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Special Considerations in the Formulation of Suspension Type Metered Dose Inhalers

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The delivery of drugs by oral inhalation to the respiratory tract, for local and systemic therapy, is of continuing interest. This has led to the development of several novel pressurized metered dose inhaler (MDI) formulations, expansion chambers (spacers), breath actuated inhalers, multi-dose dry powder inhaler devices and hand held nebulizers. These developments have been driven by diverse goals, such as, for example, a (some would say misguided) desire to replace environmentally hostile chlorofluorocarbon (CFC) propellants, or to produce aerosols with a higher respirable output of particles or to facilitate the administration of moieties that cannot conveniently be dosed by oral or other parenteral routes. Despite these advances, the most common way of delivering drugs to the majority of patients requiring inhalation therapy remains the "conventional" MDI.

There are basically two types of metered dose inhaler formulations available today. Those in which the active constituent is dissolved, and those in which it is suspended. Dissolution may be possible if the drug is extremely lipophilic in nature (because CFCs have small dielectric constants) or when a co-solvent (such as ethanol) is added to the CFC propellant or blend to enhance the solubility of more hydrophilic compounds. The latter approach is known to produce aerosols with a low respirable fraction following inhalation, probably due to the low volatility of the co-solvent, or the generally lower vapor pressure of these formulations. Since the majority of FDA approved drugs useful by the inhaled route show very low solubility in CFC propellants, suspension type MDIs

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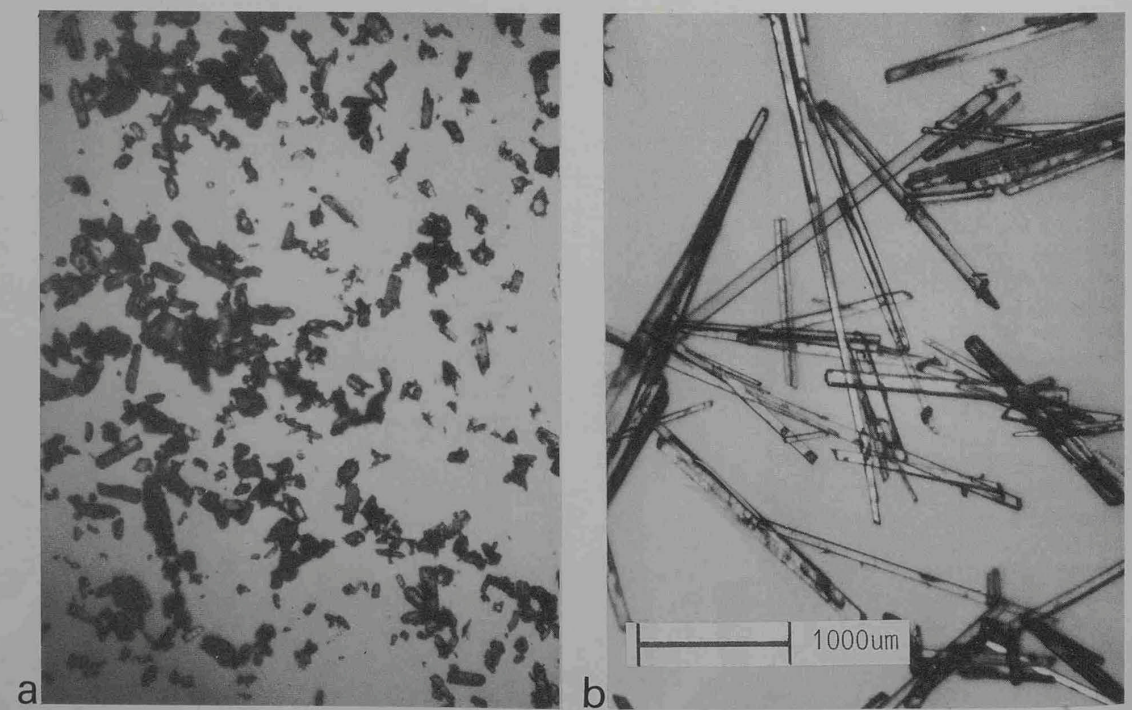

Figure 1. Salicylic acid crystals (a) initially, (b) after approximately one month in CFC-11.

have become the most predominant. Terbutaline sulfate, albuterol, metaproterenol sulfate, ipratropium bromide, beclomethasone diproprionate, flunisolide and disodium cromoglycate are common examples of drugs delivered in this type of formulation. Suspension type MDIs are likely to remain popular, since the much forecast replacement of dichlorodifluoromethane (CFC-12) by 1,1,1,2 tetrafluoroethane (HFC-134a)* is likely to produce propellants with even less drug solubilizing potential than those in use today. The advantages of suspension type MDIs are:

A. Wide Applicability—No minimum solubility is required, though it is probable that Ostwald ripening will be a problem if the drug exhibits "significant" solubility in the propellant, but not enough to allow its formulation as a high volatility solution aerosol.

B. Improved Chemical Stability—Drug remains in the solid phase, reducing the probability of chemical degradation.

C. Relatively large doses of drugs can be delivered per actuation—For example, Intal® MDI (Fisons) delivers 5mg of disodium cromoglycate per shot.

Unfortunately, suspension type MDIs have some disadvantages associated with them:

A. Reduced Physical Stability—Suspended drug particles have a tendency to either sink or float unless their density exactly matches that of the propellant. This potentially causes two problems:

1. Unreproducible dose delivery can result from delays between shaking and firing the MDI.

2. Patients must vigorously shake the MDI before use.

B. Sub-optimal Respirable Fraction—The size of the resulting aerosol cannot be less than the size of the primary particles used in its manufacture. Solution aerosols can theoretically produce infinitely small particles.

C. Suspension type MDIs are more complex to manufacture than solution MDIs.

D. Higher Propellant Leakage Rate—High concentration suspension type MDIs are potentially problematic due to drug particles preventing proper valve operation.

In order to produce a robust, efficacious product, the MDI formulator should consider several factors during the course of product development. Some of these are common to both types of MDI formulation, for example: chemical stability of the drug, uniformity of dose, total number of doses per unit, packaging component compatibility and extractables from valve elastomers. However, several factors are specifically of interest in the formulation of suspension type MDIs:

A. Starting particle size of the primary drug particles.

B. Crystal growth of the primary drug particles in the liquefied propellant.

C. Sedimentation of primary drug particles in the liquefied propellant.

D. Flocculation of primary drug particles in the liquefied propellant.

E. Effect of sedimentation and flocculation on dose uniformity.

F. Effect of suspension concentration

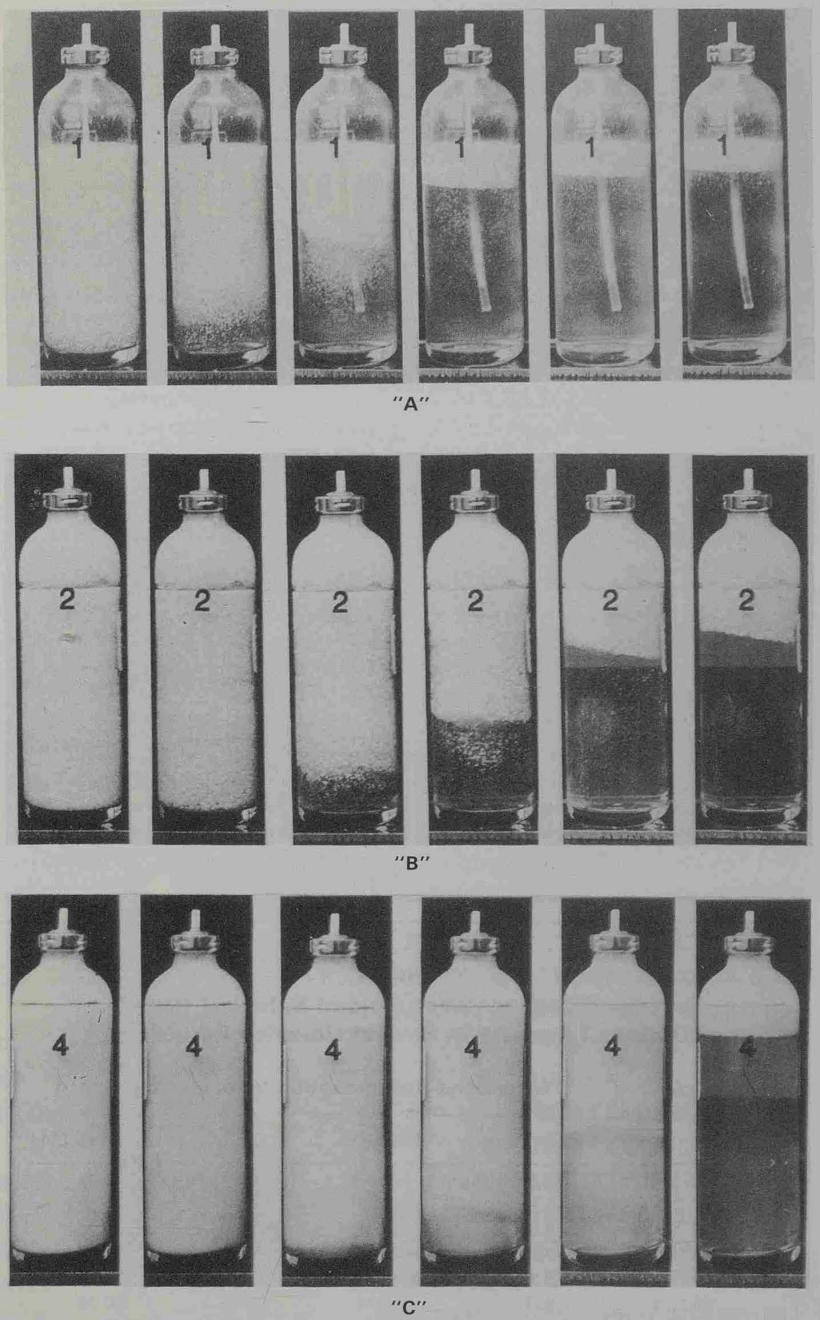

Figure 2. Appearance of several experimental MDI formulations, (left to right) 0.25, 0.5, 1, 2, 5, and 60 minutes following shaking. (A) 1%w/v drug, 0.5%w/w sorbitan trioleate in 60%w/w CFC-12 and 40%w/w CFC-114; (B) 1%w/v drug, 0.5%w/w sorbitan trioleate in CFC-12; (C) 1%w/v drug, 0.5%w/w soya lecithin in CFC-12. Courtesy of Fisons Pharmaceutical Division.

*Editor's note: A discussion of potential pharmaceutical propellants in light of the CFC phaseout can be found in the August 1990 issue of AEROSOL AGE, in the cover story "A Status Report: CFC's in Pharmaceutcal Aerosols," by Terrance M. Coyne.

on the respirable fraction of the aerosol output.

G. Effect of suspension concentration on valve metering performance and propellant leakage rate.

H. A rational strategy for manufacture of the MDI.

Size of Primary Drug Particles

New chemical entities (NCEs) are rarely synthesized with any consideration as to the physical properties required for subsequent incorporation into a viable formulation. Bulk drug destined to be delivered as a suspension type MDI is usually synthesized as a crystalline powder with a relatively large particle size. This is frequently the deliberate result of the synthetic chemist's desire to achieve rapid filtration or centrifugal separation of drug from the final recrystallization solvent. In principle at least, it is possible to crystallize drugs in the form of fine "micronized" particles by inducing extensive nucleation, but problems with separation from the recrystallizing solvent, control of growth rate and habit, and inter-particulate aggregation, particularly during drying, have limited the use of this approach. Therefore, a micronization step is almost always necessary. Since the particle size reduction realized by many fluid energy mills (the most common micronization process used for this purpose) is dependent on the particle size of the feed material, some other form of milling process is often required to comminute the raw drug particles prior to jet milling. With adequate process controls, jet milling typically yields particles with volume median diameters in the range of 2-4μm. The quantification of particle size and the setting of acceptance specifications is an important step in the formulation of all suspension type MDIs.

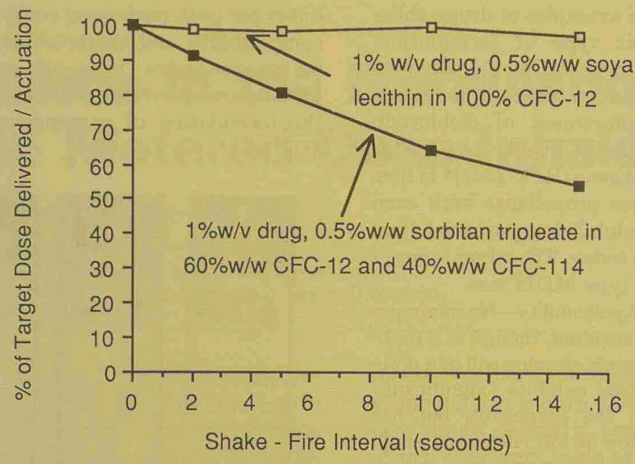

Figure 3. Effect of the interval between shaking and firing two experimental MDI formulations on the amount of drug emitted. 100% represents delivery of target dose. Courtesy of Fisons Pharmaceutical Division.

In the absence of complicating factors, decreasing particle size of the primary particles leads to aerosols with higher respirable fractions. Smaller particles also sediment in the propellant more slowly than larger particles; the significance of this will be described later. However, reducing the particle size indefinitely may lead to problems. For example, the increased surface area of smaller particles increases the tendency for strong interparticulate forces to produce multiparticle agglomerates. Increased curvature at the surface of smaller particles may cause molecules located there to exhibit a higher surface free energy compared to their counterparts on larger particles. This can lead to dissolution of drug in propellants at a concentration in excess of its equilibrium solubility. These conditions can lead to "Ostwald ripening," in which small particles dissolve completely, while larger particles grow in size. Clearly, both aggregation and crystal growth can ultimately lead to a reduced respirable fraction. In addition, micronization is an expensive and time consuming process; the production of smaller particles through low feed rates, high operating pressures and

Table 1
Calculated Sedimentation Rate of Spherical Particles (Density 1.4 gcm^{-3}) in Several Liquefied Propellants

Particle Diameter μm	Calculated Sedimentation Velocity (mm min^{-1})			
	CFC-11	CFC-114	CFC-12	HFC-134a
1	−0.006[a]	−0.005	0.01[b]	0.03
5	−0.15	−0.13	0.40	0.79
10	−0.60	−0.51	1.36	3.14
20	−2.39	−2.03	5.44	12.57
30	−5.39	−4.58	12.24	28.27
40	−9.58	−8.14	21.75	50.26
50	−14.97	−12.71	33.99	78.53

[a]Negative numbers represent floating particles.
[b]Positve numbers represent sinking particles.

Table 2
Effect of Increasing Model Drug Concentration on the Respirable Dose Delivered from an MDI

Concentration of Disodium Fluorescein (%w/w)	"Respirable Dose" % Dose ≤5.5μm
0.1	27.9
0.5	19.2
1.0	18.9
2.0	11.9

Notes
1. Sorbitan trioleate concentration = 1.4 x DF CONC.
2. Peter R. Byron, Richard N. Dalby and Anthony J. Hickey. Pharmaceutical Research, *6* (3), 225-229, 1989.

multiple passage through a fluid energy mill increases the cost.

In order to produce MDIs with an acceptable shelf life, primary drug particles dispersed in liquefied propellant must not significantly increase in size over time. Crystal growth is likely to become significant if the drug demonstrates appreciable solubility in propellant (but insufficient to make a solution MDI formulation viable). This can occur by several processes:

A. Small particles with a high surface free energy—Ostwald ripening described previously.

B. Surfactant or water induced solubilization—Micelle formation by some surfactants (eg. sorbitan trioleate) dissolved in propellant can induce dissolution of dispersed solids. This effect can be enhanced by the presence of water which is known to penetrate and accumulate in filled MDIs.

C. Cycled temperature storage—Increased temperature typically increases solubility. On cooling, re-equilibration can occur, causing previously dissolved drug to deposit on existing particles.

Figure 1 shows the size of salicylic acid crystals dispersed in trifluorochloromethane (CFC-11) for one month at room temperature compared to their initial size. In this model system salicylic acid exhibits a solubility of 1mg/ml in propellant, indicating that this level of solubility is well above that likely to yield a stable suspension MDI.

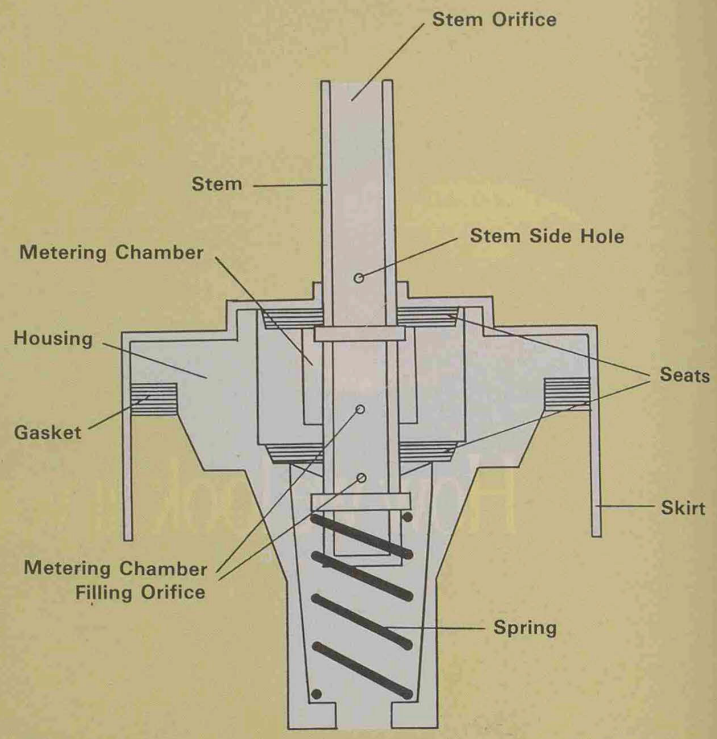

Figure 4. Schematic diagram of a typical metering valve.

Physical Stability of the Drug Suspension in Liquefied Propellant

Since micronization yields relatively few (in terms of mass) sub-micron particles, Brownian motion is not sufficient to produce a stable, homogeneous suspension of drug particles in propellant (stable being defined as an equilibrium sedimentation ratio of 1). Therefore, sedimentation occurs unless the drug and propellant blend densities are identical. In the case of the conventional CFC propellants, this is only possible in the range from 1.31 to 1.48 gcm^{-3}, the densities of CFC-12 and CFC-11, respectively at 25 °C. If it is assumed that the minimum useful vapor pressure for MDIs is around 50 psig, then this range is further restricted to 1.31 to 1.37 gcm^{-3}.

Sedimentation of particles in the size range produced by micronization is likely to occur in accordance with Stokes law (Equation 1). Therefore, it is possible to estimate the sedimentation velocity of drug particles in propellant. Table 1 shows the results of calculations for different sized particles with a density of 1.4 gcm^{-3} in several propellants. Minimizing the difference in density between the drug and propellant reduces the sedimentation rate. This is shown in Figures 2a and 2b in which the same drug (density = 1.29 gcm^{-3}) is suspended in propellants with densities of 1.37 and 1.31 gcm^{-3}, respectively. Drug and sorbitan trioleate concentration were kept constant for this comparison. Small particles (1 - 3μm) float or sink slowly compared to larger particles or multi-particulate aggregates ("floccules"). This is apparent when comparing Figures 2b and 2c. Suspended drug shown in Figure 2b is strongly flocculated (as judged by visual inspection) in the presence of sorbitan trioleate compared to drug shown in Figure 2c which contains soya lecithin but is otherwise identical. Since the drug (density = 1.29 gcm^{-3}) is less dense than CFC-12 (density = 1.31 gcm^{-3}) in which it is suspended, floating occurs at a faster rate in the highly flocculated suspension.

Care should be exercised in extra-

Table 3

Predicted Mass Median Aerodynamic Diameter for Several Concentrations of 3μm Particles of Unit Density and 30μm Droplets Sprayed from an MDI

Suspension Concentration %v/v	Average # of Particles Per		MMAD of Clusters μm
	Droplet	Cluster	
0.001	0.01	1.005	3.00
0.01	0.10	1.05	3.00
0.1	1.0	1.58	3.21
0.5	5.0	5.03	4.77
1.0	10.0	10.0	5.94
2.0	20.0	20.0	7.38
3.0	30.0	30.0	8.43

Adapted from: Igor Gonda, International Journal of Pharmaceutics, *27*, 99-116, 1985

polating the deflocculating effect of lecithin observed in this example to other formulations since its effect may be drug specific. It is also interesting to note that the lecithin formulation yielded a smaller equilibrium sedimentation ratio (negligible changes occurred after 60 minutes) than the sorbitan trioleate formulation. This provides additional evidence of deflocculation since smaller aggregates would be expected to have a tighter packing density. All the formulations shown in Figure 2 were easily redispersed by gentle shaking, and showed no tendency to "cake" during storage. This is essential if the patient is to be able to redisperse the suspension by shaking prior to inhalation. Aggregates which do not readily redisperse may be sprayed intact leading to a poor respirable fraction following aerosolization, or valve disfunction.

Good redispersibility characteristics do not guarantee reproducible dosing if the suspension is extremely unstable. Each point in Figure 3 shows the percentage of target dose of drug delivered from 10 consecutive actuations from a single MDI with a fixed delay between shaking and firing each shot. The upper (horizontal) curve was obtained from a relatively stable suspension (1%w/v drug, 0.5%w/w soya lecithin in 100% CFC-12, shown in Figure 2c), while the lower, downward sloping curve was obtained for an unstable suspension (1%w/v drug, 0.5%w/w sorbitan trioleate in 60%w/w CFC-12 and 40%w/w CFC-114, shown in Figure 2a).

The dose of drug released from the lecithin / CFC-12 formulation is independent of the shake-fire delay. However, as the shake-fire interval of the sorbitan trioleate / CFC-12 / CFC-114 formulation is increased from 0 to 15 seconds, the emitted dose decreases to approximately 50% of its initial value. This can be explained by drug floating away from the valve during the interval between shaking and firing, causing the metering chamber to refill with sub-optimal concentration of drug in suspension. The possibility of underdosing a patient could arise with the use of this formulation since delays of up to 15 seconds between shaking and firing the MDI might result from: attempts to coordinate firing and inhalation, loading the MDI into a spacer device or use of the MDI by an elderly patient. Inevitably, initial underdosing will lead to a high concentration of suspended drug remaining in the MDI, and the possibility of overdosing towards the end of the MDI's life. With an unstable, sinking suspension, similar problems could arise, but in reverse; the likelihood is of initial overdosing and subsequent underdosing. Whether regulatory authorities will see fit to set specifications in this area remains to be seen.

It is interesting to note that the unstable formulation (0.5%w/w sorbitan trioleate / 60%w/w CFC-12 / 40%w/w CFC-114) fails to deliver its target dose of 500μg in the absence of a shake-fire interval. This gives some insight into the difficulty of uniformly filling unstable suspension formulations, on a commercial scale without adequate validation studies and process controls.

Sedimentation rate can be manipulated by altering both propellant density within the narrow range described previously, and surfactant type and concentration. The choice of surfactants already used in commercial products is limited to: oleic acid (Ventolin®, Beclovent®), sorbitan trioleate (Intal®, Alupent®, Breathaire®) and soya lecithin (Atrovent®), primarily due to the absence of toxicity data by the inhaled route for other surfactants. Typical surfactant concentrations range from 0.01 to 1.00%w/w, higher concentrations being used for higher suspension concentrations. In addition to reducing inter-particulate association, the surfactant also lubricates the metering valve.

Suspension Concentration

Doses of drug delivered from suspension type MDIs varies from 20μg (Atrovent®) to 5mg (Intal®). The dose of drug emitted following actuation is determined by the product of metering valve volume, and suspension concentration (usually between 0.05 to 5.00%w/v).

Several studies have investigated the correlation between suspension concentration and respirable fraction of the resulting aerosol. The data in Table 2 (Byron et.al.) indicate that as the concentration of suspended disodium fluorescein in propellant increases, the respirable fraction (defined as the % of particles ≤5.5μm) in the emitted aerosol is reduced. For this, and other reasons described later, high suspension concentrations are often impractical, which imposes a major restriction on the dose of drug that may be delivered from an MDI.

Gonda has provided a theoretical basis to explain the above observations. His calculations indicated that for suspension concentrations ≤0.1%v/v (of unit density particles) sprayed propellant droplets are likely to contain one or no primary drug particles. Therefore, in the absence of

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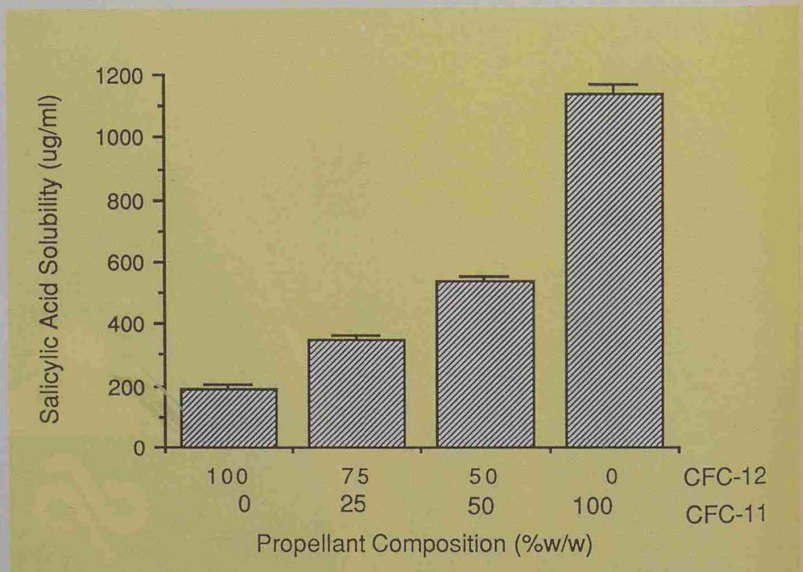

Figure 5. Effect of propellant composition on the solubility of salicylic acid (mean and standard deviation, n = 6). Richard N. Dalby, Elaine M. Phillips and Peter R. Byron; unpublished results.

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dissolved surfactant, and assuming complete propellant evaporation, the mass median aerodynamic diameter (MMAD) of the particles in the aerosol cloud at equilibrium will match the intial volume median diameter of the primary particles. However, further increases in suspension concentration increase the likelihood of multiple particle inclusion in sprayed droplets, leading to multi-particulate aggregate formation, and an increased MMAD following aerosolization. Table 3 shows an example of this model applied to 3μm particles of unit density, suspended in a propellant system that generates 30μm droplets following spraying.

Valve Performance and Manufacturing Considerations

The metering valve is an integral part of any MDI formulation. The metered volume is one of the determinants of the emitted dose, and is typically in the range of 25 to 100μl. A typical valve is shown in Figure 4. Smaller metered volumes are associated with short duration sprays and smaller droplet emission, while larger volumes produce sprays of longer duration containing larger droplets. Larger volumes permit more drug to be delivered, at the expense of number of doses per unit. Valve components must be compatible with all ingredients in the formulation, not leach toxic moieties into the propellant, and accurately meter quantities of product throughout the life of the MDI.

Suspension formulations place more stress on the metering valve than solution MDIs, particularly when the solids content is high. This necessitates meticulous attention to valve design. Examples of factors for consideration include: minimization of nooks and crannies where powder could accumulate, determination of what stem side hole diameter provides reproducible metering without blockage, and what materials are resistant to abrasion. Deposits of suspended drug in the side holes and stem orifice can render the MDI non-functional. This is usually more severe when a hygroscopic drug is involved, since water is absorbed from the atmosphere, causing the formation of strongly bound aggregates. Incomplete occlusion of the side holes may cause slow or partial product discharge during use. Deposition of drug aggregates within the metering chamber or on the valve seats may cause unreproducible suspension metering or propellant leakage. Since concentrated suspensions of jet milled particles can be abrasive, valve seats can be eroded during filling through the valve or during use, again leading to unacceptable rates of propellant loss. For these reasons, adequate valve lubrication and reduction of inter-particulate aggregation must be provided by surfactants incorporated into the formulation. The optimum combination of valve performance, metering volume, suspension concentration, surfactant type and concentration needed to maximize formulation "ruggedness" and drug delivery to the respiratory tract is a delicate balance.

The efficacy of an otherwise well formulated MDI can be compromised during scale up and manufacture if attention is not paid to various aspects of the process. Some concerns of interest for suspension formulations are outlined below.

Many MDI filling processes involve the preparation of a "concentrate." This contains suspended drug, dissolved (or dispersed) surfactant and a low volatility propellant, typically CFC-11. This may be done at low temperature or under pressure to prevent propellant evaporation. Concentrate is metered into a pressure resistant vial for subsequent dilution with the more volatile component, usually CFC-12. This may occur either before the valve is crimped (using propellant cooled to around −60°C), or via the valve after crimping (using overpressurized propellant). CFC-11 is a better solvent than CFC-12 for most drugs, allowing the possibility of drug dissolution (potentially aided by high surfactant concentrations) during concentrate preparation, and subsequent crystal growth or precipitation when CFC-12 is added. This phenomenon may become more prevalent with the introduction of HFC-134a, which is an extremely poor solvent. Figure 5 highlights a model system in which particles might be expected to grow or precipitate if manufactured by the process described above. Dissolved salicylic acid in a "concentrate suspension" of salicylic acid in CFC-11 may be precipitated by the addition of CFC-12, in which it is much less soluble. In practice most drugs are much less soluble than salicylic acid in CFC-11, but if problems do develop, CFC-114, a poor solvent compared to CFC-11, may be utilized for concentrate preparation. An alternative way of avoiding such problems involves preparation of bulk suspension using premixed propellants, followed by cold or pressure filling.

Preparation of a deaggregated suspension may be achieved using only gentle stirring (using a magnetic or impeller type stirrer), or may require the use of a high shear mixer or homogenizer. In either case it is important to ensure that the micronized drug comes into contact with the mixing device. If drug rapidly floats to the surface of the propellant, a bottom mounted magnetic stirrer or homogenizer may provide insufficient agitation to deaggregate the particles. Appropriately located additional stirrers may be required, although usually the problem can be avoided by optimizing the flow rate through the recirculation system to ensure a homogeneous drug distribution in the batching vessel. Failure to achieve this can result in poor uniformity of drug content throughout the batch and/or the presence of aggregates.

The recirculation of bulk or "concentrate" suspension between the batching vessel and metering chambers of the filling heads is necessary to avoid sedimentation in the filling lines. Recirculation, usually achieved using centrifugal pumps, may generate considerable heat. This is particularly likely when fast recirculation is necessary (as in the case of a very unstable suspension) or when the solids concentration of the suspension is very high. This can produce dangerously high pressures in the batching vessel and filling lines, cause product density to fall, leading to low fill weights or induce drug dissolution. The presence of heat exchangers on the filling lines can be used to alleviate the problem.

Conclusion

This paper has attempted to high-

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Table Four
Mexican Productions for 1989 and 1990 (est.), by Product Category

Category	1989	1990 (est.); & percentages	
Personal Products	17.1MM	17.9MM	34%
Insecticides	14.9	15.2	29
Household Products	5.0	5.3	10
Industrial Products	4.5	4.7	9
Paints	4.6	5.2	10
Medical Products	3.0	3.7	7

quet, tennis and domino tournaments and other opportunities for communication. Some of the most magnificent prehistoric ruins in the Western Hemisphere are within a 90 minute drive from Cancun. They include the mile-square archeological site of Chichen Itza, where an estimated 12,000 virgins were thrown into a huge well with unscalable limestone walls, the famous ruins of Tulum, with the main pyramid and altar built overlooking the Caribbean, and even a small ruin on Cancun itself. Many of the delegates brought their families and stayed two or three extra days in order to see and enjoy this picturesque Mayan area of Mexico, some 1200 miles by road from Mexico City. All in all, this was a convention to be remembered, sparked by the vigor and confidence of the Mexican aerosol industry as they move forward into the 1990s. □

Metered Dose Inhalers

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light some of the pitfalls that may be encountered during the formulation, scale-up and manufacture of suspension type metered dose inhalers. In order to produce an elegant, safe, and efficacious product the formulator should try to minimize apparently trivial idiosyncracies associated with the formulation. The additive effect of these "minor" problems can conspire to prevent commercialization of an otherwise effective drug. These challenges are likely to increase over the coming years since formulators will be presented with alternatives to CFC propellants, with which they have little experience. □

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