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Effects of surfactants on aerosol powders in suspension. Implications for airborne particle size

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This work is related to a recent theoretical treatment of suspension aerosols by Gonda (1985) and a claim by Ranucci et al. (1987) that "flocculation heights" are a means of "optimizing" metered dose inhaler (MDI) formulations. The success of an MDI is based on its ability to deliver a drug in a uniform dose and a size range capable of penetrating the lung (Byron, 1986a and b, 1987). As we demonstrate below, this capability may or may not be associated with sedimentation volumes determined in controlled flocculation studies on the suspensions.

Manufacture of an aerosol unit usually involves (a) micronizing and drying the drug; (b) dispersal in a low-volatility non-aqueous concentrate containing a hydrophobic surfactant; (c) packaging; and (d) high volatility propellant addition (Sciarra, 1980; Byron, 1986a). The technology associated with the dispersal technique is very important; the product may contain aggregated material in suspension due either to unsuccessful deaggregation during manufacture, inappropriate formulation, or aggregate formation during storage. Aggregates with increased aerodynamic diameters are known to be emitted by MDIs (Gonda, 1985 and references therein). Although "preformed particle aggregates" are mentioned by Gonda (1985), his theory assumes complete deaggregation in suspension and cluster formation by multiple particle inclusion in evaporating spray droplets. Sedimentation volumes provide little information concerning the adequacy of deaggregation in a suspension, even though they can be related sometimes to the ease of "redispersibility" (Hiestand, 1964). Observing that a suspension is "redispersible", is no guarantee of deaggregation. Unfortunately, the degree of aggregation within a pressurized MDI cannot be measured directly, without invading and disturbing the closed system. To demonstrate the apparent dependency (or independency) of aerosol characteristics upon suspension behaviour, we sized the output of several, easily dispersible, aerosol formulations and correlated these with the observed sedimentation ratios.

Ten different suspension aerosols were prepared using 1% disodium fluorescein (DF) by weight, as a model drug. This drug concentration is similar to some commercial preparations (Byron, 1986a) and corresponds approximately to the 1% volumetric concentration which theory predicts should display some aggregation problems (Gonda, 1985). Batches differed with respect to sorbitan trioleate concentration and whether micronized or unmicronized drug was employed. The propel-

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lants, containers, valves and actuators were held constant. To provide a difference in original size distribution the compound was employed in both the unmicronized (volume median diameter = 7.6 μm, $\sigma g = 1.9$, 26% of total volume < 5 μm) and micronized (VMD = 5.4 μm, $\sigma g = 1.7$, 44% of total volume < 5 μm) forms. These distributions were determined microscopically and were apparently log-normal. Sphericity was assumed. Manufacturing techniques were identical to those described previously (Dalby and Byron, 1987). Resultant aerosol units were fitted with a 25 μl inverted metering valve (Valois DF10, BLM Packaging Inc., Greenwich, CT). Units contained 1% DF, variable surfactant concentrations (Table 1; Span 85, Fluka AG, Ronkonkoma, NY) and a propellant blend (1 : 2 : 1 Dymel 11, 12 and 114 by weight, Du Pont, Wilmington, DE) with a calculated vapour pressure = 41.4 psig (21° C). Each unit was tumble-mixed (Turbula model T2C, Glenn Mills Inc., Maywood, NJ) at maximum speed for 1 h. Sedimentation ratios (settled height/original height), redispersibility and aerosol characteristics were determined for each formulation after standing for 20 days at 21° C. The method of aerosol sizing has been reported in detail elsewhere (Dalby and Byron, 1987). In brief, each container was shaken, fitted with a Valois IN1 actuator, and actuated into a 380-ml chamber fitted atop a calibrated cascade impactor through which air was drawn at 12.45 liter/min. Fluorescein was determined spectrophotometrically in the actuator, expansion chamber and impactor.

Table 1 shows the sedimentation and aerosol output characteristics for each formulation. All formulations appeared to exhibit controlled flocculation. Sedimentation ratios determined after either 24 h or 12 months differed only marginally from the data presented in the Table. The density of this propellant blend was 1.40 g/cm^3 (21° C). Disodium fluorescein has a density of 1.46–1.49 g/cm^3 (Hering et al., 1979, Groom, 1981). The trend of increasing sedimentation ratio with increasing surfactant concentration occurred for both micronized and unmicronized DF. For micronized material, the existence of maximum sedimentation volumes at surfactant/drug ratios of 1.2 and 1.8 was pronounced. All formulations were easily redispersible; after 12 months storage, a single inversion of the containers was sufficient to produce a homogeneous dispersion. There was no correlation between "redispersibility" and the

TABLE 1

Sedimentation ratios and aerosol characteristics of MDIs formulated as 1% suspensions with different surfactant concentrations

DF [b]	Surf/DF [c]	F [d]	Percentage of dose [a]		
			(Act. + Exp. ch.) [e]	> 5.5 μm [f]	< 5.5 μm [g]
U	1.0	0.35	82.6 (5.5)	10.3 (1.0)	7.2 (0.4)
U	1.2	0.50	87.2 (3.7)	7.9 (0.9)	4.9 (1.4)
U	1.4	0.50	84.5 (5.4)	9.9 (0.8)	5.6 (0.2)
U	1.6	0.60	88.8 (3.3)	8.5 (0.6)	2.7 (0.1)
U	1.8	0.60	90.7 (5.1)	6.2 (0.7)	3.1 (0.1)
M	1.0	0.40	68.3 (5.0)	18.0 (2.2)	13.7 (0.5)
M	1.2	0.70	73.2 (8.0)	15.5 (1.6)	11.2 (0.6)
M	1.4	0.50	57.3 (4.4)	22.2 (3.1)	20.6 (1.4)
M	1.6	0.50	80.5 (2.4)	12.7 (0.2)	6.8 (0.4)
M	1.8	0.85	78.6 (4.3)	13.9 (2.2)	7.5 (0.8)

[a] $n = 3$, values in parentheses are 0.5 × experimental range.
[b] U = unmicronized, M = micronized.
[c] (Amount sorbitan trioleate)/(Amount DF).
[d] Sedimentation ratio. Values are rounded to nearest 0.05.
[e] (Act. + Exp.ch.) shows retention of DF retained by the actuator and 380 ml expansion chamber (atop the cascade impactor). This material has aerodynamic diameters > 11.2 μm.
[f] 5.5–11.2 μm aerodynamic diameter.
[g] Aerodynamic diameter.

sedimentation volumes; all the formulations were "optimal" in this sense. This latter observation is fairly typical for well-manufactured non-aqueous suspensions containing large concentrations of sorbitan triesters. Simple calculations (Schneider et al., 1978), which show that potential energies of repulsion due to steric interactions are much more significant than their electronic counterparts in such low dielectric media, imply that steric stabilization is probably the most important suspending mechanism for these systems. Even so, it is worth noting that adsorption equilibria may take considerably longer to establish in non-aqueous media than they do in water (Shinoda, 1967). Observations like those of Ranucci et al. (1987), who found differences in sedimentation ratios as a function of the time lag between packaging their aerosol concentrate and addition of the high vapour pressure propellants, could be due to this or partial drug dissolution in the concentrate and subsequent precipitation and re-equilibration after propellant addition.

The second stage of the cascade impactor used in these experiments has a 50% cut-off diameter of 5.5 μm. Drug penetrating beneath this stage is usually considered to be "respirable" (Byron, 1986a and b). Comparing the sedimentation ratios in Table 1 to the values for the percentage of each dose which was < 5.5 μm in aerodynamic diameter shows clearly that choosing the formulation with the largest sedimentation ratio will cause the formulator to discard the best preparation. Comparing the aerosol data presented in the last 3 columns of Table 1 with the sedimentation data shows consistent trends; larger values for sedimentation ratio coincide with increased aerosol retention in the actuator and expansion chamber (aerodynamic diameters > 11.2 μm; Dalby and Byron, 1987). In general, a greater percentage of either the unmicronized or micronized DF product was emitted as a smaller aerosol when the sedimentation ratio was low.

Changing the surfactant concentration in these studies induced variations in the amount of DF emitted as small aerosol particles or droplets. Although there are many complications (Byron, 1987), two explanations are possible. First, droplet evaporation rate may be retarded increasingly by higher surfactant concentrations. Secondly, DF may be sprayed as aggregates, the existence and cohesive nature of which are varied as a function of increasing the surfactant : DF ratio. In a separate series of experiments in which 0.1% drug formulations were compared, containing either 0.14% or 1.4% sorbitan trioleate as surfactant, aerosols were smaller (than those containing 1% drug) but showed size distributions in both cases which were explained most simply by accounting for the large differences in non-volatile contents (results were probably affected insignificantly by changes in evaporation kinetics). Thus, we believe that the aerosol size differences shown in Table 1 are due to the spraying of particle aggregates. These must remain as aggregates after both the mild agitation prior to actuation and the shear forces due to passage through the spray nozzle. The terms "flocculation" and "controlled flocculation" refer to aggregation. Both of these terms are poorly defined (Hiestand, 1964). Sedimentation volumes may possibly be modified by changing interparticulate distances or co-ordination numbers for the loosely-packed floccules. Changing these and other interactive phenomena by modifying surfactant concentration provides no indication of the strength of interparticulate attraction or the ease of floccule deaggregation. The data presented here seem to indicate that once "redispersibility" is attained, further increases in sedimentation ratio only succeed in making products worse in terms of respirable dose. To determine whether this observation generally holds true requires further investigation. Even so, optimization of pressurized inhalation aerosol suspensions requires a more refined approach than that described by Ranucci et al. (1987). Also, while Gonda's theoretical approach to the prediction of changes in aerosol characteristics as a function of suspension concentration is useful, further developments should address the problem of preformed particle clusters passing through the spray jet.

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