

# The development of a new rapid screening test for evaluating the non-stick performance of MDI canisters

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## Summary

Loss of active substance to the walls of Metered Dose Inhaler (MDI) canisters by a process of deposition is a potential failure mode for certain suspension formulations. Such deposition behaviour can be mitigated by the incorporation of a suitable non-stick (release) coating. In order to develop and improve the performance of non-stick coatings, it is highly advantageous to have a fast and reproducible screening test to assess the non-stick performance of new coating systems on MDI canisters. This paper deals with the development of such a technique.

The new rapid screening technique for MDI canister deposition employs a micronised Active Pharmaceutical Ingredient (API) dispersed in the model hydrofluoroalkane (HFA), decafluoropentane (DFP). The dispersed API is deposited onto the can surface in a controlled manner. After deposition, the deposits are sequentially rinsed in a systematic way and then the remaining deposition after rinsing is assayed using a suitable assay technique for the API. The sensitivity of the test may be modified by incorporating API with a known low or high level of surface amorphicity. The described test has been found to be fast to perform, reproducible and sensitive to subtle changes in non-stick canister behaviour and has enabled the rapid screening and optimisation of a large number of new coating systems including in particular, the 3M Plasma Coated Canister.

## Background

Quantification of API deposition on MDI canisters provides an interesting challenge to the product formulator. Results obtained are highly dependant on the test method used. For example, the test canister may be employed in an MDI system whereby the MDI, containing formulation, is actuated through-life via a metering valve. After firing through life, the valve is then removed and residual deposits on the canister are assayed. This method is time consuming, especially when the firing interval is increased in order to reflect more closely, patient use. In addition, the shake type and duration have been found to be additional sources of variation in this test scenario. Furthermore the question of whether to actuate the unit fully to extinction, or to stop at the target number of doses for the product provides an additional complication. In either of the latter scenarios, the question remains of how to differentiate between API residues that will result simply from not being able to fully empty the can, versus the mass of API that is actually surface-bound to the canister – the material of interest.

Against this background it was decided to explore the possibility of creating a canister deposition screening test with the targets of speed, reproducibility and sufficient sensitivity to detect differences in the non-stick behaviour of different MDI canister types. In order to achieve the above it was decided to experiment with dispersions using the model, high boiling point hydrofluoroalkane (HFA) propellant, decafluoropentane ( Bpt 53.6°C) to avoid the need to use pressurised systems.

## Experimental

The concept of the screening test was to create adhesion of a set mass of target particles to test canisters in a reproducible way and then to create fluid shear to allow for their removal in a reproducible way that would mirror MDI use. Initial trials of the test concept used a mixed dispersion of micronised brilliant blue dye and micronised lactose monohydrate.

### Example 1 (brilliant blue/lactose monohydrate deposition)

#### 1. Particle adhesion process

Micronised brilliant blue (1.02g) and micronised lactose monohydrate (4.1g) were dispersed in decafluoropentane (320g) and the mixture was sonicated for 1 minute. Using a variable volume Eppendorf pipette, the latter suspension (0.5g) was dispensed into each of three of a selection of test canister types and the canisters were then immediately placed on a horizontal rolling mixer operating at 35RPM, for 10 minutes. After this stage, the decafluoropentane carrier fluid had evaporated and the micronised particles had formed an even coating on the canister internal surface. The canisters were then placed in an oven at 50°C for 5 minutes to complete the particle adhesion process by driving off any moisture.

## 2. Particle removal process

Decafluoropentane (5ml) was dispensed into each test canister. Then after placing a ferrule with a sealing gasket onto the lip of the canister, the canister was shaken vigorously for 10 vertical cycles. The fluid was then discarded and a further 5ml fresh decafluoropentane added. This process was repeated a further two times ie 4 shake/wash cycles in total. The internal canister surface was then rinsed with deionised water to remove and dissolve any remaining surface bound lactose/brilliant blue residues and the washings made up to 100ml. The solution was then assayed by visible light photometry at the lambda max for brilliant blue (629nm). This process was repeated for each test canister.

## Results

### % deposition

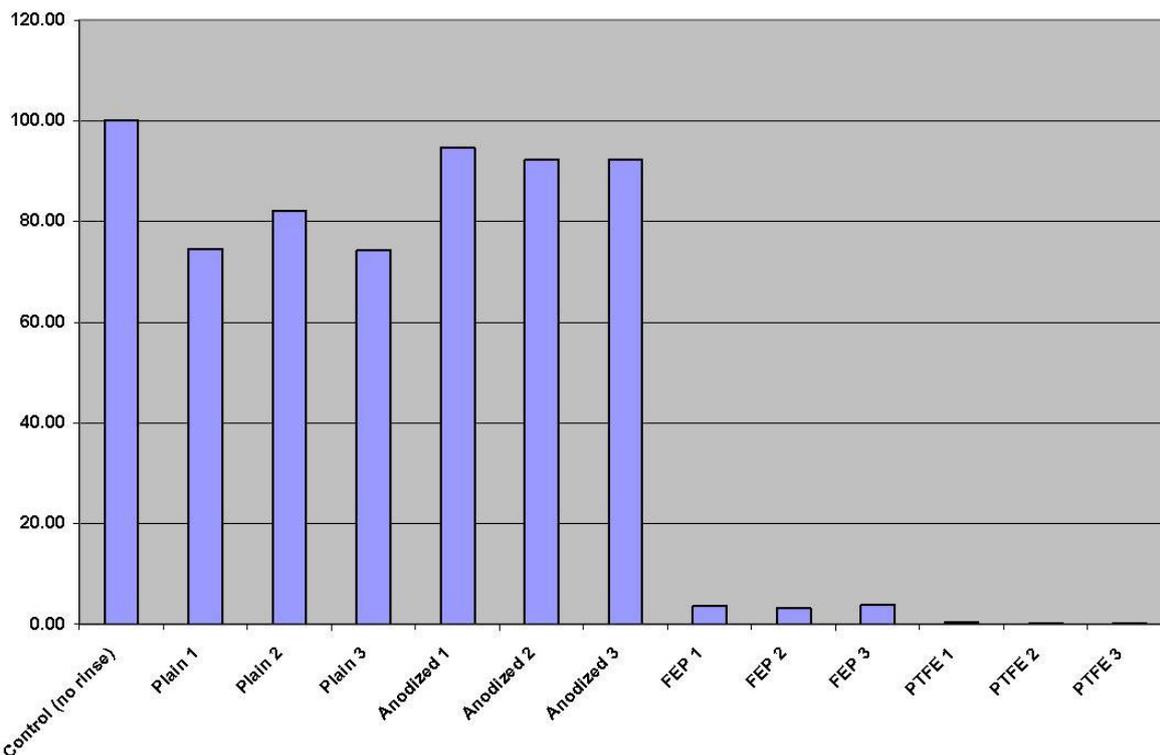


Fig 1 Comparative deposition of model suspension system (micronised brilliant blue/micronised lactose) onto different canister types (% deposition on individual canisters relative to deposited but un-rinsed control canister)

Results shown in Fig 1 from this pilot test run were highly encouraging in that the test was clearly of sufficient sensitivity to differentiate between canisters with and without non-stick coatings. Equally encouraging was the low variability for deposition values within each of the canister groups, suggesting that the particle adhesion and removal processes were both reproducible. Interestingly, the anodized (aluminium) canisters exhibited slightly higher deposition than plain (aluminium) canisters in this test, possibly due to higher surface energy and the FEP (fluorinated ethylene propylene) and the PTFE (polytetrafluoroethylene) coated canisters showed deposition levels less than 5 % of the originally applied particle mass.

Following the success of this pilot test run, it was decided to switch to the use of common inhalation APIs for the depositing particles.

### Example 2 (budesonide deposition)

The particle deposition process was performed as Example 1 with the exception that the dispersion fluid consisted of micronised budesonide.(1.0g) in decafluoropentane (400g). The particle removal process was performed as described in Example 1 and the cans were assayed for residual budesonide by UV spectrophotometry.

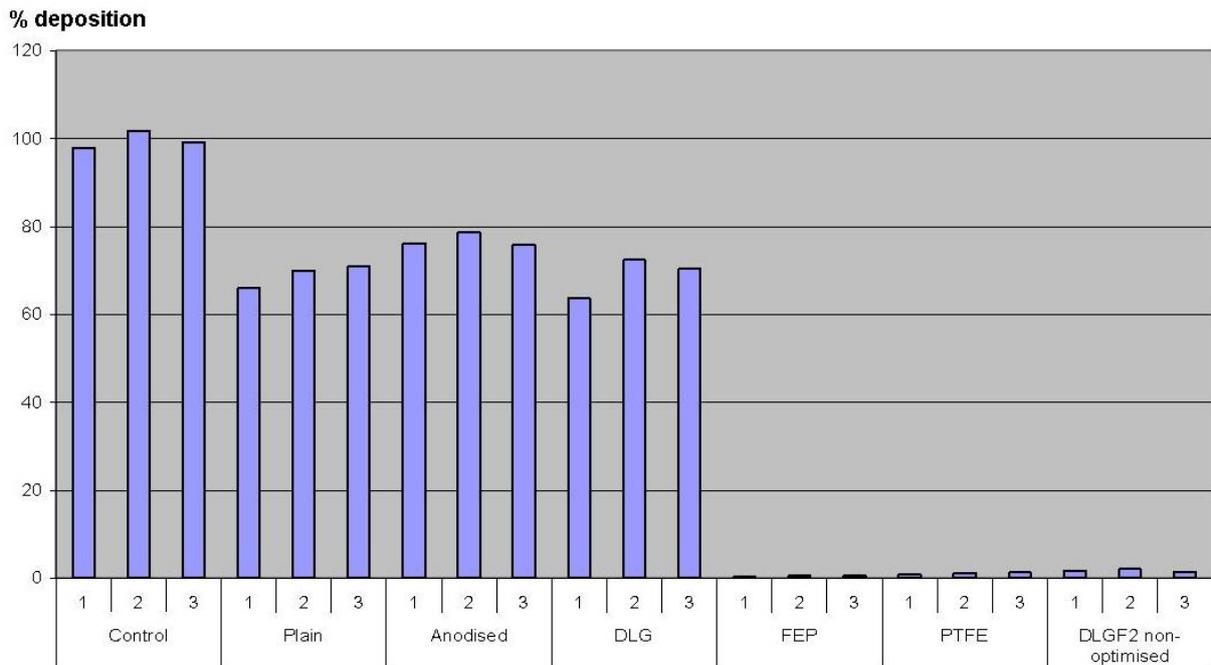


Fig 2 Comparative deposition of model suspension system (micronised budesonide) onto different canister types (% deposition on individual canisters relative to the mean of the 3 deposited but un-rinsed control canisters)

The deposition results for budesonide shown above in Fig 2, show similar trends to those of brilliant blue/lactose in Fig 1, with both PTFE and FEP fluoropolymer lacquer coatings showing excellent non-stick performance. Also included in this data set is an example of the new high-performance, 3M Plasma Coated Canister (designated DLGF2 on the chart) featuring DLG (diamond like glass), a barrier coating, with a covalently bonded fluorine-containing networked layer, to provide both additional barrier properties and excellent non-stick performance.

### Example 3 (salbutamol sulphate deposition)

The particle deposition process was performed as Example 1 with the exception that the dispersion fluid consisted of micronised salbutamol sulphate (1.0g) in decafluoropentane (400g). The particle removal process was performed as described in Example 1 and the cans were assayed for residual salbutamol sulphate by UV spectrophotometry.

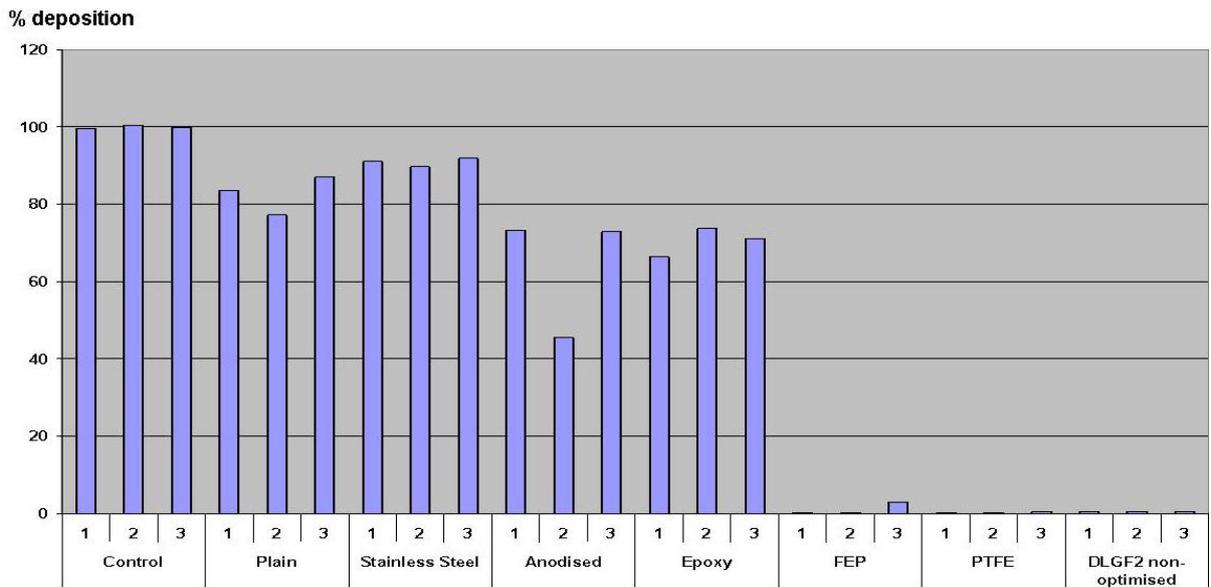


Fig 3 Comparative deposition of model suspension system (micronised salbutamol sulphate) onto different canister types (% deposition on individual canisters relative to the mean of the 3 deposited but un-rinsed control canisters)

The results for salbutamol deposition shown in Fig 3 above, demonstrate broadly similar performance as for budesonide deposition, with FEP, PTFE and DLGF2 performing well in the test with virtually no residual canister deposition and the plain, anodised, stainless steel and epoxy coated cans all showing relatively high levels of deposition.

#### Example 4 (salbutamol sulphate deposition) (test tuned for high sensitivity)

During deposition screening tests employing salbutamol sulphate it was noticed that on certain occasions the sensitivity of the test appeared to change. This phenomenon was investigated and found to be related to the micronised salbutamol sulphate and in particular the recentness of micronisation. The effect is believed to be due to freshly micronised material having high surface amorphicity, which creates higher particle adhesion forces to the canister in the screening test. In this example freshly micronised salbutamol sulphate was employed.

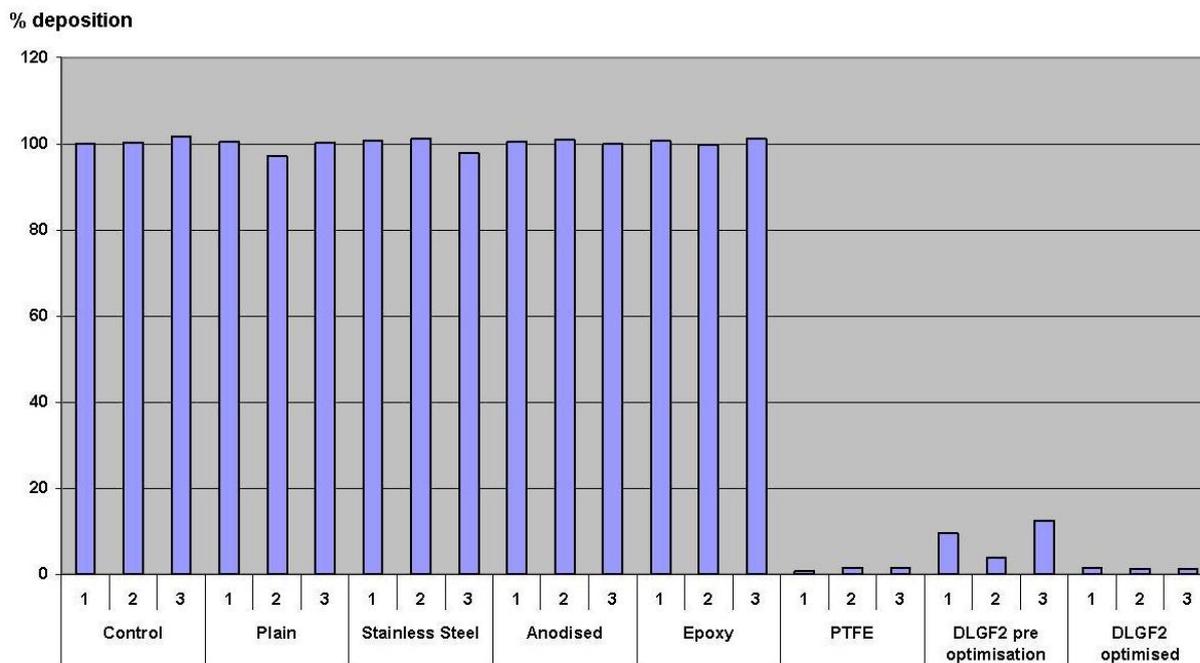


Fig 4 Comparative deposition of model suspension system employing freshly micronised salbutamol sulphate onto different canister types (% deposition on individual canisters relative to the mean of the 3 deposited but un-rinsed control canisters)

The results for the deposition test shown in Fig 4 using freshly micronised salbutamol sulphate show the performance of the screening test using salbutamol sulphate in high sensitivity mode. Here it can now be seen that plain, stainless steel, anodized and epoxy coated cans all show essentially 100% deposition in the test and that the pre-optimised DLGF2 cans now show some slight deposition. By employing the test extensively throughout DLGF2 process designed experimentation studies, it was possible to optimise the coating to achieve essentially no deposition in this highly challenging, high sensitivity test.

#### Conclusions

A new deposition screening test was devised with the aim of providing a rapid screening approach to assess the non-stick performance of MDI canisters. Results using different APIs show highly reproducible data and the ability to differentiate between coating types with different non-stick performance. Use of the test in different sensitivity modes by deliberately employing surface amorphicity effects with salbutamol sulphate, was found to be an invaluable tool in the screening and subsequent optimization of new coatings.

#### Acknowledgements

Many thanks to Chris Blatchford and Mike Forster for API assay work and data processing.