Inhalation

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Intelligent sorbents in respiratory drug delivery devices

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The role of intelligent sorbents in respiratory drug delivery devices

Intelligent sorbents can remove moisture-induced dosing inconsistencies and protect the drug stability profile of moisture sensitive drugs.

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Introduction

Inhalation therapy has become a commonly used method for drug delivery as it offers several advantages over conventional delivery methods, including precise dosing, speed of action and convenience. Pressurized metered dose inhalers (pMDIs) and dry-powdered inhalers (DPIs) are two common devices used for targeted delivery of an active drug ingredient into the lungs. Although these devices offer many advantages, challenges can arise when designing a device that will protect the drug efficacy and provide proper dosing. One such challenge is moisture. Drug suspensions in pMDIs and micronized powders and mixtures in DPIs can be sensitive to moisture ingress. Moisture management plays a major role in ensuring that the drug formulation remains stable and that the correct dosage is delivered. Moisture within the device can negatively impact the stability of certain drugs as well as create flow and dosing issues during dispensing.

Impact of relative humidity on pMDIs and DPIs

Since 1956, the pMDI has been used as a respiratory drug delivery system for the treatment of diseases, such as asthma and chronic obstructive pulmonary disease.[1] When actuated, the pMDI emits a drug aerosol driven by propellants, such as hydrofluoroalkanes (HFAs), through a nozzle at high velocity. Through inhalation, the active drug reaches the target area of the lungs.

Moisture ingress into the pMDI device is of great concern as it may decrease aerosol performance and negatively impact drug stability. Hydrofluoroalkane (HFA-134a and HFA-227) propellants are very sensitive to moisture.[2] Additionally ethanol, which is used as a co-solvent for pMDI formulations, causes the formulations to be more hydrophilic and can increase moisture uptake.[3]

In one study, moisture ingress into the canister was demonstrated when it was placed under accelerated stress conditions at 40°C and 75% relative humidity (RH). Increased moisture caused an increase in drug aggregation in the liquid HFA, resulting in a reduction in the homogeneity of the suspension. This created a lack of uniformity in the delivered dose.[2] In the presence of moisture, the solubility of suspended polar drug particles may increase or the solubility of hydrophobic compounds may decrease.[3]. Additionally, increased moisture will reduce the HFA's evaporation rate, leading to an apparent particle size increase of the

aerosol mist, which consists of unevaporated propellant droplets that coat the drug particles with a non-volatile suspending agent.[2,4].Not only is the aerosolization performance negatively impacted by moisture, moisture may also alter the physical and chemical stability of the formulation. An additional concern is corrosion of the aluminum canister over the shelf life of the product.[3]

As with a pMDI, moisture ingress can contribute to physical and chemical instability of a DPI formulation and aerosolization inconsistency from the device, creating dosage concerns. In the last decade, DPI usage has increased for the treatment of both local and systemic disorders. Drug formulations, including the powder's properties and the physical mechanisms used for aerosolization, device design and proper patient usage are all considerations for achieving proper dosage.[5] DPIs contain a blend of micronized drug particles and larger carrier particles. The purpose of the carrier is to promote dispersion of cohesive drug particles to facilitate proper dosing, to increase the flowability of the powder during filling from the reservoir into the dosing chamber and to function as a diluent for low dose applications.[4-6]

Unlike pMDIs which contain propellants, DPIs are breath-actuated. The drug/excipient mixtures must be dispersed so the active drug particles can deagglomerate from the carrier particles. When the device is activated through inhalation by the patient, shear and turbulence are created as the powder is fluidized, separating the carrier particles from the drug particles, which permits the drug particles to enter the oropharynx and airways. For drug substances to effectively deliver therapeutic functions, they must be deposited in the central or peripheral airways of the lungs, depending upon the site of action. The drug particles must deagglomerate to a size in the range of about 2 to 5 μm diameter; larger particles will primarily deposit in the upper airways or oropharyngeal region while much smaller particles may be exhaled.[5]

Dose reproducibility and particle size distribution are critical attributes for DPIs.[7] DPIs have been shown to demonstrate large variability in drug dosage with a drug dispersion range from 12% to 40% of the load dose, which may be due to inability to effectively deagglomerate particles.[5] The interaction strength between the drug and the excipient carrier or the propensity for particles to detach is dependent on the forces between the particles (van der Waals, electrostatic and capillary forces).[8] These forces can be influenced by the relative humidity within the device. At lower RH, the adhesion force is mainly comprised of van der Waals and electrostatic forces. As RH increases above 50%, capillary forces become prominent.[6] A thin layer of water will appear on the surface of the drug and carrier particles, creating a liquid bridge[8] as the RH increases and capillary forces are demonstrated. The pore diameter of the particle and surface tension influence the degree of the force.[1] A study evaluating a binary drug system composed of two powders showed no significant change in adhesion forces between 30-60% RH; however, a 30% increase in interaction force between particles took place when the humidity was increased to 60-75% RH. A comparative decrease was seen when the humidity was lowered.[7]

Chemical and physical instability is a great concern if the formulation contains hygroscopic drugs or excipients. Additional moisture within the device may cause solid bridges to form between particles as dissolution and subsequent solidification of particle surfaces result in fused particles and, therefore, larger particle size,[1] leading to particles that may not be of a respirable size.

Use of rotating impellers, turbulence impaction grids, cyclone and reverse cyclone flow paths and pressure drop devices may improve deagglomeration efficiencies in DPI devices.[5] However, the device design must protect against fluctuations in atmospheric humidity. Capillary forces can be lowered by reducing moisture within the device. However, there is a danger of increasing surface charge of the particles when RH becomes too low.

Over-desiccation of a DPI can lead to triboelectrification. This condition occurs when particles make frequent contact with each other or the walls of the DPI by impact, sliding or rolling.[9] This can occur during the aerosolization process though shaking, priming, metering and dispersion.[10] During these actions, particle electrification takes place. The resulting charged fine particles can adhere to grounded surfaces and attract or repel each other.[11] Electrostatic forces are considered significant for attraction and adhesion between the active drug particles, excipient particles and device surface.[7]

The physical and chemical characteristics of the powders, the contact surfaces (contact between particles as well as between particles and device surfaces) and environmental conditions, such as RH, all have an effect on electrostatic charging of the particles. Typically, the active drug particle will charge to a higher extent with greater variability than is seen with the excipient. The lower level of charging seen with the excipient may be due to its lower surface area as well as its affinity for moisture.[11] Triboelectrification will prevent the particles from being properly propelled from the device and result in an unacceptable dosing variance.

Where moisture reduction is required, a properly-sized traditional desiccant will lower the RH within the device. For complex moisture management where over-desiccation will lead to triboelectrification, an intelligent sorbent is required. The use of an intelligent sorbent within the device design can manage the RH within the device, facilitating drug stability and aiding in proper dosing by preventing particle agglomeration, triboelectrification and decreased aerosol performance. An intelligent sorbent will play the role of an environmental manager within the device, maintaining a desired equilibrium relative humidity (ERH). An intelligent sorbent will also react to RH changes within the device and adsorb or desorb moisture to maintain the desired water activity or moisture content of the drug.

Determining the correct sorbent formulation

Since product stability and proper dosage are directly related to moisture management within the device, forced degradation studies are often used to reveal if a sorbent is required. Determining the proper sorbent formulation can be time consuming using traditional calculations and sorbent ranging studies. Eliminating sorbent ranging studies, which are performed to determine the best sorbent formulation out of several that are tested, can expedite the start of registration stability testing and regulatory submission. Pseudo-empirical modeling has been successfully used to eliminate sorbent ranging studies. By using a predictive model of moisture permeation and adsorption, an optimized sorbent solution can be selected.

Pseudo-empirical modeling predicts the internal conditions of the drug product within the device based on a given set of external conditions and selected input criteria, such as weight of the drug as packaged, packaging or device dimensions and moisture ingress rates for materials. The modeling is based on the internal/external ERH gradient with time (including in-use time when required) and the adsorption profiles (isotherm) of the drug product and sorbent. The modeling assumes that at any given time the system (i.e., internal headspace, drug formulation and sorbent) is in a state of equilibrium.

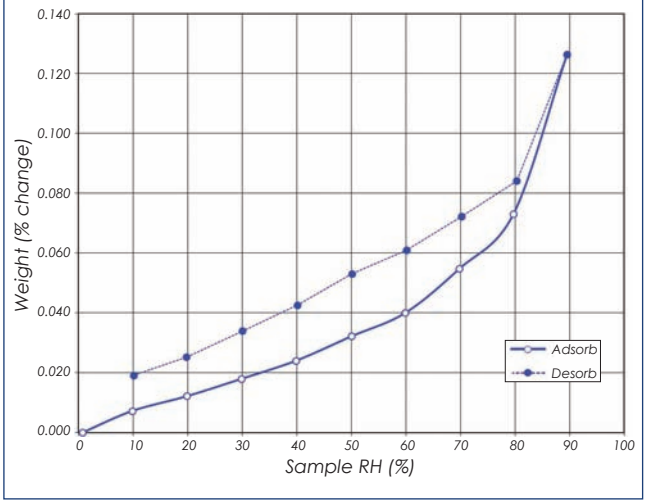
The difference between the external and internal RH environments of the device is the driving force for water vapor ingress. Water vapor will permeate the device or packaging until equilibrium is achieved between the external environment and the internal spaces in the device. The measure of the rate of passage of water vapor through the structure, called the water vapor transmission rate (WVTR), is evaluated at a given temperature and a fixed RH difference between the external and internal environments. The individual water vapor permeability rates of the materials used to make a device or packaging can be used to predict its overall WVTR. Water vapor ingress is controlled by the surface area of the package, the WVTR and the sorption isotherms of the components within the system, including the drug and desiccant. Moisture ingress into the device package is usually relatively slow, allowing for rapid equilibration and uniform ERH of all the components.

A given drug product has a water content often consisting of a combination of bound water and free water. Bound water is not available for reaction and cannot be released by adding a desiccant. Unbound water is more loosely held and is available for chemical activity; this water makes up the drug's water activity (a_w).

The a_w of a given drug product can be determined by equilibrating the liquid water phase in the sample with the vapor phase in the headspace and measuring the RH of the headspace. Sorption isotherms, which plot a substance's affinity for moisture at varying RH and a given temperature, can be used to correlate a_w and water content within the drug product. The drug formulation and the sorbent each has its own sorption isotherm. Figure 1 shows adsorption/desorption isotherms of an inhalation drug product with a lactose carrier. Figure 2 shows an adsorption isotherm of the same drug formulation in comparison to that for silica gel to highlight the large capacity that silica gel has

Figure 1

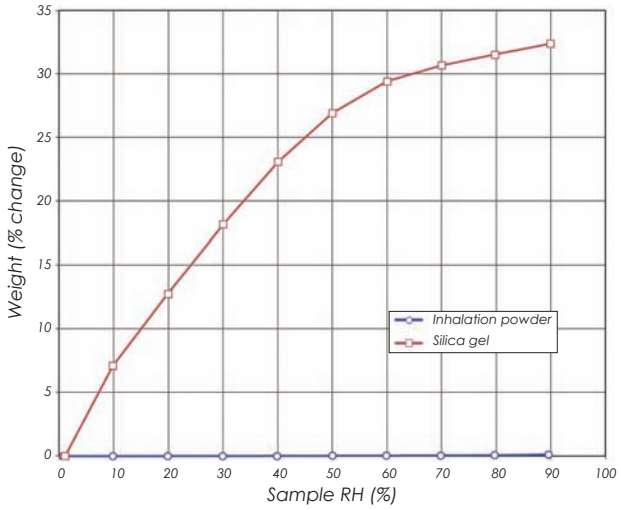
Adsorption/desorption isotherm, inhalation powder, lactose carrier



for moisture at increasing RH. In Figure 2, the drug formulation appears almost as a straight line because silica gel has a much higher capacity for water vapor adsorption as the RH increases. Using these isotherms, the internal conditions of the device can be modeled over time at a given, constant, external temperature and RH conditions.

Figure 2

Adsorption isotherms, inhalation powder, lactose carrier versus silica gel



When a desiccant or intelligent sorbent is used in the device or packaging, it will first adsorb the moisture within the headspace and then adsorb moisture from the drug product. Ingressed water vapor will be adsorbed by the desiccant and the drug product according to their respective isotherms. An aggressive desiccant, because of its strong affinity for water, can draw more free water from the drug than is desired, negatively impacting the desired a_w of the drug and potentially creating a triboelectrification effect that can lead to DPI dosing inconsistencies. Intelligent sorbent formulations will manage the internal environment to a specific ERH. Through use of pseudo-empirical modeling, the proper desiccant formulation and amount required for a given inhalation device to maintain its drug stability profile over a specified time can be accurately predicted.

Typical formal stability studies, which incorporate the sorbent as an element of the packaging materials, are performed according to the International Conference on Harmonization (ICH) and FDA guidance document, Q1A (R2) using real-time test conditions (two years, typically at 25°C and 60% RH).[12] Pseudoempirical modeling simulations can predict the RH of the packaging system under these conditions.

To facilitate flowability during the filling processes, the a_w may be somewhat higher than that required for long-term stability. The use of an intelligent sorbent can remove this final process moisture and maintain the RH at a specified level, providing long-term chemical and physical stability.

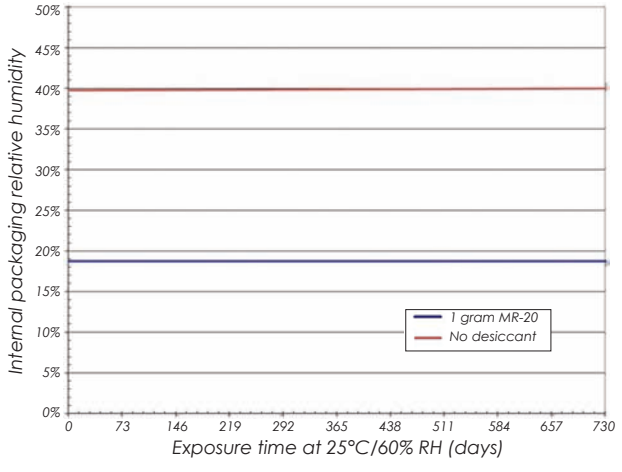
A simulation was performed comparing a packaged drug substance with and without a sorbent. Figure 3 compares the predicted 2-year RH of a packaging system containing 600 mg of drug substance in a dry powder inhaler packaged in a foil pouch with no desiccant to the same system containing a 1 gram of intelligent sorbent. The following assumptions are made:

- The external conditions are 25°C/60% RH.
- Since foil has a very low WVTR, ca 0.001 mg/day at 25°C and 75% RH,[13] it is assumed there is negligible moisture vapor ingress over time.
- The plastic components of the inhaler do not significantly contribute to the adsorption profile of the system.
- The 600 mg drug substance is at an ERH of 40% when packaged (or 0.4 a_w).
- The intelligent sorbent (1 gram Multisorb Technologies MR-20, Multisorb Technologies, Buffalo, NY, US) has an ERH of 20 ± 5%, preventing the drug's a_w from dropping below a level that may cause triboelectrification.

The RH of the internal packaging system without a desiccant remains at 40% RH (drug product at 0.4 a_w) for 2 years. When the intelligent sorbent is added, the RH of the internal packaging is lowered and maintained at approximately 19% for 2 years, protecting the drug's chemical and physical stability profile.

Figure 3

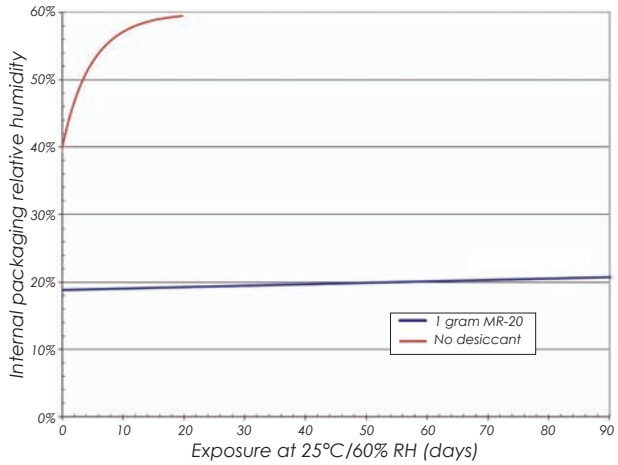
Predicted relative humidity of a packaging system, DPI foil pouch with and without desiccant



Desiccants and intelligent sorbents come in several formats, including packets that are placed into the primary packaging and those that are incorporated directly into the device itself, either as a compressed sorbent placed inside the device or the sorbent material is incorporated into thermoformed plastic components of the device. Building the sorbent into the device provides in-use protection. Figure 4, which shows the same packaging system as Figure 3, demonstrates moisture ingress once the DPI is removed from the primary packaging. The red line indicates no sorbent protection while the blue line indicates an on-board sorbent solution. Assuming a 0.2 mg/day ingress rate into the inhaler, in less than 20 days, the internal RH has jumped to nearly 60%. If the drug's in-use time is expected to be 30 days, this would fall significantly short. Further, storage in a humid environment, such as a bathroom, will increase the ingress and RH. The increased RH will lead to instability as well as dosing variability. In contrast, adding a 1 gram of intelligent sorbent (Multisorb Technologies' MR-20) into the device or device materials can maintain the RH within the device at the desired range of 20 ± 5% for more than 90 days during consumer use.

Figure 4

Predicted relative humidity of a packaging system, DPI in use with and without desiccant



Inhalation drug therapy has long been a popular method for local and systemic drug delivery. Maintaining the drug's physical and chemical stability, as well as protecting the drug dosage, are of highest importance. Managing RH within the device through use of an optimized desiccant or intelligent sorbent is a critical step in achieving this. Through use of predictive modeling, the proper sorbent formulation and sizing can be predicted with accuracy. The use of an optimized sorbent formulation and format will ensure the drug formulation's chemical and physical stability and will protect its flow and deagglomeration characteristics, resulting in the proper dosage being delivered to the patient.

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