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Research paper

A study of an epoxy aerosol can lining exposed to hydrofluoroalkane propellants

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Abstract

The surface properties of an epoxy aerosol can lining used for pressurized metered-dose inhaler products were investigated. The cans were filled with either tetrafluoroethane (HFA 134a) or heptafluoropropane (HFA 227) and equilibrated at different temperatures for 3 months. Scanning electron microscopy (SEM), atomic force microscopy (AFM), fourier transform infrared reflection absorption spectroscopy (FTIR-RA), and contact angle were determined on each sample. Similar surface morphological images and topographical images were obtained from scanning electron microscopy. Fourier transform infrared reflection absorbance spectroscopy gave similar spectra for all epoxy lined samples. Atomic force microscopy indicated that differences in surface roughness were a function of storage temperature and propellant type. No significant differences were found for the contact angle measurements. Atomic force microscopy was shown to be a useful technique to study can linings. © 1997 Elsevier Science B.V.

Keywords: Epoxy lining; Metered-dose inhaler; HFA 134a; HFA 227; AFM; FTIR-RA; SEM; Contact angle

1. Introduction

Pressurized metered-dose inhalers (pMDIs) have been used as delivery devices for pharmaceutically active agents for many years. They are used for the treatment of pulmonary diseases such as bronchial asthma and chronic obstructive pulmonary disease. The pMDIs employ propellants with a high vapor pressure to discharge the drug from the inhaler device in the form of an aerosol cloud, which is inhaled by the patient [1–4]. Some advantages of this route of administration include (1) rapid and predictable onset of action, (2) smaller dose of drug required compared to the oral route, (3) decreased incidence of systemic adverse effects and (4) accessibility of the respiratory tract through the nose and mouth [5–7]. The pMDIs consist of a canister containing active drug, a valve, and an actuator. The drug is formulated in the canister as a suspension or solution dispersed in a propellant. Hydrofluoroalkanes (HFA) are of significant interest as propellants because of the ban on the use of chlorofluorocarbons (CFC) [8]. The physical and chemical properties of the HFA propellants, such as water solubility, solvent strength, density, and polarity, are different from the CFC propellants [9]. The stability of the formulation and the accuracy of the emitted dose are influenced by formulation composition and the choice of the material composition of the delivery device [10]. Adsorption of drugs onto valve gaskets, plastic valve parts, and internal container linings has been reported in the literature [11,12].

Various materials such as glass, aluminum and tinplate are used to manufacture pMDI containers. Gener-

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ally, the internal surface of the container is lined with an inert organic coating, such as phenolic-epoxy resin. The composition of the epoxy-type resin comprising the final coated film varies according to the coating procedures employed by the manufacturer [13]. The reformulation of the currently marketed CFC containing pMDI products with ozone-friendly HFA propellants requires that the inert lining in the container be non-reactive with the propellant system.

The objective of this investigation was to investigate the influence of propellants HFA 134a and HFA 227 on the internal epoxy lining of an aluminum aerosol can stored at various conditions, and confirm if the phenolic-epoxy resin changes with time.

2. Materials and methods

2.1. Materials

Tetrafluoroethane (HFA 134a, Dymel®134a, Du Pont Chemicals, Wilmington, DE, USA) and heptafluoropropane (HFA 227, Hoechst Celanese Corporation, Sommerville, NJ, USA) were used as received. Aluminum cans (ϕ23.6 × 60 × 20 mm) were kindly supplied by Cebal (Bellegarde, France). Valves (DF10/50 RC; Valois of America, Greenwich, CT, USA) were used as received. Purified water was obtained using Milli-Q UV plus ultra-pure water system (Millipore S.A., Molsheim, France). Methanol and chloroform were obtained from EM Science (Gibstown, NJ, USA) and used as received. Ethanol (200 proof, Midwest Grain Products of Illinois, Pekin, IL, USA) was used as received.

2.2. Methods

2.2.1. Preparation of samples

A Pamasol P2005 small scale crimper and propellant filler (Pamasol Willi Mader AG, Switzerland) were used to crimp valves onto cans and then pressure fill HFA 134a or HFA 227 into empty canisters. The pMDI cans were filled with either 5 ml of HFA 134a or HFA 227 through the valve. The filled canisters were stored upright at 0, 25 and 40°C. Sample canisters were removed from each storage condition after 2 weeks, 1, 2 and 3 months. The valves were removed and the cans were cut open and separated into two parts. The bottom part of the can represented the portion that was exposed to liquid propellant, and the top of the can represented the area that was exposed to the vapor phase of the propellant. The internal epoxy lining of each part was rinsed with distilled water, ethanol, and methanol. It was dried using nitrogen prior to testing, in order to clean and dry the surface using a standardized procedure.

2.2.2. Scanning electron microscopy

A Philips 515 Scanning Electron Microscope (SEM) (Philips Electronic Instruments company, Mahwah, NJ, USA) was used to image the epoxy surface of the samples. A sample measuring 1 × 1 cm was cut from each aerosol can and mounted using double-sided conductive carbon tape on an aluminum stub. This specimen was coated with gold/palladium (60:40) using a Ladd Bench Top Sputter Coater (Ladd Research Industries, Inc., Burlington, VT, USA) at 2.5 kV and 20 mA for 45 s. The images of the samples were recorded on Polaroid PIN 55 film.

2.2.3. Atomic force microscopy

A three-dimensional topographical image of a piece of sample was obtained at high resolution using an Auto Probe CP Atomic Force Microscope (AFM; Park Scientific Instrument, Sunnyvale, CA, USA) operating in the intermittent-contact mode under ambient air and temperature conditions. The measurement of the topography of the epoxy lining was performed with sharp Si_3N_4 tips, which have a height of 4 μm, attached to a cantilever with a nominal spring constant of 15 N m^{-1}. The resonance frequencies of these tip-cantilever systems were about 300–360 kHz. The force gradient sensed by the tip was measured by detecting the deflection of a laser beam bounced off the cantilever. The closed-loop feedback control system for the tapping mode AFM was employed to control the variation in height across the sample surface. The sample with an area measuring 1 cm^2 was mounted to the disc stage using double-sided tape and slid onto the magnetic sample holder at the end of the scanner tube. The servo gain, set point, and force gradient were optimized so that the feedback system could track the sample surface satisfactorily. The topographical features of the epoxy lining were collected as 3-dimensional ordinate data in Cartesian coordinate by scanning a sample area of 10 × 10 mm with 512 × 512 pixels (Pi) at a scan rate range of 0.5–1.0 Hz. The acquired data were presented as 3-dimensional topographical graphs, and analyzed to obtain peak-to-valley roughness (Rp-v), average roughness (Rave), root-mean-squared roughness (Rms), mean height (Zm), median height, volume, and bearing ratios.

2.2.4. Fourier transform-reflection absorption infrared spectroscopy

A Nicolet Magna-IRTM 550 Spectrometer (Nicolet, Madison, WI, USA) equipped with a VeeMaxTM variable angle specular reflection accessory (Spectra-Tech Inc., Stamford, CT, USA) was used to obtain the fourier transformed-reflection absorption infrared

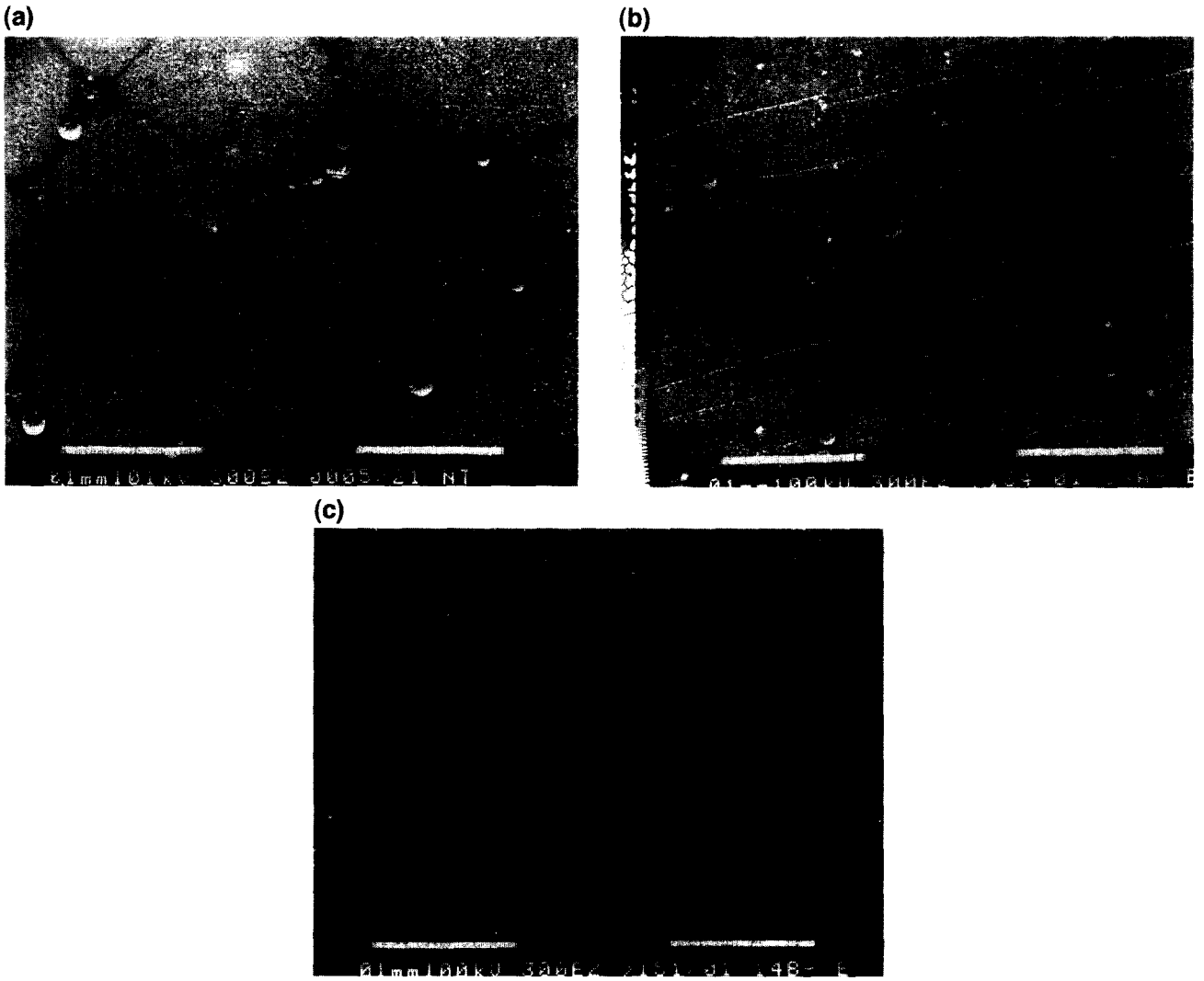

Fig. 1. SEM photomicrographs of the epoxy lining of pMDI cans following exposure to liquid hydrofluoroalkane propellants for 3 months. Magnification 300 ×: (a) control; (b) exposure to HFA 134a at 40°C; (c) exposure to HFA 227 at 40°C.

(FTIR-RA) spectra. The surface of the sample was analyzed with a grazing-angle reflection module (Refractor, Harrick Scientific Corporation, Ossining, NY, USA) with a fixed incident IR beam angle of 75° normal to the sample surface. The spectrometer was equipped with a liquid nitrogen-cooled mercury cadmium telluride detector, and was purged with dry nitrogen to exclude the moisture. The instrument also was equipped with a laser reference interferometer to ensure wavelength accuracy. Single reflection at specified angles of incidence was employed for FTIR-RA analysis. Peak frequency was recorded by the computer. The aluminum was scanned and recorded to obtain the blank spectrum from which the sample spectrum ratio was subtracted. The washed sample then was placed in the spectrometer and the spectrum was collected. All spectra were composed of 128 co-additions and were taken at 4 cm^{-1} resolution. The spectra are shown in the transmission mode.

2.2.5. Determination of contact angle

The contact angle of water on the internal epoxy lining of pMDI containers was measured using an optical-bench-type NRL Contact Angle Goniometer 100-00-115 (ram-hart, Inc., Mountain Lakes, NJ, USA) at ambient temperature conditions. A drop (0.5–1 ml) of purified water was carefully placed onto the epoxy lining of the samples using a micro-syringe. The contact angle of water on the sample was read from the internal protractor-readout though a microscope. Five measurements were taken for each sample at five locations on the sample surface.

3. Results and discussion

The extraction of constituents from the epoxy lining by the propellant, or the absorption of propellant into the internal epoxy lining are possible occurrences that

Table 1
Parameters determined by atomic force microscopy for epoxy linings exposed to HFA 134a and HFA 227 for 3 months

Parameter	Initial	HFA 134a			HFA 227		
		0°C	25°C	40°C	0°C	25°C	40°C
Rp-v (Å)	754.5 (23.9)	792.0 (165.3)	963.6 (414.7)	991.2 (190.9)	707.7 (28.8)	597.3 (93.9)	615.3 (122.4)
Rms (Å)	83.3 (12.4)	88.2 (6.9)	80.3 (5.6)	78.9 (4.9)	84.0 (4.0)	72.1 (8.3)	80.1 (13.1
Rav (Å)	63.4 (10.7)	59.5 (15.7)	61.5 (2.8)	59.6 (3.9)	65.9 (2.5)	55.8 (6.2)	61.8 (9.2)
Mean height (Å)	283.8 (37.0)	315.0 (41.8)	293.0 (70.0)	264.8 (43.9)	300.4 (69.1)	241.9 (64.3)	233.1 (55.6)
Median height (Å)	274.8 (37.1)	311.0 (41.4)	285.0 (170.5)	255.9 (41.6)	295.1 (72.2)	236.6 (63.0)	224.8 (54.0)
Volume (μm^3)	2.8 (0.35)	3.1 (1.12)	2.88 (1.67)	2.61 (0.43)	2.96 (0.68)	2.39 (0.64)	2.30 (0.55)
Bearing ratio at 75% (Å)	224.1 (34.3)	253.0 (60.8)	193.0 (173.3)	212.1 (44.3)	227.7 (89.0)	193.5 (59.9)	175.9 (44.6)

Mean and S.D. are given in parenthesis.

must be investigated during pMDI development. These interactions not only influence the surface properties of the lining and can lead to unacceptable extractives appearing in the product, but also may result in lower drug levels in the suspension if the drug adsorbs onto the internal lining. Therefore, the characterization of the surface properties of the can lining following exposure to the liquid propellants is necessary to investigate the compatibility of the internal lining with the propellants.

SEM has been used widely in combination with other analytical techniques to characterize surface morphology in the material sciences, chemical engineering, chemistry and pharmaceutical sciences [14]. SEM was employed in this study to characterize the surface morphology of the internal epoxy linings following exposure to propellants HFA 134a and HFA 227. The morphology of the epoxy lining for each sample was examined periodically by SEM during 3 months exposure to propellants HFA 134a and HFA 227 at 0, 25, and 40°C. The bottom of the can wall, which was exposed to liquid propellant, was examined and compared to a sample of the wall exposed only to vapor. Stange et al. observed multi-sided polygonal surface patterns on spin-coated polystyrene film and explained that the coating process involves spraying the polymer solution onto the surface [15]. Upon exposure to heat during the curing process, the solution film reaches a critical thickness and ruptures as it becomes thinner due to convective flow and evaporation of the solvents. The ruptured film then retreats from the nucleation site until it meets another retreating film from an adjacent nucleation site. This process results in a network being formed. Stange et al. [15] also found that the formation of the network is similar to the generation of Voronoi tessellation structures simulated on computer. Representative examples of SEM photomicrographs of the surfaces are shown in Fig. 1. It can be seen that most of the space between the vertices of the polygons contain circular structures, which appear to be bubbles that burst during release of trapped solvent during the curing process. This may be the nucleation site of the ruptured film. The SEM photomicrographs of the epoxy lining before exposure to liquid HFA 134a (Fig. 1(a)), and following exposure to liquid propellants HFA 134a (Fig. 1(b)) and HFA 227 (Fig. 1(c)) at 40°C for 3 months exhibited no discernible differences in the patterns or physical dimensions of the multi-sided polygons. Similar results were found for the samples exposed to liquid HFA 134a and HFA 227 at 0 and 25°C for 3 months, and the samples exposed to the vapor phase of HFA 134a and HFA 227 at the same storage conditions (not shown). The SEM photomicrographs revealed that the polygons consisted of five or six sides with slightly rounded edges and measured from 120 to 180 mm in diameter. The diameter of the bubbles at the vertices ranged between 15 and 20 mm. Many of the vertices contained numerous smaller bubbles that measured between 1 and 5 mm in diameter. The SEM results suggested that this type of epoxy lining did not change following exposure to propellants HFA 134a and HFA 227 for 3 months at 0, 25 and 40°C.

AFM is a technique employed to quantitatively image the surfaces of materials. It has been extremely useful for nondestructively imaging nonconductive substrates [16]. This technique utilizes the force acting between a surface and a probing tip resulting in a spatial resolution of up to 0.01 nm for imaging. In this method, a sharp tip attached to a cantilever is used to measure the surface topography of the samples which is scanned in the $x-y$ plane. The displacement of the tip, detected by a reflected laser beam and photodiode, is used to adjust the sample position in the z direction in order to maintain constant force. The feedback voltage provides the topographical data [17]. The AFM method has been used widely to image solid surfaces [15], integrated circuits, and to characterize pharmaceutical particles [18]. The advantages of AFM include simple sample preparation as no vacuum or coating is needed

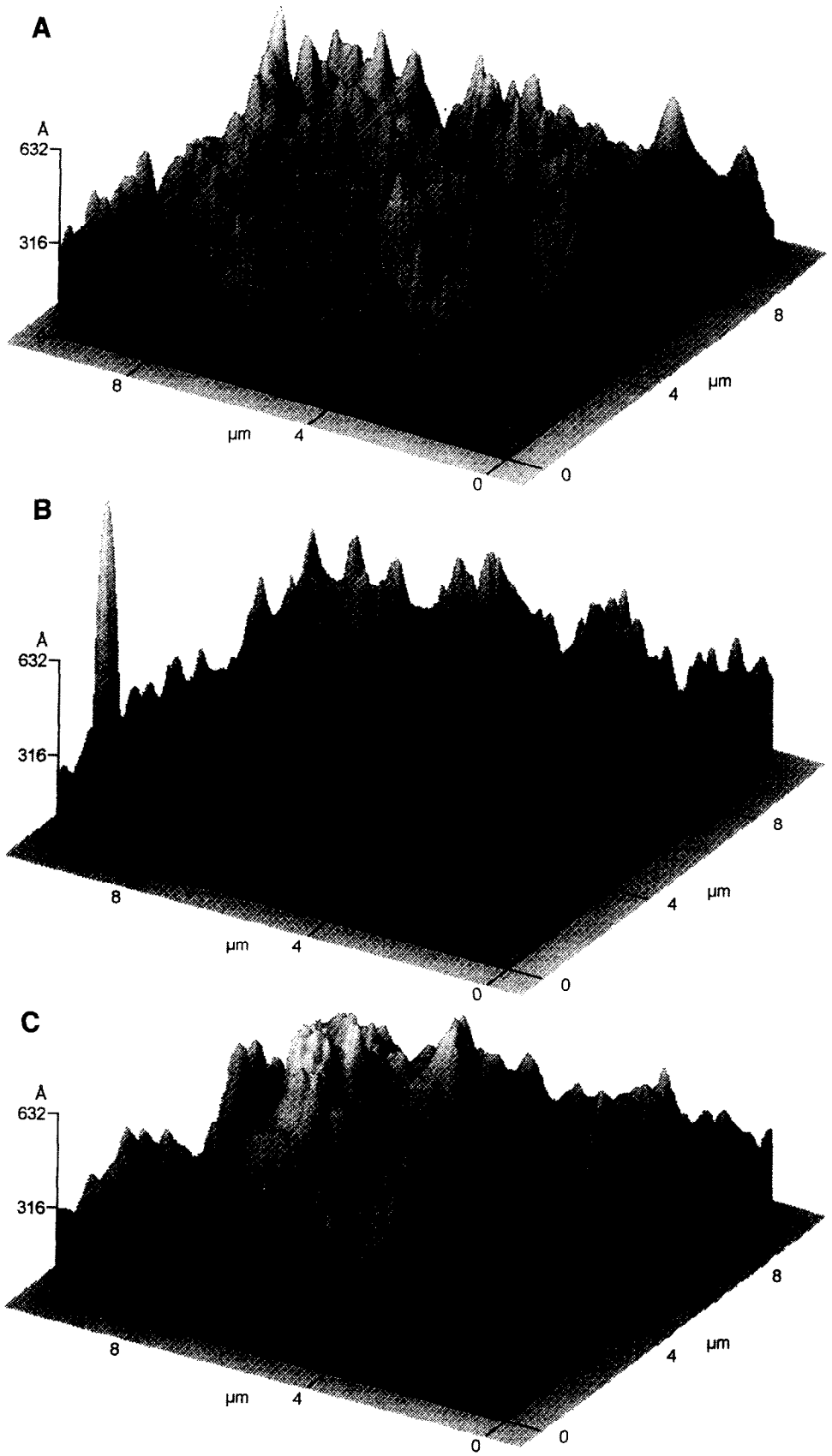

Fig. 2. AFM images of the epoxy lining of pMDI cans following exposure to liquid hydrofluoroalkane propellants for 3 months: (A) control; (B) exposure to HFA 134a at 40°C; (C) exposure to HFA 227 at 40°C.

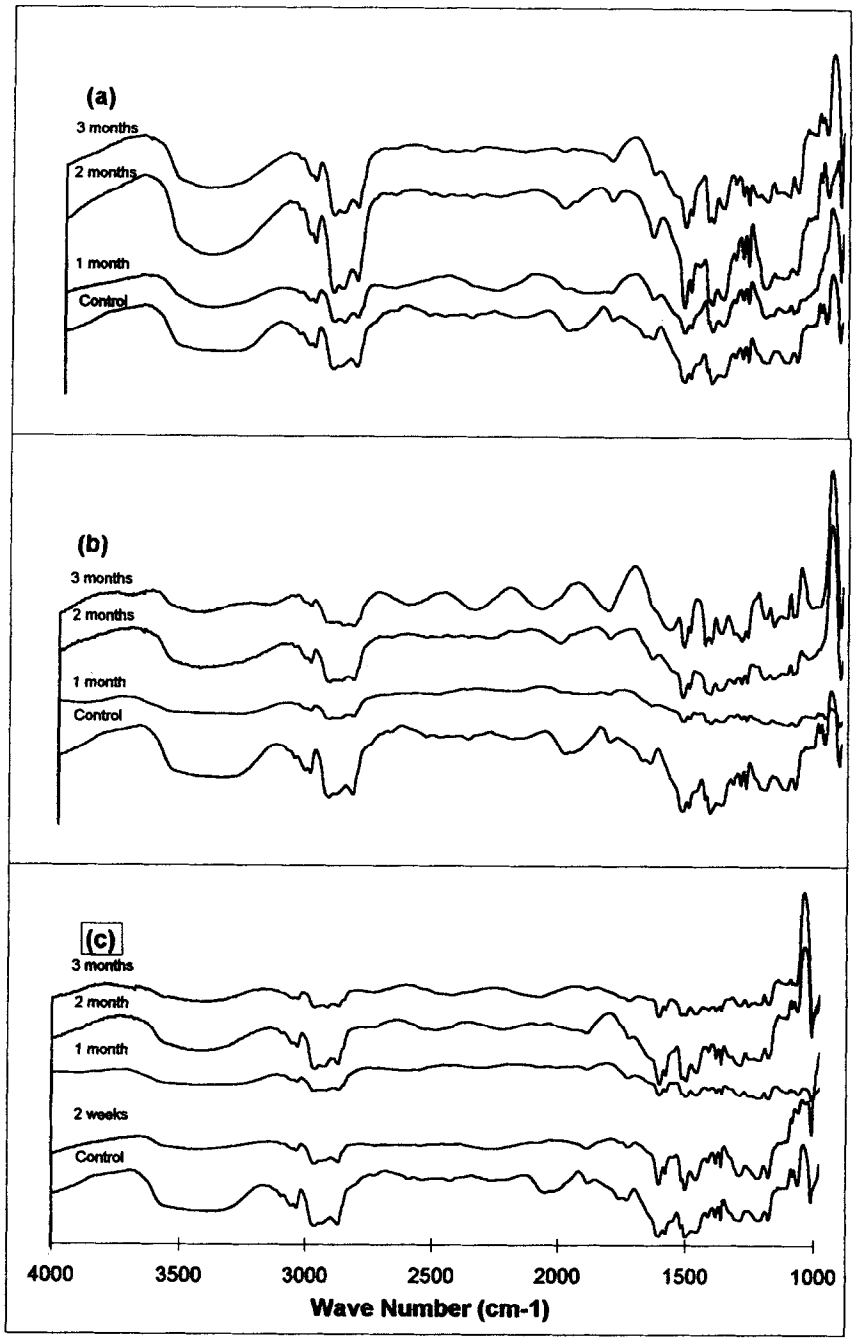

Fig. 3. FTIR spectra of the epoxy lining of pMDI cans following exposure to liquid propellant HFA 134a for 3 months: (a) stored at 0°C; (b) stored at 25°C; (c) stored at 40°C.

during operation, and the sample does not need to be conductive [19]. AFM generates topographical parameters to quantitatively characterize the surface properties. AFM was utilized in this work to characterize the topography of the internal epoxy lining and to quantitatively calculate topographical parameters such as surface roughness, height, volume and bearing ratio.

The AFM imaging of the topography of the epoxy linings was performed prior to and after 3 months exposure to liquid propellants HFA 134a and HFA 227 at 0, 25 and 40°C. The results obtained for the control and test samples stored for 3 months at 40°C are shown in Fig. 2. The AFM scan area of 10×10 mm was chosen from one polygon observed from the SEM images. The 3-dimensional images of the epoxy lining from the bottom of the pMDI can prior to exposure to the liquid propellants (Fig. 2(a)), and following exposure to liquid propellants HFA 134a (Fig. 2(b)) and HFA 227 (Fig. 2(c)) for 3 months at 40°C exhibited similar topographical patterns. Similar observations

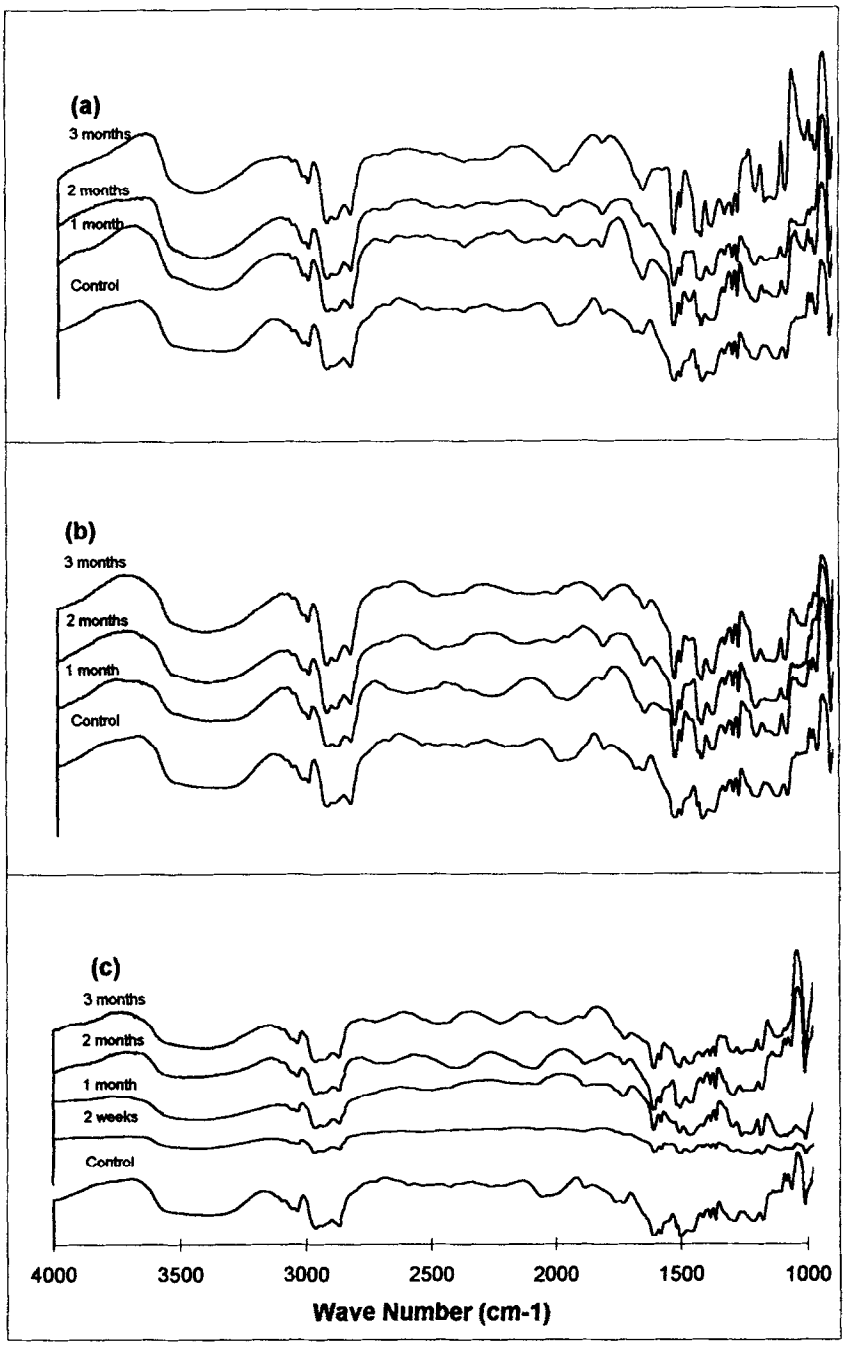

Fig. 4. FTIR spectra of the epoxy lining of pMDI cans following exposure to liquid propellant HFA 227 for 3 months: (a) stored at 0°C; (b) stored at 25°C; (c) stored at 40°C.

were found for samples stored for 3 months at 0 and 25°C (not shown). The topographical parameters of Rp-v, Rms, Rav, mean height, median height, volume, and bearing ratios are presented in Table 1. The measurement of Rp-v gives the maximum peak to valley distance within the included areas. Rav is given by the average deviation of the height values from the average value of all height data within the included scan area. The Rms is given by the S.D. of the data. The median height is the height value which divides the height histogram into two equal areas. At the median value, 50% of the data points have higher values, and 50% have lower values. The volume measurement gives the volume between the included surface and the plane which includes the minimum data point of the entire image, and parallels to the surface. The bearing ratio is essentially an integral of the height histogram. A bearing ratio curve plots the percentage of the data points that lie above a given height in the height histogram. The bearing ratio gives a measure of how 'jagged' a

Table 2
Water contact angle on the epoxy lining exposed to propellants HFA 134a and HFA 127

Temp (°C)	Time (months)	HFA 134a		HFA 227	
		LP[a]	VP[b]	LP	VP
0	0	86.2 ± 1.9	86.2 ± 1.9	86.2 ± 1.9	86.2 ± 1.9
	1	87.2 ± 1.6	84.2 ± 1.3	89.0 ± 1.0	83.4 ± 1.7
	2	89.4 ± 0.9	88.8 ± 0.8	88.6 ± 0.5	83.6 ± 1.8
	3	86.4 ± 1.1	86.2 ± 2.8	88.4 ± 0.9	89.4 ± 0.9
25	0	86.2 ± 1.9	86.2 ± 1.9	86.2 ± 1.9	86.2 ± 1.9
	1	86.0 ± 1.6	88.6 ± 0.5	86.8 ± 1.3	87.8 ± 0.8
	2	89.8 ± 0.4	89.4 ± 0.9	87.4 ± 1.9	87.8 ± 1.6
	3	89.0 ± 1.0	88.0 ± 0.7	87.8 ± 1.3	84.8 ± 1.6
40	0	86.2 ± 1.9	86.2 ± 1.9	86.2 ± 1.9	86.2 ± 1.9
	0.5	88.2 ± 0.8	89.2 ± 0.8	86.8 ± 1.3	84.6 ± 2.2
	1	89.4 ± 0.9	88.4 ± 0.5	88.8 ± 1.3	86.6 ± 2.2
	2	88.0 ± 0.7	87.2 ± 2.0	86.6 ± 1.9	84.0 ± 1.4
	3	87.6 ± 0.9	85.8 ± 1.3	89.8 ± 0.4	82.4 ± 1.1

Data is presented as mean ± S.D. ($n = 5$).
[a] Exposed to liquid phase of propellant.
[b] Exposed to vapor phase of propellant.

surface is. The magnitude of Rp-v increased significantly after exposure to liquid propellant HFA 134a for three months at 0, 25 and 40°C, and decreased significantly after exposure to HFA 227 at the same conditions. The magnitude of Rms and Rav decreased slightly following exposure to liquid propellants HFA 134a or HFA 227 for 3 months at 25 and 40°C. The mean height, median height, and the magnitude of the volume increased following exposure to HFA 134a for 3 months at 0, 25°C, and exposure to HFA 227 at 0°C, but decreased following exposure to HFA 134a for 3 months at 40°C and HFA 227 at 25 and 40°C. The values of the bearing ratio at 75%, at which 75% of the points in the scanned area had a greater height than this value, increased following exposure to HFA 134a for 3 months at 0°C, and decreased following exposure to HFA 134a or HFA 227 for 3 months at HFA 227 at 25 and 40°C. These results on the bearing ratio indicated that the jaggedness of the lining decreased following exposure to propellants for 3 months at 25 and 40°C. The jaggedness is related to the surface area available as potential nucleation sites for drug adsorption, and hence must be controlled. The change in jaggedness as a function of time and temperature is the subject of an ongoing investigation.

FTIR-RA, commonly referred to as external reflection infrared spectroscopy, has become a powerful, nondestructive technique for investigating the film on the surface of substrates [20]. FTIR-RA measures an absorption band of a surface film by measuring the change of the substrate reflectivity due to the surface film. When infrared radiation strikes a polished metal surface, an electric field is generated near the surface. FTIR-RA can be used for studies of both thin (monolayer) and thick (> 1000 nm) films. Under optimal conditions, a reflection absorption spectrum of a thin film on a surface can be 25 times stronger than the corresponding transmission spectrum of the same film on a transparent substrate [21–23]. A single reflection is sufficient for a thick film. The intensity and shape of the absorption bands obtained by this technique are different from those obtained by the conventional transmission technique, and are a complex function of numerous parameters, such as the angle of incident beam and the thickness of the analyzed film [24]. FTIR-RA has been used to study the degradation of the protective coating films [25,26]. The FTIR-RA spectra obtained from samples exposed to liquid propellants HFA 134a and HFA 227 are shown in Fig. 3 and Fig. 4, respectively. The broad peak band from 3200 to 3550 cm^{-1} was attributed to the absorbance of the stretching phenolic hydroxyl group in the chain of the phenolic epoxy, which was the primary constituent in the lining. The peak band between 1550 and 1610 cm^{-1} was attributed to the bending and stretching of other epoxy lining ingredients containing N–H, C–N, and N–C=N groups. Other peaks resulted from the $-CH_2-$ or $-CH_3$ normal vibrations. The main feature peak bands from 1550 cm^{-1} to 1610 cm^{-1} and from 1550 cm^{-1} to 1610 cm^{-1} appeared at the same wave numbers on all spectra. The results of FTIR-RA suggested that the epoxy linings were not influenced by exposure to HFA 134a or HFA 227, and were chemically compatible with the HFA.

A method for the investigation of surface properties is the determination of the contact angle on a surface.

The contact angle of water on the surface of the internal epoxy lining represented the affinity of water to the surface, and may be used as a reference for the film's affinity to other compounds. Contact angles of water on the epoxy lining were measured initially, 2 weeks, 1 month, 2 months, and 3 months following exposure to propellants HFA 134a and HFA 227 at 0, 25 and 40°C. The results presented in Table 2 show the contact angle for each film tested. The contact angle of cans containing either HFA 134a or HFA 227 ranged from 84.2 to 89.4°, and 82.4 to 89.8°, respectively. The S.D. of the contact angles determined by this method were less than 3°. The results indicated that the exposure of the epoxy lining to propellants HFA 134a and HFA 227 did not influence the surface properties of the film following storage at the different storage conditions. The results indicated very good precision in the data.

4. Conclusions

The results obtained from SEM, FTIR-RA, and contact angle indicated that the epoxy lining of the pMDI can did not change over 3 months storage at 0, 25 and 40°C when exposed to either HFA 134a or HFA 227. The topographical parameters obtained from AFM showed slight differences in the surface properties of roughness, and the magnitude was dependent on the propellant system. AFM, contact angle, SEM, and FTIR-RA are useful tools to investigate the influence of the propellants on the can.

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