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Prediction and Assessment of Flammability Hazards Associated with Metered-Dose Inhalers Containing Flammable Propellants

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Several potential replacements for chlorofluorocarbons (CFCs) in metered-dose inhalers (MDIs) are flammable. The flammability hazard associated with their use was assessed using a range of MDIs containing 0–100% (w/w) *n*-butane (flammable) in HFC-134a (nonflammable) fitted with either 25-, 63-, or 100-μl metering valves or continuous valves. In flame projection tests each MDI was fired horizontally into a flame, and the ignited flume length emitted from the MDI was measured. Flame projections of ⩾60 cm were produced by all formulations fitted with continuous valves which contained ⩾40% (w/w) *n*-butane in HFC-134a. Using metering valves the maximum flame projection obtained was 30 cm. This was observed with a formulation containing 90% (w/w) *n*-butane in HFC-134a and a 100-μl valve. For a particular formulation, smaller metering valves produced shorter flame projections. Because many MDIs are used in conjunction with extension devices, the likelihood of accidental propellant vapor ignition was determined in Nebuhaler and Inspirease reservoirs and a Breathancer spacer. Ignition was predictable based on propellant composition, metered volume, number of actuations, and spacer capacity. Calculated *n*-butane concentrations in excess of the lower flammability limit [LFL; 1.9% (v/v)] but below the upper flammability limit [UFL; 8.5% (v/v)] were usually predictive of flammability following ignition by a glowing nichrome wire mounted inside the extension device. No ignition was predicted or observed following one or two 25-μl actuations of 100% *n*-butane into large volume Nebuhaler (750 ml) or Inspirease (660 ml) devices. Additionally, several other formulations containing lower proportions of *n*-butane also remained nonflammable, due to failure to reach the LFL. In the small-volume Breathancer spacer (140 ml), nonflammability was usually due to *n*-butane exceeding its UFL. In this situation further dilution during respiration could result in a flammable mixture. Using a carefully selected propellant blend, metering volume, and spacer design, environmentally acceptable flammable propellants may have considerable utility in MDIs reformulated without CFCs.

KEY WORDS: metered-dose inhaler (MDI); aerosol; formulation; flammability; propellant; spacer; reservoir.

INTRODUCTION

Due to their deleterious effect on the atmosphere, chlorofluorocarbons (CFCs) are being phased out. This includes their use as propellants in metered-dose inhalers (MDIs). Among the foreseeable alternatives are several flammable propellants (1), including HCFC-141b, (1,1-dichloro-1-fluoroethane), HCFC-142b (1-chloro-1,1-difluoroethane), HFC-152a (1,1-difluoroethane), propane, *n*-butane, isobutane (2-methylpropane), *n*-pentane, isopentane (2-methylbutane), neopentane (2,2-dimethylpropane), and DME (dimethylether). Preliminary inhalation toxicity studies on several of these are under way or have been performed in the past because of their desirable properties for aerosol and other industrial applications (2–4 and references therein). How to assess and minimize the hazards associated with the use of flammable propellants in aerosol formulations designed for inhalation, or whether they have any place in this application at all, has not been studied in detail. Dalby and Byron (1) have considered some of the challenges associated with the manufacture and testing of flammable MDIs, in addition to addressing some common attitudes which are encountered in this field. However, if the MDI is to remain a popular inhalation delivery device, it must be safe and convenient to use.

One of the dual aims of this investigation was to determine how MDIs containing flammable propellants behave in a flame projection test. One such test is performed using the Department of Transportation (Bureau of Explosives) Flame Projection Apparatus, which is derived from the analogous Chemical Specialties Manufacturers Association (CSMA) test (5). It is one of the tests used to determine whether an aerosol should carry warning labels and which transportation regulations apply. Because MDIs contain less than 4 oz of product, they are exempt from these regulations (6), nevertheless, the test should provide useful comparative data. It should be noted that the CSMA does not consider this test to be applicable to aerosols containing metering valves (5). The second aim was to predict the potential for ignition following actuation of MDIs containing potentially flammable propellants into commercially available spacer devices.

The use of a spacer or reservoir device in conjunction with an MDI is a common practice; indeed several MDIs are sold in combination with such devices (7). Spacers (essentially tubes connecting the actuator to the mouth) are known to benefit patient subpopulations which would otherwise derive little therapeutic advantage from the MDI alone (8,9, and references therein). Typically, only single actuations are made into spacer devices after the patient's mouth has closed around the mouthpiece, and he/she has begun to inhale. In a reservoir device (a large-volume chamber between the actuator and the patient's mouth) synchronization becomes unnecessary. Patients may, for convenience, make multiple actuations into such devices before inhaling, although the respirable fraction of the aerosolized drug may decrease (9).

When used in conjunction with an MDI containing one or more flammable propellant components, a spacer or reservoir provides a buffer between flammable vapor in the aerosol flume and any ignition source in the vicinity. Theoretically, if the flammable vapor concentration in the extension device is below that which can support combustion (the lower flammability limit; LFL), then a patient cannot inhale, or be capable of exhaling, a flammable mixture. Such a situation would seem to offer a wide safety margin in all reasonably foreseeable situations. This paper attempts to predict which propellant blend and valve metering combinations might be expected to yield nonflammable vapor concentra-

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tions following spraying into commercially available spacers.

THEORY

Metering valves function by releasing a specific volume of liquified product, V_M (ml), following actuation. The theoretical weight of product released per actuation, W_M (g), is given by Eq. 1, where ρ is product density (g/ml).

$$W_M = V_M \rho \tag{1}$$

If the product contains F (% by weight) of liquified flammable propellant, the number of moles of flammable propellant released, $\mathrm{Mol_F}$, is given by

$$\mathrm{Mol_F} = nW_M F/100\ M_F \tag{2}$$

where M_F is the molecular weight of the flammable propellant, and n is the number of actuations. If the sprayed product contains two or more flammable propellants, then $\mathrm{Mol_F}$ can be calculated from

$$\mathrm{Mol_F} = nW_M/100\left(\sum_{i=n}^{i=1} F_i/M_{F,i}\right) \tag{3}$$

If it is assumed that the propellant behaves ideally, then 1 mol of propellant occupies 22400 ml following complete vaporization at atmospheric pressure and 25°C. The volume of flammable propellant vapor generated in these circumstances, V_F (ml), is

$$V_F = 22400\ \mathrm{Mol_F} \tag{4}$$

If the product is sprayed into a spacer or reservoir device of volume V_S (ml), the concentration of flammable vapor in air, C_F (% by volume), is

$$C_F = 100\ V_F/V_S \tag{5}$$

For a blend containing only one flammable component, if C_F falls outside the flammable range (between the lower and the upper flammability limit) of the propellant vapor, no ignition is expected.

MATERIALS AND METHODS

Preparation of Metered-Dose Inhalers. Two component propellant blends of *n*-butane (A17, Phillips 66, Bartlesville, OK) and HFC-134a (Du Pont, Wilmington, DE) or DME[2] (Dymel A, Du Pont, Wilmington, DE) were prepared. These contained from 0 to 100% by weight of each propellant. All propellants were filled using a pressure burette (Aerosol Laboratory Equipment Corporation, New York), overpressurized with nitrogen, into aerosol bottles precrimped with appropriate valves. All crimping was performed using small-scale aerosol pressure packaging equipment (Pamasol, Pfaffikon, Switzerland). The total fill weight was 20 g in all cases. Aerosols were packaged in 120-ml plastic-coated glass pressure-resistant bottles (Wheaton Glass, Mays Landing, NJ) fitted with 25-, 63-, or 100-μl metering valves (BK356 series valves, Bespak, Cary, NC) or BK356 valves modified to provide continuous operation by deliberately enlarging the lower seat orifice to prevent metering chamber isolation during actuation. No drug or surfactant was incorporated into the aerosols. Valve metering reproducibility was determined in triplicate from average container weight loss following 10 actuations of each formulation. Propellant density was determined at 25°C using a vibrating U-tube densitometer (Model DMA 55, Anton Parr AG, Graz, Austria) modified to accommodate volatile propellants.

Flame Projection Tests. Each MDI was fired horizontally from a distance of 10 cm into the tip of a 2-cm-long, continuously burning propane flame. An oral inhalation actuator with an orifice diameter of 0.4 mm was used for each test (Model BK648 prototype, Bespak, Cary, NC). The distance flames from the MDI flume projected beyond the propane flame was visually determined against a linear scale mounted horizontally behind the apparatus. Triplicate experiments were performed inside an extraction hood with the fan switched off, to avoid altering the flume characteristics.

Flammability Assessment in Spacers. Each formulation was actuated one, two, or three times into commercially available spacer or reservoir devices modified to include an ignition coil. Reservoir devices tested were the Nebuhaler (Astra Pharmaceuticals, in conjunction with a BK648 actuator) and the Inspirease[3] (Key Pharmaceuticals). The Breathancer spacer device (Geigy Pharmaceuticals) was tested with a sealing gasket around the valve stem/actuator junction to prevent propellant leakage and with the mouthpiece blocked. The ignition coil consisted of 20 cm of nichrome wire wound into a 1-mm-diameter, 4-mm-long coil. The coil protruded from the tip of a 1-cm-diameter, heat-resistant micarta tube (Acme Plastics, Inc., Alexandria, VA) inserted into the center of each device. Shorting was prevented by glass-fiber sheaths around the leads to the coil. Immediately following the last actuation the ignition coil was supplied for 5 sec with a 20-V ac current from a variable autotransformer (Fisher Scientific, Type 9-521-110V2, St. Louis, MO). This induced an intense orange/yellow glow. Following either ignition or no response, the contents of the spacer were removed using a vacuum. Each experiment was repeated five times. The experiment was performed behind a polycarbonate shield inside an extraction hood. The volume of each spacer was determined from the amount of water it was able to hold with all openings blocked.

RESULTS

Table I indicates the measured density of each liquified propellant blend. The measured container weight loss per actuation was typically within 10% of the expected weight

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[2] *n*-Butane a is low-vapor pressure propellant that could replace CFC-11 in MDIs. HFC-134a (1,1,1,2-tetrafluoroethane) and DME are examples of nonflammable and flammable high-vapor pressure propellants, respectively. They are potential alternatives to CFC-12 in the reformulation of MDIs.

[3] The thin, collapsible plastic cylinder that comprises this spacer was replaced with a Plexiglas tube (Plywood and Plastics, Inc., Richmond, VA) with the same internal dimensions as the fully extended original device. The original device melted during repetitive testing.

Table I. Measured Density of Propellant Blends

% (w/w) *n*-butane in HCFC-134a	Liquid density (g/ml, 25°C)	% (w/w) *n*-butane in DME	Liquid density (g/ml, 25°C)
0	1.21	0	0.66
10	1.06	10	0.65
20	0.95	20	0.63
30	0.86	30	0.62
40	0.80	40	0.62
50	0.74	50	0.60
60	0.69	60	0.60
70	0.66	70	0.59
80	0.62	80	0.58
90	0.60	90	0.58
100	0.57	100	0.57

loss per actuation [Eq. (1)]. Formulations containing a high proportion of DME were slightly more erratic, probably as a result of elastomer swelling in the metering valve. The flame projection for the HFC-134a/*n*-butane formulations fitted with metering and continuous valves is shown in Fig. 1. Flame projections of greater than 60 cm could not be quantified due to the dimensions of the extraction hood.

The internal volume of the Nebuhaler, Inspirease, and Breathancer devices was found to be 750, 660, and 140 ml, respectively. Figures 2–4 show the calculated percentage of flammable (*n*-butane) vapor in air (by volume) following one, two, or three actuations from the HFC-134a/*n*-butane formulations into each spacer from 25-, 63-, and 100-μl valves. Figures 5–7 show the calculated *n*-butane, DME, and total vapor concentrations in each extension device, following one, two, or three shots from each *n*-butane/DME formulation fitted with a 63-μl metering valve. An experimentally observed ignition event is shown by a filled square (■), while failure to ignite is shown by an open square (□). An ignition event was defined as either an explosion or sustained burning during one or more tests. Each test was replicated a minimum of five times. The lower flammability limit (LFL) and upper flammability limit (UFL) of *n*-butane [1.9–8.5% (v/v)] (10) and DME [3.3–27% (v/v)][4] (10) are also indicated and represent the concentration below and above which *n*-butane or DME are not expected to ignite in air when present as the only flammable propellant.

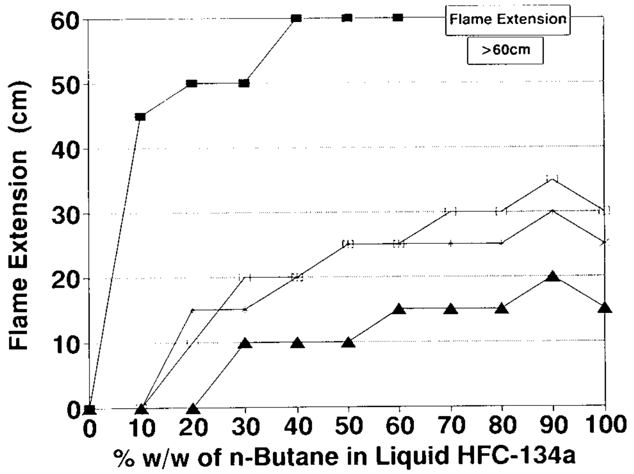

Fig. 1. Effect of valve type and volume and propellant composition on the length of flame projection. Continuous valve (■). Metering valves: 100 (□), 63 (*), and 25 (△) μl. Measurements were made to the nearest 5 cm. *n* = 3 for each propellant/valve combination.

DISCUSSION

Flame Projection Tests. Metering valves with volumes typically encountered in metered-dose inhalers (25–100 μl) dramatically reduced the flame projection of all propellant blends compared to similarly designed continuous valves (Fig. 1). The reduction in flame projection was more dramatic in the case of 25-μl valves compared to 63- and 100-μl valves. Typically, 25- and 63-μl valves reduced the observed flame projection to one-quarter and one-half, respectively, of the projection produced by an analogous continuous valve. This was accompanied by a reduction in the incidence of burning propellant remaining in the actuator following termination of the spray. If a patient were unfortunate enough to ignite the flume leaving the actuator mouthpiece of an MDI, the resulting burn due to flammable propellant would be of very short duration (too short for accurate, unaided measurement) and length, compared to that from a similar propellant system employing a continuous valve.

Single Flammable Propellant Studies in Reservoirs. Figures 2 and 3 show generally excellent agreement between a calculated *n*-butane concentration in the flammable range [1.9–8.5% (v/v)] following actuation and an experimentally observed ignition event. It was impossible to ignite (using a glowing coil inside the reservoir cavity) 100% *n*-butane containing formulations following one or two 25-μl actuations into a Nebuhaler (Fig. 2c) or Inspirease (Fig. 3c) reservoir. This observation was in agreement with a calculated *n*-butane concentration below the LFL of 1.9% (v/v). However, following three 25-μl actuations, formulations containing more than 50% (w/w) *n*-butane in HFC-134a did ignite (Figs. 2c and 3c) as the *n*-butane concentration exceeded 1.9% (v/v). The same predictable ignition pattern was observed with 63- and 100-μl valves fired one, two, or three times. Only 100-μl valves fired three times produced calculated *n*-butane concentrations which slightly exceeded the UFL [8.5% (v/v)] following spraying into the Nebuhaler or Inspirease device. Unexpected flammability in these formulations could be due to erratic valve metering, incomplete vapor mixing, vapor layering due to density differences, or erroneous theoretical assumptions. Patients are typically instructed to actuate a MDI into a reservoir device once prior to inhalation. However, formulations showing no ignition following two or three actuations have an inherent additional safety margin if misused. With all propellant compositions and valve metering volumes where ignition was not observed, it is reasonable to suggest that the use of an MDI in combination with a Nebuhaler or Inspirease reservoir is likely to preclude risk from flammability, even with an ignition source inside or just beyond the device mouthpiece. Hydrocarbons are generally flammable at lower concentra-

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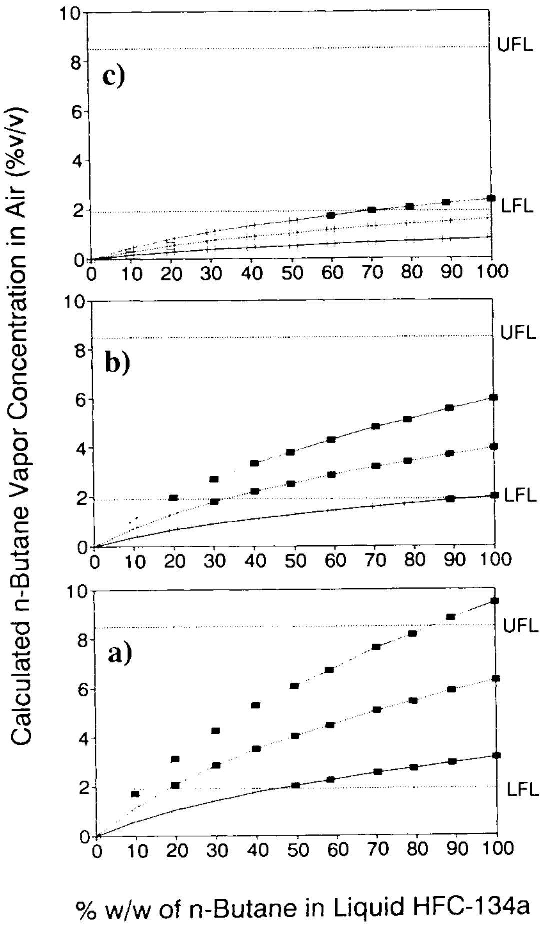
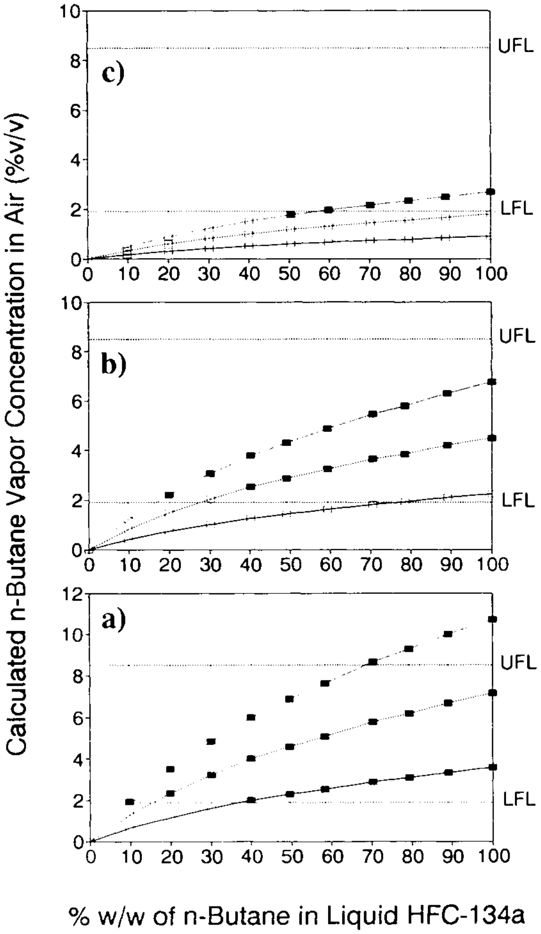
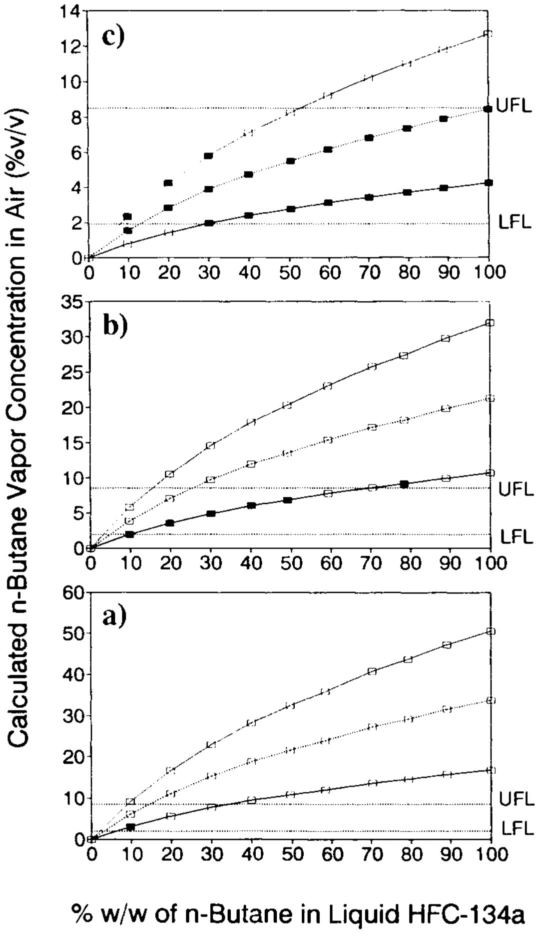
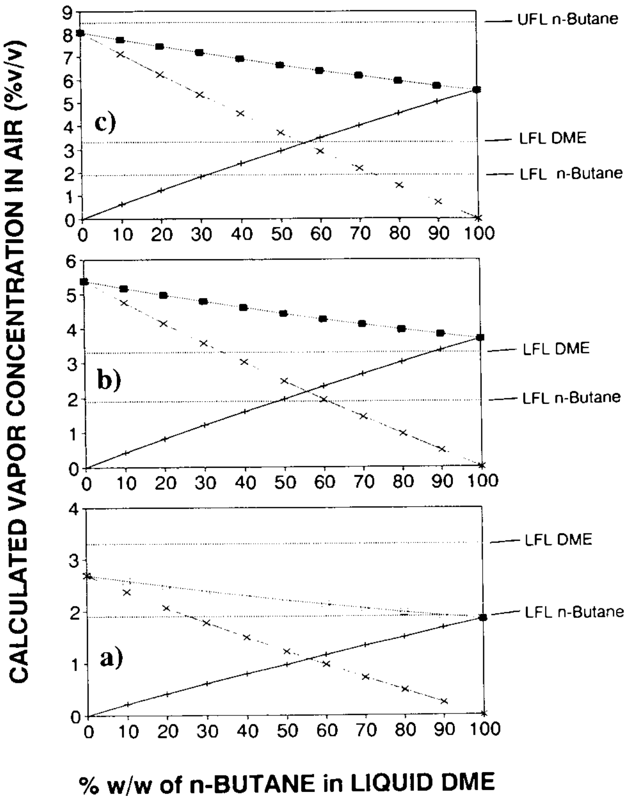
[4] The flammability limits for DME quoted in Ref. 11 are 3.3–18% (v/v); those quoted in Ref. 10 are 3.4–27% (v/v). The flammability limits of DME are assumed to be 3.3–27% (v/v) in this paper.

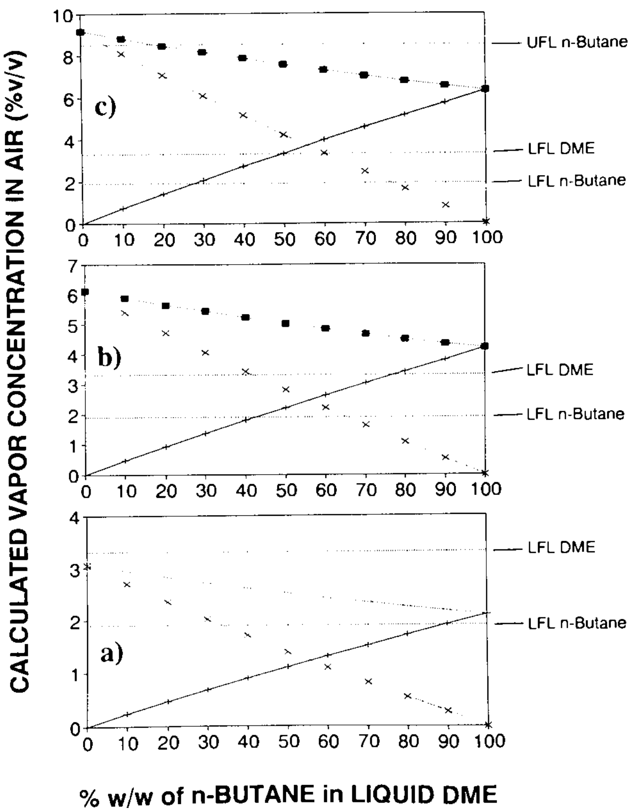


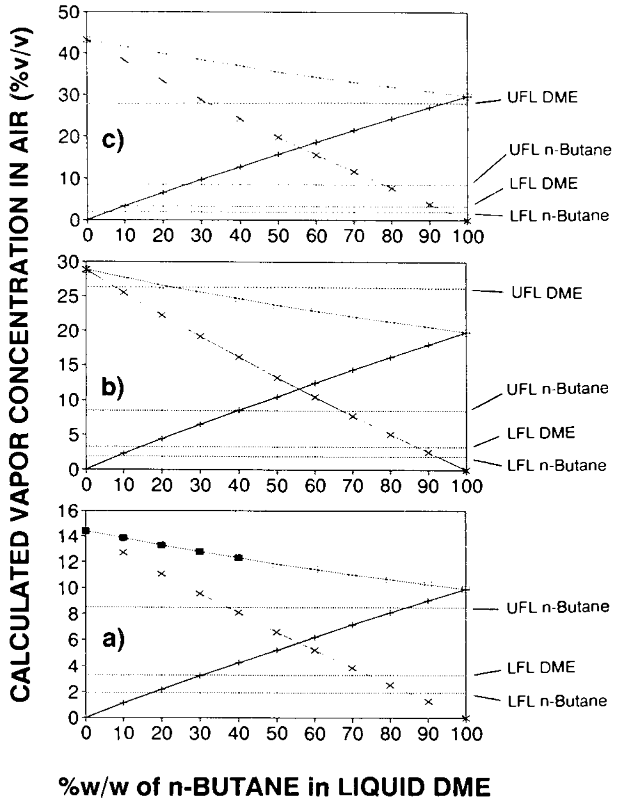




Figs. 2–4. Calculated *n*-butane vapor concentrations in the Nebuhaler (Fig. 2, upper left), InspirEase (Fig. 3, upper right), and Breathancer (Fig. 4, lower left), following one (lower curve), two (middle curve), or three (upper curve) shots of each HFC-134a/*n*-butane formulation from 100-μl (a), 63-μl (b), and 25-μl (c) metering valves. Filled squares represent formulations which ignited, while failure to ignite is shown by an open square. The upper (UFL) and lower (LFL) flammability limits of *n*-butane are also indicated.







Figs. 5–7. Calculated *n*-butane (+), DME (x), and total vapor concentrations (■ and □) in the Nebuhaler (Fig. 5, upper left), InspirEase (Fig. 6, upper right), and Breathancer (Fig. 7, lower left), following one (a), two (b), or three (c) shots of each DME/*n*-butane formulation from a 63-μl metering valve. Filled squares represent formulations which ignited, while failure to ignite is shown by an open square. The upper (UFL) and lower (LFL) flammability limits of *n*-butane and DME are also indicated.

tions in air than other flammable propellants. For example, the LFL of DME (11), HFC-152a (12), and HCFC-141b (13) is 3.3, 3.9, and 7.6% (v/v), respectively, compared to the LFL of iso-butane (10), *n*-butane (10), and propane (10), which is 1.9, 1.9, and 2.3% (v/v), respectively. Therefore, these data represent a worst-case scenario, with most other flammable propellants presenting an even lower risk than *n*-butane. Safety would be further enhanced in the Inspirease reservoir, which incorporates the valve stem seat and spray orifice within the spacer molding so that it is possible to fire the MDI only into the spacer cavity. A conventional actuator connects the MDI to the Nebuhaler, so it is possible to detach the actuator and inadvertently fire into an ignition source in the vicinity.

Single Flammable Propellant Studies in a Spacer. The incidence of ignitions following spraying into a Breathancer spacer was again predictable based on calculated *n*-butane vapor concentrations (Fig. 4). For 25-μl valves (Fig. 4c), *n*-butane contents up to only 20% (w/w) remained unignitable following a single shot due to failure to reach the LFL. Due to the small volume of the Breathancer spacer (140 ml), the *n*-butane vapor concentration exceeded the LFL in all other propellant blends after two or three shots. Predictably, three shots of formulations containing more than 30% (w/w) *n*-butane failed to ignite, probably as a result of the *n*-butane concentration exceeding the UFL. Failure to ignite due to the UFL being exceeded cannot be considered as safe as nonignition due to failure to reach the LFL, because subsequent dilution, for example, by inhalation, could result in a flammable mixture. Using 63- and 100-μl valves in combination with a Breathancer (Figs. 4a and b) produced generally predictable results, except that no ignition occurred with occasional valve/propellant compositions predicted to yield *n*-butane concentrations in the flammable range. This may have been due to reasons mentioned earlier, the collapsible (nongastight) design of the Breathancer spacer or propellant vapor displacing air, and therefore oxygen, from the interior of the device. The latter effect should be more significant in a small-volume spacer such as the Breathancer, where the percentage of air displaced by propellant vapor should be larger than in a high-capacity reservoir device. For completeness, multiple actuations were made into the Breathancer spacer. However, in practice a patient would be ill advised to attempt such a procedure due to the necessity of at least attempting to coordinate actuation with inhalation in order to obtain an adequate respirable dose.

Two Flammable Propellants in Reservoir and Spacer Devices. When mixtures of two flammable propellants (*n*-butane and DME; Figs. 5–7) were fired one, two, or three times into a Nebuhaler or Inspirease spacer, ignition was observed only when the vapor concentration of *n*-butane exceeded its LFL [1.9% (v/v)] and/or the DME vapor concentration exceeded its LFL [3.3% (v/v)]. Ignition was not observed when the total flammable vapor concentration exceeded the LFL of an individual propellant, but the concentration of that propellant failed to reach its particular LFL. An example of this characteristic is shown in Fig. 5a for 30% (w/w) *n*-butane in DME. The calculated total flammable vapor concentration exceeded the LFL of *n*-butane, but the concentration of *n*-butane failed to reach its LFL, and no ignitions were observed. This observation cannot be generalized to all combinations of flammable propellants without further testing.

Due to the small volume of the Breathancer spacer, there were no ignition failures attributable to both flammable propellants failing to reach their associated LFL, even after only one 63-μl shot. However, ignition failures did occur due to one or both flammable propellant vapor concentrations exceeding their UFL. Ignitions were not generally observed when one flammable propellant vapor exceeded its UFL, while the other was in its flammable range. Following one 63-μl shot of 50–80% (w/w) *n*-butane in DME into a Breathancer, no ignitions were observed despite calculated *n*-butane and DME vapor concentrations in their respective flammable range. This again suggests that oxygen displacement is a significant factor in suppressed flammability in small-volume spacers.

CONCLUSIONS

Following actuation of MDIs containing flammable propellants into commercially available reservoir and spacer devices, a strong correlation was observed between predicted flammable vapor concentrations in air and experimentally observed ignition events. Therefore, the maximum proportion of flammable propellant in a liquified product that should result in a nonflammable vapor concentration below the LFL after spraying into an extension device can be determined a priori. For example, the maximum percentage of *n*-butane [molecular weight = 58.1 g/mol, LFL = 1.9% (v/v)] in nonflammable HFC-134a that should result in a nonignitable vapor following a single 63-μl actuation into a 500-ml reservoir device is 39% (w/v) or 55% (w/w).[5] This information is useful during the initial preparation of test formulations. Additionally, the data suggest that when an extension device is permanently attached to an MDI, ignition of the flammable flume produced by some formulations will be practically impossible, even if an ignition source (such as a cigarette) is introduced into the spacer immediately following spraying. The design of Nebuhaler and Inspirease reservoir devices is superior to that of the Breathancer for this purpose due to their large dilution effect. The presence of obstacles to the inadvertent introduction of an ignition source into the spacer cavity, namely, an exit valve in the Nebuhaler mouthpiece and a reed in the Inspirease mouthpiece, is also a useful, though presumably unintentional, design feature.

Even in the absence of ancillary extension devices, a MDI formulated with a single flammable component was found to produce a significantly shorter flame projection than the same formulation packaged using a continuous valve. A carefully selected combination of propellant, valve, and (optional) spacer can conspire to produce an acceptably safe MDI formulation containing one or more flammable propellants.

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[5] From the density information in Table I, 50 and 60% (w/w) *n*-butane in HFC-134a correspond to 37 and 41% (w/v), respectively, at 25°C. Linearly interpolating between these values, 39% (w/v) is equivalent to 55% (w/w).

REFERENCES

1. R. N. Dalby and P. R. Byron. Metered dose inhalers containing flammable propellants—perspectives and some safety evaluation procedures. *Pharm. Tech.* 15(10):54–66 (1991).
2. S. Zakhari. Propane (Chap. 4), Butane (Chap. 5), and Isobutane (Chap. 6). In L. Goldburg (ed.), *Non-Fluorinated Propellants and Solvents for Aerosols,* CRC Press, Boca Raton, FL, 1977, pp. 49–72.
3. S. Zakhari and D. M. Aviado. Cardiovascular toxicology of aerosol propellants, refrigerants and related solvents. In E. W. Van (ed.), *Cardiovascular Toxicology,* Raven Press, New York, 1982, pp. 281–326.
4. J. J. Daly, Jr. Properties and toxicology of CFC alternatives. *Aerosol Age* February:26 (1990).
5. Revised flammability test methods for aerosol products. In *Aerosol Guide,* 7th ed., Chemical Specialties Manufacturers Association, Inc., Washington, DC, 1981, pp. 13–23.
6. *Code of Federal Regulations,* Part 49 (Transportation), Section 173.306, Government Printing Office, Washington, DC, October 1990.
7. *Physicians Desk Reference,* 45th ed., Medical Economics Co., Oradell, NJ, 1991.
8. P. R. Byron. Aerosol formation, generation and delivery using metered systems. In P. R. Byron (ed.), *Respiratory Drug Delivery,* CRC Press, Boca Raton, FL, 1990, p. 173.
9. A. R. Clark, G. Rachelefsky, P. L. Marson, M. J. Goldenhersh, and A. Hollingworth. The use of reservoir devices for the simultaneous delivery of two metered-dose inhaler aerosols. *J. Allergy Clin. Immunol.* 85(1):75–79 (1990).
10. N. I. Sax and R. J. Lewis, Sr. (eds.). *Dangerous Properties of Industrial Materials,* 7th ed., Vols. I–III, Van Nostrand Reinhold, New York, 1989.
11. *Material Safety Data Sheet (MSDS) on Dymel A Aerosol propellant* (E-97118-1), Du Pont Company, Wilmington, DE, 1989.
12. *Material Safety Data Sheet (MSDS) on Dymel 152a Aerosol propellant* (E-94824-1), Du Pont Company, Wilmington, DE, 1989.
13. *Product Safety Data Sheet on HCFC-141b,* Allied Signal, Inc., Morristown, NJ, 1989.