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International Journal of Pharmaceutics 275 (2004) 155–164

international journal of pharmaceutics

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Moisture transfer into medicament chambers equipped with a double-barrier-desiccant system

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Received 15 October 2003; received in revised form 1 December 2003; accepted 23 January 2004

Abstract

The present study illustrates and evaluates the capability of the double-barrier-desiccant system to regulate the humidity inside a medicament powder chamber. The model medicament chamber chosen was the reservoir-based dry powder inhaler Taifun®. The study was focussed to screen the critical parameters affecting the function of the desiccant system. For this purpose a novel simulation method was developed and applied to predict the progress of the internal relative humidity of the powder chamber. The simulation method showed good correlation with the measurement results and, hence, it was concluded that it was valid for the system. According to the simulations, effective regulation of the humidity inside a closed powder chamber with the double-barrier-desiccant system is possible for a prolonged time. However, this can be achieved only if the critical parameters, such as the permeabilities of the desiccant container and the powder chamber, the amount of the desiccant and the initial moisture content of the desiccant, can be accurately specified and strictly controlled in the production of the components comprising the medicament chamber.

Keywords: Dry powder inhalers; Modeling; Moisture permeation; Packaging; Relative humidity; Stability

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1. Introduction

The negative effects of moisture on the chemical and physical stability of pharmaceutical drug products are widely recognized. For the materials or products known or suspected to be moisture sensitive, efforts to protect the product from the adverse effects of moisture are made by modifying the product so

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Abbreviations: ABS, polyacrylonitrile–butadiene–styrene; C_L, Langmuir constant; Δt, time interval between the steps of the iterative simulation cycles; m_{ingr}, weight of the moisture adsorbed on the desiccant during the measurement; m_{init}, initial moisture content (mg) of the desiccant; m_{desc}, dry weight of the desiccant (mg) loaded in the desiccant container; m_{max}, the maximum amount of moisture (mg) in the head space of powder chamber, i.e. the product of the water content at the dew point (23.0 g/m^3 at 25 °C and 51.1 g/m^3 at 40 °C) and the head space volume (2.42 ml); PC, polycarbonate; PP, polypropylene; PTFE, polytetrafluoroethylene (Teflon); $\mathrm{RH}_{\mathrm{ch}}$, relative humidity (% RH) inside the powder chamber; $\mathrm{RH}_{\mathrm{con}}$, relative humidity (% RH) inside the desiccant container; $\mathrm{RH}_{\mathrm{env}}$, relative humidity (% RH) of the environment, i.e. ambient humidity; $\mathrm{RH}_{\mathrm{init}}$, relative humidity (% RH) inside the powder chamber when the chamber is closed; RH_x, ambient humidity (% RH) in equilibrium with the desiccant; W_m, Langmuir constant, the weight of the adsorbed molecules forming a monomolecular layer per the weight of the dry desiccant

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doi:10.1016/j.ijpharm.2004.01.026

as to be more resistive against moisture, by treating the surface of the material with a hydrophobic excipient (Keller and Müller, 2000) or by incorporating the moisture-sensitive material into a protective matrix via freeze- or spray-drying (Yu, 2001; Hinrichs et al., 2001). However, perhaps the most common and simplest way to protect the product from moisture is to utilize protective packaging material and include a desiccant inside the package, if necessary. The function of the desiccant is to preferentially sorb the moisture permeating through the package wall material, and to maintain such a low humidity level inside the package that moisture is unable to interact adversely with the moisture-sensitive product. It should be kept in mind that all plastic materials are permeable to moisture, even polytetrafluoroethylene (PTFE; Teflon).

A widely used approach to control the internal humidity of closed packages is to use water-insoluble absorbents that have a large capacity to sorb moisture. An alternative is to use chemical absorbents that irreversibly sorb water molecules in their structures. Another possibility is to apply desiccants that adsorb moisture at their surfaces or in pores more or less reversibly. Widely used examples of this category are molecular sieves and silica gel. Silica gel is a very popular desiccant due to its high moisture capacity and its non-toxic nature, and because it is inexpensive.

On the other hand, it is possible to use water-soluble solutes and their ability to form a saturated salt solution that tends to generate a constant water pressure above the solution. The practical utilization of this kind of desiccant requires the physical separation of the solution from the medicament product, and hence is not convenient.

Regarding water-insoluble adsorbent-type desiccants, the sorption–desorption moisture transfer (SDMT) model has been developed and successfully used to predict moisture transfer between a solid product and a desiccant inside a closed package (Zografi et al., 1988). The SDMT model takes into account the initial masses, moisture contents and moisture sorption profiles of the product and the desiccant to predict the redistribution of moisture inside the sealed package, as well as the final internal relative humidity. The model ignores the transmission of moisture through the package walls. Theoretical simulations extended the use of the SDMT model to take into account the moisture permeation properties of the package (Kontny et al., 1992). The simulated results were successfully correlated with the chemical stability results of a moisture-sensitive drug (Badawy et al., 2001). The applied simulations are valid with certain precautions for the so-called single-barrier-desiccant system where the equilibrium of moisture with the solid components inside the package is achieved rapidly relative to the permeation into the package. The single-barrier-desiccant system is defined as a system in which the desiccant is packed in a very permeable or porous container, which does not constitute any barrier against moisture transfer, and where the desiccant material is in equilibrium with the humidity of the head space of the package. The only barrier against the moisture transfer is the walls of the package itself.

The above-mentioned desiccant set-up has certain disadvantages, one being the fact that the internal humidity of the package will initially be low if dry desiccant is loaded in the package. In addition, the humidity can reach the environmental level quite rapidly if the desiccant capacity is exhausted. With reservoir-based dry powder inhalers (DPIs), where the dosing mechanism consists of moving parts, the electrostatic forces can readily reach a level, especially under dry conditions (Busnaina and Elsawy, 2000), that can adversely affect the function of the DPI. It is also recognized that low relative humidity enhances the generation of electric charging due to the triboelectrification of flowing powders (Eilbeck et al., 2000; Greason, 2000; Woodhead and Armour-Chélu, 2003). Beside this, especially with DPIs, variations in humidity are undesirable since the capillary forces between the particles comprising the dry powder formulation are known to increase with rising humidity (Podczeck et al., 1997; Kappl and Butt, 2002; Bérard et al., 2002; Price et al., 2002) resulting in variation of aerosolization efficiency, delivery efficacy and the performance of the inhalation device (Jashnani and Byron, 1996; Young et al., 2002). The most dramatic and noticeable manifestation of the increased capillary forces is the formation of liquid bridges between the particles due to the hygroscopic components of the formulation. Moreover, adhesion forces between the particles and the substrate (e.g. the primary polymeric components of DPIs) are humidity dependent, thus affecting the performance of the inhaler (Busnaina and Elsawy, 2000; Sedin and Rowlen, 2000).

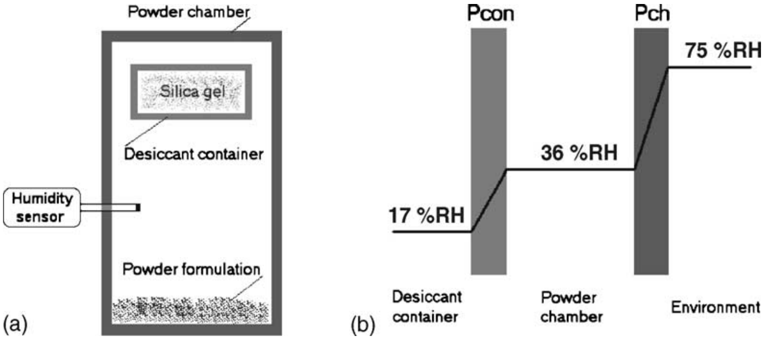

Fig. 1. (a) Schematic drawing of the medicament chamber of the double-barrier-desiccant system consisting of the powder chamber and the desiccant container. Also the humidity sensor to measure the internal humidity RH_{ch} is represented. (b) Generation of RH_{ch} according to Eq. (1) when $RH_{con} = 17\%$ RH, $RH_{env} = 75\%$ RH, $P_{con} = 40$ ng/(min %RH) and $P_{ch} = 20$ ng/(min %RH).

On the basis of the above-mentioned studies, it can be concluded that to avoid the risk of the variable performance of DPIs it would be beneficial to reduce the adverse changes in interparticulate and particle/substrate adhesions by regulating the humidity level within a narrow range of variation, e.g. 30–60% RH inside the medicament chamber. Within this range, the electrostatic forces can be expected to be minimized by relatively high humidities, and the capillary forces can be expected to be minimized by relatively low humidities. Of course, the limits of the internal humidity range are characteristic for the specific formulation depending on the physico-chemical properties of the ingredients of the formulation, as well for the polymer materials the components are made of. A solution to regulate the internal humidity could be the use of the so-called double-barrier-system (Lankinen, 2000), where the water molecules have to penetrate through both the medicament (powder) chamber wall and the desiccant container wall before they will be scavenged by the desiccant (Fig. 1). The relative values of the permeabilities for the chamber and the container are crucial, as are their absolute values, and the amount of the desiccant. The aim of the present study is to elucidate the function and performance of the double-barrier-desiccant system, develop a simulation method to predict the progress of humidity within the medicament chamber as a function of time under variable environmental conditions, and compare the measurement and simulation results to validate the method.

2. Materials and methods

2.1. Theory

The schematic drawing of the double-barrier-desiccant system is presented in Fig. 1a. With the desiccant set-up, the factors affecting the internal humidity of the powder chamber (RH_{ch}) are mainly the same as with the normal single-barrier-desiccant system. The factors determining the progress of RH_{ch} are the dry mass (m_{desc}), the initial moisture content (m_{init}) and the moisture uptake profile (adsorption isotherm) of the adsorbent in addition to the total effective permeabilities of the powder chamber (P_{ch}) and the desiccant container (P_{con}). To calculate the evolution of RH_{ch} as a function of time, the head space volume and the relative humidity when the chamber is closed (RH_{init}) are also needed. When the head space volume is multiplied with the water amount at the dew point at a particular temperature, the maximal water content (m_{max}) that the head space volume is capable of holding is obtained. In the present study, no powder formulation has been included in the container. Nor is the water solubility of the polymeric chamber and container materials taken into account but, regarding the simulations, they are estimated with separate measurements.

When the powder chamber containing the desiccant container is closed and moved into another humid condition, the RH_{ch} value generated within the chamber after the parts have reached equilibrium with the new condition can be estimated with a simple rate balance equation

$$P_{\mathrm{con}}(\mathrm{RH}_{\mathrm{ch}} - \mathrm{RH}_{\mathrm{con}}) = P_{\mathrm{ch}}(\mathrm{RH}_{\mathrm{env}} - \mathrm{RH}_{\mathrm{ch}}) \qquad (1)$$

where $\mathrm{RH}_{\mathrm{env}}$ and $\mathrm{RH}_{\mathrm{con}}$ are the relative humidities of the environment and the desiccant container generated by the desiccant, respectively. The other parameters are as stated above. The equation is based on the fact that the total effective transmission rates of moisture through the container and chamber walls must be equal in the equilibrium. If the situation depicted in Fig. 1b, where $P_{\mathrm{ch}} = 20\,\mathrm{ng/(min\,\%RH)}$ and $P_{\mathrm{con}} = 40\,\mathrm{ng/(min\,\%RH)}$ is considered, the generated humidity $\mathrm{RH}_{\mathrm{ch}}$ at the beginning of the measurement would be 36% RH.

Under humid conditions more moisture will penetrate through both of the walls and $\mathrm{RH}_{\mathrm{con}}$ will also increase in accordance with the adsorption isotherm. The process will proceed gradually, slowing down as the humidity gradients diminish until the desiccant is in equilibrium with the environmental humidity and $\mathrm{RH}_{\mathrm{con}} = \mathrm{RH}_{\mathrm{ch}} = \mathrm{RH}_{\mathrm{env}}$. This process can be simulated with iterative calculation cycles at certain intervals Δt by calculating the following steps for the cycles:

A_i: The total moisture content (mg) inside the powder chamber calculated at the previous time point excluding the initial water content when the chamber was closed ($\mathrm{RH}_{\mathrm{init}}$).

B_i: The amount of water that permeates from the environment into the chamber during Δt.

C_i: The humidity (% RH) inside the chamber calculated from A_i, B_i and $\mathrm{RH}_{\mathrm{init}}$ (i.e. $\mathrm{RH}_{\mathrm{ch}}$).

D_i: The amount of water that permeates from the chamber into the container during Δt as calculated from C_i and F_{i-1}.

E_i: The total amount of water that has permeated into the container calculated from D_i and E_{i-1} (i.e. the amount of water adsorbed by the adsorbent, m_{ingr}).

F_i: The humidity (% RH) inside the container as calculated according to E_i, the Langmuir constants W_m and C_L, the dry mass of the desiccant (m_{desc}) and its initial moisture content m_{init} (i.e. $\mathrm{RH}_{\mathrm{con}}$).

The capital letters above can be regarded as the columns of Exel® and the equations for each column are presented in Appendix A. The moisture uptake profiles for the used desiccant are described in the present work with the Langmuir equation

$$\Delta m\ (\%) = \frac{W_m C_L \mathrm{RH}_x}{1 + C_L \mathrm{RH}_x} \qquad (2)$$

where RH_x is the relative humidity in the unit of % RH.

2.2. Materials

White granular silica gel (Grace Davison, Columbia, USA) was used as the desiccant material. The Langmuir constants (Eq. (2)) were determined gravimetrically at 25 and 40 °C, and were as follows: $W_m = 84.03/C_L = 0.00827$ and $W_m = 82.66/C_L = 0.00670$, respectively.

The model medicament chamber was the Taifun® (Focus Inhalation, Finland) dry powder inhaler that is described in detail elsewhere (Lankinen, 1994, 2000). The chamber utilized in the present work comprised of the body and the lid (the powder chamber), the dose pin and the desiccant container. The dose pin was equipped with a dose slot for the volumetric metering of the dose. For the proper transfer of the metered dose out of the chamber, the holes at both ends of the chamber were equipped with compliant seals. The head space volume of the chamber was 2.42 ml, and thus m_{max} equals 0.0557 and 0.1237 mg at 25 and 40 °C, respectively. The wall materials of the chamber were polypropylene (PP) and of the container polycarbonate (PC). In the measurements at 25 °C a mechanical holder made of polyacrylonitrile–butadiene–styrene (ABS) was also used. The holder showed no effect on the permeation of the water into the chamber.

In the measurements of the internal humidity $\mathrm{RH}_{\mathrm{ch}}$ the silica loaded in the container ($m_{\mathrm{desc}} = 670\,\mathrm{mg}$) was premoisturized with 9 mass% of water ($m_{\mathrm{init}} = 60.3\,\mathrm{mg}$). The use of totally dry silica was avoided in the inhaler since it was found to enhance adverse electrostatic effects that dramatically affected the performance of the inhaler in everyday use.

2.3. Measurements of internal humidity

Monitoring the progress of the internal humidity $\mathrm{RH}_{\mathrm{ch}}$ of the powder chamber was performed with humidity sensors soldered into the walls of the containers by their wires (Fig. 1a). The humidity sensors utilized at 25 °C were Humicap® (Vaisala Oyj, Finland), and the readings of the sensors were done at certain intervals with HM34 (Vaisala Oyj). Before the actual measurements, the sensors were calibrated. The calibrations were performed by determining the readings of the sensors at six different humid conditions generated with six distinct salt solutions. The actual values of humidities were then obtained by applying the linear calibration curve. At 40 °C, the utilized RH sensors were SHT75 (Sensirion AG, Switzerland), and the readings were done with EK-H2 (Sensirion AG). As the sensors were calibrated beforehand by the manufacturer, no calibration was needed.

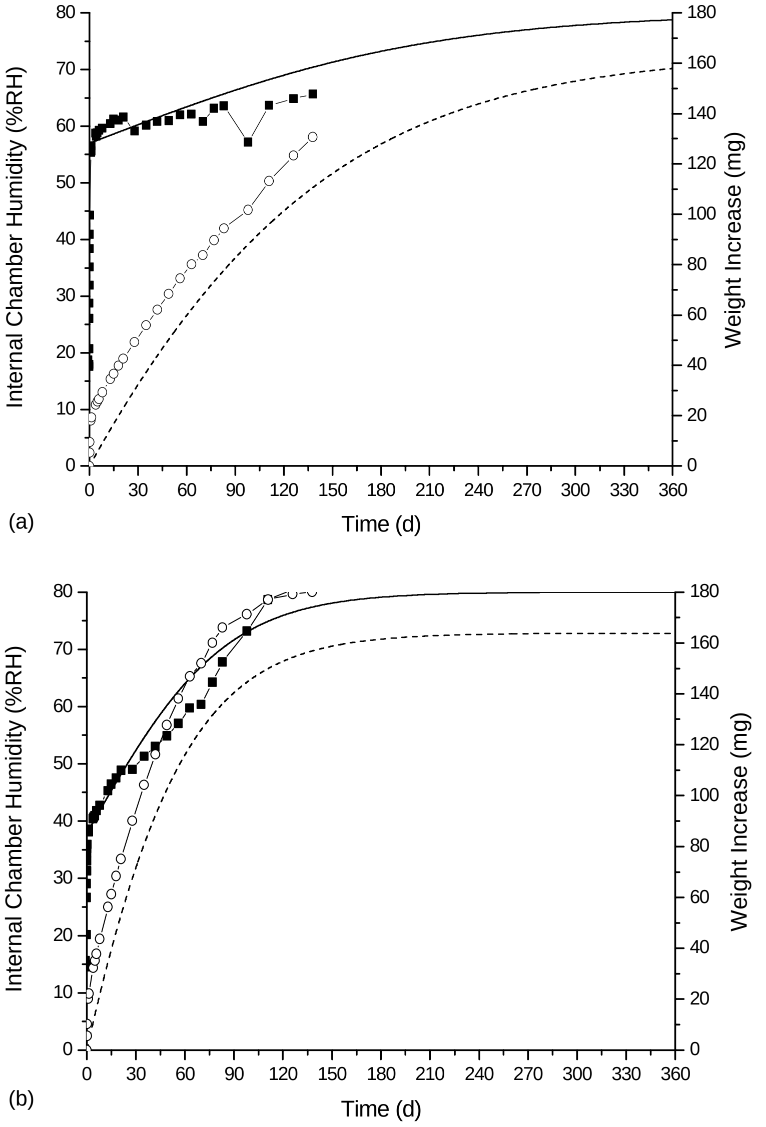

Fig. 2. Measured and simulated data for the internal humidity of the powder chamber (RH_{ch}) (solid symbols and solid line, respectively), the measured weight increases of the medicament chambers (open symbols) and the simulated amounts of water adsorbed by the desiccant (m_{ingr}) (dashed line) as a function of time under the condition of 25 °C/80% RH. Values for the permeabilities used in the simulations are: (a) $P_{ch} = 33$ ng/(min %RH) and $P_{con} = 19$ ng/(min %RH), and (b) $P_{ch} = 44$ ng/(min %RH) and $P_{con} = 86$ ng/(min %RH).

The test conditions of 25 °C/80% RH and 40 °C/75% RH were maintained by means of climate test cabinets. At certain intervals, the readings of the humidity sensors were monitored in the storage condition, i.e. the medicament chambers were not pulled out from the climate test cabinet since a change in temperature has a great influence on the measured RH values inside a closed package.

2.4. Determination of permeabilities

The permeabilities of the desiccant containers were determined gravimetrically by weighing the containers at certain time intervals while stored under three distinct humid conditions at 25 and 40 °C. The silica loaded in the container contained 9 mass% of water and generated RH values of 17 and 18% RH inside the container at 25 and 40 °C, respectively. The corresponding permeability values were 19 and 44 ng/(min %RH). When the containers were pierced to improve the permeability, the obtained value for P_{con} was 86 ng/(min %RH) at 25 °C.

In the case of the powder chambers, the values of the permeabilities clearly varied due to the inconsistent quality of the compliant seals around the dose pin holes, and the permeabilities could not be determined before the chambers were closed. Because of this, not only the internal humidities RH_{ch}, but also the weights of the medicament chambers were recorded. After the polymeric components had reached their equilibrium solubility under humid conditions, which was recognized as a rapid weight increase at the beginning of the measurement (Fig. 2), the observed weight increase was mainly due to the moisture adsorbed by the desiccant. The weight increase curve can be used to calculate the permeability of the chamber since the internal humidity RH_{ch} is measured and environmental humidity RH_{env} is constant. Thus, when the slope of the weight increase curve (mg/min) is divided by the humidity gradient, the value of P_{ch} is obtained.

3. Results and discussion

3.1. Humidity measurements

Figs. 2 and 3 present the results of the internal humidity RH_{ch} and the weight increase measurements at 25 °C/80% RH and 40 °C/75% RH, respectively. The measured weight increase curves represent the weight changes of the total medicament chamber employed in the study and consist of the moisture absorbed by the desiccant in the desiccant container and the water absorbed by all the polymeric components comprising the medicament chamber under study. The sharp stepwise increase of about 18.5 mg in the weights at the beginning of the measurement (Fig. 2) were due to the moisture absorbed by the polymeric components when the humidity was raised from the ambient condition (21 °C/20% RH) to the storage condition (25 °C/80% RH). This stepwise increase in the weight was caused mainly by the holder made of ABS, since the water absorption for ABS is at least 10 times that for PC. Regarding the powder chamber, it must be borne in mind that the higher the internal humidity the more water is absorbed into the PP polymer. However, this effect was minor due to the modest absorption of PP. Since no ABS holder was employed at 40 °C, the stepwise increase (about 1 mg) was much more minor.

At 25 °C, the permeability of the solid desiccant container P_{con} was found to be equal to 19 ng/(min %RH) with separate measurements as described in Section 2.4. For the chamber, it was found that $P_{ch} = 33$ ng/(min %RH) according to the slope of the mass increase curve (0.04475 mg/h) and the humidity gradient of 23% RH (80% RH versus 57.5% RH) over the wall (Fig. 2a). When applying Eq. (1) it was obtained, e.g. that $RH_{ch} = 57\%$ RH. Thus, the results showed good correlation. When the container was pierced to verify the influence of the improved permeability on the internal humidity, the obtained value for P_{con} was 86 ng/(min %RH). Now, the slope of the mass increase equaled 0.11065 mg/h and the humidity gradient 41.5% RH, and thus $P_{ch} =$ 44 ng/(min %RH) (Fig. 2b). Applying Eq. (1) yielded the value of 38% RH for RH_{ch}.

At 40 °C, two measurements were performed to test the significance of the moisture transmission resistivity of the powder chamber in the internal humidity (Fig. 3). With separate measurements, it was found that $P_{con} = 44$ ng/(min %RH). In the measurements with the more permeable powder chamber (Fig. 3a) it was found that the slope of the mass increase curve was 0.08099 mg/h and $RH_{ch} = 49\%$ RH, and thus $P_{ch} = 52$ ng/(min %RH). The corresponding values for the less permeable powder chamber (Fig. 3b) were

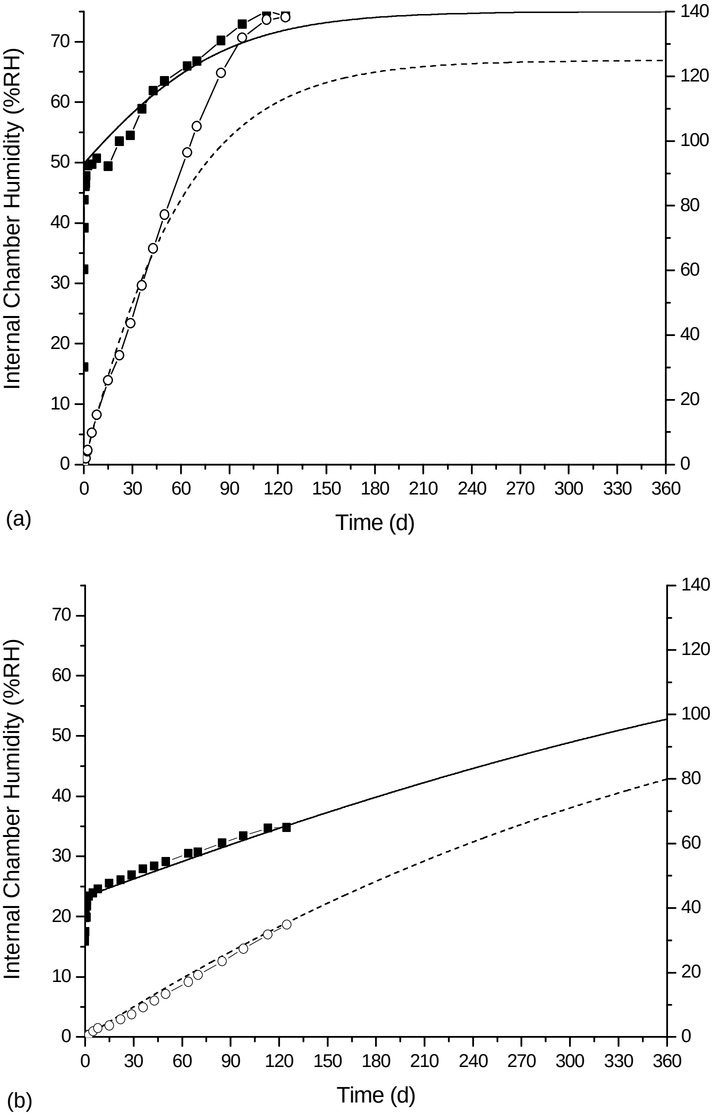

Fig. 3. Measured and simulated results of the internal humidity of the powder chamber (RH_{ch}) (solid symbols and solid line, respectively), the measured weight increases of the medicament chambers (open symbols) and the simulated amounts of water adsorbed by the desiccant (m_{ingr}) (dashed line) as a function of time under the condition of 40 °C/75% RH. Values for the permeabilities used in the simulations are(2004) (a) $P_{ch} = 52$ ng/(min %RH) and $P_{con} = 44$ ng/(min %RH), and (b) $P_{ch} = 4.3$ ng/(min %RH) and $P_{con} = 44$ ng/(min %RH).

0.01331 mg/h and $RH_{ch} = 23\%$ RH, respectively, yielding the value of 4.3 ng/(min %RH) for P_{ch}. Also here, applying Eq. (1) gave good correspondences.

3.2. Humidity simulations

The principle of the simulation is to calculate the amounts of moisture that transfer through the walls of the chamber and the container, and the effects that these tiny amounts of moisture have on the relative humidities inside both the chamber and the container during a short time interval. The correlation of the adsorbed moisture and the generated humid condition for the desiccant must be known (adsorption isotherm) so that the RH_{con} can be calculated. During the calculation cycle it must also be considered that a part of the moisture permeated into the chamber will permeate into the container. The calculation cycle is iterated after a short interval to obtain the progress of the internal humidity as a function of time. Utilization of a short enough interval during the calculation cycles is critical for the successful simulation. It was demonstrated that applying time intervals shorter than or equal to one minute would yield simulated $\mathrm{RH_{ch}}$ curves that differ less than 1% RH from each other at maximum.

3.2.1. *Validation of simulations*

The simulated curves for $\mathrm{RH_{ch}}$ and the moisture uptake by the adsorbent are represented in Figs. 2 and 3, together with the measurement results. For the humidity values the consistency was good considering that the error limits for the RH sensors has usually been filed as ±2% RH. The discrepancy between the measured and simulated weight increase curve is explained by the solubility of the polymeric components, especially at 25 °C, when ABS holders were used with the chambers (Fig. 2). The deviation of the simulated curve from the measured data at 40 °C (Fig. 3) at high moisture uptake values was obviously due to poor correlation between the Langmuir parameters and the actual adsorption isotherm. In addition, the possibility that the permeability properties of the chambers changed due to swelling as moisture was absorbed by the polymers over a long period under humid conditions could not be excluded. Overall, the simulations succeeded satisfactorily to predict the progress of the internal humidity of the powder chamber, and hence validated the method for use in other applications.

3.2.2. *Effect of* P_{ch}

It is obvious that the permeability of the powder chamber plays an important role in the evolution of $\mathrm{RH_{ch}}$. However, it is very laborious and time-consuming to study the influence of the permeability P_{ch} on the internal humidity $\mathrm{RH_{ch}}$ with measurements, especially when other factors than P_{ch} are also crucial. Fig. 4 shows the simulation curves of $\mathrm{RH_{ch}}$ for varied values of P_{ch}. The environmental conditions were 25 °C/75% RH, and the amount of dry silica was 700 mg containing 9 mass% of water. The permeability of the desiccant container P_{con} equaled 20 ng/(min %RH). In the case of a dry powder formulation with a critical humidity value of 60% RH at 25 °C, after which the formulation suffers adverse changes affecting the shelf life or functionality of the powder, it could be seen from the simulations that when P_{ch} had the values of 50, 20, 10 and 5.0 ng/(min %RH), the corresponding threshold times were 13, 145, 295 and 568 days, respectively.

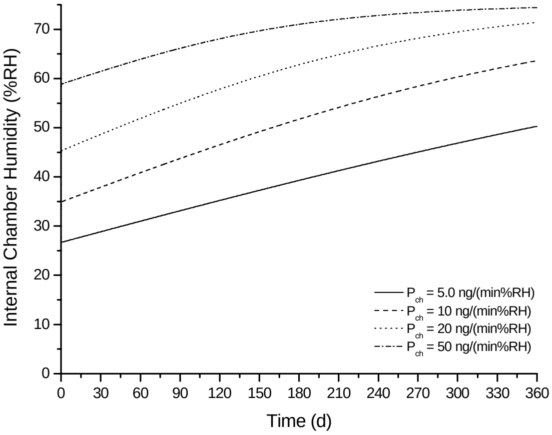

Fig. 4. The effect of the various powder chamber permeability values (P_{ch}) on the internal humidity values of the powder chamber ($\mathrm{RH_{ch}}$) at 25 °C/75% RH when $P_{\mathrm{con}} = 20$ ng/(min %RH).

3.2.3. *Effect of* P_{con}

Beside P_{ch}, the permeability of the desiccant container P_{con} is the other main parameter determining the initial internal humidity of the powder chamber $\mathrm{RH_{ch}}$. It also influences the evolution of the internal humidity as a function of time. Considering a situation identical to the previous example (Fig. 4), but where P_{con} was varied, the simulated curves of $\mathrm{RH_{ch}}$ are shown in Fig. 5. The permeability of the chamber P_{ch} had been chosen to equal 20 ng/(min %RH). The effect of P_{con} on the progress of $\mathrm{RH_{ch}}$ was more complicated than if P_{ch} had been varied. If the limit value for $\mathrm{RH_{ch}}$ was considered as 60% RH, the times needed to reach the threshold value were 98, 145, 145 and 137 days for the $\mathrm{RH_{con}}$ values of 10, 20, 40 and 100 ng/(min %RH), respectively. Thus, it was difficult to predict the effect of the various permeabilities of the container on the internal humidity without a proper simulation or measurements. This is understandable since P_{con} affects not only the rate of the moisture ingress into the desiccant container but also the humidity gradient between the powder chamber and the environment, and thus, in turn, the moisture ingress into the powder chamber.

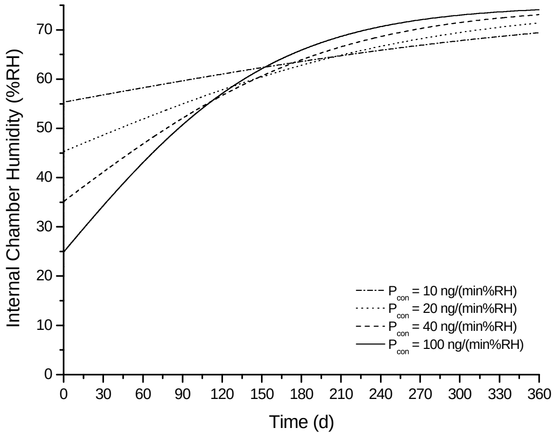

Fig. 5. The effect of the various desiccant container permeability values (P_{con}) on the internal humidity values of the powder chamber ($\mathrm{RH_{ch}}$) at 25 °C/75% RH when $P_{\mathrm{ch}} = 20$ ng/(min %RH).

3.2.4. *Effect of* m_{desc}

The more desiccant a chamber contains the longer time is needed to reach the environmental humidity inside the powder chamber. The role of m_{desc} is presented in Fig. 6, where $P_{\mathrm{ch}} = 20$ ng/(min %RH) and $P_{\mathrm{con}} = 40$ ng/(min %RH), the other parameters being the same as in the previous cases (Figs. 4 and 5). The times to reach the threshold humidity of 60% RH inside the chamber were 103, 207, 310 and 621 days for the desiccant dry weights of 500, 1000, 1500 and 3000 mg, respectively. As expected, the effect was rectilinear.

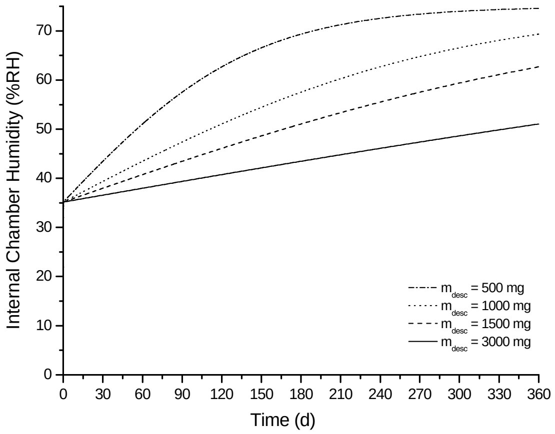

Fig. 6. The effect of the various amounts of dry desiccant (m_{desc}) on the internal humidity values of the powder chamber ($\mathrm{RH_{ch}}$) at 25 °C/75% RH when $P_{\mathrm{ch}} = 20$ ng/(min %RH) and $P_{\mathrm{con}} = 40$ ng/(min %RH).

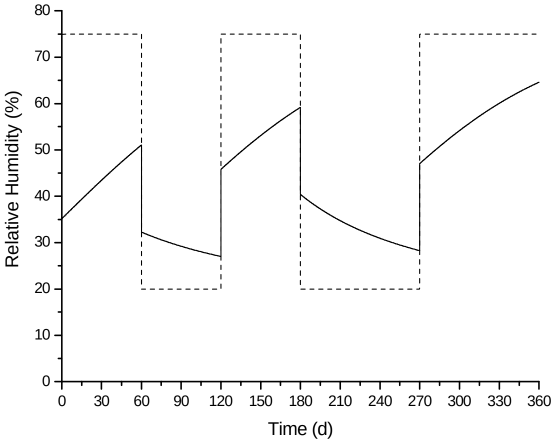

Fig. 7. The regulation effect of the double-barrier-desiccant system on the $\mathrm{RH_{ch}}$ (solid line) against the changes in $\mathrm{RH_{env}}$ (dashed line) between 20 and 75% RH at 25 °C when $P_{\mathrm{ch}} = 20$ ng/(min %RH), $P_{\mathrm{con}} = 40$ ng/(min %RH) and $m_{\mathrm{desc}} = 500$ mg.

3.2.5. *Variable environmental humidity*

As the desiccant used in the present study showed reversible sorption–desorption behavior, if hysteresis was ignored, and as the walls of the chamber and the container formed barriers against moisture transmission, one excellent feature of the set-up was its tendency to attenuate the ambient humidity variations. Fig. 7 shows the simulation curve in the situation where $P_{\mathrm{ch}} = 20$ ng/(min %RH), $P_{\mathrm{con}} = 40$ ng/(min %RH) and the environmental humidity has been changed between 20 and 75% RH (25 °C) at certain time points. Due to the double-barrier-desiccant system, $\mathrm{RH_{ch}}$ was regulated between 27 and 60% RH for the first 330 days. This effect was obtained with a dry desiccant of 500 mg, initially containing 9 mass% of water for the powder chamber of 2.42 ml. With increasing chamber volume more desiccant is also needed.

4. Conclusions

The present study showed the novel double-barrier-desiccant system to be a potential method to regulate the humidity inside a closed medicament chamber.

The simulation method for the system was developed, validated and applied to demonstrate the effects of various parameters on the progress of the internal humidity of the powder chamber. On the basis of the simulations, it is ease to estimate the appropriate values for, e.g. the permeabilities of the desiccant container and the powder chamber, plus the desiccant amount, so that the desired humidity can be controlled within a specified range for the defined time. In the present study, the role of the formulation itself on the evolution of the internal humidity was ignored as the normal lactose-based formulations show moderate moisture uptake behavior, but in future the method will be extended to cover also this factor.

Acknowledgements

The authors wish to thank Mr. M. Aarnio for the construction of the computer program for the simulation and Mrs. S. Rankonen for the readings of the RH and weight increase values.

Appendix A. Equations for the steps of the iterative calculation cycle (Exel® columns)

$$A_i = A_{i-1} + (B_{i-1} - D_{i-1})$$

$$B_i = P_{\mathrm{ch}}\Delta t\left(\mathrm{RH}_{\mathrm{env}} - \left(100\left(\frac{A_i}{m_{\max}}\right) + \mathrm{RH}_{\mathrm{init}}\right)\right)$$

$$C_i = 100\left(\frac{A_i + B_i}{m_{\max}}\right) + \mathrm{RH}_{\mathrm{init}}$$

$$D_i = P_{\mathrm{con}}\Delta t(C_i - F_{i-1})$$

$$E_i = E_{i-1} + D_i$$

$$F_i = \frac{(100m_{\mathrm{init}} + 100E_i)}{(m_{\mathrm{desc}}W_mC_L) - C_L(100m_{\mathrm{init}} + 100E_i)}$$

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