

## **A Study on the Drug Deposition Mechanisms of Surface-treated pMDI Canisters**

**Athina Skemperi<sup>1</sup>, David Worrall<sup>1</sup> Gary Critchlow<sup>2</sup> & Phil Jinks<sup>3</sup>**

<sup>1</sup>Chemistry Department, Loughborough University, Loughborough, Leicestershire, UK

<sup>2</sup>Materials Department, Loughborough University, Loughborough, Leicestershire, UK

<sup>3</sup>3M Drug Delivery Systems, Loughborough, Leicestershire, UK

### **Summary**

The aim of this project was to explore drug deposition mechanisms on the aluminium canisters employed with Pressurised Metered Dose Inhalers (pMDIs). The investigation explored the influence of various surface treatments, applied to the canisters, to drug deposition phenomena. Physicochemical characterisation of the canisters was performed after the application of different surface treatments to explore potential links between: surface topography, surface chemical composition, total surface energy, and drug caking appearing on the canister walls. The coating treatments which were tested were; Fluorinated Ethylene Propylene (FEP) lacquer, vapour deposited Parylene and a 3M-proprietary, fluid-applied fluorosilane. Anodisation was also explored both with and without additional fluorosilane treatment. A number of surface physicochemical characterisation techniques were employed, namely; Scanning Electron Microscopy (SEM), X-Ray Photoelectron Spectroscopy (XPS) and Contact Angle (CA) analysis. The data from these analyses were correlated with those from a Drug Deposition test employing drug quantification by UV spectrophotometry. The results obtained indicated a direct correlation of drug deposition on canister walls to the total surface free energy. The lowest total surface free energy values and lowest deposition values were seen when the 3M-proprietary fluorosilane coating was applied as the final treatment. In this case a surface free energy value of 15.73 mN/m and a percentage drug deposition of 7% compared to the calibration can, were achieved.

### **Introduction**

Aerosol Inhalation therapy is the most widely used treatment for the common diseases of the lungs namely: Chronic Obstructive Pulmonary Disease (COPD), and asthma. The key advantages of inhalation therapy arise from the direct targeting of the drug to the site of action. This results in more rapid onset of therapeutic effect, fewer systemic side effects and lower doses, giving an improved safety profile in comparison with for example, oral therapy [1, 2]. pMDIs are the most popular aerosol devices used for inhalation therapy. However, one of the most significant drawbacks of pMDI systems is that drug deposition commonly appears on the hardware of the device, from suspension-based formulations [2, 4]. Such drug deposition (caking), may result in ineffective drug therapy due to low or inconsistent dosing [5, 6]. There are several published studies on drug deposition phenomena in pMDI devices, most of which focus on stabilisation of the formulation by the use of either excipients, surfactants or particle engineering techniques [7, 8]. Further studies focus on the effect of both moisture and temperature storage conditions to the drug caking appearing on the device [9, 10]. Other investigations explore the effect of hardware design to the performance of pMDIs [11, 12]. However, there are limited studies concerning surface treatments applied to the hardware of the inhaler i.e. cleaning methods and coating procedures [13, 14]. The aim of this study was to explore drug deposition behaviour on pMDI canisters employing a range of surface treatments and to relate this to surface topography and surface chemistry.

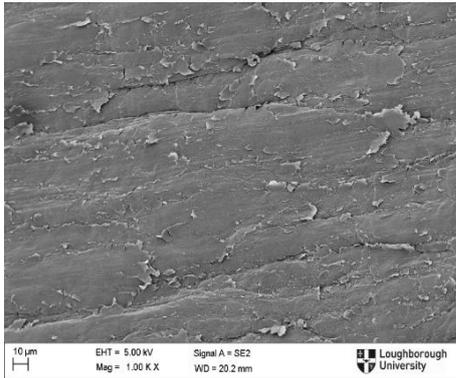
### **Experimental**

#### **Section 1** Physicochemical characterisation of the aluminium canisters,

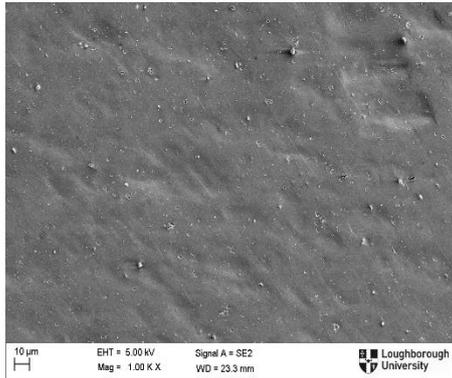
In order to observe the effect of different surface treatments on surface morphology, surface elemental composition and total surface energy of the samples, three different techniques were applied to the samples: Scanning Electron Microscopy (SEM), X-Ray Photoelectron Spectroscopy (XPS), and Contact Angle (CA) analysis. The results obtained are presented below.

**Scanning Electron Microscopy (SEM)**

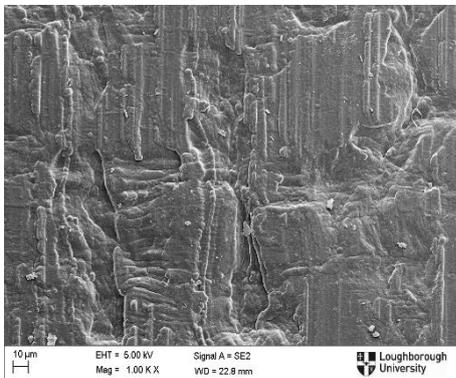
The SEM technique was used to acquire high resolution information on sample surface topography. The results are presented in Fig 1.



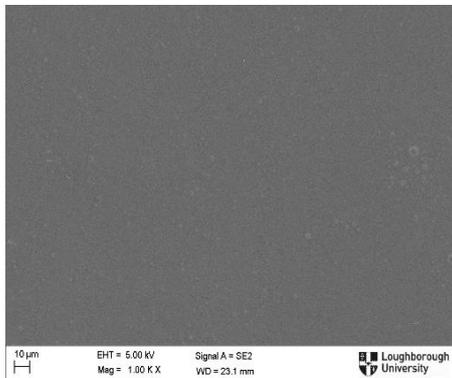
**Figure 1a:** Surface of the Aluminium Can after solvent cleaning process x1000 Magnification



**Figure 1b:** Surface of the Aluminium Can after Anodisation Surface treatment x1000 Magnification



**Figure 1c:** Surface of the Aluminium Can after Parylene coating Surface treatment x1000 Magnification



**Figure 1d:** Surface of the Aluminium Can after FEP coating Surface treatment x1000 Magnification

**Figure 1:** Surface topography of aluminium canisters after various surface treatments were applied

In Figure 1, it is seen that the anodisation treatment produced a significantly smoother surface topography (Figure 1b) compared to the original surface (Figure 1a). In contrast the Parylene coating treatment masked only the fine topography of the sample (Figure 1c). Finally, complete masking of the aluminium surface irregularities was observed with the FEP coating treatment (Figure 1d).

**X-Ray photoelectron Spectroscopy Analysis**

The aim of the XPS analysis was to determine the surface chemical composition of the aluminium canisters before and after coating application. The results are shown in Table 1.

**Table 1:** Surface chemical composition atomic%, excluding H and He, of the aluminium canisters after various coating treatments applied

Sample	Al	C	Cl	F	Mg	O	S	Si	N	Ni
Novec 72DE cleaned can	26.46	26.80	0.00	0.00	5.30	41.40	0.00	0.00	0.00	0.00
FEP coated can	0.00	35.30	0.00	64.7	0.00	0.00	0.00	0.00	0.00	0.00
Parylene coated can	0.00	83.80	12.68	0.31	0.00	2.28	0.00	0.92	0.00	0.00
Anodised can	22.57	33.00	0.00	0.00	0.00	38.50	3.10	0.00	0.86	2.00
Anodised + 3M fluorosilane can	13.71	31.73	0.00	26.89	0.00	22.87	1.83	0.00	0.67	2.30
3M fluorosilane can	6.55	29.22	0.00	48.62	0.00	15.61	0.00	0.00	0.00	0.00

In Table 1 the surface elemental composition of the cans, after the application of various treatments is shown. These data indicate that the coatings have created specific surface chemistry. The absence of detectable aluminium at the surface for both the FEP and the Parylene coatings suggests that both coating types completely mask the surface. The high percentages of fluorine for both the FEP coating and for the 3M fluorosilane coating applied directly onto the aluminium canister suggest that effective non-stick performance might be expected for these systems. The high percentages of both carbon and chlorine are both characteristic of the Parylene coating and the high percentages of aluminium along with oxygen were seen with the anodised canister surface.

#### Contact angle analysis

The aim of the Contact Angle technique was to quantify the surface hydrophobicity and the total surface energy of the samples. The results are shown in Table 2.

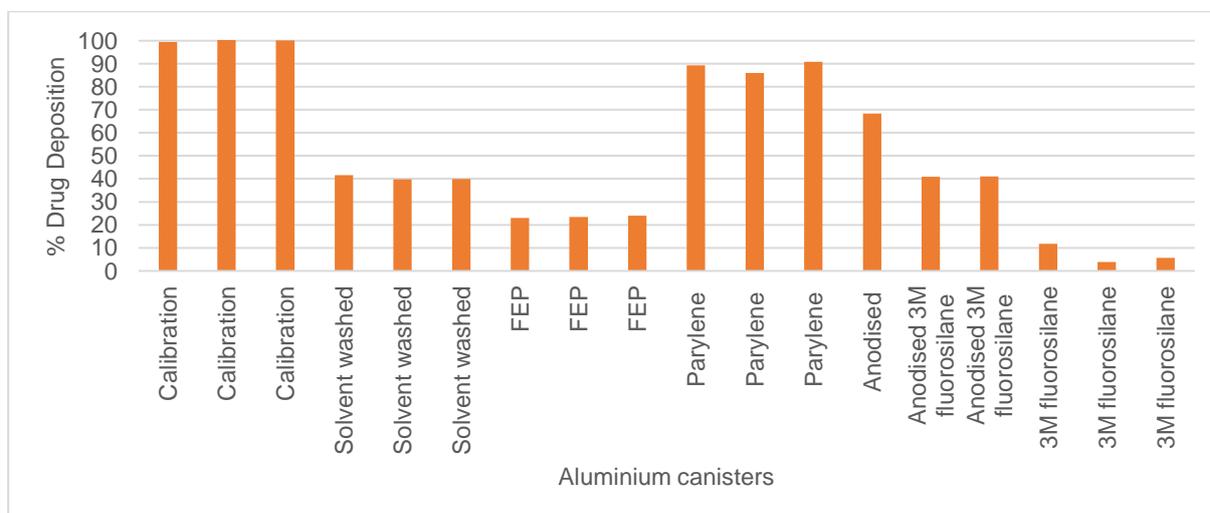
**Table 2** Contact Angle and total Surface Energy of the aluminium canisters after surface treatment application

Sample	CA Water(°)	CA DIM (°)	Total Surface Energy (mN/m)	Dispersive component (mN/m)	Polar component (mN/m)
Novec 72DE cleaned alum can	87.90	56.80	30.05	27.46	2.59
FEP coated alum can	101.70	77.40	18.59	17.27	1.32
Parylene coated alum can	84.10	39.70	39.17	37.48	1.69
Anodised alum can	80.60	41.30	38.44	35.36	3.08
Anodised+3M fluorosilane alum can	106.50	86.00	15.87	14.53	1.34
3M fluorosilane coated alum can	112.60	84.20	15.73	15.41	0.32

The sessile drop technique was used for the acquisition of the contact angle data. The Surface Energy calculation employed was that of Owens-Wendt and Kaelble (OWK). A two-liquid method was employed using Deionised Water (a polar liquid) and Diiodomethane (DIM) (a non-polar liquid). This method allows the surface energy to be expressed in terms of polar and dispersion components. The DIM is used in order to detect surface energy due to dispersive interactions and water is used to detect surface energy due to polar interactions [15, 16]. The results indicated a range of values of the total surface energy and of the polar and dispersive elements of the surface energy across the samples. The lowest total surface energy was seen with the use of the 3M fluorosilane final treatment, while the highest total surface energy was observed with the Parylene coated sample. Notable is the significant decrease of the total surface energy observed with the anodised can, following application of the 3M fluorosilane as a final treatment.

#### Section 2 Application of drug deposition testing to the treated aluminium canisters.

The canisters were subjected to a previously published rapid screening deposition test based on the controlled deposition of micronised salbutamol sulphate particles on the internal surface of canisters, followed by rinsing steps, followed by the assay of residual surface salbutamol sulphate deposition [14]. The results are shown in Figure 2.



**Figure 2** Deposition performance of aluminium canisters with different surface treatments

In Figure 2, the deposition performance of the aluminium canisters, after different surface treatments, is shown. Two to three replicates were used in each case. The canisters labelled “Calibration” provide a test reference point defining 100% deposition, as the salbutamol sulphate suspension has been applied to these canisters but without subsequent rinsing. The salbutamol sulphate suspension was applied to the remaining test canisters with the addition of two separate fluid rinses, employing decafluoropentane (5ml) with five 180 degree inversion shakes of 1 second cycle duration for each rinse. From the results obtained it is observed that the highest drug deposition occurred with the Parylene coated sample, while the lowest drug deposition occurred with the 3M fluorosilane coated sample. Notable is the decrease in drug deposition for the solvent-washed and the anodised sample, when followed by the 3M fluorosilane as a final treatment.

## Discussion

Viewing all experimental data as a whole, it can be seen that, in general terms, FEP and fluorosilane coatings give rise to high measured surface fluorine levels, which in turn correlate to low deposition performance. Although FEP provides the smoothest coating, the key driver for deposition appears to be surface energy, since the fluorosilane coatings do not significantly alter the topography of the can surface, yet perform slightly better than the FEP coating in terms of measured deposition. The Parylene coated canister shows both higher surface energy and higher deposition than the uncoated canister yet is topographically smoother than the uncoated canister, which further supports the argument that surface energy is the key driver to reducing deposition.

## Conclusions

Drug deposition on pMDI canisters was shown to vary considerably across a range of samples with different coatings applied. Deposition was found to correlate very strongly with total surface energy rather than surface topography. Hence coatings depositing high surface fluorine and providing low surface energy, irrespective of topography, gave the best performance. Further work will focus on developing a deeper understanding of the variables in coating application, deposition test methodology and fluorosilane chemistry on measured deposition performance.

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