Improving dose reproducibility from MDIs

Using a particulate semi-permeable matrix (PSPM) foam component as a holding chamber for a valve improves sampling consistency in flocculating suspensions

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Many of the formulations delivered by metered dose inhalers (MDIs) marketed today consist of suspensions of solid active pharmaceutical ingredient (API) material in the form of particulates suspended in a propellant. Such formulations, which may also include various excipients and stabilizers, have a tendency to flocculate rapidly, with particulates suspended within the liquid moving close together and forming a loose association, a process that can lead to dosing inconsistencies.

The loose associations formed by flocculation cause heterogeneity within the formulation. Not only are dense areas of particulates formed, but the rates of sedimentation, where the material falls out of the suspension, and creaming, where the particulate material collects at the surface, can also be affected. Whether flocculation leads to creaming or to sedimentation depends on the relative density of the API materials compared to the density of the chosen propellant.

Whether the flocs remain distributed in the liquid, form a sediment, or cream, such behavior may give rise to inconsistent dosing performance due to the sampling mechanism employed by typical MDI valves. In these devices, once the patient fires a shot, formulation passes through one or more sampling channels into the metering chamber. That dose is then stored in the chamber prior to firing the next shot. If flocculation occurs within the formulation, and the particulates are not distributed homogenously, formulation sampling is likely to be inconsistent, resulting in variations in dosing.

Recently, researchers have been exploring the use of a novel, semi-permeable system component made of a reticulated foam for use with suspension formulations to alleviate valve sampling problems. Reticulated foams feature open pore structures with specified numbers of pores per inch. Using the foam as a holding chamber adjacent to the valve sampling point prevents flocs forming in a suspension formulation from growing any larger than the volume of the pores.

The pore structure of the foam results in consistently sized flocs and also prevents their migration, which might otherwise cause valve oversampling or undersampling. The ultimate result is greatly improved MDI dosing consistency from suspension formulations.

Flocculation in HFA vs. CFC formulations

Initial research began with an analysis of the problem using some commonly employed pulmonary APIs in an HFA propellant. The suspension characteristics of a selection of currently marketed HFA-based MDI suspension products 30 seconds after shaking showed a variety of behaviors (Fig 1), and a study evaluating the rapidity of flocculation between CFC propellants (soon to be phased out under the Montreal Protocol) and HFAs found that flocculation is more problematic with HFA propellants. The rapidity of flocculation between a CFC formulation of Ventolin and an HFA-based formulation (Ven-

tolin Evohaler) showed great variability in dosing for the HFA product in a Timed Medication Delivery Test (Fig 2).

The Timed Medication Delivery Test (TMDT) quantifies how robust the dosing performance of a product is compared to the delay between shaking and firing [1]. In this test, assessment of dosing performance takes place following different time intervals between the cessation of shaking and firing a shot from the inhaler. The data obtained show that the rapidity of flocculation for Ventolin Evohaler underpins its performance in the TMDT, where the HFA product performs less well than its more slowly flocculating and creaming CFC-based predecessor.

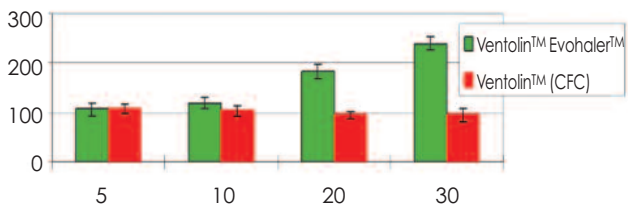
The strongly electronegative mantles of the HFA suspension formulations, which can cause more intense interparticulate interactions [2], may bear responsibility for this behavior. Some researchers have postulated that the electronegative fluorine atoms in an HFA molecule form an electronegative mantle around the carbon backbone of the molecule, which has been observed to act as a repulsive barrier [2].

Figure 1

Suspension dynamics of marketed HFA MDI suspension products at 30 seconds post shaking. From left to right the products shown are Ventolin Evohaler, Flixotide 50 Evohaler, Flixotide 250 Evohaler, Seretide 250 Evohaler, Salamol, and Airomir.

Figure 2

Timed Medication Delivery testing of Ventolin versus Ventolin Evohaler



Research suggests that some flocculation behavior can actually help improve dosing consistency since the metering valve may be unable to retain the correct amount of active after periods as short as a single 12 hour dosing interval if the suspension flocculates unevenly [3]. The rapid flocculation exhibited by some HFA products such as Ventolin Evohaler may on balance, be a positive attribute in terms of MDI dosing uniformity since the formation of coarse flocs that build up over time can reduce particulate mobility and also prevent the sediment (or cream) from becoming too compacted and concentrated.

A new MDI sampling concept

Employing a fluid permeable, particulate semi-permeable matrix (PSPM) within the MDI can minimize the sensitivity of suspension-based HFA formulations to the effects of a time delay between shaking and firing a shot from the unit. Cutting cylindrical shaped PSPM components allows them to fit within a zone above the sampling point of the metering valve (Fig 3).

The open pore structure of the PSPM foam component (Fig 4) allows free passage of a formulation that has been fully dispersed during shaking, so the foam allows the dispersed particulate formulation access to the sampling points of the valve. After particulate flocculation has occurred within its matrix, the PSPM then acts as a reservoir for the formulation, trapping flocs within its pores.

Figure 3

Samples of PSPM that have been cut to size in order to fit around the sampling points of the Spraymiser valve.

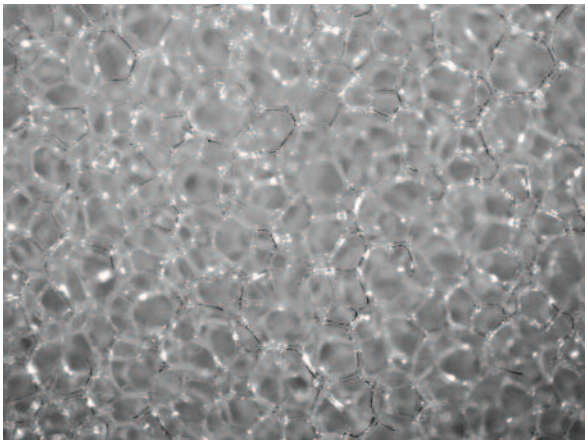
The foam component therefore allows the valve to sample the correct concentration of formulation even if particulates within the bulk formulation have creamed or sedimented. In simplistic terms, the PSPM foam acts as a flocculation limiter, preventing the buildup of particularly large particulate associations within its structure. Shaking the unit causes the elimination of smaller associations of particulates suspended within the matrix of the PSPM back into the canister. Once that portion of the suspension returns to the canister, those smaller flocs redisperse and mix with the rest of the bulk formulation.

Testing of valves equipped with the PSPM component took place using MDI units containing a model suspension formulation comprised of micronized brilliant blue food dye and micronized lactose bulking agent in a P134a-based propellant system. The model formulation, while behaving in a similar manner to the marketed suspension HFA formulations shown in Figure 2, has the advantage of being simple to assay using visible light photometry. Inserting the formulation and the PSPM material into a transparent PET (polyethylene terephthalate) vial allows for observation of the formulation's interaction with the PSPM materials (Fig 5).

Assessment of the dosing performance of the MDIs was performed using a Timed Medication Delivery protocol. The data indicate that the inclusion of the PSPM components adjacent to the valve sampling points significantly improves the dosing robustness of the model suspension MDI system when the unit is challenged with a 30 second delay between shaking and firing (Fig 6). The blue line in Fig 6 indicates the valve incorporating the PSPM material and shows a stable dosing performance.

Figure 4

Photo showing the open pore nature of the PSPM material.



Testing demonstrated that selecting the correct pore size for the foam components is critical to improving the dosing consistency. The PSPM material itself clearly shows the even entrapment of flocculated formulation within its porous structure (Fig 5). Flocs unable to navigate around the cell walls of the matrix remain locked within the structure until they are reintroduced into the bulk of the formulation by shaking the unit.

Ideally, formulation regions above and below the PSPM component will have the same height ratio of suspended solids after inversion of the unit. Achieving the same height ratio indicates that the formulation

Figure 5

Appearance of model HFA suspension formulation in contact with polyester reticulated foams of varying pore sizes 5 minutes post shaking

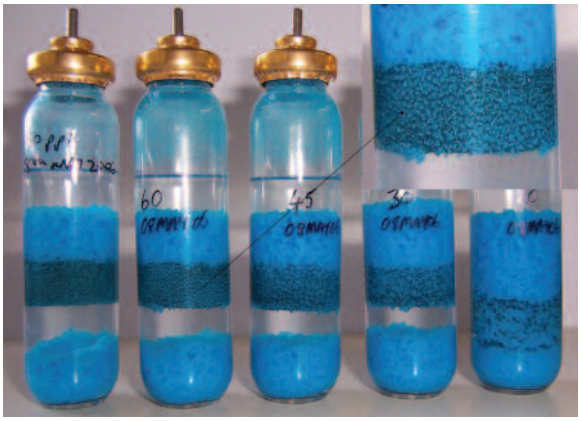
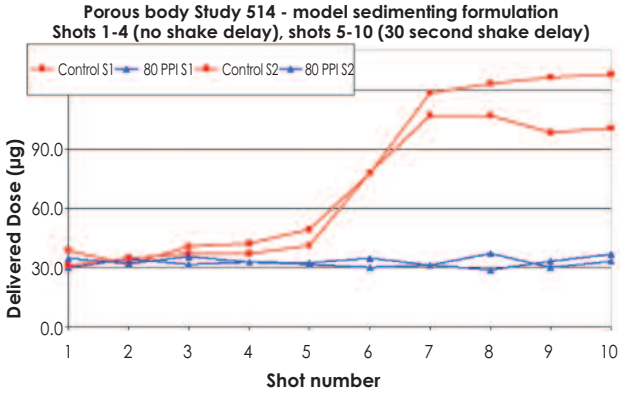


Figure 6

Timed Medication Delivery study on valves modified by the incorporation of polyester reticulated foam PSPM components with a range of pore sizes versus unmodified controls



has passed through the PSPM material unhindered during agitation but that the foam provided a barrier during the subsequent flocculation and sedimentation phase.

Through Life Medication Delivery (TLMD) studies have demonstrated that inclusion of the PSPM component causes no untoward dosing behavior or excessive residues on the component. Tests assessing various shots throughout the lifetime of the unit, usually performed at the start, middle, and end of the unit's "shot" life, showed no significant changes in TLMD dosing performance, and residues remained less than 5 µg when testing a system formulated at 5 µg per actuation.

Work is ongoing to explore the use of this novel system of PSPM components in both the valve metering tank and flow channels with the aim of addressing loss of dose behavior. This concept may eventually prove useful with other metering valve designs as well.

References

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