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RESEARCH PAPER

Compatibility Evaluation of Metered-Dose Inhaler Valve Elastomers with Tetrafluoroethane (P134a), a Non-CFC Propellant

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ABSTRACT

Compatibility of propellants, excipients, and solvents with the components of the valve greatly influences performance of metered-dose inhalers (MDIs). Ozone-friendly hydrofluoroalkane propellant 134a has potential for use as a chlorofluorocarbon (CFC) replacement. No suitable replacement for propellant 11 and 114 has yet been found and the problems arising from this may be overcome by use of ethanol as a solvent. In this study, compatibility of MDI valve elastomers Dowty Nitrile 0117, White Buna, and Type 674 (B) with P134a placebo formulations having different concentrations of ethanol was investigated. The results indicate that formulations containing no ethanol adversely affected the functioning of the valves. Higher concentrations of ethanol improved valve performance, but showed increased leakage. Physical characteristics of the valve elastomers evaluated by determining swelling caused after exposure to the P134a placebo formulations exhibited increased swelling with increasing concentrations of ethanol in the formulation.

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INTRODUCTION

Metered dose inhalers (MDIs) are the preferred means of delivering drugs to the lungs for treatment of asthma and chronic obstructive pulmonary disease (1). MDIs contain an active drug dissolved or suspended in a propellant. Typically chlorofluorocarbons (CFCs) are used as the solvent (P11/P114) and propellant (P12) in MDI formulations (2). However, CFCs currently used in most MDI products cause environmental damage because they deplete the stratospheric ozone (3). Non-ozone-depleting hydrofluoroalkane propellant 1,1,1,2-tetrafluoroethane (P134a) is considered as the most viable CFC alternative for use in MDIs by the International Pharmaceutical Aerosol Consortiums for Toxicology Testing (IPACT) (4). There are still no suggested replacements for propellants 11 and 14. The problems arising from this may be overcome by the use of ethanol as a solvent with P134a to replace P11 and P114. Ethanol is a suitable choice because it is the most commonly used solvent and has a long history of acceptable use (5).

Two major problems associated with metered valve performance are valve sticking and can leakage (6). High vapor pressure in the MDI requires the seal to be efficient to prevent leakage during storage. Elastomeric gaskets of the MDI valve give a satisfactory seal. However, they may swell or shrink in presence of propellant, adversely affecting the valve function. Therefore, the compatibility of P134a with the MDI valve elastomers needs to be evaluated.

EXPERIMENTAL

Materials

Neotech Spraymiser 25 μl valve (Neotechnic Limited, Lancashire, England), Valois DF30 50 μl valve (Valois, 78160 Mauli-Le-Hois, France), Bespak 356 compound B 50 μl valve (Bespak, Norfolk, England), Propellant 134a (Dupont, Wilmington, DE), Cebal Mikoflex lined aluminum cans (Press Part Manufacturing, England), and absolute ethyl alcohol (Florida Distillery Company, Lake Afred, FL) were used.

Formulation

Placebo aerosol formulations were prepared by using four concentrations of ethanol (0, 2, 10, and 30% v/v). These four formulations were prepared for the MDI valves Neotech 25 μl, Valois 50 μl, and Bespak 50 μl, containing Dowty Nitrile 0117, White Buna, and Type 674 (B) as the elastomer. The required amount of ethanol was filled in each aerosol can and sufficient propellant 134a was added by pressure filling after crimping the valves according to the manufacturer's recommended specifications onto the cans. Each can had a total fill volume of 16 ml. Twenty cans from each batch were stored at 24 (room temperature), 37, and 45°C for 1, 2, and/or 3 months in inverted (IV) and/or upright (UP) positions.

Shot Weight Study

Shot weight is the term used to indicate the total weight of contents (drug + propellant + excipient) that is emitted (shot) from the can when it is actuated, and is measured by container weight loss. Ten cans from each batch at their storage conditions were tested for shot weight studies. The shot weight was determined at three points of the can usage, in the beginning, middle, and at the end. The stepwise procedure for this determination was as follows:

The valve was primed by actuating the inverted can five times and then the can was weighed. One shot was fired and the can was reweighed. The difference in weight gave the weight of the first shot. The process was repeated to obtain the weight of 10 individual shots. An average of these determinations represented the shot weight in the beginning of the product use. The contents of the can were then purged to about 50% of the initial contents by actuating the can for the required number of times, and then the weight of 10 individual shots were determined. The average of these represented the shot weight at the middle of the product use. The contents of can were purged again until about 20% of the initial weight was left in the can. The weight of 10 individual shots was determined, and the average of these represented the end of the product use.

Leakage Test

Ten cans of each batch at their storage conditions were tested for leakage. The cans were stored at storage conditions for a minimum of 4 weeks. Each can was weighed before and after storage and any loss from initial weight was determined. The loss of weight was extrapolated for 1 year by the following formula given in the USP (7):

$$L/Y = (365)(24/T)(W_1 - W_2)(100)(1/W_0)$$

where L/Y is loss of weight per year, T is storage time in hours, W_1 is initial weight of the can, W_2 is final weight of the can after it has been stored for T hr, and W_0 is net fill weight of the can.

Gasket Swelling

Gasket swelling was determined by measuring the expansion in diameter and thickness of the gasket after it had been exposed to the can contents. The diameter was measured with a Vernier caliper and the thickness was measured using a thickness gauge. The average determination of the 10 gaskets before exposure was taken as the average initial diameter and thickness. After the leakage test was performed, 5 cans from each of the differently stored 10 cans were selected randomly for gasket diameter and thickness measurement. The gaskets were removed from valve after puncturing each can to allow the propellant to escape, and measurements (thickness and diameter) were taken immediately. The average of five determinations was used to compute the percent swelling of the gasket using the following relationship:

$$\text{Percent swelling} = \frac{(\text{increase in thickness or diameter})\,(100)}{(\text{initial thickness or diameter})}$$

RESULTS AND DISCUSSION

The metering valve has the essential function of measuring accurately and repetitively small volumes of the MDI formulations. The effect of P134a on MDI valve performance was evaluated by determining the shot weights during the beginning, middle, and end of MDI usage. The average of the cumulative shot weights (10 shot weights of each of the 10 cans) for all the prepared formulations was determined. Formulations containing 0% v/v ethanol were found to have two major defects in valve functioning. These were either sticking (valve did not spray) or continuous spray (valve sprayed continuously) problems. The problems of sticking and continuous spray were observed with the Dowty Nitrile 0117 MDI valve elastomer, while the Type 674 (B) and White Buna elastomers showed only the sticking problem.

The valve malfunctioning was reduced with the introduction of 2% v/v ethanol in the formulations and was totally eliminated when higher concentrations of ethanol (10% v/v) were used. The detailed results of this evaluation are presented in Tables 1–3. The reason for better valve performance at higher ethanol content in the MDI formulations appears to be the lubrication provided by ethanol to the valves. This would also explain the reduction of sticking problem with an increase in ethanol content.

The storage positions (UP and IV) and temperature at which MDIs were stored did not appear to affect the valve performance.

Leakage Rate

The leakage rate was determined by finding the difference in weight of each can before and after storage at the specified conditions. In the case of MDI valve containing Dowty Nitrile 0117 elastomer, a rank-order correlation was observed between the percent loss per year and the storage temperature (Fig. 1). The loss was less when the cans were stored at room temperature (RT) than when the cans were stored at 37°C. The position of the can during storage (UP or IV) did not appear to influence leakage rate. Percent loss per year increased with increasing concentrations of ethanol in the formulations. This increase in loss was more pronounced when the cans were stored at 37°C than when cans were stored at room temperature.

The effect of ethanol, storage temperature, and storage position on percent loss per year of MDI valve formulations containing White Buna and Type 674 (B) elastomers were similar to that shown by Dowty Nitrile 0117 valve elastomer formulations (Figs. 1–3).

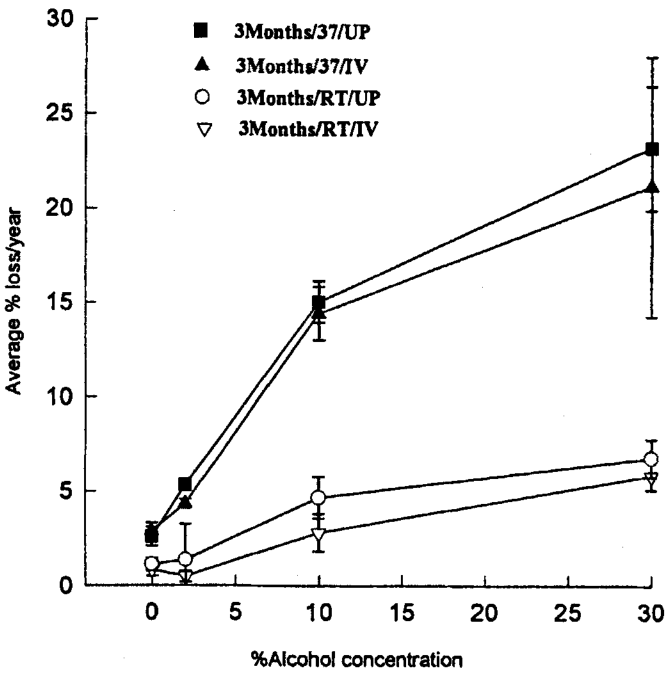

Figure 1. Leak rate plot for Dowty Nitrile 0117 elastomer.

Table 1

Dowty Nitrile 0117 Elastomer Metering Valve Performance

Formulation Description		Shot Weights in mg (%RSD) 1 Month 37 IV	45 IV	3 Months RT UP	RT IV
P134a with 0% v/v alcohol	Beginning	35.3 (2.0%)	36.4 (4.8%)	36.1 (0.9%) 3/10 ST	35.1 (1.3%) 2/10 CS
	Middle	34.9 (2.9%) 3/10 ST	36.3 (3.1%) 2/10 ST	35.6 (1.1%) 1/10 ST	34.9 (1.7%) 1/10 ST
	End	35.6 (3.1%) 2/10 ST	36.5 (4.2%) 2/10 ST	6/10 ST	34.1 (7.5%) 2/10 ST
P134a with 2% v/v alcohol	Beginning	34.0 (2.3%)	34.5 (4.6%) 1/10 CS	35.0 (0.7%)	34.6 (1.3%)
	Middle	33.5 (2.2%)	33.6 (2.4%) 1/10 CS	33.9 (1.1%)	34.0 (1.8%) 1/10 CS
	End	33.6 (2.5%)	33.7 (2.6%)	33.9 (1.4%)	34.4 (1.4%)
P134a with 10% v/v alcohol	Beginning	32.4 (2.1%)	32.6 (1.6%)	33.1 (0.9%)	31.7 (1.4%)
	Middle	31.6 (2.3%)	32.4 (2.3%)	32.5 (1.3%)	31.6 (1.3%)
	End	32.3 (2.8%)	32.7 (2.2%)	32.5 (1.2%)	30.0 (1.6%)

ST: Valve sticking; CS: valve sprays continuously (e.g., 3/10 ST indicates that 3 out of 10 tested valves were sticking); %RSD: percent relative standard deviation (N = 100).

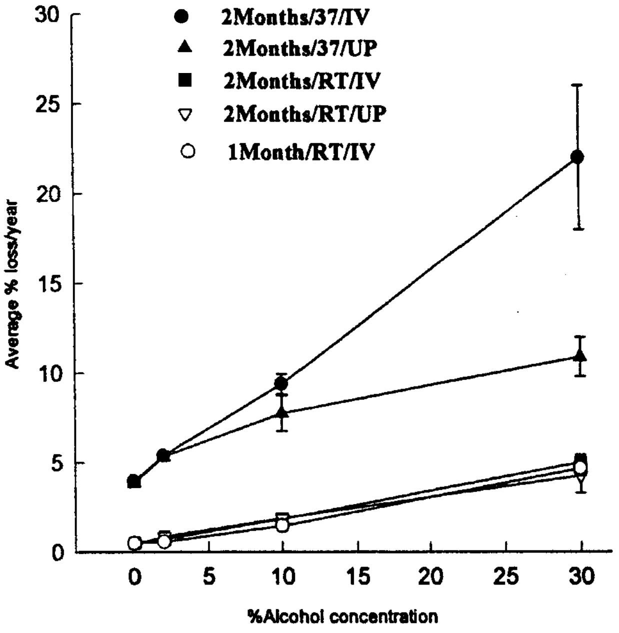

Figure 2. Leak rate plot for White Buna elastomer.

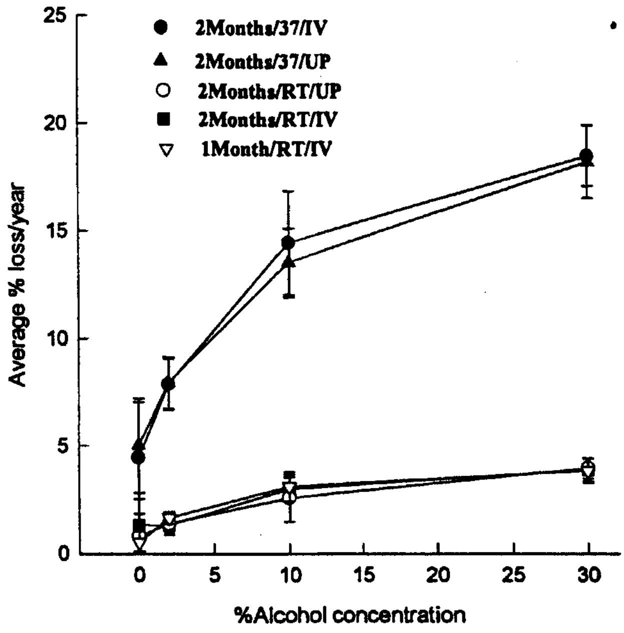

Figure 3. Leak rate plot for Type 674 (B) elastomer.

Table 2

White Buna Elastomer Metering Valve Performance

Formulation Description		Shot Weights in mg (%RSD) 1 Month RT IV	1 Month RT UP	2 Months RT IV	2 Months 37 IV
P134a with 0% v/v alcohol	Beginning	59.68 (1.62)	58.07 (2.70)	58.88 (2.38)	61.6 (2.89)
	Middle	59.72 (2.66)	59.15 (1.51)	59.5 (1.48)	60.4 (2.93) 2/10 ST
	End	60.26 (1.80)	59.56 (1.35) 1/10 ST	59.19 (1.61) 3/10 ST	60.3 (2.75) 3/10 ST
P134a with 2% v/v alcohol	Beginning	56.33 (2.56)	57.19 (2.34)	57.30 (2.90)	59.99 (2.39)
	Middle	27.26 (1.24) 1/10 ST	56.19 (1.41)	55.83 (2.55)	57.29 (1.47) 1/10 ST
	End	56.49 (1.33) 2/10 ST	54.92 (3.94) 1/10 ST	54.94 (2.72)	55.50 (1.95)
P134a with 10% v/v alcohol	Beginning	53.39 (2.53)	51.00 (3.45)	52.58 (3.59)	53.23 (20.7)
	Middle	51.79 (1.84)	51.4 (4.22)	50.99 (1.96)	52.71 (3.44)
	End	50.65 (2.89)	50.2 (3.71)	51.33 (5.62)	52.71 (3.44)

ST: Valve sticking (e.g., 3/10 ST indicates that 3 out of 10 tested valves were sticking); %RSD: percent relative standard deviation (N = 100).

No significant difference between the leakage rates of the MDI stored at 1 month/RT/IV and 2 months/RT/IV was observed for MDI valve formulations containing White Buna (Fig. 2) and Type 674 (B) (Fig. 3) elastomers. Similar results were obtained for MDI formulations containing Dowty Nitrile 0117 elastomer stored at 1 month/37/UP and 3 months/37/IV (Fig. 1). Hence, no difference in the leakage rate was observed for MDI stored under similar conditions for 1, 2, or 3 months. The valve elastomers appear to reach an equilibrated state with their can contents when stored for 1 month or longer.

Swelling Characteristics

According to the manufacturers of the valves, swelling in excess of 5–10% in valve elastomer dimensions may affect the metering valve performance. Swelling of valve elastomer was observed in all MDI valve formulations. In the case of Dowty Nitrile 0117 elastomer, the increase in swelling increased with an increase in ethanol concentration in the formulation (Table 4). This increase was more pronounced in thickness than in diameter. Temperature and duration of the storage did not appear to have any affect on the Dowty Nitrile 0117 elastomer swelling.

The White Buna elastomer also showed increase in swelling with an increase in ethanol concentration in the formulations with one exception (Table 5). The elastomer for the 2% v/v ethanol formulation stored at 1 month/RT/IV showed 1.65% increase in diameter and 3.64% increase in thickness compared to the increase of 2.53 and 7.48%, respectively, for 0% v/v formulation stored under the similar conditions. The effect of ethanol on Type 674 (B) elastomer was similar to the effects observed for Dowty Nitrile 0117 valve elastomers (Table 6).

Table 3

Type 674 (B) Elastomer Metering Valve Performance

Formulation Description		Shot Weights in mg (%RSD) 1 Month RT IV	1 Month RT UP	2 Months RT IV	2 Months 37 IV
P134a with 0% v/v alcohol	Beginning	59.00 (1.57) 2/10 ST	57.12 (2.14)	59.74 (2.76)	59.61 (2.17)
	Middle	57.72 (1.46)	56.51 (1.77)	57.14 (1.69) 1/10 ST	60.82 (1.81)
	End	6/10 ST	55.70 (2.10) 2/10 ST	57.32 (1.95) 1/10 ST	60.30 (1.26)
P134a with 2% v/v alcohol	Beginning	59.07 (1.21)	56.8 (2.24)	58.51 (2.04)	60.90 (1.91)
	Middle	56.40 (1.56) 1/10 ST	55.4 (1.70)	55.56 (2.19) 1/10 ST	58.40 (1.83)
	End	56.07 (1.30)	55.7 (1.77)	55.91 (0.87)	58.20 (1.74)
P134a with 10% v/v alcohol	Beginning	55.71 (2.00)	54.21 (2.61)	55.30 (1.95)	59.60 (1.93)
	Middle	54.16 (1.57)	56.28 (1.28)	54.30 (1.86)	57.12 (2.60)
	End	54.49 (1.52)	59.26 (4.63)	54.70 (1.48)	56.72 (3.28)

ST: Valve sticking; (e.g., 3/10 ST indicates that 3 out of 10 tested valves were sticking); %RSD: percent relative standard deviation ($N = 100$).

Table 4

Dowty Nitrile 0117 Elastomer Swelling

Formulation Description	% Increase in Diameter (%RSD) 1 Month 45°C IV	% Increase in Diameter (%RSD) 1 Month 37°C IV	% Increase in Thickness (%RSD) 1 Month 45°C IV	% Increase in Thickness (%RSD) 1 Month 37°C IV
P134a with 0% v/v alcohol	0.30 (0.6)	1.20 (0.6)	3.90 (1.2)	2.89 (1.6)
P134a with 2% v/v alcohol	1.20 (0.4)	1.80 (0.2)	4.28 (0.9)	2.51 (0.8)
P134a with 10% v/v alcohol	2.30 (0.4)	2.50 (0.3)	6.60 (1.6)	5.03 (1.7)
P134a with 30% v/v alcohol	2.90 (0.4)	2.70 (0.5)	9.18 (1.1)	6.29 (1.3)

(%RSD): Percent relative standard deviations are given in parentheses ($N = 5$).

Table 5

White Buna Elastomer Swelling

Formulation Description	% Increase in Diameter (%RSD) 1 Month RT IV	% Increase in Diameter (%RSD) 2 Months RT IV	% Increase in Thickness (%RSD) 1 Month RT IV	% Increase in Thickness (%RSD) 2 Months RT IV
P134a with 0% v/v alcohol	2.53	3.20	7.10	7.49
	(0.9)	(0.7)	(3.8)	(2.3)
P134a with 2% v/v alcohol	1.65	3.51	4.03	5.76
	(2.2)	(0.3)	(4.8)	(1.7)
P134a with 10% v/v alcohol	4.03	4.44	8.64	9.45
	(0.9)	(0.3)	(1.9)	(2.1)
P134a with 30% v/v alcohol	4.13	-	19.96	-
	(0.8)		(4.4)	

(%RSD): Percent relative standard deviations are given in parentheses ($N = 5$).

Table 6

Type 674 (B) Elastomer Swelling

Formulation Description	% Increase in Diameter (%RSD) 1 Month RT IV	% Increase in Diameter (%RSD) 2 Months 37°C IV	% Increase in Thickness (%RSD) 1 Month RT IV	% Increase in Thickness (%RSD) 2 Months 37°C IV
P134a with 0% v/v alcohol	1.73	1.62	3.38	6.62
	(0.7)	(1.1)	(1.5)	(1.8)
P134a with 2% v/v alcohol	3.45	5.07	7.03	6.89
	(0.8)	(1.4)	(1.7)	(3.1)
P134a with 10% v/v alcohol	4.97	5.23	10.14	11.49
	(0.9)	(0.8)	(1.2)	(1.5)
P134a with 30% v/v alcohol	4.97	-	10.68	-
	(0.3)		(0.8)	

(%RSD): Percent relative standard deviations are given in parentheses ($N = 5$).

CONCLUSIONS

Placebo formulations of P134a with no ethanol adversely affected the functioning of the valve. Higher concentrations of ethanol in the formulation improved the valve performance. However, higher concentrations of ethanol in the formulations also increased the leakage rate of the MDI. Elastomer of MDI valves swelled in the presence of P134a and ethanol.

REFERENCES

1. W. F. Miller, Aerosol therapy in acute and chronic respiratory diseases, Arch. Intern. Med., 131, 148 (1973).
2. M. E. Boulden, Dymel 134a/P for aerosol pharmaceuticals, Respiratory Drug Delivery IV Proceedings, Richmond, VA, 334 (1994).
3. M. J. Molina and F. S. Rowland, Stratospheric sink for chlorofluoromethanes: chlorine atom catalyzed destruction of ozone, Nature, 249, 810 (1974).

4. M. E. Whitman and A. M. Eagle, Alternate propellants: proprietary rights, toxicological issues and projected licensing problems, Respiratory Drug Delivery IV Proceedings, Richmond, VA, 203-209 (1994).
5. G. S. Hallworth, The formulation and evaluation of pressurized metered dose inhales, in *Drug Delivery to Respiratory Tract*, (D. Ganderton and T. M. Jones, eds.), Academic Press, New York, 1987, p. 87.
6. D. Tiwari, Evaluation of the propellant 134a as a chlorofluorocarbon replacement for albuterol metered dose inhaler formulations, M.S. Thesis, College of Pharmacy & Allied Health Professions, St. John's University, New York, 1993, p. 32.
7. *United States Pharmacopeia*, 22nd ed., The United States Pharmacopeial Convention, Inc., Rockville, MD, 1990, p. 1556.