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Research paper

Application of co-grinding to formulate a model pMDI suspension

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Abstract

The objective of this study was to investigate the effect of co-grinding the model drug, triamcinolone acetonide (TAA), with a polymeric surfactant on the in vitro performance of a model pMDI suspension system. The physicochemical properties of TAA after co-grinding with the surfactant, Pluronic F77®, were determined by laser light diffraction, helium pycnometry and equilibrium solubility measurements. TAA-surfactant interaction was investigated by differential scanning calorimetry and Fourier transform infrared spectroscopy (FTIR). The suspension characteristics of pMDI formulations prepared with co-ground TAA and surfactant were investigated by determining their in situ sedimentation, rheological profiles and vapor pressure. The performance characteristics of the pMDI formulations were determined by cascade impaction and dose delivery through-the-valve (DDV) measurements. It was found that the presence of Pluronic F77® decreased the solubility of TAA in the propellant medium. Co-grinding TAA particles with Pluronic F77® influenced the particle size distribution, sedimentation and flocculation characteristics of the pMDI suspension formulation. The addition of Pluronic F77® decreased the viscosity of the pMDI formulation. Formulating the suspension pMDI system with co-ground TAA and Pluronic F77® decreased the mass median aerodynamic diameter (MMAD) of the emitted aerosol and increased the percent respirable fraction (%RF). The co-ground TAA and Pluronic F77® pMDI suspension formulation exhibited greater physical stability which was due to the influence of the co-grinding technique on the physicochemical properties of the TAA particle surface and the propellant dispersion medium. The changes induced by co-grinding with Pluronic F77® improved the performance characteristics of a pMDI suspension formulation by stabilizing the suspension and influencing the flocculation characteristics. Co-grinding is a process which may be useful when developing new pMDI systems containing HFA propellants.

Keywords: Co-grinding; Pressurized metered dose inhaler; Suspension; Co-polymer; Surfactant; Pluronic F77®

1. Introduction

Due to their reported depletion of ozone in the atmosphere, chlorofluorocarbon (CFC) propellants which are used in pressurized metered dose inhalers (pMDI), are being phased out and replaced by hydrofluoroalkane (HFA) propellants [1]. Differences in polarity between the CFC and the HFA propellants have presented significant obstacles in the development of new pMDI systems [2,3]. Drugs which were not soluble in the CFC propellants and were formulated as suspension pMDI systems may be appreciably soluble in the HFA propellants. Although the surfactant, oleic acid, was found to be soluble in P134a, other surfactants such as lecithin and sorbitan trioleate are not soluble in HFA media [2]. Reports of the influence of HFA propellants, P134a and P227, on the vapor pressure, density and aerodynamic particle size distribution of model pMDI suspension systems have indicated a need for further investigation [3].

Some researchers have focused on identifying and investigating new surfactants for the dispersion and stabilization of HFA based pMDI formulations. A recent US patent describes the use of polyglycolyzed glycerides in aerosol drug formulations containing P134a and P227 for preventing unwanted aggregation of a suspended medicament [4]. Another US patent documents the use of surfactants having a hydrophilic-lipophilic balance (HLB) greater than 9.6 in pMDI formulations containing P227 [5]. Polymeric surfactants such as the block copolymers of ethylene oxide (EO) and propylene oxide (PO), may also be suitable for dispersion and stabilization of HFA based pMDI formulations. The block copolymers of EO and PO, also referred to as poloxamers, behave differently from nonionic hydrocarbon lipophiles. Their HLB depends on the ratio of the number of EO groups in the hydrophilic chain and the number of PO groups in the hydrophobic chain [6]. Co-grinding water insoluble drugs with various types of water soluble poly-

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mers and surfactants has been utilized to enhance drug dissolution and solubility by improving the wetting of drug particles [7]. Changes in drug particle size and the molecular interactions between the drug and polymeric surfactant may affect the enthalpy of the solid and influence the dissolution properties of the drug [8]. Co-grinding solid drug particles with these polymeric surfactants may influence suspension characteristics and drug solubilization properties in HFA propellants. Pluronic F77® is a solid at 20°C, has a molecular weight of 6,600 and an HLB of 25 [9]. Although it is highly hydrophilic, the solubility in a 1:1 (w/w) P134a and P227 propellant mixture was found to be greater than 0.1% (w/w). Therefore Pluronic F77® was chosen as a model polymeric surfactant for co-grinding with the model drug, TAA.

The objectives of this study were to investigate the effect of co-grinding the model drug, triamcinolone acetonide (TAA), with a polymeric surfactant on the physicochemical properties of TAA and to determine the influence on the in vitro performance of a model pMDI suspension system.

2. Materials and methods

2.1. Materials

The hydrofluoroalkane propellants used were Dymel Ultrapure P134a (P134a; 1,1,1,2-tetrafluoroethane; DuPont Chemicals; Wilmington, DE) and Solkane 227 Pharma (P227; 1,1,1,2,3,3,3-heptafluoropropane; Solvay Fluorides, Greenwich, CT). Methanol (EM Science; Gibbstown, NJ) and the model drug, Triamcinolone Acetonide USP (The Upjohn Co.; Kalamazoo, MI) was used. The surfactant investigated was the Pluronic grade F77® Prill (BASF; Mount Olive, NJ).

2.2. Co-grinding procedure

A 10 g aliquot of TAA and a 10 g aliquot of 3:1 (w/w) TAA and Pluronic F77® were ground in a porcelain centrifugal ball mill grinding apparatus (US Stoneware, Inc.; East Palestine, OH). The ball mill apparatus consisted of a 237 ml chamber and 20 zirconia balls measuring 3/8 inch in diameter. Test samples were ground at 20 rev./min for 6 h at 24°C and 55% RH. Also, a 10 g aliquot of a 3:1 (w/w) TAA and Pluronic F77® physical mixture was prepared by geometric dilution using a glass mortar and pestle.

2.3. Preparation of suspension pMDI formulations

Suspension pMDI formulations were prepared by measuring 30 mg of control TAA (not subjected to grinding), ground TAA, and 40 mg of co-ground or physical mixture of 3:1 (w/w) TAA and Pluronic F77® blends into aluminum cans (Cebal S.A.; Bellegarde, France) crimped with 75 μl metering chamber valves (Model DF10; Valois of America; Greenwich, CT). The canisters were filled with 5 g of P134a and 5 g of P227 using a Pamasol crimping and propellant filling unit (Models P2005 and P2008; Pamasol Willi Mader AG; Pfaffikon, Switzerland). The suspension pMDI formulations were prepared in triplicate.

2.4. Dose delivery through-the-valve

The dose delivery through-the-valve (DDV) was determined by collecting the contents of the metering chamber emitted for each pMDI formulation in a dosage unit sampling tube equipped with a firing adapter (26.6 × 37.7 × 103.2 mm; 50 ml volume, Jade Corporation; Huntingdon Valley, PA). Three actuations from each pMDI formulation were collected. Methanol was added to the dosage unit and the amount of drug emitted per actuation was determined by HPLC [10]. A Shimadzu Liquid Chromatography system (Model 6A with CLASS-VP automated software system; Shimadzu Inc., Columbia, MD) was used. The mobile phase was composed of phosphate buffer (pH = 3.0)/methanol (63:37). A 150 × 4.6 mm Inertsil 5μ ODS 2 column (MetaChem Technologies Inc., Torrance, CA) and a Shimadzu UV detector operating at 240 nm were employed. The flow rate was controlled at 1.5 ml/min. The HPLC analysis met all system suitability requirements for precision and accuracy.

2.5. Aerodynamic particle size distribution

An 8-stage cascade impactor (Andersen I ACFM Non-Viable 8-Stage Cascade Impactor with a USP Induction Port, Mark II, Graseby-Andersen; Smyrna, GE) was used to determine the aerodynamic particle size distribution of the dose emitted from the pMDI systems investigated. Twenty-five actuations were collected for each cascade impaction determination. Glass fiber filter paper (Graseby–Andersen) was used as the collection substrate. Methanol was used to solubilize TAA from the glass filter substrate. The mass of TAA deposited on each stage of the impactor, the induction port and the actuator was determined by HPLC [10]. The mass median aerodynamic diameter (MMAD) was determined from a plot of the cumulative percent mass of drug versus the particle size less than stated on log-probability paper. The percent respirable fraction (%RF) was calculated as the mass fraction of drug emitted from the test pMDI system which was less than 4.7 μm.

2.6. In situ sedimentation and velocity

The method used to determine the in situ sedimentation of the test pMDI suspension formulations was adopted from a method recently described by Miller et al. [11]. Briefly, a dosage unit sampling tube equipped with a firing adapter was used to collect the dose of drug emitted from the valve. Each test pMDI system was shaken manually, then the valve stem was immediately depressed and held down for 0, 5, 10 and 15 s into a waste sampling tube. As a result, the meter-

Table 1
The aerodynamic particle size distribution and DDV of test pMDI systems after storage for five days at 25°C. Standard deviations (SD) are given in parenthesis

PMDI formulation	MMAD (μm)	SD	GSD	%RF	SD	DDV (μg)	SD
Ground TAA	4.6	(0.29)	2.2	23.5	(7.13)	170.8	(16.31)
TAA/F77 physical mixture	3.5	(0.17)	2.0	30.9	(2.65)	184.3	(8.108)
TAA/F77 co-ground	2.7	(0.26)	2.6	33.6	(1.60)	197.8	(24.73)

ing chamber of the valve was loaded with formulation at the designated loading interval. The drug content of the loaded metering chamber was collected by actuating once into separate dosage unit sampling tubes corresponding to each time interval. The drug collected in the sampling tube was dissolved in methanol and analyzed by HPLC [10]. The theoretical sedimentation velocity of the suspension pMDI formulations was calculated using the Stokes law equation and their corresponding experimentally determined values for density, particle size and viscosity [12].

2.7. Helium pycnometry

An AccuPyc 1330 (Micrometrics, Inc.; Norcross, GA) was used to determine the true density of ground TAA, co-ground TAA and Pluronic F77® and the TAA and Pluronic F77® physical mixture ($n = 5$).

2.8. Vapor pressure

The vapor pressure of the test pMDI formulations was determined using a head pressure test gauge (Model P700; Pamasol Willi Mader AG; Pfaffikon, Switzerland). The vapor pressure of the pMDI systems at 25°C was recorded by coupling the test gauge to the valve stem and opening the pMDI system by depressing down on the valve ($n = 3$).

2.9. Particle size distribution

The particle size distribution of control TAA, ground TAA, co-ground TAA and Pluronic F77® and the physical mixture of Pluronic F77® and TAA were measured with a Shimadzu SALD-1100 laser light diffraction particle size analyzer (Shimadzu Inc., Columbia, MD). The median diameter (M50) was determined at the 50th percentile of particles undersized. The polydispersity was given by a span index which was calculated by (M90 - M50)/M50 where M90 is the particle diameter determined at the 90th percentile of particles undersized [13]. The co-ground and physical mixture were washed with cold water to remove the surfactant prior to measurement. Dispersions of washed TAA were prepared in an aqueous 0.01% Tween 80 solution utilizing a water bath with sonication ($n = 3$).

2.10. Triamcinolone acetonide solubility

The equilibrium solubility of TAA in purified water and in a 1:1 (w/w) P134a and P227 propellant blend was determined after storage for five days at 25°C. To determine the equilibrium solubility in purified water, 30 mg of TAA and 40 mg of 3:1 (w/w) TAA and Pluronic F77® blends were dispersed in 10 ml water and placed in an automatic shaker. The test samples were filtered and the concentration of TAA in the filtrate was measured by HPLC analysis [10]. A similar method to that described by Dalby et al. was used to determine the solubility of TAA in liquid propellant [14]. Briefly, a donor canister containing the test pMDI formulation was crimped with a continuous spray valve then stored inverted in an automatic shaker. After five days at 25°C, the donor pMDI systems were coupled to an empty receiver canister by a modified Gelman filtration apparatus (25 mm In-line Delrin® Filter Holder; Pall Gelman Sciences; Ann Arbor, MI). The soluble contents of the test pMDI formulations were passed through the filter into the empty receiver canister, and the concentration of TAA in solution was measured by HPLC analysis [10].

2.11. Fourier-transform infrared spectrophotometry

FTIR chromatographs were obtained using a Nicolet Magna-IR® Spectrometer 550 (Nicolet Instrument Corporation; Madison, WI) and Omnic 1.20 FT-IR data acquisition software. Test samples were mixed with potassium bromide, FTIR grade (Aldrich Chemical Co.; Milwaukee, WI) and packed in a sample holder to make pellets. The percent transmittance spectral data was collected over a wavenumber range of 500–4000 cm^{-1}.

2.12. Modulated differential scanning calorimetry

Differential scanning calorimetry (DSC) was performed with a DSC 2920 Modulated DSC and Thermal Analyst 2000 software (TA Instruments, New Castle, DE). An aliquot of 5.0 mg of each test sample was hermetically sealed in aluminum pans. An empty sealed pan was used as a reference. The heating program was conducted using the modulated setting at 10°C/min over a range of 20–320°C ($n = 3$). Temperature oscillation rate was 0.32°C every 60 s.

2.13. Rheology of pMDI formulations

An in-line viscometer (Model SPC-371; Cambridge Applied Systems, Inc., Medford, MA) was employed to perform the viscosity measurements. The viscometer was fitted with a continuous flow valve at the inlet and a metered flow valve so that the sampling chamber could be completely filled and sealed with the pMDI test samples. The viscometer was calibrated with a piston suitable for viscosity measurements in the range 0.2–2.0 cp. The temperature of

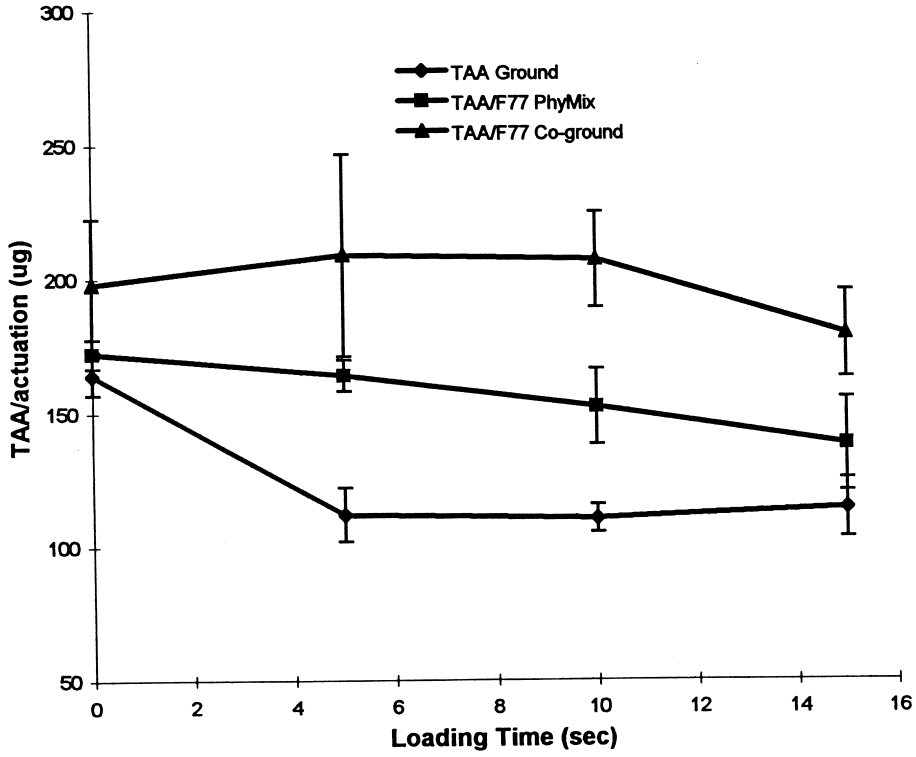

Fig. 1. Sedimentation properties of ground TAA, co-ground and TAA and Pluronic F77 physical mixture pMDI suspension formulations after storage for five days at 25°C.

the pMDI test samples was controlled at 25°C during the experiment with a refrigerated circulation bath. The viscosity measurements were determined on replicates of five samples.

3. Results

3.1. Mass median aerodynamic diameter and %RF of pMDI Formulations

The effect of co-grinding TAA particles with Pluronic F77® on the aerodynamic particle size distribution of the emitted aerosol is described in Table 1. The MMAD of the aerosol prepared from a pMDI formulation of ground TAA was 4.6 μm. The MMAD of the aerosol prepared from a pMDI formulation of co-ground TAA and Pluronic F77® was 2.7 μm. The MMAD of the aerosol generated from a TAA and Pluronic F77® physical mixture pMDI formulation was 3.5 μm. The %RF of the co-ground TAA and Pluronic F77® pMDI formulation was 33.6%, and the %RF of the pMDI formulation prepared with the physical mixture of TAA and Pluronic F77® was 30.9%.

3.2. Dose delivery through-the-valve of pMDI formulations

Matching the density of the dispersion medium and the dispersed phase will reduce the tendency toward creaming or settling of a suspension formulation [15]. Therefore a 1:1 (w/w) P134a and P227 propellant blend was chosen as the dispersion medium for the pMDI formulations since the calculated liquid density of the propellant blend (1.35 g/ml) was similar to the density of the test samples determined experimentally by helium pycnometry. However the pMDI formulations prepared in this study were observed to settle in the 1:1 (w/w) P134a and P227 propellant system. The DDV of a pMDI is a measurement of the amount of drug that is loaded into and expelled from the metering chamber immediately after actuation and may be influenced by the sedimentation characteristics of the formulation. As shown in Table 1, each test pMDI formulation emitted less than the theoretical amount of TAA per actuation (300 μg). However the magnitude of the DDV found for the co-ground TAA and Pluronic F77® pMDI formulation was most similar to the theoretical value.

3.3. In situ sedimentation of pMDI formulations

Information about the physical stability of the suspension pMDI formulations may be obtained by measuring the amount of drug that is loaded into the metering chamber after allowing designated time intervals for the suspension to equilibrate after shaking. Fig. 1 describes the in situ sedimentation of the test pMDI formulations by measuring the amount of TAA that was loaded into the metering chamber after allowing 0, 5, 10 and 15 s for the suspension to equilibrate with the metering chamber held in the open

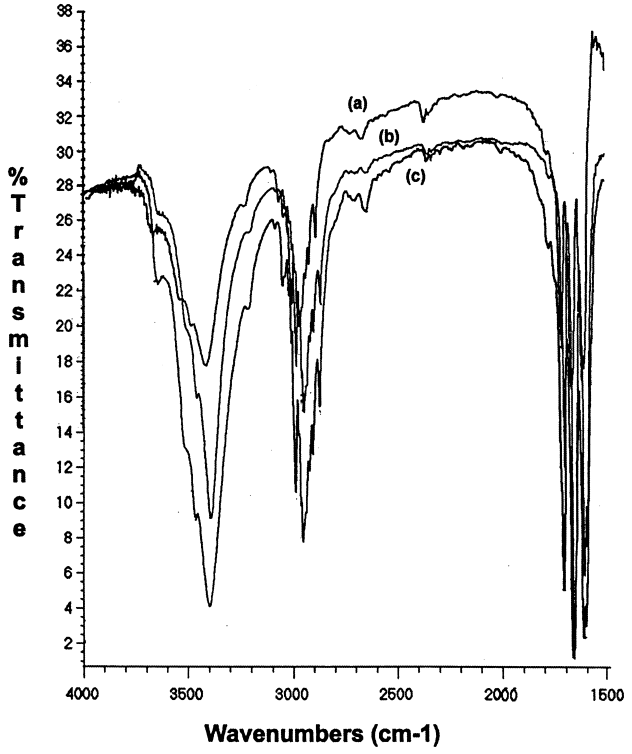

Fig. 2. FTIR chromatograms of: (a) ground TAA, (b) co-ground TAA and Pluronic F77 and (c) TAA and Pluronic F77 physical mixture.

position after shaking. It was found that the concentration of TAA emitted from the valve was influenced by the time allowed for loading the metering chamber. The concentration of TAA loaded into the metering chamber from the ground TAA pMDI formulation decreased after 5 s then did not change for 15 s. A decreasing trend was found for the concentration of TAA loaded and emitted by the TAA and Pluronic F77® physical mixture pMDI during the 15 s allowed for loading the metering chamber. Although not significantly different, the concentration of TAA loaded and emitted by the co-ground TAA and Pluronic F77® pMDI formulation after 5 and 10 s was slightly greater than at 0 s. After allowing 15 s for loading the metering chamber the TAA concentration emitted by the co-ground TAA and Pluronic F77® pMDI formulation decreased.

3.4. Density of dispersed phase

The density of the dispersed phase was not influenced by co-grinding process. The average density of the test samples was 1.33 ± 0.14 g/ml.

3.5. Vapor pressure of pMDI formulations

The addition of co-solvents and surfactants has been found to affect the vapor pressure of pMDI formulations [16]. However the addition of Pluronic F77® did not influence the vapor pressure of a 1:1 (w/w) P134a and P227 propellant mixture. Also the vapor pressure of the pMDI formulation prepared from co-ground TAA and Pluronic F77® was not significantly different from the pMDI formulation prepared with a physical mixture of TAA and Pluronic F77®. The average vapor pressure of the pMDI formulations was 89.1 ± 0.623 psi. The vapor pressure of the pMDI formulations was found to deviate slightly from the theoretical vapor pressure of the propellant blend which was calculated by Raoult's law to be 87.1 psi.

3.6. Triamcinolone acetonide -surfactant interaction

Hydrogen bonding between TAA and Pluronic F77® was shown by FTIR spectrophotometry. The FTIR chromatograms in Fig. 2 show an increased peak corresponding to the —OH stretch between 3650 and 3200 cm^{-1} and the —CH stretch in the range 3000–2840 cm^{-1}. Interactions such as hydrogen bonding between TAA and Pluronic F77® may be indicated by an increase in the parameters of melting point, heat capacity and heat of fusion [19]. Thermal graphs of TAA and blends of TAA and Pluronic F77® are presented in Fig. 3a–d. The melting point of control TAA was found to be 279.4°C and was not significantly different from ground TAA ($P < 0.05$). The DSC thermograms reveal an increase in the melting point of TAA in the presence of Pluronic F77®. The melting point of the co-ground and physical mixture of TAA and Pluronic F77® was found to be 291.8 and 294.3°C, respectively. Also an increase in the heat of fusion, ΔH_{fus}, was found by combining Pluronic F77® with TAA. The ΔH_{fus} increased from 46.3 to 66.5 J/g for the physical mixture and to 69.5 J/g for the co-ground mixture of TAA and Pluronic F77®.

Table 2
The viscosity of control samples and test pMDI formulations after storage for five days at 25°C

pMDI formulation	Average viscosity at 25°C (cp)	Standard deviation	% Relative standard deviation
100% P134a	0.202	0.005	2.56
100% P227	0.245	0.002	0.789
1:1 (w/w) P134a/P227	0.215	0.001	0.529
0.1% (w/w) Pluronic F77	0.239	0.007	2.97
0.3% (w/w) TAA	0.389	0.016	4.21
3:1 (w/w) Physical-mixture	0.280	0.005	1.60
3:1 (w/w) Co-ground	0.265	0.003	1.15

Table 3
The particle size distributions of test samples after co-grinding and after storage of test pMDI formulations for five days at 25°C

Test sample description	After co-grinding		After formulation	
	M50 (μm)	Span index	M50 (μm)	Span index
Control TAA	4.0	1.6	NA	NA
Ground TAA	4.5	1.6	6.4	2.9
TAA/F77 Physical mixture	5.8	1.0	4.7	2.0
TAA/F77 Co-ground	5.3	1.1	3.7	2.6

3.7. Rheology of pMDI formulations

Polymers may be excellent viscosity modifiers and therefore the impact of the selected poloxamer on the viscosity of the 1:1 (w/w) P134a and P227 propellant system was measured. The results of these measurements are described in Table 2. The average viscosities of P134a and P227 were found to be 0.202 ± 0.005 and 0.245 ± 0.002 cp, respectively. The average viscosity of a 1:1 (w/w) blend of P134a and P227 was found to be 0.215 ± 0.001 cp. The addition of Pluronic F77® added directly into propellant, at a concentration of 0.1% (w/w), was found to increase the viscosity of the propellant blend to 0.239 ± 0.007 cp. Dispersion of ground TAA particles at a concentration of 0.3% (w/w) in the propellant also increased the viscosity to 0.389 ± 0.016 cp. The 3:1 (w/w) combination of TAA and Pluronic F77® increased the viscosity of the 1:1 (w/w) P134a and P227 blend to 0.280 ± 0.005 cp for the physical mixture and to 0.265 ± 0.003 cp for the co-ground pMDI system.

3.8. Particle size distribution of triamcinolone acetonide

The particle size distribution of the test samples was determined prior to formulating in a pMDI and is presented in Table 3. Grinding did not significantly influence the M50 of TAA, however co-grinding TAA with Pluronic F77® increased the M50 to 5.3 μm and the physical mixture was further increased to 5.8 μm ($P < 0.05$). The dispersity of the particle size distribution was not influenced by grinding but the span index was found to decrease when Pluronic F77® was combined with TAA by co-grinding and by physical mixture. The particle size distribution of the test samples recovered by filtration after formulation in a pMDI system using a 1:1 (w/w) P134a and P227 propellant blend is also described in Table 3. The M50 of the ground TAA pMDI

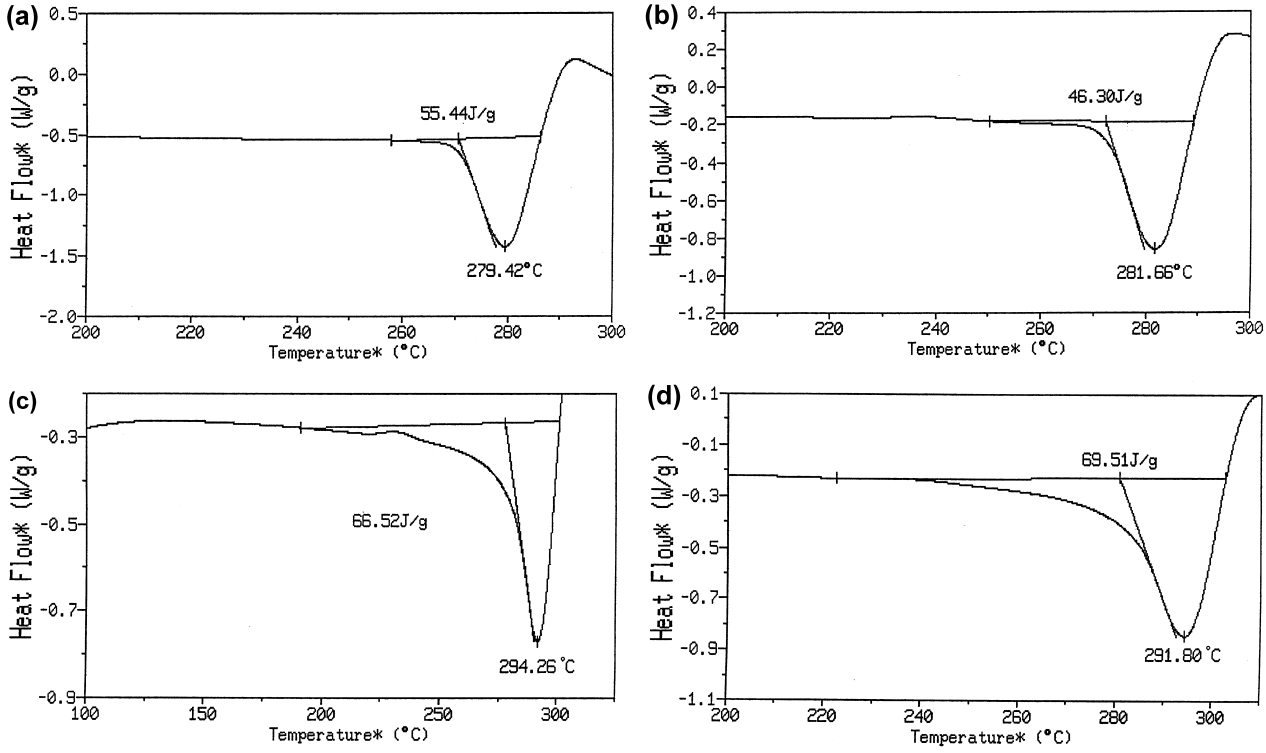

Fig. 3. DSC thermograms of: (a) control TAA, (b) ground TAA, (c) co-ground TAA and Pluronic F77 and (d) TAA and Pluronic F77 physical mixture.

Table 4
The solubility of TAA in water and in a 1:1 (w/w) P134a/P227 propellant blend after five days at 25°C. Standard deviations (SD) are given in parenthesis

Sample description	Solubility in water (μg/ml)	SD	Solubility in propellant (μg/ml)	SD
Control TAA	17.0	(0.333)	71.7	(6.47)
Ground TAA	18.0	(0.400)	79.6	(6.11)
TAA/F77 Physical mixture	20.9	(0.350)	42.2	(6.30)
TAA/F77 Co-ground	19.5	(0.957)	57.2	(7.05)

formulation was found to be 6.4 μm which is larger than the M50 of the ground TAA before dispersion and storage in propellant. The addition of Pluronic F77® as a physical mixture decreased the M50 of the ground TAA suspension pMDI formulation to 4.7 μm ($P < 0.05$). Co-grinding TAA with Pluronic F77® further decreased the M50 of the pMDI formulation to 3.7 μm ($P < 0.05$). The dispersity of the particle size distribution increased due to formulation and storage in the propellant system. The span index of ground TAA increased from 1.6 before formulation and storage to 2.9 after formulation and storage and the span index was found to increase two times when Pluronic F77® was incorporated ($P < 0.05$).

3.9. Triamcinolone acetonide solubility

The solubility of TAA in water and in a 1:1 (w/w) P134a and P227 propellant blend is shown in Table 4. Grinding did not significantly influence the solubility of TAA in water since the solubility of control TAA and ground TAA in water was 17.0 and 18.0 μg/ml, respectively ($P > 0.05$). However, the addition of Pluronic F77 as a physical mixture and by co-grinding significantly increased the solubility of TAA in water ($P < 0.05$) to 20.9 and 19.5 μg/ml, respectively. The solubility of the TAA and the TAA and Pluronic F77® blends in the non-polar propellant medium was significantly greater than in water. The solubility of control TAA in a 1:1 (w/w) P134a and P227 was found to be 71.7 μg/ml, and was increased to 79.6 μg/ml after grinding ($P < 0.05$). However, the addition of Pluronic F77® to the pMDI formulation decreased the solubility of TAA in the propellant blend. The solubility of the TAA and Pluronic F77® physical mixture and the co-ground TAA and Pluronic F77® formulation was 42.2 and 57.2 μg/ml, respectively. Co-grinding significantly increased the solubility of TAA in the 1:1 (w/w) P134a and P227 propellant medium compared to the physical mixture ($P < 0.05$).

4. Discussion

As seen in Table 1, the performance characteristics of the pMDI formulation were influenced by the addition of the polymeric surfactant, Pluronic F77® and by the co-grinding process. The pMDI formulations containing Pluronic F77® significantly increased the %RF of the emitted dose and co-grinding TAA with Pluronic F77® resulted in an MMAD of the emitted aerosol that is optimal for deposition in the lower respiratory tract [20]. Although, Finlay et al. reported that such changes in MMAD or RF may not give much change in lung deposition since lung deposition is only a weak function of MMAD when the GSD is large [21]. The differences in the performance characteristics are likely due to differences in the physicochemical properties of the pMDI suspension formulations. Without the polymeric surfactant, the dispersed phase of the pMDI formulation was flocculated and settled. Addition of Pluronic F77® by physical mixture with TAA decreased the time for the dispersed phase to settle and co-grinding TAA with Pluronic F77® further decreased the settling time. The factors which influence sedimentation velocity are described by Stoke's law which is written: $\nu = 2r^2 \cdot (\rho_s - \rho_0)g/9\eta_0$, where ν is the sedimentation velocity, r is the radius of the dispersed particles, ρ_s is the density of the dispersed phase, ρ_0 is the density of the dispersion medium, g is the gravitational force constant and η_0 is the intrinsic viscosity of the dispersion medium [12]. The average density of the TAA particles was found to be 1.33 ± 0.014 g/ml and was not influenced by the technique used to incorporate Pluronic F77® into the formulation. Changes in the density of the liquid propellant dispersion medium due to the addition of the soluble polymeric surfactant were assessed by measuring the vapor pressure of the pMDI formulations. Since the average vapor pressure measured for the pMDI formulations was found to be 89.1 ± 0.623 psi, the density of the propellant was not influenced by the addition of the soluble surfactant. However the vapor pressure of the pMDI formulations was found to deviate slightly from the theoretical vapor pressure of the propellant blend which was calculated by Raoult's law to be 87.1 psi.

Using the experimentally determined values for the particle size of TAA, the viscosity of the propellant, the density of TAA and the density of the propellant, the theoretical sedimentation velocities of the pMDI formulations were calculated based on the Stokes law equation. The calculated sedimentation velocities were found to be close to zero. However, visual observation of the pMDI formulations indicated that flocs were readily formed and settled rapidly. Therefore Stokes law was not useful in determining the sedimentation velocity of the drug dispersions. Stokes law is applicable only if particle-to-particle and particle-to-solvent interactions are negligible. The deviation from Raoult's law found for the pMDI formulations indicated the presence of weak intermolecular forces between the dispersed phase and the dispersion medium [12]. It is likely

that these interactions played a significant part in the characteristics of the suspension formulation since extensive flocculation of the pMDI formulations was observed. Aggregation of the dispersed phase commonly occurs in non-polar media due to the high surface area and the associated free energy of the micronized drug [22]. Suspension pMDI formulations are usually deflocculated and stabilized by the addition of surfactants [23]. Surfactants have been shown to influence the surface properties of the dispersed phase and inhibit inter-particulate interaction and flocculation by modifying the surface charge of the particles or through a steric hindrance mechanism [24]. Since co-grinding TAA with Pluronic F77® may enhance the interaction between the drug and the polymeric surfactant, changes in the characteristics of the pMDI system may be observed [7,8]. Hydrogen bonding is a common mechanism by which adsorption of the polymeric surfactant onto solid drug particles occurs [18]. This type of interaction between TAA and Pluronic F77® may be inferred by the increase in peak area of the FTIR chromatogram corresponding to the -OH stretch between 3650 and 3200 cm^{-1} and the —CH stretch in the range 3000–2840 cm^{-1} [17,18]. Furthermore, DSC thermograms presented in Fig. 3a–d show that the melting point of the TAA was increased in the presence of Pluronic F77® which may be a result of the additional energy required to break the hydrogen bonds [19]. Melting is accompanied by a positive molar enthalpy change (ΔH_{fus}) and occurs at a specific temperature. A measure of how much energy that must be added to a substance to produce a given temperature increase may be described as the molar heat capacity of the substance, $C_{P,m}$ and may be used to relate the change in enthalpy to a change in temperature [25]. The more ways (translation, rotation, vibration, intermolecular interactions) a substance has of absorbing added energy, the greater will be its $C_{P,m}$ [26]. The increased ΔH_{fus}, found in the presence of Pluronic F77® is also an indication of intermolecular interactions such as hydrogen bonding [25]. Pluronic F77® has been shown to adsorb to hydrophobic drugs and influence the physicochemical properties and surface characteristics of solid drug particles. Also, the adsorption process was shown to be influenced by the hydrophobicity and the chemical structure of the adsorbent [27]. By simple structural analysis, Pluronic F77® may be a potential proton acceptor and may hydrogen bond with the hydroxyl groups of TAA. These interactions may be enhanced by the co-grinding process and influence the extent of adsorption and the resulting steric stabilization of the suspension in the non-polar propellant medium may be increased.

Polymers act as flocculating agents in suspension formulations because part of the chain is adsorbed onto the particle surface, with the remaining parts projecting out into the dispersion medium. Formation of flocs may occur through bridging between the adsorbed portions of the polymer and by desorption of the polymer from the drug particle surface [28]. Any mechanism that may decrease the attractive energy of the suspended particles will reduce aggregation and flocculation [24]. The magnitude of the attractive energy of the suspended particles is dependent upon the relative polarity and molecular interactions between the surface of the dispersed phase and the dispersion medium. Viscosity measurements of suspension pMDI formulations has been utilized to characterize the attractive energy associated with flocculation by determining the shear force required to disrupt the flocculated system [29]. The relative viscosity of the pMDI formulations listed in Table 3 may be used to compare the inter-particulate binding strength of their dispersed phases [30]. The addition of Pluronic F77® as a physical mixture decreased the flocculation strength and co-grinding TAA with Pluronic F77® further decreased the flocculation strength of the pMDI suspension formulation. The effectiveness of a surfactant may be correlated to its extent of adsorption at the surface of the dispersed phase which in turn is influenced by its interaction with the dispersion medium. Repulsion due to steric interactions depends on the nature, thickness, and completeness of the surfactant adsorbed layers on dispersed particles [18]. Thus, enhancing the interaction between TAA and Pluronic F77® by employing the co-grinding process the surface coverage of the TAA particles by the surfactant may be increased and the particle-to-particle attraction reduced.

Differences in the aerodynamic particle size distribution of the emitted aerosols may have been due to the relative binding strength of the aggregates and their subsequent breakdown upon the application of shear forces as the aerosol was emitted from the valve of the pMDI systems. Without the polymeric surfactant, the increased MMAD of the pMDI system may be due to the spraying of particle aggregates that remain as aggregates after both the mild agitation prior to actuation and the shear forces due to passage through the valve stem [31]. The MMAD produced by the co-ground TAA and Pluronic F77® pMDI formulation was similar to the initial median particle size of the TAA prior to formulation. The formation of weakly attractive flocs in the co-ground TAA and Pluronic F77® pMDI formulation would corroborate the observed in situ sedimentation characteristics and the favorable performance characteristics of the pMDI system. An added advantage imparted by the use of the polymeric surfactant was the increase in viscosity of the liquid propellant. Physical stabilization of suspension formulations is typically enhanced by increasing the viscosity of the dispersion medium [28].

Other modifications of the physicochemical properties of the pMDI formulations, such as particle size and TAA solubility due to the addition of Pluronic F77® and the co-grinding process were also determined. The results shown in Table 4 describe the mean particle diameter of TAA after being subjected to the grinding process and after formulation and storage of the pMDI for 5 days at 25°C. The addition of Pluronic F77® either as a physical mixture or by co-grinding resulted in an increase in the median particle diameter of the TAA particles. Conversely, the median

particle size of the TAA formulated in a pMDI was found to decrease with the addition of Pluronic F77®. The differences in the particle size distributions may have been due to the influence of the polymeric surfactant on the solubility of TAA in aqueous and in the non-polar propellant dispersion medium. In Table 4 the solubility of TAA in water was found to increase in the presence of Pluronic F77®. In the presence of the surfactant, smaller particles are more readily solubilized in aqueous media than larger particles, resulting in an increase in the particle size distribution [12]. The fact that the span index decreased in the presence of the surfactant is further evidence that the smaller particles were dissolved and removed from the distribution. In the non-polar propellant medium, the opposite trend was observed. The presence of the surfactant resulted in a decrease in the median particle size of TAA after storage of the pMDI formulation for five days at 25°C. In addition, co-grinding TAA with Pluronic F77® resulted in a median particle diameter comparable to the median particle diameter of TAA before formulation. Likewise the solubility of TAA in the propellant was found to decrease by the addition of Pluronic F77®. By adsorption of the polymeric surfactant to the surface of the TAA particles, the interaction of the TAA particles with the non-polar dispersion medium was diminished and the dissolution of TAA in the propellant was reduced. The presence of the surfactant may have decreased the solubility of TAA by saturating the propellant medium and preferentially occupying the binding sites that TAA would require for dissolution to occur in the aprotic propellant solvent [32]. In addition, the adsorbed segments of the polymer may have inhibited crystal growth of a drug because they form a barrier that impedes the approach of the drug molecules from the solution to the crystal surface [12,28]. The benefit of reducing the solubility of TAA in the propellant may be further recognized in the long term since the potential of particle growth due to Ostwald ripening may be inhibited. This observation is of interest and additional studies are required to provide an explanation.

5. Conclusions

In conclusion, co-grinding TAA drug particles with Pluronic F77 promoted their interaction and possibly enhanced the adsorption of the surfactant onto the drug particle surface when formulated in a pMDI system. The interaction of TAA and Pluronic F77 influenced the dispersion, flocculation and sedimentation characteristics of a pMDI suspension formulation. Differences in the performance characteristics of the pMDI system may be attributed to interactions between TAA and Pluronic F77. In addition, the use of a polymeric surfactant may further stabilize a suspension pMDI formulation by modifying the viscosity of the propellant and decreasing drug solubility. The process of co-grinding drug particles with a polymeric surfactant may be utilized for the development of new pMDI systems containing HFA propellants that give desirable performance characteristics.

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