.3	<0.01	<0.01
Glycomul O	∞	≈21.6	≈40.6	∞	<0.01	<0.01
Arlacel 60	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Macol SA 2	≈11.8	≈0.02	<0.01	≈9.8	<0.01	<0.01
Centrolex P	≈22.7	≈43.9	<0.01	≈0.3	<0.01	<0.01
Transcutol	∞	∞	1.4–12.0[b]; 34.2–100[b]	∞	∞	∞
Brij 30	∞	≈23.5	10.1–100	∞	≈1.8	0.8–1.2[b]
Tween 80	≈0.1	<0.01	<0.01	≈27.1	<0.03	0–10.0[b]; 25.0–89.8[b]
Tween 20	≈0.1	<0.01	<0.01	8.6–35.0[b]	≈0.1	1.4–3.5[b]
Carbowax Sentry PEG 300	<0.01	<0.01	<0.01	∞	≈4.0	1.5–4.3[b]; 16.1–100[b]
Carbowax Sentry PEG 8000	<0.01	<0.01	<0.01	<0.02	<0.01	<0.01
Aerosol OT	≈21.2	≈41.2	≈36.1	≈32.9	<0.01	<0.02

[a] Determined as the maximum % w/w to produce a single clear phase except where noted.
[b] Existed as one clear phase only in this concentration range.
[c] Approximately equal to.
[d] Appeared miscible in all proportions.

able van der Waal's interactions (dispersion forces) between the propellant and the lyophilic tails of the surfactant molecules. Similarly, the HCs were not expected to dissolve the polar surfactants. Some combination of these factors, polar and nonpolar behavior, was found in DME, a known solubilizer (20). The ability of DME to form hydrogen bonds [acceptor only (21)] as well as interact via van der Waal's forces allowed this propellant to dissolve almost all of the surfactants investigated, regardless of their polarity.

Table 3

Physical Properties of Propellants[a]

Propellant	Molecular Weight	Boiling Temp (°C)	Vapor Pressure[b]	Solubility Parameter $(cal/ml)^{1/2}$	Dipole Moment	Dielectric Constant (Liquid)
CFC-11	137.4	23.8	13.4	7.6	0.46	2.3
n-Butane	58.1	−0.5	31.7	6.6	0	1.8
Propane	44.1	−42.1	123.7	5.8	0.084	1.7
DME	46	−24.8	77.7	7.3	1.3	5.0
HFA-134a	102	−25.8	85.7	6.6	2.06	9.51
HFA-227ea	170	−17.3	59.7	6.6	0.93	4.07

[a] Adapted from Ref. 5.
[b] Pounds per square inch absolute (psia) (21°C). Absolute pressure 14.7 psia = 1 atm = 101.3 kPa.

The dissolution of some of the high HLB, nonionic surfactants investigated in the present study (Brij 30, Tween 20, Tween 80, and Carbowax Sentry PEG 300) in the high-volatility HFAs is the subject of two United States patents (17,18), and may be of considerable importance during the formulation of both suspension and solution type MDIs. These surfactants are well known pharmaceutical excipients with acceptable toxicity profiles (9). Although their suspension-stabilizing behavior in HFAs is undoubtedly drug-dependent, they may act as valve lubricants, a property of some importance to the reproducible function of many pressurized formulations (14).

Iodine Solubilization

Propellant–surfactant systems were chosen for further investigation when apparent surfactant dissolution was ≥ 2% by weight (Table 2). Table 4 shows that 12 of the 22 systems investigated showed promise as iodine solubilizers (360-nm absorbance at ≥ 2% surfactant by weight was >0.2). The use of the iodine solubilization method was not possible in DME. Addition of any amount of DME to the iodine solution in hexane resulted in an immediate color change from violet to yellow, and therefore to a high 360-nm absorbance value, owing to the formation of a charge-transfer complex between the iodine and combined oxygen (13).

Water Solubilization

Twenty propellant–surfactant systems were investigated for their ability to dissolve or solubilize water. Representative phase diagrams of these systems may be found in Figs. 2–6. In each of the diagrams, water content (% by weight) includes all of the water in the system, whether this was derived from the surfactant (Table 1) or added independently. Thus, the results shown in Table 2 for surfactant solubility in propellants are plotted as open circles (= one clear phase) on or near the right-hand axis of Figs. 2–6. Surfactants with high initial water contents displaced the plotted constitutions of propellant–surfactant mixtures further from the right-hand axis and toward the apex of the triangle labeled "Water" [Fig. 4(b); e.g., Tween 20). All diagrams show systems containing ≥ 80% propellant by weight and thus ≤ 20% water-plus-surfactant. Ternary diagrams were constructed conventionally (22), and for this reason Point A in Fig. 2(b), for example, was a two-phase ternary system with the constitution 82.5% n-butane, 12.5% water, and 5% Aerosol OT.

Interpretation of the diagrams in Figs. 2–6 is straightforward with one exception: although many phase diagrams in the literature fail to illustrate uninvestigated regions, these are shown as hatched areas in Figs. 2–6 for several reasons. In Fig. 2(b), for example, at the point where the propellant n-butane was added to a 3:1 Aerosol® OT–water mixture (follow 15 on the left-hand axis through 100 on the right), crosses (two–phase region) turn to circles (single-phase region) through a hatched area containing Point B. The precise point at which the two-phase system becomes a single clear phase is between 83.5% and 86% n-butane. The region around point B is shown with hatching because of this practical uncertainty. Second, in pressurized systems, analytical determination of the constitution of consolute phases (which are in equilibrium with each other) is impractical because of the volatile nature of the blends, making the connection of tie lines and firm establishment of phase boundaries extremely difficult. Finally, and from a theoretical viewpoint, there is a further difference between conventional ternary-phase diagrams (at fixed temperature and pressure) and those describing blends of liquified propellants (23) that are maintained as liquids in closed vessels in equilibrium with their own vapor. The vapor pressure at each point in these phase diagrams is fixed, yet it varies throughout the diagram (temperature is fixed throughout). Conventional ternary-phase diagrams, showing behavior at constant temperature and pressure (22), would be of no practical value to the formulator. Nevertheless, the application of the phase rule in the case of Figs. 2–6 is instructive. Even though pressure is a variable throughout the diagrams (generally increasing in the direction of 100% propellant), at any given point in a diagram, temperature and pressure are fixed. Thus, for a phase constitution to be fixed [zero degrees of freedom in the phase rule, $F = 0 = C - P$ for a system with fixed temperature and pressure (22)], the number of components or chemical species, C, must equal the number of phases, P. Provided the system is truly ternary ($C = 3$), a maximum of three phases, each with a defined constitution, can coexist. As expected in a conventional phase diagram of this kind, this statement ensures that any three-phase region in Figs. 2–6 must actually be triangular, with the apices of the triangle representing the constitution of each of the consolute phases (22). The three phase regions are not represented as triangles in Figs. 2–6, but more accurately as actual observations at the corresponding constitutions.

Much of the work needed to replace the CFCs in pressurized MDIs requires empirical review of a large number of drug-containing alternative formulations. Al-

Table 4

Approximate 360-nm Absorbance Values Obtained by Visual Comparison with Hexane Standards

System	Surfactant Conc.[a]	Absorbance[b]	Surfactant Conc.[a]	Absorbance[b]	Surfactant Conc.[a]	Absorbance[b]
Hexane–Oleic acid	0.20	0.01	1.95	0.116	9.04	0.314
n-Butane–Oleic acid	0.20	0.01	1.96	0.03	9.08	0.2
Hexane–Span 85	0.20	0.132	1.95	0.530	9.04	1.496
n-Butane–Span 85	0.20	0.01	1.96	0.5	9.07	1.5
Propane–Span 85	0.20	0.01	1.96	0.5	9.08	1.5
Hexane–Antarox 31R1	0.20	0.043	1.95	0.266	9.04	1.430
HFA-134a–Antarox 31R1	0.20	0.1	1.96	1.4	4.77	N/O
HFA-227ea–Antarox 31R1	0.20	0.04	1.96	1.4	9.09	N/O
Hexane–Glycomul SOC	0.20	0.011	1.95	0.944	9.04	0.519
n-Butane–Glycomul SOC	0.20	0.01	1.96	0.9	9.08	0.5
Propane–Glycomul SOC	0.20	0	1.96	0.9	9.08	0.5
Hexane–Glycomul O	0.20	0.002	1.95	0.690	9.04	0.830
n-Butane–Glycomul O	0.20	0	1.96	0.7	9.09	0.8
Propane–Glycomul O	0.20	0	1.96	0.7	9.11	0.8
Hexane–Centrolex P	0.20	2.025	1.95	2.004	9.04	2.836
n-Butane–Centrolex P	0.20	2.0	1.95	2.0	9.06	2.8
Hexane–Transcutol	0.20	0.012	1.95	0.034	9.04	0.103
n-Butane–Transcutol	0.20	N/O	1.95	0.03	9.09	0.1
HFC-134a–Transcutol	0.20	0.03	1.96	0.06	9.10	0.1
HFC-227ea–Transcutol	0.20	0.03	1.96	0.03	9.10	0.06
Hexane–Brij 30	0.20	0.004	1.95	0.007	9.04	0.206
n-Butane–Brij 30	0.20	0	1.97	0.01	9.09	0.2
HFA-134a–Brij 30	0.20	0.01	1.96	0.03	4.77	N/O
HFA-227ea–Brij 30	0.20	0	1.96	0	9.09	0
HFA-227ea–Tween 20	0.20	N/O	1.96	N/O	9.10	N/O
HFA-227ea–Tween 80	0.20	N/O	1.96	N/O	9.10	N/O
HFA-134a–Carbowax Sentry PEG 300[c]	0.20	0.1	1.96	0.5	4.76	1.5
HFA-227ea–Carbowax Sentry PEG 300[c]	0.20	0	1.96	0.1	9.10	1.5
Hexane–Aerosol OT	0.20	0.022	1.95	0.209	9.04	0.737
n-Butane–Aerosol OT	0.20	0.7	1.96	0.7	9.09	0.7
Propane–Aerosol OT	0.20	0.1	1.96	0.7	9.09	0.7

[a] Expressed as % w/w.

[b] Absorbance determined by UV spectroscopy in the case of hexane samples and by visual comparison in all other cases.

[c] Samples compared to Hexane–Span 85 standards.

N/O Not obtainable from the data collected. The samples were either cloudy or colorless.

though the drug itself must eventually be included along with various packaging components, a knowledge of the interactive properties of a number of likely alternative propellants with toxicologically acceptable surfactants and water can be used to avoid unnecessary experimentation. In pressurized MDIs with contents formulated as suspensions, vapor pressures of about 3 atm measured by gauge (4 atm absolute) are quite usual (14), while solution (as opposed to suspension) formulations and increased pressures have been proposed (7,14) as means of increasing the fraction of the inhaler output that forms droplets and particulates small enough to be considered respirable. One purpose of the present study was to chart those blends in which single-phase systems coincided with high propellant concentrations and thus with high vapor pressures (no attempts were made to monitor vapor pressure during the present study, because to do so would have prevented the construction of accurate phase dia-

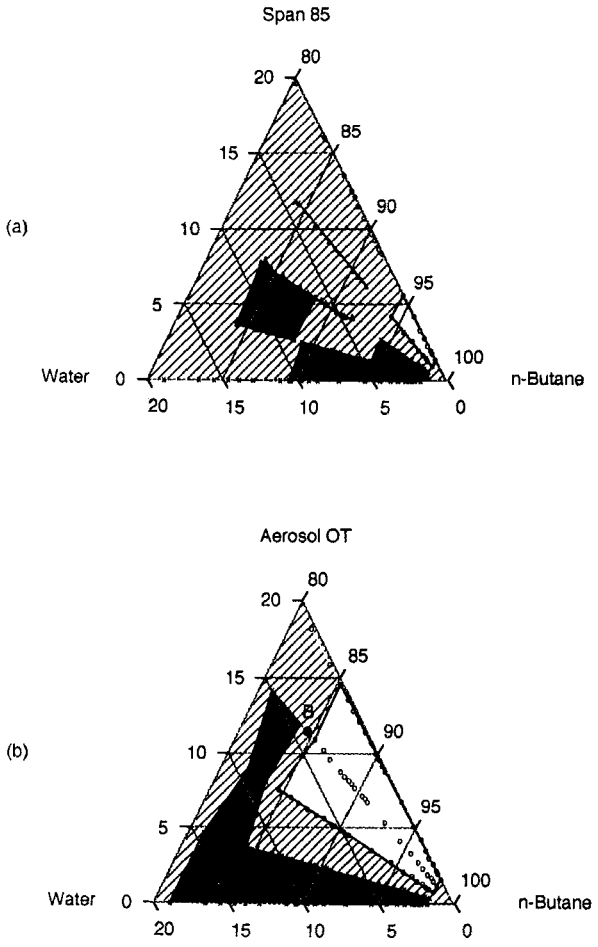

Figure 2. Ternary-phase diagram of n-Butane–surfactant–water for (a) Span 85 and (b) Aerosol OT, where: (□) o one clear phase region; (■) x one cloudy or two-phase region; (■) Δ three-phase region; (/ /) uninvestigated region.

grams). Any of the systems contained within a clear region in Figs. 2–6, or described by an open circle, may thus be considered as viable alternative propellant formulations. In each case, a move toward the 100% propellant apex of each triangle can probably be considered to increase the vapor pressure of the formulation toward that of the pure propellant (Table 3).

The behavior of each propellant–surfactant mixture with water is important for several reasons. First, and most obvious, if water can be solubilized by a surfactant in a nonaqueous propellant, it may also be possible to dissolve polar drugs in these blends, and therefore to form high-pressure solution aerosols with high respirable

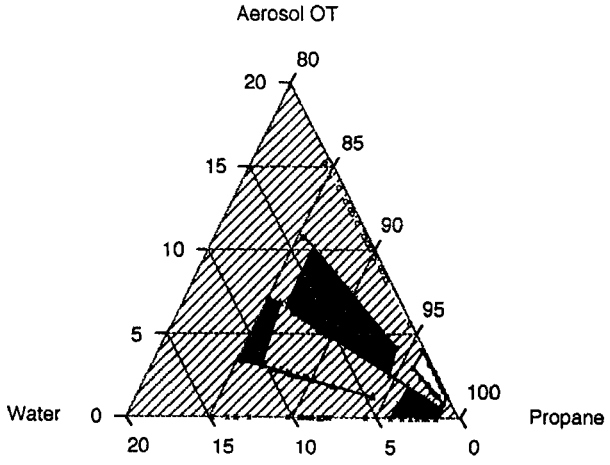

Figure 3. Ternary-phase diagram of Propane–Aerosol OT–water. where: (□) o one clear phase region; (■) x one cloudy or two-phase region; (■) Δ three-phase region; (/ /) Uninvestigated region.

fractions (7,24). Furthermore, with the current interest in peptide and protein aerosols (11), the molecular environment of water in a solubilized system (25) may prevent hydrophilic peptide denaturation in hydrophobic propellants. The single-phase regions in Figs. 2–6 may be due either to surfactant micellization around groups of water molecules [this is known to be true for Aerosol OT in n-butane and Aerosol OT in propane; (26)], and/or to the cosolvent properties of the surfactant in the propellant–surfactant blend. However, from the viewpoint of the aerosol formulator, the way in which a drug is dissolved to form a stable solution may be unimportant; true solutions and microemulsions containing larger droplets may be physically stable for extended periods of time (27). Several of the propellant–surfactant systems investigated in the present study were able to solubilize more water in the presence of surfactant than in its absence (n-butane–Span 85, n-butane–Aerosol OT, propane–Aerosol OT, and DME–Brij 30). With these exceptions, only DME (which dissolves approximately 4.5% water in the absence of surfactant) displayed appreciable single-phase regions including both added water and nonionic surfactants. Thus, if the addition of a propellant-miscible cosolvent such as ethanol is to be avoided, these single-phase systems represent likely alternative propellant blends for the creation of pressurized nonaqueous-solution formulations.

Conversely, in MDIs with contents formulated as nonaqueous suspensions, water diffusion into a formulation

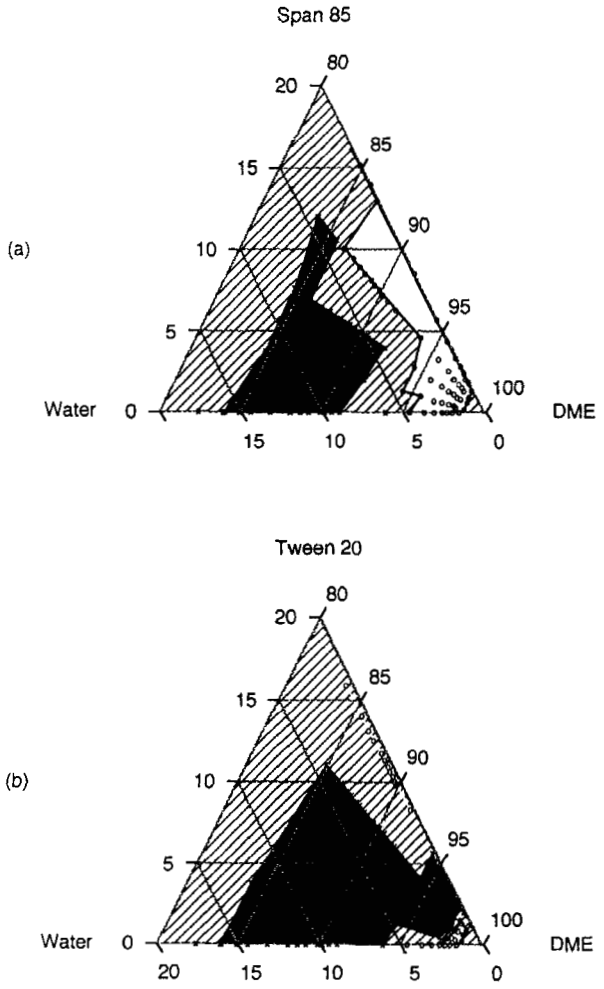

Figure 4. Ternary-phase diagram of dimethyl ether (DME)–surfactant–water for (a) Span 85 and (b) Tween 20 where: (□) o one clear phase region; (■) x one cloudy or two-phase region; (■) Δ three-phase region; (/ /) uninvestigated region.

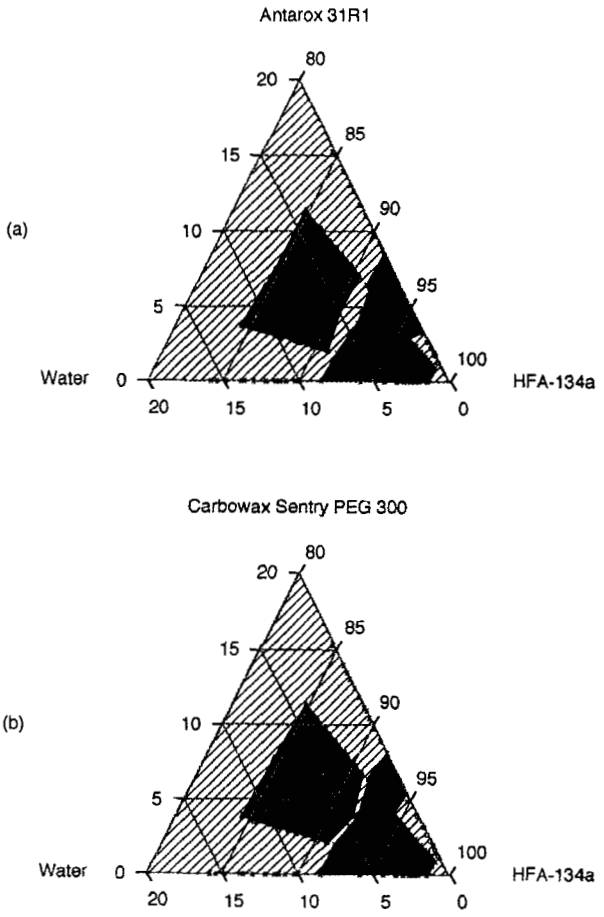

Figure 5. Ternary-phase diagram of 1,1,1,2-tetrafluoroethane (HFA-134a)–surfactant–water for (a) Antarox 31R1 and (b) Carbowax Sentry PEG 300 where: (□) o one clear phase region; (■) x one cloudy or two-phase region; (■) Δ three-phase region; (/ /) uninvestigated region.

can destroy the stability of the suspension in a variety of ways (28). Moreover, in pressurized-suspension formulations, the use of dissolved surfactants at concentrations that both solubilize and disperse drug may be contraindicated because of the possibility of promotion of crystal growth over time (8). Provided that drug solubility in a propellant is small and/or has only a slight temperature dependence (5,29,30), pressurized-suspension formulators may wish to avoid the use of blends that show a tendency to solubilize drugs, and perhaps water, in propellants by choosing the appropriate systems from Figs. 2–6. Surprisingly, Figs. 5 and 6 show that the leading contenders as alternative propellants in MDIs, HFA-134a and HFA-227ea, have difficulty in dissolving added water, even though they are more polar than the CFCs (5) and dissolve the higher-HLB surfactants (5,17,18). Unfortunately, this statement may not mean that it is easy to avoid crystal growth for all compounds in HFAs when suspension formulations are prepared, because the solubilities of several drugs are much higher in pure HFAs than they are in CFCs. In practice, with drugs like beclomethasone dipropionate, dissolution in HFAs can be substantial (5), and so much so that the addition of even a small amount of ethanol as a cosolvent can produce a high-volatility solution MDI

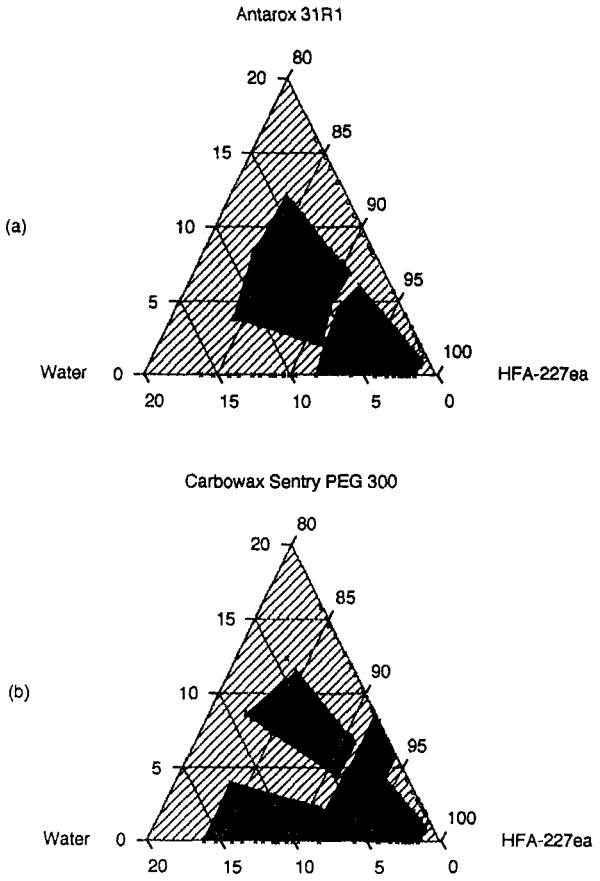

Figure 6. Ternary-phase diagram of 1,1,1,2,3,3,3-heptafluoropropane (HFA-227)–surfactant: water for (a) Antarox 31R1 and (b) Carbowax Sentry PEG 300 where: (□) o one clear phase region; (■) x one cloudy or two-phase region; (■) Δ three-phase region; (/ /) uninvestigated region.

formulation with an unknown chemical-stability profile (31).

ACKNOWLEDGEMENTS

F. E. B. acknowledges financial support from Rhône-Poulenc Rorer. The authors wish to thank the suppliers of the surfactants, Wheaton Coated Products, and Bespak for their gifts.

REFERENCES

1. *Montreal Protocol on Substances That Deplete the Ozone Layer*, Liaison Office of the United Nations Environmental Program, New York, 1989.
2. J. J. Daly, Jr. and M. L. SanGiovanni, Replacement for CFC propellants: A technical/environmental overview, Spray Tech Marketing, 3, 34–38 (1993).
3. A. R. Ravishankara, A. A. Tumipseed, N. R. Jensen, S. Barone, M. Mills, C. J. Howard, and S. Solomon, Do hydrofluorocarbons destroy stratospheric ozone?, Science, 263, 71–75 (1994).
4. R. N. Dalby and P. R. Byron, Metered-dose inhalers containing flammable propellants: perspectives and some safety evaluation procedures, Pharm. Tech., 15, 54–66 (1991).
5. P. R. Byron, N. C. Miller, F. E. Blondino, J. E. Visich, and G. H. Ward, Some aspects of alternative propellant solvency, in *Respiratory Drug Delivery IV* (P. R. Byron, R. N. Dalby, and S. J. Farr, eds.), Interpharm Press, Philadelphia, PA, 1994, pp. 231–242.
6. T. S. Purewal and D. J. Greenleaf, Medicinal aerosol formulations, European Patent #0,372,777 (1990).
7. R. N. Dalby and P. R. Byron, Comparison of output particle size distributions for pressurized aerosols formulated as solutions or suspensions, Pharm. Res., 5, 36–39 (1988).
8. E. M. Phillips and P. R. Byron, Surfactant promoted crystal growth of micronized methylprednisolone in trichloromonofluoromethane, Int. J. Pharm., 110, 9–19 (1994).
9. Y. C. J. Wang and R. R. Kowal, Review of excipients and pH's for parenteral products used in the United States, J. Parent. Drug Assoc., 34, 452–462 (1980).
10. R. M. Evans, S. J. Farr, N. A. Armstrong, and S. M. Chatham, Formulation and in vitro evaluation of pressurized inhalation aerosols containing isotropic systems of lecithin and water, Pharm. Res., 8, 629–635 (1991).
11. P. R. Byron and J. S. Patton, Drug delivery via the respiratory tract, J. Aerosol Med., 7, 49–75 (1994).
12. S. Ross and J. P. Oliver, A new method for the determination of critical micelle concentrations of un-ionized association colloids in aqueous or in non-aqueous solutions, J. Phys. Chem., 63, 1671–1674 (1959).
13. S. Ross and V. H. Baldwin, Jr., The interaction between iodine and micelles of amphipathic agents in nonaqueous solutions, J. Colloid Inter. Sci., 21, 284–292 (1966).
14. P. R. Byron, Aerosol formulation, generation, and delivery using metered systems, in *Respiratory Drug Delivery* (P. R. Byron, ed.), CRC Press, Boca Raton, FL, 1990, pp. 167–205.
15. *United States Pharmacopeia and National Formulary*, USP Convention, Inc., Rockville, MD, 1995, pp. 547, 2259, 2290, 2307, 2308.
16. J. H. Fendler, Surfactants in apolar media, in *Membrane Mimetic Chemistry. Characterizations and Applications of Micelles, Microemulsions, Monolayers, Bilayers, Vesicles, Host-Guest Systems, and Polyions* (J. H. Fendler, ed.) John Wiley & Sons, New York, 1982, pp. 48–77.
17. P. R. Byron and F. E. Blondino, Metered dose inhaler formulations which include the ozone-friendly propellant HFC 134a and a pharmaceutically acceptable suspending,

solubilizing, wetting, emulsifying or lubricating agent, U.S. Patent #5,492,688 (1996).
18. P. R. Byron and F. E. Blondino, Pharmaceutically acceptable agents for, solubilizing, wetting, emulsifying or lubricating in metered dose inhaler formulations which use HFC-227 propellant, U.S. Patent #5,508,023 (1996).
19. T. Higuchi, Solubility, in *Pharmaceutical Compounding and Dispensing*, (R. A. Lyman, ed.) Lippincott, Philadelphia, PA, 1949, pp. 159–190.
20. M. E. Boulden, Use of dimethyl ether for reduction of VOC content, Spray Tech. Marketing, 2, 30–36 (1992).
21. L. J. M. Bohnenn, Recent European developments in DME technology, Aerosol Age, September, 26–29 (1988).
22. A. Martin, J. Swarbrick, and A. Cammarata, States of matter and phase equilibria, in *Physical Pharmacy*, 3rd Ed. (A. Martin, J. Swarbrick, and A. Cammarata, eds.) Lea & Febiger, Philadelphia, PA, 1983, pp. 62–92.
23. DuPont. Blends of Dymel®22/A (40/60) azeotrope and hydrocarbons provide virtually constant pressure over wide range of component concentration, Dymel Aerosol Propellants Information, Technical Bulletin #ATB-10 Wilmington, DE.
24. R. M. Evans, D. Attwood, S. M. Chatham, and S. J. Farr, A novel strategy for the formulation of medicinal aerosols, J. Aerosol Sci., 20, 1309–1312 (1989).
25. P. L. Luisi and L. J. Magid, Solubilization of enzymes and nucleic acids in hydrocarbon micellar solutions, CRC Crit. Rev. Biochem., 20, 409–474 (1986).
26. J. Eastoe, W. K. Young, B. H. Robinson, and D. C. Steytler, Scattering studies of microemulsions in low-density alkanes, J. Chem. Soc. Faraday Trans., 86, 2883–2889 (1990).
27. S. Ross and I. D. Morrison, Emulsions, in *Colloidal Systems and Interface* (S. Ross and I. D. Morrison, eds.) John Wiley & Sons, New York, NY, 1988, pp. 267–293.
28. N. C. Miller, The effects of water in inhalation suspension aerosol formulations, in *Respiratory Drug Delivery* (P. R. Byron, ed.) CRC Press, Boca Raton, FL, 1990, pp. 249–257.
29. R. N. Dalby, E. M. Phillips, and P. R. Byron, Determination of drug solubility in aerosol propellants, Pharm. Res., 8, 1206–1209 (1991).
30. E. M. Phillips, P. R. Byron, and R. N. Dalby, Axial ratio measurements for early detection of crystal growth in suspension-type metered dose inhalers, Pharm. Res., 10, 454–456 (1993).
31. W. H. Soine, F. E. Blondino, and P. R. Byron, Chemical stability in pressurized inhalers formulated as solutions, J. Biopharm. Sci., 3, 41–47 (1992).