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Surfactant promoted crystal growth of micronized methylprednisolone in trichloromonofluoromethane

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Abstract

The effect of drug concentration and particle size, as well as surfactant type and composition, on the apparent solubilities and crystal growth of methylprednisolone (MP) in trichloromonofluoromethane (CFC-11) was examined. Apparent solubilities of micronized MP in CFC-11 were consistently greater than those of the unmicronized drug. Although the micronized and unmicronized drug were the same polymorph (form I), micronized MP was higher in amorphous content. Despite the existence of apparent supersaturation, micronized MP suspended in CFC-11 in the absence of surfactant showed no crystal growth over a 120 day period. Lipophilic surfactants showed differing abilities to solubilize MP in CFC-11. High concentrations of sorbitan trioleate (Span 85; 10^{-2} M) increased the apparent solubility of micronized MP 3-fold. This resulted in net crystal growth (increasing volume median diameter, Dvm) of drug suspended at concentrations $\leq 0.01\%$ by weight. Oleic acid and lower concentrations of Span 85 solubilized drug to lesser extents and failed to promote detectable growth. Greater suspension concentrations of drugs ($\geq 0.03\%$ w/w) also showed negligible changes in Dvm, even when formulated with 10^{-2} M Span 85. Preformulation of drugs in metered dose inhalers (MDIs) should include crystal size measurements in propellant-surfactant blends as functions of time. In some cases, changes in crystal size may be avoided by appropriate selection of surfactant, surfactant concentration and drug concentration in suspension.

Key words: Crystal growth; Surfactant; Pressurized suspension; Solubility; Propellant; Methylprednisolone; Physical form

1. Introduction

Crystal growth in aqueous pharmaceutical suspensions has been reported previously (Higuchi and Lau, 1962; Carless and Foster, 1966; Mehta et al., 1970; Simonelli et al., 1970). However, there is little information on the growth of compounds in nonaqueous, low dielectric media, and the important effects of formulation variables which should be reviewed during metered dose inhaler (MDI) development. The particle size distribution of suspended, microcrystalline drug is probably the single most important factor defining shelf life. We (Phillips et al., 1990) and others (Miller, 1990) have shown that suspension MDIs

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can be subjected to conditions which promote crystal growth and result in their physical instability. In some cases, net growth is accompanied by even more rapid changes in crystal habit (Phillips et al., 1993). Chlorofluorocarbon (CFC) propellants, used presently, must soon be replaced by 'ozone friendly' alternatives like hydrofluorocarbons (HFCs). A small but potentially variable concentration of dissolved surfactant is usually included in MDIs to prevent drug particles from aggregating irreversibly, and to keep the metering valve lubricated. Drug concentration in suspension can also be varied substantially because of the wide range of metering volumes available as valve options (drug concentration is dictated by the ratio of required dose to valve metering volume). As a result, there are numerous permutations possible for the product formulator and presently, little published information or theory relating to the effects of major variables upon crystal growth and crystal growth kinetics.

This paper reports the effect of drug concentration and particle size, as well as surfactant type and composition, on the apparent solubility and crystal growth of methylprednisolone (MP) in trichloromonofluoromethane (CFC-11). MP is similar to many steroids formulated in aerosols and the micronized form may be sufficiently small to promote Ostwald ripening (Ostwald, 1900; May and Kolthoff, 1948; Mullin, 1972). CFC-11 was chosen for ease of handling during experimentation. It is included in all existing MDI formulations and, among the CFCs, it has relatively high polarity. It is liquid at room temperature with a boiling point of 23.8°C.

2. Materials and methods

The particle size distributions of micronized methylprednisolone suspended in different trichloromonofluoromethane formulations were investigated as functions of storage time.

2.1. Preparation of methylprednisolone (MP) suspensions

MP (methylprednisolone USP, micronized lot 145CY, non-micronized USP lot 289DS, Upjohn Co., Kalamazoo, MI) was suspended in CFC-11 (Dymel-11, Dupont, Wilmington, DE) in the presence and absence of surfactants (Span 85, Fluka, Ronkonkoma, NY and oleic acid, Fisher, Columbia, MD) at surfactant concentrations ranging from 10^{-4} to 10^{-2} M. Suspensions were prepared and stored in 2 oz glass compatibility containers (Aerosol Laboratory Equipment, NY) or 4 oz aerosol bottles (Wheaton Glass, NJ). These were fitted with PTFE screwtops or valves (BK356 modified to continuous, Bespak, Cary, NC). The mean particle size of micronized MP, as determined by optical microscopy, was 3.0 μm with a standard deviation of 1.2 μm. Initial drug concentration (> 99.8% in suspension, < 0.2% dissolved in all cases) was either 0.01, 0.03 or 0.1% w/w in CFC-11. All formulations were shaken (wrist action shaker, Fisher) for 2 h immediately after preparation and stored under ambient conditions (21.3–22.4°C).

2.2. Iodine solubilization in CFC-11

Iodine solubilization (Ross and Olivier, 1959; Ross and Baldwin, 1966) was employed to determine the solubilizing power of Span 85, oleic acid and isopropyl myristate (Sigma Chemical Co., St. Louis, MO) in CFC-11. 2×10^{-4} M I_2 in CFC-11 was added to different quantities of each surfactant, to form solutions containing zero and 10^{-4}–10^{-2} M surfactant. Containers were sealed and shaken for 12 h prior to scanning (Varian DMS 100S, Varian Instrument Division, Palo Alto, CA) from 600 to 250 nm vs a CFC-11 reference. Absorbances due to solubilized iodine were determined relative to 2×10^{-4} M I_2 in CFC-11 at 355 nm.

2.3. Solubility determinations

A filtration apparatus, which has been described in detail (Dalby et al., 1991) and validated for drug solubility determinations in propellants, was used to determine apparent MP solubility in CFC-11 in the presence and absence of Span 85. Briefly, suspensions were filtered through 0.22 μm CFC-11 compatible membranes (GVWP, Millipore, MA) into preweighed receiving containers

crimped with continuous valves. Once sufficient filtrate had been collected, the containers were reweighed, propellant allowed to evaporate and drug residue reconstituted with a water/methanol (1:1) mobile phase. MP was determined by reverse-phase HPLC analysis using an autoinjector (Perkin-Elmer ISS 100, Norwalk, CT), 150 mm, 5 μm C-18 column (Spherisorb ODS-2, Alltech, Deerfield, IL) and a flow rate of 1.0 ml/min (Perkin-Elmer pump, model 250). A guard column (Spherisorb 5 μm C-18 cartridge, Alltech, Deerfield, IL) was used and replaced every 20th sample. Drug was detected at 254 nm (Shimadzu SPD-6, Shimadzu Corp., Kyoto, Japan) 19 min after each 20 μl injection. Calibration curves were linear from 0.2 to 7 μg/ml and the detection limit of the assay was 0.05 μg/ml. Each formulation was sampled five times. Results are presented in terms of μg of MP per g of filtrate. Samples containing Span 85 were first centrifuged to separate the surfactant from the drug-containing mobile phase. No significant quantities of drug were lost by partitioning into surfactant and MP spiked samples indicated that Span 85 did not interfere with chromatograms for drug.

2.4. Crystal characterization

Solid micronized and unmicronized MP was characterized at different points during this investigation. When necessary, the material was isolated from suspension in CFC-11 by filtration, washed three times in surfactant-free CFC-11 and the propellant removed by evaporation at room temperature and pressure. Melting points, heats of transition (ΔH_t) and heats of fusion (ΔH_f) were determined using differential scanning calorimetry (DSC; Perkin-Elmer PC Series DSC7). Accurately weighed samples were sealed in aluminum pans (item no. 0219-0014, Perkin-Elmer) and heated at 2°C/min under dry nitrogen flowing at 25 ml/min. Melting points were assigned at the onset of melting. Hot stage microscopy was performed using transmitted light under crossed and uncrossed polars, also under dry nitrogen flowing at 25 ml/min (Nikon Optiphot Polarizing Microscope and Mettler Hot Stage FP 80 and FP 82 Processor). The furnace of the hot stage (heating rate 2°C/min) and DSC were cross-calibrated at the melting transitions of stearic acid (69–70°), indium (156.6°) and tin (231.9°) reference standards. The maximum recorded deviation from these standard values was −2.0° (melting point of tin on DSC7). Polymorphism was assessed by X-ray powder crystallography. The formation of solvates or other reaction products between MP, CFC-11 and Span 85 was investigated by performing elemental analysis (C, H, O and Cl) on micronized MP before and after 3 months storage in suspension.

2.5. Crystal size analysis

Crystal size distributions were determined as a function of time on samples from suspension formulations by forward laser light scattering (Malvern 2600c, Malvern Instruments, Southboro, MA). Formulations were shaken for 2 h and sonicated for 5 min (to break down aggregates) before pipetting into an air-tight, pressure-resistant cell (PS1 cell, Malvern) containing CFC-11 as diluent (there were no differences in measured crystal size distributions when diluent CFC-11 was previously saturated with MP). The cell was placed in the path of the helium neon laser and diffracted light intensity patterns were transformed into model independent particle size distributions. Most samples were analyzed with a 63 mm range lens. Results were expressed in terms of volume median diameter (Dvm) vs time with error bars as the experimental range for the three determinations. Monodisperse polystyrene latex spheres (Polybead, Polyscience, Warrington, PA) were sized in water as external standards to ensure consistent instrument performance. Suspensions were subsequently examined by optical microscopy (Nikon Optiphot, Tokyo, Japan) to confirm results from the laser light scatterer.

3. Results and discussion

Fig. 1 compares the thermograms for unmicronized and micronized (jet milled) MP heated at 2°C/min after initial rapid heating (200°C/

min) to either 150 or 200°C. Rapid heating to 200°C gave a broad endotherm with onset at 210°C and another with onset at 238°C for the unmicronized drug, while the micronized MP apparently showed a single endotherm at 238°C. Running the thermogram from 150 instead of 200°C showed similar differences between micronized and unmicronized MP although the major (melting) endotherm occurred at 220 instead of 238°C.

Literature values (Guillory, 1967; Moffat, 1986; Merck, 1989) for MP melting points range from 209 to 243°C, probably reflecting the compound's thermolability (visual examination under hot stage microscopy indicated that decomposition had occurred when the upper temperature limit of 260°C had been reached even though the compound was heated under nitrogen; the melt failed to recrystallize when seeded). Lower apparent melting points (Fig. 1, curves C and D) consistently coincided with increased exposure to high temperatures. Coincidentally perhaps, the data in curve A of Fig. 1 agreed well with that of Guillory (1967) who performed differential thermal analysis on MP. He stated that MP form I undergoes an endothermic transition at 209–213°C (ΔH_t of 1380 ± 50 cal/mol), with fusion occurring at 239–242°C (ΔH_f of 5350 ± 200 cal/mol). These values compared well with the 1372 and 5560 cal/mol determined, respectively, from curve A of Fig. 1 for the unmicronized MP. The apparent absence of a transition endotherm for the micronized MP implied that it was the metastable polymorph of MP, form II (Phillips, 1991; Phillips and Byron, 1991). However, this was not the case and, in this respect, the DSC data were misleading. The interplanar distances, determined by X-ray powder diffraction for the micronized and unmicronized MP, were entirely consistent with values for MP form I, the stable polymorph, in both cases. Our values for interplanar spacings (Å) determined from the powder diffraction data

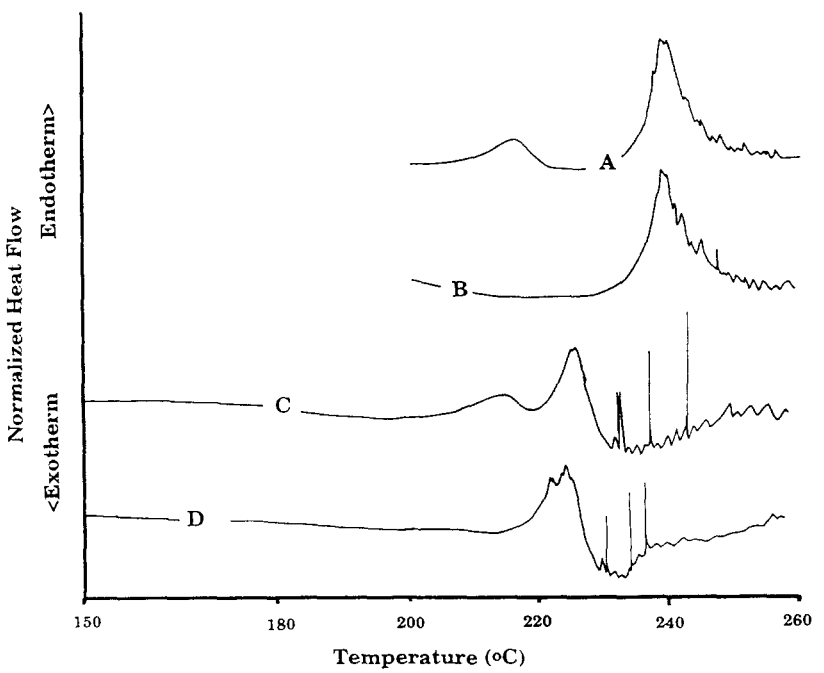

Fig. 1. Thermograms from differential scanning calorimetry for unmicronized and micronized MP heated at 2°C/min under dry nitrogen after rapid heating to 200°C (curves A and B, respectively). Curves C (unmicronized MP) and D (micronized MP) show the effect of rapid heating to 150°C followed by a 2°C/min temperature ramp from 150°C. The large endotherms indicate fusion accompanied by decomposition in all cases. The small endotherms shown for the unmicronized drug illustrate the transition from polymorph I to polymorph II; these merged with the baseline for micronized MP.

according to Stout and Jensen (1989) were: 9.92, 9.19, 8.39, 7.09, 5.95, 5.47, 4.94, 4.58, 4.19, 3.92, 3.66, 3.52, 3.38, 3.29, 3.12 and 2.95. These compared with those reported by Higuchi et al. (1963) of 9.87, 9.21, 8.42, 7.08, 5.94, 5.50, 5.01, 4.59, 4.19, 3.93, 3.67, 3.51, 3.39, 3.29, 3.11 and 2.96. Those authors also reported values for the metastable polymorph II of MP commencing at 12.1, 8.58, 7.37, 6.32 Å, clearly showing the ability of X-ray powder diffraction to discriminate between the two polymorphs in this case. Microscopy under crossed polars, DSC data, X-ray diffraction, and hot-stage microscopy, however, all indicated an increase in the content of amorphous MP due to the process of micronization, but no change in polymorphic form. The absence of a clear transition endotherm in the thermograms for micronized MP (Fig. 1, curves B and D) appeared to be due to the broadening of this endotherm and its merger with the baseline. The transition endotherm reported by Guillory (1967) and confirmed in Fig. 1 (curves A and C) was only visible when MP crystals were relatively large.

The micronization process, which may increase the content of high energy amorphous material, or induce polymorphic change, usually produces polydispersed log-normal distributions ranging from < 1 to approx. 5 μm in diameter. It is also believed to produce powders with numerous high-energy surface sites (Miller, 1990). Drug may have greater escaping tendencies from these sites, leading to supersaturation, and/or particles may be more prone to aggregation because of them. Fig. 2 compares the apparent solubilities of micronized and unmicronized MP in CFC-11 in the absence of surfactant. At all suspension concentrations tested, micronized drug had a significantly higher apparent solubility than the unmicronized compound (when data were pooled for micronized and unmicronized drug, the average value of 0.404 μg/g for micronized MP was 82% greater than the solubility of unmicronized MP). Micronized MP contained a higher proportion of high-energy amorphous material and smaller particles, both with greater escaping tendencies than the unmicronized drug. The Kelvin effect (Martin et al., 1983), which is believed to describe the increased escaping tendency due to surface curvature, is described mathematically for solid spheres in suspension by the Ostwald-Freundlich equation (May and Kolthoff, 1948):

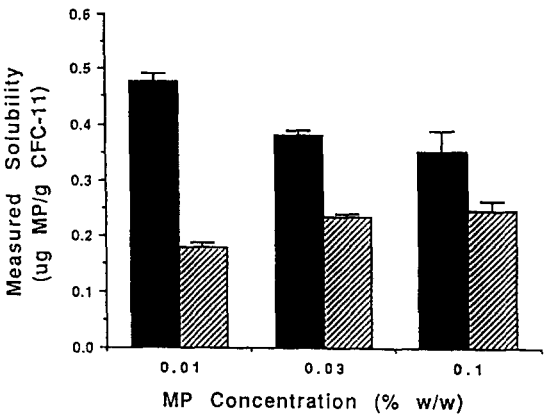

Fig. 2. Measured solubility of micronized (■) and unmicronized (□) MP in CFC-11 at three separate MP suspension concentrations. Error bars are standard deviations with $n = 5$.

$$\ln(S_r/S_0) = (2\gamma_{s/l}V)/(RTr) \quad (1)$$

where S_0 is the intrinsic solubility above a non-curved solute surface, S_r denotes the solubility of a spherical particle of radius r, V is the molar volume of the solute, $\gamma_{s/l}$ represents the solid-solution interfacial tension, and RT is the product of the universal gas constant, R, and absolute temperature, T. The net effect of this equation is that S_r decreases exponentially toward S_0 as r is increased from zero to values above 1 μm. Although there are theoretical and practical limitations (Aveyard and Haydon, 1973; Buckton, 1988) to the use of Eq. 1 for solid/liquid systems in which solids display non-uniform surface free energy, the Kelvin effect failed to account convincingly for the large differences in apparent solubility between micronized and unmicronized MP. Calculations of S_r/S_0 for MP in CFC-11 indicated that a 1 μm sphere should only have an increase in solubility of about 1.5%. However, apparent solubilities also showed a marked suspension concentration dependence and no inclination to change within a realistic time frame. The same formulations tested 36 days after the initial experiment gave equivalent solubilities and, as we will discuss later, showed no increases in

crystal size. Observations of this kind are not unusual in MDI formulations (Miller, 1990), nor are they without precedent in the literature (Buckton and Beezer, 1992). The data presented in Fig. 2 were reproducible and indicative of the existence of metastable steady states in the different CFC-11 suspensions. Accordingly, none of the values reported in Fig. 2 can be considered to be the equilibrium solubility of MP form I (Buckton and Beezer, 1992). Note also that dissolution of MP in CFC-11 (dielectric constant = 2.28; Handbook of Chemistry and Physics, 1987) is presumably due almost entirely to dispersion forces and is consistently less than 0.5 ppm.

It is difficult to explain the suspension concentration dependency of the results in Fig. 2. The filtration technique used for these determinations has been validated (Dalby et al., 1991; Phillips, 1991) using MP and other compounds. The results were reproducible and independent of the volume of filtrate collected. One plausible explanation for the trend shown for unmicronized MP could be the dissolution of a very small, but finite, amorphous content (0.025–0.2% of suspended MP was dissolved in these cases) and metastable maintainence of the resulting supersaturated state. Micronized MP, however, showed the opposite trend (decreasing concentrations in solution with increasing suspension concentrations). The trend in this case was fortunately coincident with the occurrence of extremely rapid flocculation; particle aggregation into flocs occurring faster at higher suspension concentrations. This is consistent with theory (Miller, 1992) where interparticulate contacts in flocs favor those points with high surface free energies. Thus, the occlusion of high-energy active sites (with higher escaping tendencies) may have occurred increasingly at higher suspension concentrations, resulting in lower values for apparent solubility.

3.1. Crystal growth

In the absence of surfactant, there were no significant changes in volume median diameter, Dvm, of the suspended drug over a 120 day period. Suspensions with concentrations > 0.01% w/w MP showed a greater range in measured median sizes using this technique due to rapid crystal flocculation and the measurement of aggregates in suspension. However, microscopic examination of these formulations at 120 days confirmed the absence of growth. All subsequent sizing experiments without surfactant were performed with 0.01% w/w MP in order to minimize variability in results due to aggregation.

Fig. 3 shows the crystal growth of 0.01% MP in CFC-11 containing various concentrations of Span 85. In the presence of zero, 10^{-4} M (not shown) and 10^{-3} M Span 85, Dvm was unchanged over a 120 day period. Supersaturation due to the presence of 0.01% micronized MP alone (Fig. 2) was insufficient to promote observable growth. However, in the presence of 10^{-2} M Span 85, Dvm increased from an initial size of approx. 4.7 to 9.5 μm over the study period. Fig. 4 shows a similar growth effect due to 10^{-2} M Span 85, this time at various suspension concentrations of MP (flocculation during sampling was not a problem in the presence of Span 85 even at increased suspension concentrations).

It is well known that some steroids solvate in the presence of chlorinated fluorocarbons to form 'clathrates' or molecular associations of variable stoichiometry (Cook and Hunt, 1976). Indeed, beclomethasone dipropionate is marketed in an MDI as a 'clathrate with trichloromonofluo-

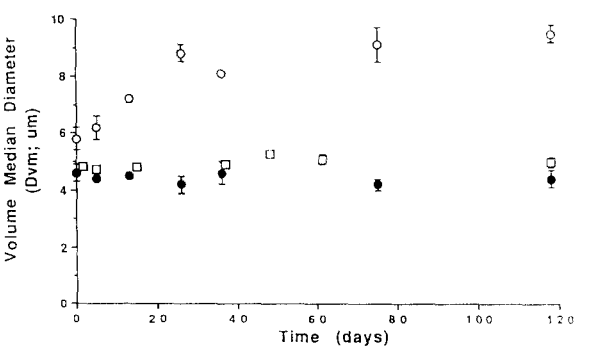

Fig. 3. Volume median diameter (Dvm) for 0.01% w/w micronized MP formulations as a function of time following suspension manufacture. Formulations differ with respect to their Span 85 content; (○) 10^{-2} M; (□) 10^{-3} M; (●) no surfactant. Error bars show experimental ranges for three samples. Absence of error bars indicate that the range was less than the symbol size.

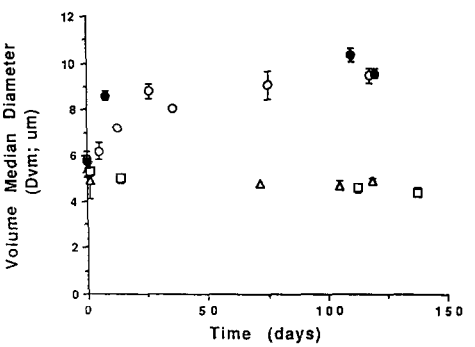

Fig. 4. Volume median diameter (Dvm) vs time for formulations containing 10^{-2} M Span 85 and different micronized MP concentrations; (●) 0.005% w/w MP; (○) 0.01% w/w MP; (△) 0.03% w/w MP; (□) 0.10% w/w MP. Error bars show experimental ranges for three samples. Absence of error bars indicate that the range was less than the symbol size.

romethane'. In this study, however, elemental analyses of MP before and after growth were identical and in agreement with theory. After growth, MP was isolated from suspension and washed with surfactant-free CFC-11. The solvent was then allowed to evaporate for 24 h under ambient conditions in the hood (beclomethasone dipropionate clathrates retain CFC-11 under identical conditions). Chlorine was notably absent from the MP crystals grown in the presence of the surfactant and thus, there was no detectable reaction with Span 85 or CFC-11 during the crystal growth process. Powder X-ray diffraction data were also collected on these crystals. The data indicated maintainence of crystalline MP form I.

Thus, while the presence of Span 85 promoted an increase in Dvm, it was incapable of promoting discernable crystal growth at drug concentrations greater than 0.01% w/w (Fig. 3 and 4). Furthermore, in the increasingly dilute 0.005% w/w formulation, Dvm changed from 5.7 to 9.6 μm, the initial rate of change occurring more rapidly than with the 0.01% suspension. This concentration dependence may be partly because precipitation of a finite drug mass has a smaller and slower effect when it occurs on a larger number of particles. Independent of the explanation, however, it is clear that the MDI formulator should review the influence of suspension concentration when confronted by an apparent growth problem.

Fig. 5 shows the absorbance of the iodine-surfactant complex at 355 nm vs $\log_{10}$ surfactant concentration for three surfactants. Iodine in Span 85 showed a progressive increase in absorbance to a maximum at approx. 10^{-2} M while oleic acid only showed significant increases in absorbance at concentrations greater than 10^{-2} M. Isopropyl myristate showed no evidence of solubilizing iodine in this medium. These results for iodine solubilization by Span 85 in CFC-11 were in good agreement with those of Evans et al. (1988, 1989) who performed a similar experiment in 1,1,2-trichloro-1,2,2-trifluorethane and showed that solubilization was due to the formation of reverse micelles. Results for apparent MP solubilities determined in the presence of Span 85 at different concentrations (0.01% w/w MP suspensions) are shown in Table 1. The dramatic increase in iodine solubilization by Span 85 at 10^{-2} M correlated well with the surfactant's ability to solubilize the steroid. Taken with the results for crystal growth in the presence of 10^{-2} M Span 85 (Fig. 3), the presence of reverse micelles seemed somehow implicated in the growth process. Oleic acid, on the other hand, had a much a smaller effect on iodine or MP concentrations in non-aqueous solution (Fig. 5, Table 1). Values for Dvm of MP in suspensions containing 10^{-4} to 10^{-2} M oleic acid were assessed, but did not

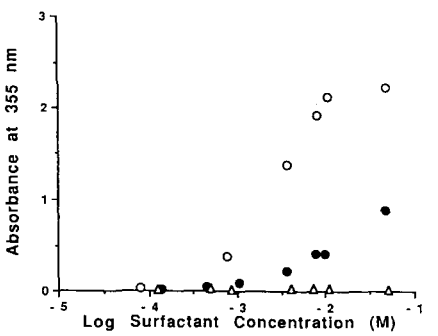

Fig. 5. Solubilization of iodine in CFC-11 by Span 85 (○), oleic acid (●) and isopropyl myristate (△). Absorbance values at 355 nm in CFC-11 represent the surfactant-iodine complex and exclude absorbance due to free iodine and/or free surfactant.

Table 1
Effect of surfactant type and concentration on the apparent solubility of 0.01% w/w micronized MP suspended in CFC-11

Surfactant	Concentration (M)	Solubility of MP (μg MP/g CFC-11)
Span 85	2.0×10^{-4}	0.545 (0.009)
	1.1×10^{-3}	0.715 (0.050)
	1.0×10^{-2}	1.57 (0.080)
Oleic acid	3.9×10^{-4}	0.621 (0.010)
	1.1×10^{-3}	0.865 (0.032)
	0.9×10^{-2}	0.645 (0.082)

Values in parentheses are standard deviations for $n = 5$.

change over the study period. Crystal size changes were not studied in the presence of isopropyl myristate.

Many studies have examined the effect of surfactants on aqueous solubility and crystal growth in high dielectric media. Higuchi and Lau (1962) found that the addition of one drop of Tween 80 to an aqueous MP suspension decreased its rate of crystal growth 500-fold, while the addition of sodium lauryl sulfate or Tertigol 4 did not alter the crystal growth kinetics. In a study examining the effect of temperature cycling on crystal growth, Carless and Foster (1966) performed experiments incorporating three different surfactants in sulfathiazole suspensions, all at concentrations above their aqueous critical micelle concentration. They found that increasing concentrations of cetomacrogol inhibited crystal growth of sulfathiazole despite the fact that increased concentrations of the surfactant also increased the drug's solubility. Both groups suggested that surfactants produced an interfacial barrier to drug transport between solution and solid surfaces. Mehta et al. (1970) concluded in their study that aqueous crystal growth of MP was surface and not diffusion controlled. In the present case, suspensions of micronized MP in CFC-11 prepared in the absence of surfactant, failed to show changes in Dvm over the 120 day study period. If the data and discussion surrounding Fig. 2 above are interpreted to indicate that solutions were supersaturated with respect to MP form I when suspensions were formed with micronized MP at 0.01% by weight, then this degree of supersaturation was apparently stable for the duration of the growth experiments. Even if MP had precipitated from solution to reduce this supersaturation, calculations revealed that the available drug mass, deposited over the entire suspended surface, would not have produced a detectable change in Dvm. However, 10^{-2} M Span 85 promoted an increase in median diameter without inducing any other measurable change in the physical form of suspended MP (Fig. 3 and 4).

Despite considerable efforts to characterize this system, we were unable to define the mechanism whereby Dvm increased in the presence of Span 85. It is impossible to say whether MP solubilization could itself modify the true supersaturation ratio (concentration/S_0) or the degree of supersaturation (concentration $- S_0$) with respect to crystalline form I, and then bring about changes in nucleation and/or growth kinetics. It is possible that the increase in apparent supersaturation brought about by surfactant-drug complexation (Table 1) may act as a reserve of drug which can more readily assist in growth. Net growth in this system however (increasing values for Dvm; Fig. 3 and 4), involves a net reduction in total crystal number and the surface area presented to the liquid propellant. If nucleation continues to be an important phenomenon in these suspensions it is equally plausible that the surface affinity of Span 85 and/or its ability to hinder nucleation may impede the creation of new crystals yet favor the growth of the old. Such an explanation is consistent with a previous report of the importance of surface control during MP crystal growth (Mehta, 1970), however, it appears to conflict with the data showing the effect of MP suspension concentration on Dvm (Fig. 4). In the more concentrated suspensions, however, surfactant concentration in solution may have been lowered by adsorption to the powder surface.

Table 2 summarizes the degree of polydispersity and Dvm for three of the formulations shown in Fig. 4 during the study period. It is included here for completeness, because the formulator of an MDI frequently considers that the geometric standard deviation of the micronized product is an important property to control (Byron, 1990). In the case of formulations showing an increase

Table 2
The degrees of dispersity (D_{90}/D_{10}) or ratios of diameters below which either 90% (D_{90}) or 10% (D_{10}) of the particle volume appeared to exist following model-independent curve fits of the forward light scattering data collected from the Malvern 2600

Time (days)	0.01% w/w MP		0.03% w/w MP		0.10% w/w MP	
	Dvm (μm)	D_{90}/D_{10}	Dvm (μm)	D_{90}/D_{10}	Dvm (μm)	D_{90}/D_{10}
<1	6.3	9.5–12.6	6.3	6.1–8.7	5.3	8.5–9.6
1– 14	6.7	5.9– 7.0	ND	ND	5.2	5.3–8.3
15– 28	8.8	5.7– 6.6	5.8	3.9–7.7	ND	ND
29– 77	9.1	4.9– 6.9	5.7	4.4–5.0	ND	ND
78–113	ND	ND	5.9	5.0–5.6	4.6	5.1–6.6
113–140	9.5	4.8– 4.9	6.0	5.2–5.6	4.4	5.3–6.2

Values for dispersity and average volume median diameter, Dvm, are presented for suspensions containing 10^{-2} M Span 85 at varying suspension concentrations (% w/w) of MP in CFC-11 at different times. Ranges shown are the full range of three determinations; ND, not determined.

in Dvm with time, we hypothesized that this may coincide with decreasing polydispersity in their particle size distributions. Polydispersity of the formulations was estimated by taking the ratio of D_{90}/D_{10} which are the calculated volume diameters below which 90 and 10% of the total volume of particles occur in suspension. Volume size distributions were calculated by the Malvern 2600 by a process of constrained least squares fitting of theoretical scattering characteristics to the observed data (Malvern, 1985). The values presented in Table 2 are observed experimental ranges. Their breadth (5.3–8.3, for example) is indicative of the poor reliability of this curve-fitting procedure at the extremities of the data. The large dispersity for all three formulations at the early time points was, however, a characteristic of formulations containing surfactants. MP suspensions containing no surfactant, and experiencing no crystal growth, had more consistent values of D_{90}/D_{10} (approx. 4.5) over the complete time frame for which suspensions were sampled. These values (D_{90}/D_{10}) are similar to those expected for a log-normally distributed powder with a geometric standard deviation of approx. 2. In the surfactant containing systems, the large degree of dispersity at the early time points suggested that the formulations had not achieved surface equilibrium. As the formulations aged, the degree of dispersity decreased to values similar to the surfactant-free systems. Table 2 shows clearly that forward laser light scattering in CFC-11 does not allow the degree of dispersity to be used alone as an indicator of net crystal growth.

4. Conclusion

In practice, the suspension formulator must avoid crystal growth problems while confronting the selection of surfactant, surfactant concentration, drug concentration and valve metering volume. In some cases there may also be a need to control the polymorphic form and/or solvate, as well as the particle size distribution, of the drug during milling. Metastable forms should not be selected and, unless solutions are to be formulated in propellants (Evans and Farr, 1992) it is clearly irrational to select surfactant concentrations which act as powerful solubilizers. Preformulation of a drug candidate should certainly include solubility measurements. Crystal size distributions should also be examined over the proposed shelf life of the formulation. Surfactant concentration and surfactant/drug ratio should probably be minimized. Also, it may be important to minimize the extent to which micronized crystalline product is rendered amorphous by the milling process although this was not shown to be a problem in this study. Whether or not significant growth occurs must still be assessed by experiment. Laser scattering is a useful method in this respect, being much more sensitive than cascade impaction (Phillips et al., 1990). However, the Malvern 2600 could not be used to assess changes in polydispersity with time even in cases of significant crystal growth. Values of Dvm can be determined at different times for true MDI formulations by sampling sprays under the surface of a collection medium in which the drug is insoluble (e.g., CFC-11). A non-solvent collection medium with minimum volatility should be used to minimize laser-induced cavitation in the suspension. Even in a pressure cell, vapor bubbles can be induced by the laser beam which then scatter light themselves. In this study, light scat-

tering in suspension was used successfully to assess both the existence and the kinetics of changing values for volume median diameter in non-aqueous suspensions.

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