

Pressurized metered dose inhalers: Chlorofluorocarbon to hydrofluoroalkane transition—Valve performance

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This article reviews the issues related to the performance of valves in metered dose inhalers with respect to chlorofluorocarbon propellant replacement. Reformulation of existing chlorofluorocarbon-based products with hydrofluoroalkane propellants has been a much more difficult task than initially anticipated, complicated by the need to concurrently develop better performing valves with cleaner extractive profiles. This paper will examine issues related to the reformulation and development of new valves and the tests and procedures used to evaluate valve performance. Evaluation of valve performance will consider the tests performed; mechanisms by which valves fail and analytic testing errors that can complicate the interpretation of results. (*J Allergy Clin Immunol* 1999;104:S230-5.)

Key words: Valve performance, propellant replacement, propellants, extractives, metered dose inhalers, chlorofluorocarbon, hydrofluoroalkane

The replacement of chlorofluorocarbon propellants in metered dose inhalers (MDIs) with hydrofluoroalkane propellants has not been as straightforward as was initially anticipated. Hydrofluoroalkane-134a and -227 have physical properties similar to the chlorofluorocarbons that they are replacing and were expected to work in place of the chlorofluorocarbons quite readily. However, there have been two major difficulties that have caused significant delays in propellant replacement, reformulating with the new propellants and compatibility of the cleaner valves. The major difficulty in reformulating has been the incompatibility of surfactants used in chlorofluorocarbon products with the hydrofluoroalkane propellants. Concurrent to the replacement of chlorofluorocarbons have been requirements to develop valves that are both better performing and that have cleaner valve materials than those used in the past.

REFORMULATION

A complete discussion of issues related to the development of hydrofluoroalkane-compatible formulations with the use of alternate propellants is beyond the scope of this paper. The discussion will be limited to those issues that have a direct impact on valve performance, the most important of which is the incompatibility of surfactants used in chlorofluorocarbon products with hydrofluoroalkane pro-

Abbreviations used

DTV:	Dose through valve
MDI:	Metered dose inhaler
PAH:	Polycyclic aromatic hydrocarbons
USP:	United States Pharmacopeia

pellants. Surfactants, such as oleic acid and lecithin, are not soluble in hydrofluoroalkane propellants; therefore it has been necessary, for the most part, to use cosolvents to solubilize the surfactants to create suspension formulations or to dissolve the drug substance for solution formulations. The need for cosolvents has significantly delayed propellant replacement for those products that do not use chlorofluorocarbon valves because of the effects of the cosolvent on gasket materials. The most commonly used cosolvent, ethanol, causes swelling of gasket materials and increases extractives. Surfactants and ethanol not only affect the stability of suspensions, but also the amount of lubrication between the valve stem and gaskets.

VALVE COMPONENTS AND EXTRACTIVES

MDI valves contain a large number of components made from a wide variety of materials that include plastics, rubbers, and metals and are required to accurately and precisely deliver a metered dose typically between 80 and 200 times over the life of the product. A typical valve will have a valve stem (plastic or metal), gaskets (rubber), o-ring (rubber), spring (metal), metering chamber (metal), and fill cup (metal or plastic). Two gaskets form the seal around the valve stem. The lower gasket seals between the metering chamber and the outside atmosphere, and the upper gasket seals between the metering chamber and the bulk formulation in the canister. An o-ring forms the seal between the canister and the valve assembly.

Any of the plastic or rubber components can be a source of extractives, with the o-ring considered the major source. These materials are extracted by the propellant, and the use of a cosolvent can exacerbate the problem. A cosolvent, such as ethanol, can increase both the number of compounds and the quantity of each extracted from polymeric (plastic or rubber) valve components.

Concurrent to the efforts to reformulate with hydrofluoroalkanes has been pressure from regulatory bodies on valve manufacturers to create valves that are both cleaner and better performing. This has meant the development of

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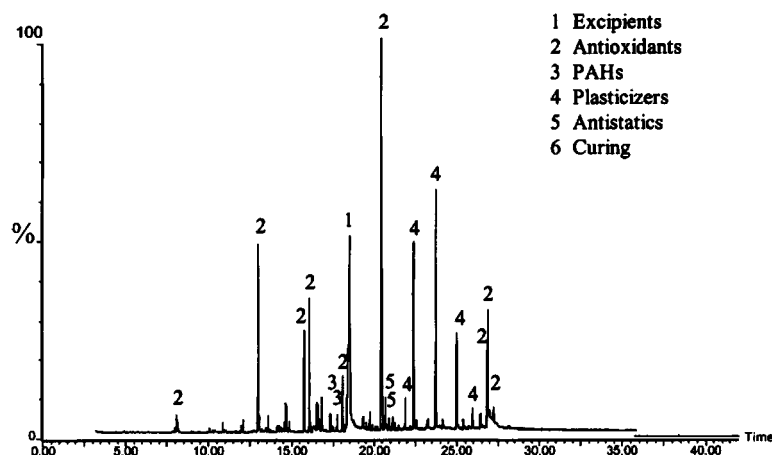


FIG 1. Gas chromatography/mass spectroscopy chromatogram of the formulation from a commercially available MDI containing chlorofluorocarbon propellants.

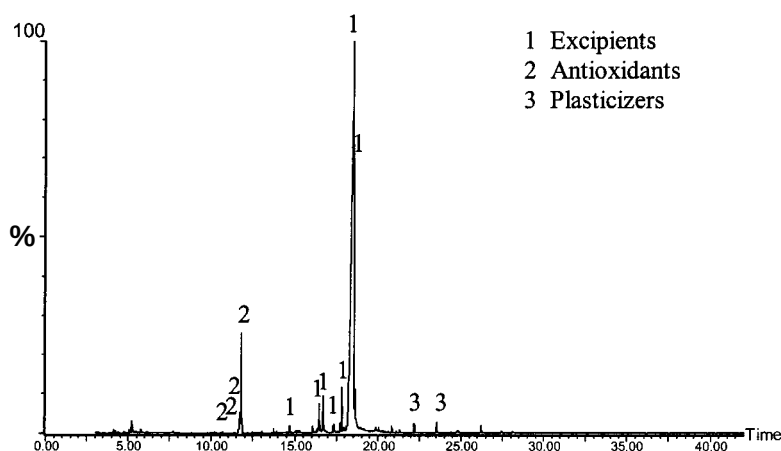


FIG 2. Gas chromatography/mass spectroscopy chromatogram of the formulation from a commercially available MDI containing hydrofluoralkane propellant.

new polymeric materials, especially gaskets and o-rings, which have cleaner extractive profiles and similar characteristics of friction, swelling, flexibility, and durability of the polymeric materials currently used. The desired characteristics of better performance and cleaner extractive profiles are in many ways conflicting goals. In general, those components and additives in rubber materials that produce undesired extractives are the same components that give the rubbers used in gaskets and o-rings the desirable characteristics of flexibility and durability. That these new materials must also be compatible with cosolvents has further complicated the development process. There still exists a general lack of agreement between regulatory groups as to what appropriate performance requirements should be.

The development of cleaner valves has required either the novel use of existing polymeric materials or the development of completely new materials. The materials used for gaskets and o-rings in chlorofluorocarbon products are made from rubbers that are crosslinked by sulfur-curing (vulcanization) and use carbon black as a

filler. These "black rubbers" can leach a wide variety of compounds into the formulation. These include organics (monomers, oligomers, stabilizers, plasticizers and lubricating agents), polycyclic aromatic hydrocarbons (PAHs), 2-mercaptobenzothiazole and nitrosamines. PAHs, 2-mercaptobenzothiazole, and nitrosamines are known or suspected carcinogens. The Food and Drug Administration requires drug manufacturers to identify and control these compounds.¹ PAHs come from the carbon black filler, and the 2-mercaptobenzothiazole and nitrosamines result from the sulfur-curing process. The use of cosolvents, currently in most hydrofluoralkane formulations, only exacerbates the problem of leaching of extractives and swelling of valve gasket materials.

The new, cleaner rubber materials are generally "white rubbers" made with the use of titanium dioxide as the filler and with peroxide-mediated crosslinking. Peroxide curing can, however, result in residual peroxides, which can cause degradation of the drug substance in the product. Care must be taken in selecting the type of peroxides

to be used and controlling reaction conditions during the crosslinking step. Valves can also be made cleaner by pre-extracting the gaskets with the intended propellant and/or cosolvent before the manufacture of the valve. Because the extraction removes plasticizers and other compounds that give the polymers their rubber-like quality, it can result in gaskets that are not flexible or durable enough and are thus prone to leaking or premature failure.

Regulatory submissions for the approval of new MDIs require characterization and control of extractives. Example extractive profiles for two commercially available MDIs are shown in Figs 1 and 2. Fig 1 shows a typical gas-chromatography/mass-spectroscopy chromatogram of the extractives found in a chlorofluorocarbon product, and Fig 2 shows the chromatogram for a hydrofluoroalkane MDI. Peaks in each chromatogram are identified by the class or source of the compound. The hydrofluoroalkane product produces a cleaner extractive profile because most of the peaks are excipiently related, while the chlorofluorocarbon product has multiple compounds from each class.

EVALUATION OF VALVE PERFORMANCE

The evaluation of valve performance can be very complicated. Not only are there multiple performance tests and failure modes, but analytical testing errors can also be misinterpreted as valve failures. The converse also occurs: valve failures are assigned to testing errors when they are not. In this section the various test procedures, failure modes, and testing errors and the ways in which test results can be misinterpreted will be discussed. The following discussion is general in nature and applicable to all MDI formulations, but comment will be made for issues that are specific to propellant replacement.

There are many tests used to evaluate MDIs,¹ some of which are intended specifically to evaluate valve performance. These include medication delivery, dose through valve (DTV), valve delivery, tail off, leakage, and priming studies. The mechanisms by which MDIs fail include blow by, continuous dosing, valve sticking, loss of prime, erratic tail off, and leakage. Analytic testing errors are related to shaking, valve actuation, canister handling, and temperature of both the canister and the test environment. All of these factors must be carefully controlled so that they are not misinterpreted as valve failure. The evaluation of data that suggest a malfunctioning valve is difficult because many analytical testing errors can produce results that look the same. Care must be taken to assure that analytical technique is not the source of failing results, and one must be equally careful not to readily assign poor valve performance or formulation problems to testing errors. In this section the performance tests, various modes of valve failure, and testing errors that affect results will be defined and their relationship to one another discussed.

Valve performance tests

Medication delivery. Medication delivery (or dose delivery) is a measure of the dose delivered past the

mouthpiece of the actuator. It is measured by delivering one dose (1 or more shots) into a collection apparatus. The dose is recovered by rinsing the apparatus with an appropriate solvent and assaying the recovered solution. The most common medication delivery collection devices are (1) a separating funnel with a cotton plug in the stem and (2) the dose collection apparatus described in the United States Pharmacopeia (USP) 23.² The latter is typically a plastic tube, with a filter in one end, that can be sealed and filled with recovery solution.

Medication delivery can be done as a through-life test; that is, throughout the labeled number of doses. Usually this means testing at the beginning, middle, and end of canister life. For the purposes of this discussion, canister life is defined as the labeled number of actuations, not shelf life.

Dose delivered through the valve. DTV is a measure of the dose delivered past the valve stem. It is measured by placing the MDI valve down into a container with a recovery solution and a retaining surface with a hole to allow the dose to be captured in the recovery solution. The bottom of the canister is pressed down to actuate the valve, releasing the dose into the recovery solution. DTV was, until recently, the basis of product labeling in Europe.

Like medication delivery, DTV can be done as a through-life test and is usually done at the beginning, middle, and end of canister life.

Valve delivery. Valve delivery, also known as shot weight, is a measure of the weight of the formulation delivered. It is measured by the difference of weight per actuation or per dose. Valve delivery is commonly determined concomitantly to medication delivery or DTV.

Tail off. Tail off is a measure of the uniformity of actuations past the label-claim number of doses as the canister is exhausted. It may be measured by medication delivery, DTV, or valve delivery. Measurement of tail off by valve delivery does not assure that the drug substance is being delivered because most of the weight of an actuation is due to the propellant. Tail off testing is performed to determine the rate at which an MDI transitions from delivering complete doses to no delivery at all. The ideal is a rapid transition from complete doses to no delivery so that the patient is receiving partial doses for as few actuations as possible.

Priming study. A priming study is an application of the medication delivery test to evaluate MDI performance under a variety of conditions that simulate patient use. These can include storing primed MDIs in various orientations (typically valve up and valve down) for defined periods of time. Shaking studies are done to determine how the MDI should be shaken to assure a good dose and whether the dose can be lost from shaking too vigorously. Information from these studies about need to prime and how to shake the MDI is provided in the patient instructions supplied with the product.

Leakage. Leaking of propellant is measured by weight change of MDIs as a function of time stored at controlled conditions. Weight loss is determined by measuring the initial weights of canisters that are placed on condition and then reweighed at subsequent time points. An alternative test, USP Leak Rate, has been used in the past, but

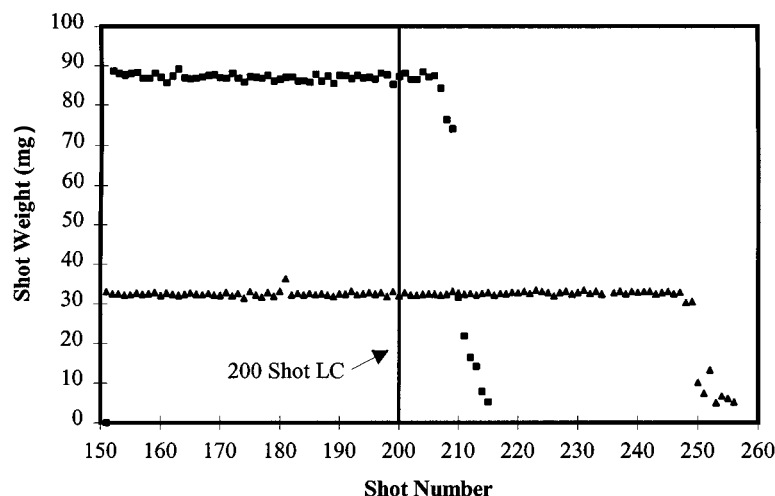


FIG 3. Valve delivery data for 2 commercially available MDIs with chlorofluorocarbon propellant (■) and hydrofluoralkane propellant (▼). LC, label claim.

was recently removed from Chapter <601>. The reader is referred to older versions of the USP for details.³

Failure mechanisms

There are a variety of ways by which valves can fail. Some of the more common mechanisms include blow by, continuous dose, valve sticking (gasket or formulation related), partial filling of the metering chamber, drain back, erratic tail off, and loss of dose because of creaming and sedimentation. In this section, the various failure mechanisms and tests by which they are detected and their relationship to the product will be defined.

Blow by. Blow by is the condition in which the lower gasket, between the metering chamber and atmosphere, leaks when the valve is actuated so that a portion of the dose passes around the outside of the valve stem. Blow by can result from a gasket that swells too much or is not flexible enough and does not fit around the valve stem well. If it does not slide along the valve stem properly, it can buckle and leak. Also, if the gasket is not durable enough, it will wear with use and leak during actuation. Gasket failure can also be formulation related (for example, if the drug product builds up or crystallizes on the valve stem, it can cause premature wear).

Blow by can be detected by medication delivery testing with confirmation from valve delivery data, if collected. Increased deposition in the mouthpiece, especially on the stem block, is a clear indication of this problem. It would not, however, be detected by DTV testing.

Continuous dose. Continuous dose (sometimes referred to as catastrophic failure) is the condition in which the upper gasket, between the metering chamber and the bulk formulation, leaks when the valve is actuated. The dose is not metered because there is now a direct path from the bulk formulation out of the canister and formulation is emitted as long as the valve is compressed. The causes for gasket failure are similar to those discussed for blow by.

Continuous dose can be detected by both medication delivery and DTV testing with confirmation from valve delivery data. Visual or audible observation of the valve failure is possible with medication delivery, depending on the experimental setup used, and can be seen and heard (depending on the severity of the problem) with DTV testing because the dose is bubbled through the recovery solution.

Sticking valve. A sticking valve can result from gasket swelling or improperly compounded gasket rubber or because the formulation does not provide sufficient lubrication. Valve stick causes the valve to not fully return after actuation that results in only partial filling of the metering chamber, which results in a low shot. A sticking valve can result in a partial fill in two ways. The valve may not return all the way to its rest position before the next actuation is delivered or it may only stick momentarily before returning to its rest position, but long enough for the analyst to move or shake the can in preparation for the next shot. Shaking or tilting of the MDI can move the liquid away from the fill hole, causing part or all of the next shot to be vapor even if the valve fully returns. A sticking valve can be detected by the dose delivery test (and valve delivery) but is often an intermittent problem that does not lend itself to investigation.

Erratic tail off. Erratic tail off is the situation in which the dose delivered after the label-claimed number of actuations is inconsistent; the patient repeatedly receives partial doses. Erratic tail off can result from a sticking valve, poor valve design, or poor analyst technique. The lower the fill hole is in the canister the more likely it is to be covered with liquid formulation when the metering chamber is refilling. The higher on the valve the fill hole is located (for example, if the metering chamber fills from the top), the sooner in canister life the occurrence of partial fills will begin.

An example of the data from a tail off study are shown in Fig 3. These are shot-weight data for two commercial-

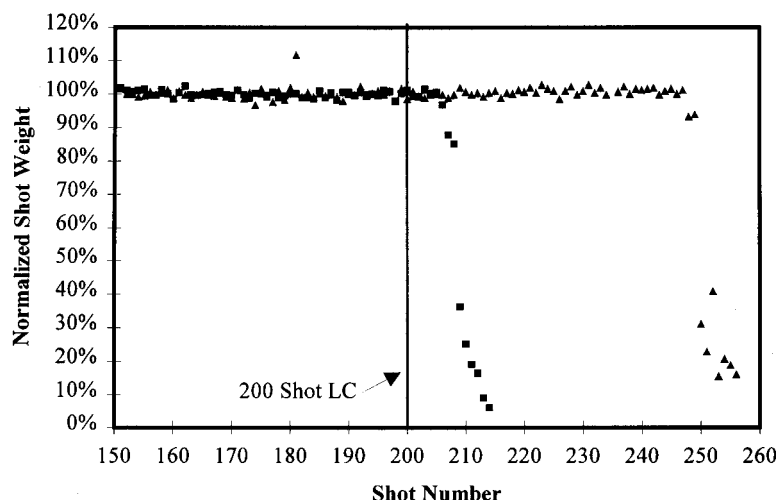


FIG 4. Normalized valve delivery data for 2 commercially available MDIs, 1 with chlorofluorocarbon propellants (■) and the other with hydrofluoroalkane (▼). LC, label claim.

ly available MDI products; data are shown for shot 150 onward. Both are 200-shot products; one is a chlorofluorocarbon product, and the other is a hydrofluoroalkane product. The chlorofluorocarbon product has a shot weight approximately 3 times that of the hydrofluoroalkane product; the same data are shown in Fig 4 with shot weights normalized. The hydrofluoroalkane product has a greater number of doses past label claim, due at least in part to the smaller shot weight; however, the variability of the shot weights and tail off characteristics are essentially the same for both products.

Loss of prime. Loss of prime, also referred to as the Cyr effect,⁴ is the result of the partitioning of suspension formulations, creaming or sedimenting, in the metering chamber. Once in the metering chamber, it usually cannot be mixed with sufficient force by shaking to resuspend the drug. As a result, the next actuation delivered is subpotent because some of the partitioned material sticks to the walls of the chamber. The mixing that occurs as the chamber refills causes the drug to be resuspended, and the second actuation delivered is superpotent.

Analytic technique related issues

Results generated from the analytic testing of MDIs are dependent on analyst technique in handling the canisters during testing and on experimental set-up. The force and timing of shaking, speed and duration of valve actuation, angle and motion of the canister during refill, and temperature of the canister and test environment can significantly influence results.

Shaking. A suspension MDI must be shaken with sufficient force to resuspend the drug substance, but not so forcefully as to cause part of the dose to come out of the metering chamber. Both the duration and force of shaking must be carefully controlled through analyst training. Errors as subtle as whether the testers bend their wrist at the end of the shaking motion can have a dramatic effect

on the results obtained. The “wrist snap” that results can input enough energy to force the dose out of the metering chamber, depending on valve design. The increased use of mechanical actuators and wasting stations cannot only reduce this type of shaking error but can also improve analyst-to-analyst and day-to-day variability and the potential for repetitive motion injuries.

Actuation technique. The valve must be compressed long enough during actuation, generally 1 second, to allow the entire contents of the metering valve to empty. In addition, when an MDI is actuated, it must be pressed directly down above the valve stem. If the canister is allowed to tip during actuation, the valve stem will push to one side and distort the gaskets in the metering, causing or exacerbating blow by. This sort of torquing of the valve stem is a common problem with the DTV testing because there is no support to guide the canister. When a mouthpiece is used, as in medication delivery testing, which fits around the canister properly, torquing is much less likely.

The rate at which an MDI is actuated, especially when waste shots to dose are delivered from the beginning of life to the middle or the middle to the end, is vital. If actuated too quickly, the valve (and gaskets) can freeze, and the gaskets can wear prematurely. Rest periods to allow the MDI to warm up should be included in the activation regimen.

Canister handling. Care must be taken after the delivery of an actuation that the canister is held vertically and still until the valve has fully returned to its rest position. If the canister is shaken or tilted while the valve is returning, a partial fill may result. If shaking is started while the valve is still compressed, the liquid formulation may be shaken away from the metering chamber fill hole(s) while the chamber is refilling, resulting in some or all of the chamber being filled with propellant vapor. Likewise, if it is tilted to the side and the fill hole is not covered with liquid, some or all of the chamber volume may be

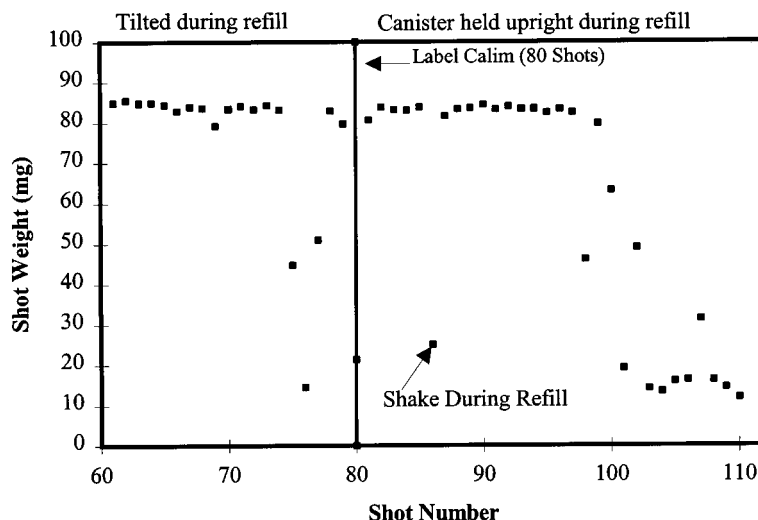


FIG 5. Valve delivery data illustrates the effect of improper handling of an MDI (tilting and shaking of canister) during refill of the metering chamber.

filled with vapor. The likelihood of this happening increases toward the end of canister life when the volume of formulation left in the canister is low.

Both of these situations, tilting and shaking of the canister during refill, are illustrated by the shot weight data shown in Fig 5. In this experiment, shot weight is measured for each actuation delivered from an 80-shot MDI. The canister was tilted at various angles after each actuation when the valve was refilling. Initially this is not a problem; however, as expected, as the canister approaches the labeled number of actuations, the frequency of low shot weights increases. After actuation 80, the canister was held vertically to demonstrate that it would continue to deliver a full shot if handled carefully. At actuation 86, the analyst intentionally started shaking the canister too soon, while the valve was returning to its rest position, which resulted in the low shot weight observed for that actuation.

Important observations, both visible and audible, can be made, depending on experimental setup. Visual observations can be made if the test apparatus is transparent (eg, separating funnel), and audible observations can be made if a remote vacuum source is used instead of a vacuum pump directly adjacent to the apparatus. These observations can be crucial in verifying valve failure or experimental error.

In evaluating the results of performance testing, there can be a tendency to ascribe testing errors to valve failures or, conversely, to identify valve or formulation failures as testing errors. The way in which these misassignments are made may depend on which part of the product development process one participates in. For example, blow by can be caused or certainly made worse by poor technique. If the valve stem is torqued during actuation or if it is actuated too quickly (causing freezing of the gaskets), the results are the same as blow by. Similarly, if continuous dose produced medication delivery values that were too high, equivalent to an extra actuation, these results could

be interpreted as miscounting on the part of the analyst. Without experimental observation, one cannot determine with certainty which is the case. Partial dosing and erratic tail off, which might both be caused by a sticking valve, could also be the result of not holding the valve fully depressed during actuation or shaking or tilting the canister during refill, as was discussed for Fig 5. It is beyond the scope of this paper to describe all of the possible ways by which valve or formulation failures could be confounded; however, the examples given make clear that great care must be taken to reach the correct conclusion.

SUMMARY

The conversion from chlorofluorocarbon to hydrofluoralkane propellants has been a difficult process that has been made harder by the need to concurrently develop cleaner valves. Surfactants traditionally used in the formulation of MDIs have not been applicable with the hydrofluoralkane propellants, and, for the most part, cosolvents have been required. As a result, it has taken years longer to develop new products than was anticipated. Performance testing, including experimental set-up and analyst training, must be done carefully because valve failure and testing errors can produce similar results. Those who interpret the results must be very circumspect in their conclusions about the cause of failure results.

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