Formulation and *in Vitro* Evaluation of Pressurized Inhalation Aerosols Containing Isotropic Systems of Lecithin and Water

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Reverse micellization of nonionic surfactants in apolar media was applied to the formulation of solution phase, pressurized inhalation aerosols, employing soya lecithin (SPC) and water in chlorofluorocarbon (CFC) blends. The use of a 30/70 mixture of trichlorofluoromethane (P11) and dichlorodifluoromethane (P12) resulted in the formation of stable, isotropic systems containing 0.5–2.0% (w/v) SPC and solubilized water; R (moles water/moles SPC), 0.9 to 4.28. In systems containing <30% P11, phase separation became apparent, particularly at higher water and surfactant concentrations. Dramatic changes in solution viscosity were noted on increasing R values and were attributed to an increase in asymmetry of SPC micelles. Dynamic fractionation of the output from pressurized aerosols using a four-stage liquid impinger showed that the respirable fraction (as measured by the percentage of emitted droplets with aerodynamic diameters <5.5 μm) was highly dependent on SPC concentration and R. A significant correlation between RF and actuator score, based on orifice diameter and length, was also found and confirmed that the highest RF values were achieved with the systems of lowest SPC and water concentrations sprayed through an actuator with the smallest and shortest orifice dimensions. This novel mechanism for the formulation of hydrophilic drugs as solutions within CFC-based pressurized aerosols may offer advantages over the traditional suspension approach to pulmonary drug delivery.

KEY WORDS: inhalation aerosol; surfactant; micellar solubilization; formulation; solution; suspension.

INTRODUCTION

Studies on human subjects administered radiolabeled aerosols emitted from pressurized, metered-dose inhalers (MDIs), formulated as suspensions, demonstrate poor efficiency in delivering drugs to the respiratory tract (1). Without the addition of a spacer or holding chamber to the device, the *in vivo* deposition pattern is largely in the oropharynx, with only 10 to 14% penetrating into the lower airways of the lung (2). Previous studies *in vivo* have demonstrated the significant effects of vapor pressure and metered volume (3,4) on the extent of lung deposition, whereas doubling of the median size of suspended particles exerts a negligible effect on the deposition profiles of aerosols emitted from MDIs (5). Hence, the deposition pattern is a function primarily of the droplet size (and velocity) compared to the original drug crystal size provided that particle aggregation within the formulation does not result in the delivery of large particle clusters through the spray jet (6). A logical method of improving lung deposition, therefore, would be to reduce the initial droplet size, leading to a significant increase in the respirable portion of the emitted aerosol cloud. A recent publication of Dalby and Byron (7) alluded to the potential benefit of formulating pressurized aerosols containing drug in solution compared to the traditional suspension, provided that the high volatility of the propellant blend could be maintained. Whereas the ultimate aerodynamic diameter of aerosols emitted from suspension systems will be no less than that of the original particles, the size of aerosols derived from solution systems will be a function of the initial droplet size and of the small nonvolatile component of the formulation. In addition and by virtue of their homogeneous nature, solution phase systems should allow modification of actuator systems to encourage more efficient breakup of emitted aerosols, which will further contribute to the production of high respirable fractions.

Several nonionic surfactants have been shown to aggregate in a model CFC solvent, trichlorotrifluoroethane (P113), and in P113:hexane mixtures of similar dielectric constant to P11/P12 blends at extremely low concentrations (10^{-3} to 10^{-5} M) dependent on their physicochemical character (8). Further work (9) has determined the size and shape of lecithin micelles in P113, demonstrating the ability of such systems to solubilize small quantities of water. In these isotropic systems, water is located within the polar interior of the micelles (10), thus forming discrete units with potential for the solubilization of hydrophilic drugs in CFC-based pressurized aerosols. This paper, therefore, extends previous fundamental studies of reverse micellization of lecithin in P113 to the formulation of similar, isotropic systems in CFC-based pressurized aerosols. Aerosol characterization was undertaken in a multistage liquid impinger (MLI) employing dual radioisotopes as markers of the micellar core and shell. The influence of surfactant concentration, solubilized water, and geometry of the actuator orifice were studied with a view to predicting the efficiency of these devices in delivering aerosol to the respiratory tract.

MATERIALS AND METHODS

Formulation of Homogeneous Pressurized Aerosols

Soya lecithin was purified by chromatographic separation (11) of a commercial source (Epikuron 200, Lucas Meyer, West Germany) to yield a pure phosphatidylcholine fraction (SPC). Pressurized packs containing SPC in the concentration range 0.5, 1.0, and 2.0% (w/v) and solubilized water, R (ratio, moles water:moles surfactant), of 0.9 to 4.28 were formulated in 10/90, 20/80, 30/70, 40/60, and 50/50

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blends of trichlorofluoromethane:dichlorodifluoromethane (P11:P12, ICI Mond Division, UK). The required volume of glass distilled water was added using a 20-μl air displacement precision pipette (Gilson) to a 20-ml plastic-coated, glass bottle (Type 37, SGD Ltd., UK) which had been previously washed, dried, and stored in a desiccator containing silica gel. The bottle was tared and the calculated volume of cooled, lecithin concentrate (20%, w/v) in P11 was added. Further P11, at 4°C, was added dropwise to an excess weight and allowed to evaporate until the required weight remained in order to facilitate evacuation of air from within the bottle. A 50-μl metering valve (Neotechnic Engineering Ltd., UK) was crimped into position and the required quantity of P12 filled through the valve. The crimping and filling procedures were undertaken using a laboratory scale apparatus (Model 2005, Pamasol Willi Mader AG, Switzerland) correctly adjusted for glass bottles with 20-mm-diameter metering valves. Gross leakage of the pressurized units was detected immediately after manufacture by immersion in a water bath at 55°C. Pressurized packs were then placed in a thermostatically controlled shaking water bath and maintained at 25 ± 0.1°C for 1 week. Daily inspections were made to ascertain the nature of the system, i.e., isotropic or anisotropic. Absolute water content of the formulations was determined by actuation of pressurized packs fitted with continuous valves to exhaustion in specially dried methanol (BDH Chemicals, UK) followed by Karl Fischer analysis (Model AF5 titrator, Baird and Tatlock, UK).

Construction of Modified Actuator Assemblies

A range of two-piece button actuators was obtained as a gift from Metal Box (UK). Each comprized of a white molded button, housing the seat for the valve stem, and an insert containing the spray orifice. These differed in terms of orifice diameter, length, and profile and are represented schematically in Fig. 1. Orifice diameters were given by the manufacturer, whereas orifice lengths were estimated from technical drawings and varied from approximately 0.9 to 3.7 mm. As these could not be accurately determined, each length was assigned an arbitrary numerical value ranging from 1 (shortest) to 5 (longest). The inserts were then classified by a alphanumeric coding derived from the orifice diameter, profile (A to E), and length (Table 1). Each button actuator was inserted into a specially modified MDI oral adaptor. This basically involved removal of a section containing the original valve seat and spray orifice by means of a cork borer and a small plastic collar inserted which functioned to support the appropriate actuator button. A precisely cut neoprene wedge was glued into the base of the plastic collar before incorporation of the button actuator in order to compensate for its tapered profile. This ensured that an even downward pressure was exerted on the metering valve during actuation.

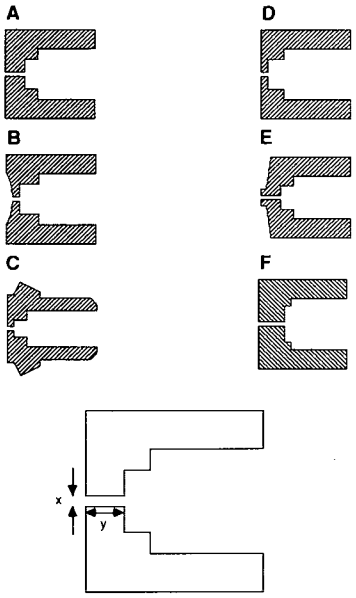

Fig. 1. Schematic diagram of the profiles of the range of button actuators obtained from Metal Box, UK. The actuators were classified according to orifice diameter (x), insert profile (A to F) and relative orifice length (y).

Aerosol Characterization

A previously calibrated four-stage MLI with a glass throat (Fisons Scientific Apparatus, UK) was employed. When operated at a 60 l min^{-1} airflow by means of a vacuum pump downstream of the terminal glass-fiber filter (Type GF/A, 47-mm diameter; Whatman, UK), the effective cutoff diameters (ECD) for stages 1 to 4 were 10.47, 5.51, 3.59, and 1.25 μm, respectively (12). Each stage was filled with 10 ml 50% (v/v) ethanol and the specially modified adaptor was clamped in a position to direct the emitted aerosol into the glass throat. For the homogeneous, pressurized systems under study, 33 kBq L-α-phosphatidylcholine, 1,2-di-[1-^{14}C]palmitoyl (^{14}C-DPPC; Amersham International plc., UK), and 100 kBq [6,6′(n)-^{3}H] sucrose (^{3}H-sucrose; Amersham International plc., UK) were additionally included in the formulation as tracers of SPC and the aqueous micellar core respectively. Following shaking and priming, each unit was secured in an inverted position in the adaptor and depressed at 5-sec intervals for 20 actuations. Nonvol-

Table I. Dimensional Description of the Actuators Employed in the Aerosol Analysis Experiments

Orifice diameter (mm)	Profile type[a]	Orifice length[b]	Code[c]
0.305	B	2	31B2
0.432	A	3	43A3
0.432	D	2	43D2
0.457	A	3	46A3
0.457	C	1	46C1
0.508	F	5	51F5
0.559	A	3	56A3
0.559	D	2	56D2
0.559	E	4	56E4

[a] As depicted in Fig. 1.
[b] Nominal length based on 1 = shortest and 5 = longest.
[c] Actuator code based on orifice diameter, profile, and length.

atile components of the emitted aerosol were quantitatively washed off the adaptor, throat, various stages, and filter and transfered to volumetric flasks. Duplicate 1-ml aliquots of each sample were mixed with 10 ml Cocktail T (BDH Chemicals, UK) before scintillation counting by the channels ratio method. The observed counts per minute (cpm) for ^{14}C and ^{3}H were corrected for chemical quenching, with reference to a previously constructed quench curve, to yield the corresponding disintegrations per minute (dpm) which were related to the amount of SPC and sucrose, respectively, in each sample.

The data are expressed as the percentage deposition in the throat and adaptor together with the percentage entering the MLI. The latter fraction is described as equivalent to the aerosol droplets delivered to the respiratory tract. Owing to the ECD of stage 2 (5.51 μm), aerosol droplets collected on stages 3 and 4 and the filter of the MLI are considered capable of penetration into the deeper airways of the lung and thus give a measure of the respirable fraction (RF) of the emitted dose (12). The mass median aerodynamic diameter (MMAD) and geometric standard deviation (σ_g) of the aerosol droplets were determined by construction of particle size-cumulative undersize plots for aerosols deposited on the four stages of the MLI.

RESULTS AND DISCUSSION

The physical stability of the combinations of propellant blend, SPC, and solubilized water studied in the preliminary formulation experiments is summarized in Table II. Stable, homogeneous systems were produced for formulations containing P11 and P12 present at the ratios of 30/70, 40/60, and 50/50 independent of both water and SPC concentration. For CFC blends containing <30% P11, however, the systems became increasingly unstable as demonstrated by a phase separation, particularly evident at higher water and surfactant concentrations. This may be attributed to a dramatic reduction in solubilizing power of the blend for the lipophilic SPC when P11 is mixed with the more weakly solubilizing P12, which is even further reduced in the presence of water. Long-term, physical stability of these formulations was assessed by periodic visual examination during 6 months of storage in the dark at room temperature. There was no apparent phase change in any system suggesting that physical instability was only an immediate phenomenon.

Table II. Physical Stability of SPC/Water Systems in Various Blends of P11 and P12[a]

CFC blend, P11/P12	SPC (%, w/v)/R					
	0.5/0.9	0.5/4.28	1.0/0.9	1.0/4.28	2.0/0.9	2.0/4.28
10/90	√	X	X	X	X	X
20/80	√	X	√	X	X	X
30/70	√	√	√	√	√	√
40/60	√	√	√	√	√	√
50/50	√	√	√	√	√	√

[a] Symbols refer to systems of observed isotropicity (√) or phase separation (X) after equilibration for 1 week at 25°C.

For the aerosol characterization studies, homogeneous formulations were prepared with a propellant blend of 30/70 P11/P12, SPC concentrations of 0.5, 1.0, and 2.0% (w/v), and three levels of solubilized water (R = 1.42, 2.82, and 4.28). These were actuated through nine variations in actuator geometry to give 81 permutations for the aerosol analysis experiments. The choice of this propellant blend allowed complete solubilization of the nonvolatile components at all levels, while exhibiting a vapor pressure (444 kPa, 21°C) typically employed in a conventional MDI. The various values of R were chosen to yield systems in which it was assumed, with reference to previous studies (9) in P113, that there would be differences in SPC micellar shape. Variability in the performance of the metering valve in this study was found to be <7%, and the percentage of the emitted dose recovered from the MLI and other locations for each of the 81 permutations was >95% as compared to ^{14}C and ^{3}H activity levels delivered by the metering valve.

Initial experiments were conducted to confirm aerosol homogeneity by monitoring the relative deposition profiles of the dual isotopes. Figure 2 shows RF values obtained for ^{14}C-DPPC and ^{3}H-sucrose as a function of surfactant concentration for the two extreme values of R investigated. Results are given for the range of pressurized pack formulations actuated through a single orifice type (56D2). In all instances, RFs obtained from the respective ^{14}C and ^{3}H deposition profiles were comparable confirming homogeneity of the various systems investigated. Accordingly, further characterization of emitted aerosols was undertaken by use of the mean value of deposition of ^{14}C-DPPC and ^{3}H-sucrose at each location in the MLI apparatus; values for the pair of nuclides were within ±6% at each location.

While data were accumulated for aerosol deposition in the adaptor, throat, and MLI, from which the MMAD, σ_g, and RF were derived, statistical treatment was performed only on the influence of formulation and actuator variables on the RF, as this parameter is considered the most important with respect to the ultimate therapeutic efficacy of a pressurized aerosol product. Two 3 × 3 × 3 analyses of

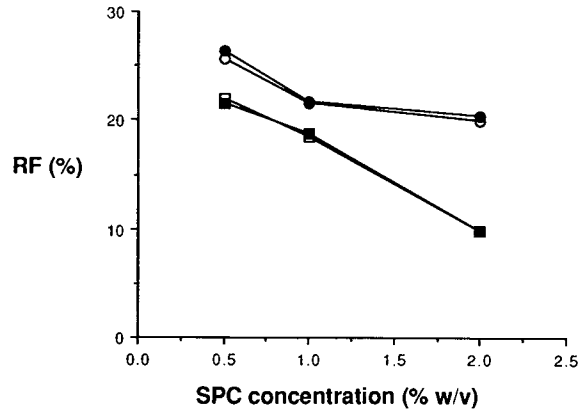

Fig. 2. RF of ^{14}C-DPPC and ^{3}H-sucrose as a function of SPC concentration for two homogeneous formulations actuated through a single orifice type (56D2). (●) ^{14}C-DPPC and (○) ^{3}H-sucrose for formulations containing solubilized water, R = 1.42; (■) ^{14}C-DPPC and (□) ^{3}H-sucrose for formulations containing solubilized water, R = 4.28.

variance (ANOVA) were employed to compare the effect of surfactant concentration and solubilized water with orifice diameter (employing actuators 43A3, 46A3, and 56A3) and orifice length (56D2, 56A3, and 56E4), respectively. Due to the lack of replicates, the triple interaction term was taken as a measure of the experimental error likely to have occured. The statistical data of both investigations are shown in Tables III and IV and depict highly significant values for the contribution of each individual variable. Only one interaction between two factors was significant, namely, surfactant concentration and solubilized water ($P < 0.05$) for variations in orifice length. Higher SPC concentrations always resulted in a proportionate reduction in the RF as a result of increased impairment of propellant evaporation following actuation. Delayed propellant evaporation will result in the existence of large aerosol droplets, thus favoring increased throat deposition at the expense of the proportion of aerosol dose entering the MLI. This effect has been previously documented (12–14) and it is dependent on the type of surfactant included within the formulation (7). For example, oleic acid, by virtue of its molecular orientation, is considered to form a condensed layer at the droplet–air interface more readily than lecithin, resulting in the formation of a more efficient barrier to evaporation. Whether these effects would prove significant when the various agents are incorporated into formulations on an equal stoichiometric rather than weight basis, however, has not been determined.

The incorporation of an additional nonvolatile component, water, leads to further, dramatic reductions in the RFs obtained. This was particularly apparent for formulations containing the higher water concentrations despite the vapor pressure of the formulation remaining unchanged. However, an increase in bulk viscosity was evident for the systems containing solubilized water in an analogous manner to SPC/water systems in P113 (9). In such systems, an increase in viscosity in solutions of higher water content occurs as a result of a change in shape of SPC micelles from oblate to increasingly prolate through a spherical intermediate. No absolute comparison can be drawn with similar systems in the P11/P12 blend, however, owing to the complexity of spectroscopic and viscometric studies of micellar shape in pressurized systems. Assuming that similar changes occur in pressurized CFC blends, the three values of R (1.42, 2.82, and 4.28) would equate to systems containing micelles of increasing asymmetry. There was no discernible effect of R on aerosol deposition profiles at the lowest SPC concentration (0.5%), probably because of the relatively low number of micelles present in solution. At higher concentrations of SPC, when the micellar concentration will proportionately increase, the micellar shape induced viscosity changes were highly significant, resulting in a dramatic reduction in RF with a concomitant increase in the extent of actuator deposition.

From the ANOVA tables, it is evident that orifice diameter and orifice length possess an equal degree of significance on the calculated values of RF. Therefore, in order to determine the effect of the actuators not included within the statistical analysis, a numerical value ranging from 1 to 5 was assigned to each orifice geometry variable such that the smallest and shortest orifice dimensions were given the lowest numerical values. Simple addition of these numbers produced an actuator "score" which was used to classify the

Table III. Data (a) for RF as a Function of SPC Concentration (%, w/v), R, and Orifice Diameter (mm) Included in 3 × 3 × 3 ANOVA (b) Used to Determine the Significance of Individual Factors and Possible Interactions Contributing to the Production of Respirable Aerosols[a]

a

	Factor A (SPC; %, w/v)								
	0.5			1.0			2.0		
	Factor B (R)								
Factor C (diameter)	1.42	2.82	4.28	1.42	2.82	4.28	1.42	2.82	4.28
0.432	46.17	52.88	47.00	53.77	43.39	32.78	33.47	19.11	18.53
0.457	37.67	38.52	40.70	34.01	41.00	26.43	29.83	22.18	13.65
0.559	30.83	30.22	29.90	29.67	28.34	24.47	21.04	15.04	11.97

b

Source	df	Sum of squares	Mean square	F	$P <$[a]
A	2	1734.0	867.0	56.5	0.005
B	2	287.7	143.9	9.4	0.01
C	2	876.6	438.3	28.6	0.005
AB	4	226.5	56.6	3.7	0.10
AC	4	107.2	26.8	1.8	
BC	4	53.0	13.3	0.9	
ABC	8	122.7	15.3		
Total	26	3407.6			

[a] P values >0.05 were taken as not significant.

Table IV. Data (a) for RF as a Function of SPC Concentration (%, w/v), R, and Orifice Length Included in 3 × 3 × 3 ANOVA (b) Used to Determine the Significance of Individual Factors and Possible Interactions Contributing to the Production of Respirable Aerosols[a]

a

	Factor A (SPC; %, w/v)								
	0.5			1.0			2.0		
	Factor B (R)								
Factor C (length)	1.42	2.82	4.28	1.42	2.82	4.28	1.42	2.82	4.28
2	26.3	26.1	21.5	21.7	22.6	18.8	20.4	14.5	9.8
3	30.8	30.2	29.9	29.7	28.3	24.5	21.0	15.0	12.0
4	25.2	28.0	23.3	23.5	19.6	17.3	15.6	13.7	7.7

b

Source	df	Sum of squares	Mean square	F	$P <$[a]
A	2	723.0	361.5	167.6	0.005
B	2	140.9	70.5	32.7	0.005
C	2	144.2	72.1	33.4	0.005
AB	4	38.0	9.5	4.4	0.05
AC	4	29.8	7.5	3.5	0.10
BC	4	4.6	1.2	0.5	
ABC	8	17.3	2.2		
Total	26	1097.9			

[a] P values >0.05 were taken as not significant.

actuators (Table V). Figure 3 shows the variation in RF with actuator score for systems representing the two extremes of formulation variables (and hence blend viscosity) studied. Linear regression of the data yielded an excellent correlation between RF and actuator score in each case (0.5, w/v, SPC—R = 1.42, $P < 0.005$, n = 9; and 2.0%, w/v, SPC—R = 4.28, $P < 0.01$, n = 9) despite differences in shape and degree of recess among the various actuators employed. This infers that these parameters are of little importance in determining the size of emitted aerosols for the range of formulations studied.

Small orifice diameters, however, resulted in higher RFs by imparting greater resistance and hence greater disruption of the aerosol upon actuation. These were further improved by combining a small orifice diameter with a short orifice length, which served to break efficiently the emitted aerosol into a wide cone of small droplets, thus maximizing the air envelope for propellant evaporation. In comparing the full deposition data for one formulation emitted through different actuators representing extreme values of orifice diameter and length employed (Fig. 4), it can be seen that adaptor deposition increased on increasing orifice diameter, with a corresponding reduction in the proportion of emitted dose entering the MLI. In such instances, the production of a wide cone of large primary droplets will favor impaction within the confines of the oral adaptor. Conversely, the amount associated with the throat substantially increased on increasing orifice length due to the aerosol cloud being effectively directed as a narrow, high-velocity stream toward the 90° bend of the throat. This was evident, even at small orifice diameters, resulting in correspondingly lower levels of aerosol deposition in the adaptor.

Despite the large variation in RF, MMADs of aerosols calculated from the proportion entering the MLI were similar when the same formulation was actuated through different orifices; MMAD increased only on increasing SPC concentration as a result of delayed propellant evaporation. For example, MMADs for formulations containing 0.5% (w/v) SPC (R = 2.82) ranged from 2.40 to 2.85 μm for the complete series of actuators tested, whereas the corresponding values for formulations containing 1 and 2% (w/v) SPC ranged from 3.03 to 3.25 and 3.60 to 3.80 μm, respectively. Values obtained for σ_g (approximately 2.2–2.3 in all cases) reflected polydisperse systems typically reported for aero-

Table V. Actuator Score Based Upon the Contribution of Orifice Diameter and Length for Each Actuator Used in the Aerosol Analysis Experiments[a]

Code	31B2	43A3*	43D2	46A3*	46C1	50F5	56A3*†	56D2†	56E4†
Score	3	5	4	6	4	9	8	7	9

[a] Superscripts * and † indicate groups of actuators used in the statistical analyses to determine the influence of orifice diameter and length, respectively.

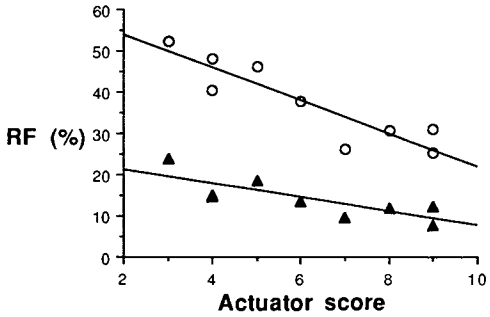

Fig. 3. RF as a function of actuator "score" for systems representing the two extremes of formulation variables examined: (○) 0.5% (w/v) SPC, R = 1.42; (▲) 2.0% (w/v) SPC, R = 4.28.

sols generated from MDIs. Such data reflect the important dependency of RF on events which occur immediately upon actuation, i.e., the primary droplet size, which in turn, is affected by orifice geometry. This conclusively emphasizes the desirability of investigations into the design of actuator systems to improve the efficiency of MDIs in delivering a therapeutic aerosol. A recent study (15) has investigated modified actuators for use with suspension formulations of pressurized aerosols. The inclusion of baffles within the actuator was seen to improve the apparent respirable fraction by retaining the larger, nonrespirable droplets within the actuator. However, there was no improvement in RF in terms of absolute dose emitted by the aerosol product using this type of approach, although the use of baffles would appear to have certain advantages in instances where it is clinically desirable to reduce unwanted oropharyngeal deposition.

The overriding conclusion from the present work points to further reductions in orifice geometry, possible with solution phase systems, in order to improve values of RF. Even with homogeneous formulations, clogging is bound to become a serious problem, particularly with systems containing higher levels of the nonvolatile components (12). However, this work has demonstrated the potential of formulating solution phase systems of SPC and water in CFC blends which are capable of generating aerosols with high RFs. These were of a similar magnitude to that reported for a recent formulation of a low-dose, lipophilic drug dissolved directly in a propellant blend (16) and substantially greater than that for conventional solution phase systems containing

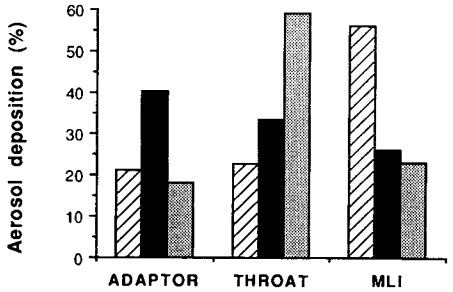

Fig. 4. Histogram representation of the relative retention of aerosols emitted from solution phase pressurized pack containing 1% (w/v) SPC and solubilized water (R = 2.82) in 30/70 P11/P12. Shadings depict retention following actuation through orifice types 31B2 (▨), 56D2 (■), and 56E4 (▩).

ethanol as a cosolvent (17). By altering the SPC concentration and the amount of solubilized water, the isotropic micellar systems would appear to have significant potential for formulating a range of hydrophilic drugs at various dose levels as solutions in pressurized CFC blends. Viscosity effects, however, should in practice limit the extent of drug solubilization possible within SPC reverse micelles and dictate that, where increased solubilizing potential is required, an increase in SPC concentration rather than an increase in R is preferable. By extrapolation of the previous data (9) obtained with SPC/water/P113 to these pressurized systems, this should lead to an increase in the number rather than the asymmetry of the micelles, thus ensuring less dramatic changes in solution viscosity. A future contribution will report on data pertaining to drug solubilization within such systems and will compare the performance *in vitro* of formulated solution systems with conventional suspension pressurized aerosols.

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