

Moisture transport into chlorofluorocarbon-free metered dose inhalers

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Moisture is known to affect the stability of some metered dose inhalers (MDIs). Hydrofluoroalkanes such as tetrafluoroethane (134a) and heptafluoropropane (227) are known to have higher affinity for moisture than the currently used chlorofluorocarbon propellents. An initial study was conducted to determine the water vapor transmission rates of various elastomers that may be used as gaskets in MDIs. A further study was conducted to measure the moisture ingress rates of various chlorofluorocarbon-free MDIs. The data indicate that moisture transport into chlorofluorocarbon-free MDIs is influenced by the elastomeric nature of the gaskets used and the type of hydrofluoroalkane formulation and storage conditions used. (*J Allergy Clin Immunol* 1999; 104:S227-9.)

Key words: *Aerosols, moisture*

The potential for moisture to contribute to instability and particle aggregation in nonaqueous pharmaceutical aerosol formulations has previously been reported by Miller.¹ Therefore moisture ingress and content are of interest to develop and manufacture stable pharmaceutical aerosol formulations. There is also some interest from the regulatory authorities with regard to moisture levels in metered dose inhalers (MDIs) and their levels over the shelf life of the product.²

The means by which moisture may enter an MDI system are shown in Fig 1. The moisture must pass from the outside environment either through the seal around the stem or the can to the valve seal and then enter the vapor phase or the condensed phase inside the MDI.

Hydrofluoroalkane 134a and 227 have higher affinities for moisture than the currently used chlorofluorocarbon propellents.³ Based on this fact, it is likely that new chlorofluorocarbon-free MDIs may be prone to increased water ingress rates and eventual water content. This situation could be worsened by the use of polar, water-miscible cosolvents, such as alcohol, and could also be influenced by the nature of the drug substance or any excipients present.

Models have previously been proposed that may predict the time dependence of water permeation, through

Abbreviation used

MDI: Metered dose inhaler

the elastomeric components or gaskets of the metered dose valve, into chlorofluorocarbon MDIs.⁴ It appears that very little has been published about moisture transport into chlorofluorocarbon-free MDIs.

MATERIAL AND METHODS

A standard International Organization for Standardization (ISO) method⁴ capable of determining the water vapor transmission rate of sheet materials was used to characterize the various rubber materials that may be used as gaskets in MDIs. Dishes containing dehydrating agent and closed by the sheet to be tested are placed in an enclosure with controlled temperature and relative humidity. The dishes are weighed at suitable intervals of time. The water vapor transmission rate is determined from the increase in mass when this increase has become proportional to the time interval.

The water content of the MDIs were determined with a Karl Fischer moisture meter.⁶ The sample is introduced into the reagent chamber through a septum plug by a syringe needle from the MDI. The method is simple, rapid, and reproducible for the measurement of low-level water content in MDIs.

MDIs were built incorporating a matrix of gasket materials in both the can-to-valve and stem-seal area. These were filled with different propellant systems and were stored under controlled temperature and humidity conditions and tested at various time intervals.

RESULTS AND DISCUSSION

The results of water vapor transmission rates for various rubber materials are given in Fig 2. The water vapor transmission rates of the materials seem to be strongly linked to the nature of the polymer base used to manufacture the rubber material.

Rubber materials containing black fillers seem to have lower water vapor transmission rates than their corresponding white rubber equivalents. Predictably, the rate of water transmission is affected by the thickness of the rubber material used for testing.

The results of the water content of MDIs containing different propellents and various gasket materials are given in Fig 3. Based on the results obtained from the use of different rubber materials in the can-to-valve seal area

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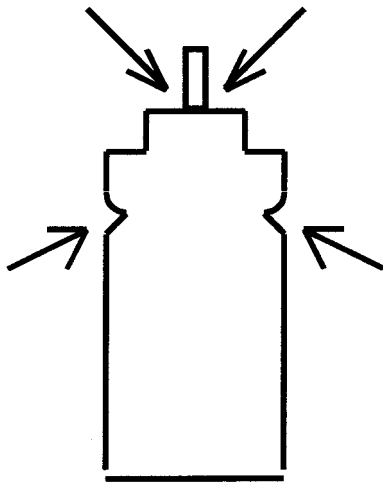


FIG 1. Possible points of moisture ingress in MDIs

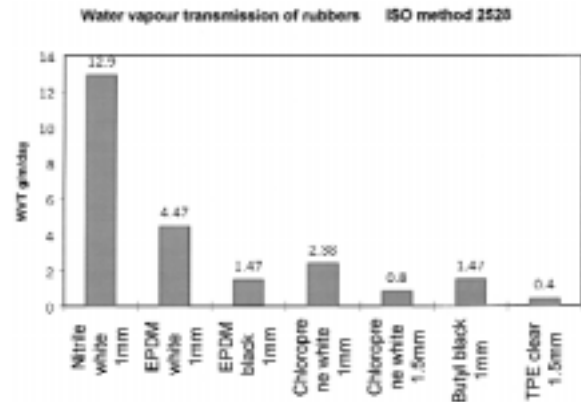


FIG 2. Water vapor transmission results for various gasket materials

Moisture ingress of MDIs @ ambient storage

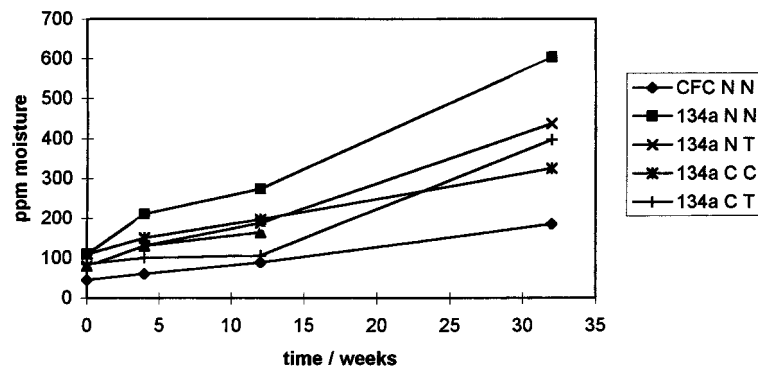


FIG 3. Water content of various MDIs. CFC N N, Propellant, stem seal, can-to-valve seal; N, nitrile rubber; C, chloroprene rubber; T, thermoplastic elastomer.

and the outer-stem seal area, it can be concluded that the major route for moisture ingress into the MDIs is through the can-to-valve seal area.

Moisture permeation of MDIs is known to increase as temperatures and humidity are raised.³ Furthermore, the rates of moisture transport into MDIs could also be influenced by the drug, excipients, and nature of any plastic

materials present in the aerosol system, although the effects of these components on the MDI systems were not considered here.

CONCLUSION

The data clearly indicates that the rate of moisture transport and the water content of the chlorofluorocarbon-free

aerosol MDIs were considerably higher after storage than that of the chlorofluorocarbon-containing MDIs that used identical gasket materials. This is explained by the hydrofluoroalkane propellants having a much greater inherent capacity for water (approximately 500-2000 ppm) as compared with the chlorofluorocarbon propellants (approximately 100 ppm). For aerosol products that may be sensitive to moisture content, it may be possible to assess their potential stability by separately determining the water vapor transmission rate of the gasket materials in the metered dose valve and the equilibrium moisture content of the proposed formulation.

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