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# An Effective Desiccant System to Regulate the Humidity Inside the Chambers of the Solid Dosage Forms

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**The most common way to protect moisture-sensitive pharmaceutical powders is to utilize protective packaging. However, the most convenient package materials are all permeable to water molecules to some extent and limited protection is normally achieved with this arrangement even though desiccants are employed. In the present study we introduce a novel system that can regulate the internal humidity of the containers used with solid dosage forms for a desired time at a requested level. Instead of the widely used solid adsorbents the system utilizes saturated salt solutions loaded in desiccant bags made of various polymer materials with appropriate permeation properties. By utilizing salt solutions the size of the desiccant bag can be further reduced. A wide variety of commonly used powder chambers and desiccant bags are tested, proving the effectiveness of the introduced system.**

**Keywords** desiccant system; drug container; moisture permeability; moisture protection; packaging; polymer bottle

## INTRODUCTION

Moisture is recognized to be the most common single reason to cause adverse effects on the chemical and physical stability of pharmaceutical products. Even though the water molecules of the product would not affect the stability, they may cause variations in the processability of pharmaceutical powders and the performance of the powder formulation, e.g., in dry powder inhalers (DPIs). The most common and simple way to protect the moisture sensitive powders is to utilize protective packaging like bottles and blisters. However, nearly all materials used for packaging are permeable to the moisture to some extent (Allinson, Danserau, & Sakr, 2001). The environmental humidity conditions can vary a lot during the shelf life of drug products and the material utilized in the package also needs to protect the product from these variations. A frequently used solution to the problem is to insert the desiccant inside the package to sorb the permeated moisture. To predict the moisture transfer in such systems the sorption-desorption moisture transfer (SDMT) model has been developed (Zografi, Grandolfi, Kontny, & Mendenhall, 1988). Later, the model was extended to take into account the moisture permeation properties of the package (Kontny, Koppenol, & Graham, 1992). The prediction of moisture content of packed products is also possible with a mathematical model (Chen & Li, 2003). In these desiccant systems the only barrier against the moisture is the package itself, i.e., the desiccant material (if used) is packed in a very permeable container.

At the beginning of the storage, the humidity inside the chamber can also be very low if dry desiccant is used. For high humidity values, dry conditions can also have adverse effects on the performance of the product. For example, in the reservoir-based DPIs low humidity level is a clear disadvantage. The generation of electric charges in flowing powders is increased at low humidity values (Eilbeck, Rowley, Carter, & Fletcher, 2000; Woodhead & Armour-Chélu, 2000). Electrostatic forces also affect the functionality of moving parts of inhaler (Busnaina & Elsawy, 2000). When the humidity increases, due to the exhausted capacity of the desiccant, capillary forces between particles also increase (Podczeck, Newton, & James, 1997; Price, Young, Edge, & Staniforth, 2002) affecting the performance of the inhaler. So-called double barrier desiccant model was presented by Lankinen and in this solution the internal humidity was regulated between 30–60% RH (Lankinen, 2000; Lehto & Lankinen, 2004). In the present study, the double barrier desiccant model was utilized, but instead of silica granules saturated salt solutions were utilized inside the desiccant bag. The performance of the desiccant system is verified and tested with commonly used powder vessels made of various polymers and of various sizes.

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## MATERIALS AND METHODS

### Theory

Regarding the double barrier moisture control system the rate balance equation

$$P_{bag} \cdot (RH_{ch} - RH_{bag}) = P_{ch} \cdot (RH_{env} - RH_{ch}) \qquad (1)$$

can be used to describe the system at the steady state. In the equation $P_{\mathrm{bag}}$ and $P_{\mathrm{ch}}$ are the effective permeabilities of the salt solution bag and the drug chamber, and $RH_{\mathrm{ch}}$, $RH_{\mathrm{bag}}$, and $RH_{\mathrm{env}}$ are the relative humidities of the drug chamber, the salt solution bag, and the environment, respectively. If the relative humidity outside the system is higher than the humidity generated by the saturated salt solution inside the bag, moisture will penetrate first through the drug chamber wall and then through the salt solution bag wall to be sorbed by the salt solution. The relative humidity inside the chamber will reach the constant value that can be calculated according to Eq. (1). This value will remain constant as long as the salt solution inside the bag remains saturated. If the environmental humidity changes, the system will seek a new steady state based on the rate balance equation Eq. (1).

By choosing the salt solution appropriately, the relative humidity values inside the chamber can be controlled. Another effective way of controlling the humidity of the chamber is to change the permeabilities of chamber and bag walls. This can be done by material choice and/or by altering the thickness of the walls. The system will maintain its capability of controlling the humidity of the chamber as long as the salt solution inside the bag remains saturated. When the operation time of the bag is estimated the solubility of the salt is also needed. The amount of water that will be transmitted inside the bag, and in the solution, $m_{H2O}$, is

$$m_{H2O} = P_{bag} \cdot t \cdot (RH_{ch} - RH_{bag}) \qquad (2)$$

where, $t$ is the elapsed time. To keep the salt solution saturated, there need to be undissolved crystals left inside the bag, meaning that $m_{H2O}$ may not dissolve all the crystals left in the bag. If the relative humidity of the environment is lower than the humidity generated by the salt solution, the bag can regulate the humidity inside the chamber providing that there exist water in the bag, i.e., the salt is not totally dry. The benefit of utilizing salt solution instead of silica gel, molecular sieves or clays is that the $RH_{\mathrm{bag}}$ value is steady over the self life of the regulator (desiccant bag) and thus also $RH_{\mathrm{ch}}$ is constant or varies a bit due to the changes in the environmental humidity.

### Materials

High-density polyethene powder chambers were donated by Orion Pharma Oy (Finland). The other chambers used in the present work were purchased from Nalgene Labware (New York, U.S.A.). Four different chamber materials were evaluated, namely polycarbonate (PC), high- and low-density polyethenes (HDPE and LDPE), and polypropene (PP) (Figure 1). With HDPE chambers four different chamber sizes, 40, 75, 120, and 200 mL were evaluated. Salt solution bags were made of three different materials, polyvinylchloride (PVC), latex, and silicone rubber. PVC and latex bags were made of plastic bags of the named material by gluing the ends together after loading the salt solutions. The sizes of the bags were ca. 1×3 cm (Figure 1). The silicon bags were made of two component silicon rubber with a particular mould (cylindrical shape of ca. 1×5 cm, Figure 1) under vacuum. The ends of the silicon bags were glued with the same two-component silicon rubber after loading the salt solutions. Saturated salt solutions were made of $MgCl_2$ or NaCl (Bayer analytical grade) and distilled water. The amount of undissolved $MgCl_2$ crystals in the salt solution bag varied between 2.4–2.6 mg and for NaCl between 2.5–3.0 mg.

### Measurements of Internal Humidity and Permeabilities

The humidity inside the drug chambers was monitored with humidity sensors SHT75 (Sensirion AG, Switzerland) as was reported by Lehto and Lankinen (2004). The sensors were factory calibrated and their specified precisions were ±2% RH and repeatability ±0.1% RH. The sensors were fastened into the caps of the chambers by their wires with a two compound epoxy glue (Araldit). The humidity values were read once a week. Between the measurements the powder chambers were stored in glass desiccators in ambient temperature and in constant relative humidity. Two different humidity values were utilized in the disiccators, 33% RH and 75% RH depending on the application. Two types of bag systems were evaluated, one designed to maintain the humidity of the chamber at a lower and the other at a higher humidity level than the humidity in the desiccator.

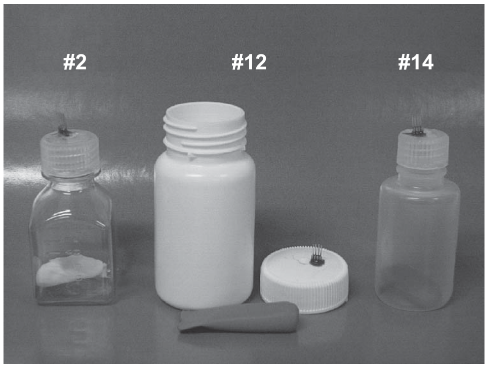

FIGURE 1. Three different drug chamber and desiccant bag combinations utilized in the study. The symbols of the combinations are the same as used in Table 1: #2 polycarbonate/latex, #12 HDPE/silicone, #14 polypropene/PVC. The humidity sensors has been glued into the caps of the chambers.

The effective permeabilities of the chamber and the bags were determined gravimetrically. The chambers were weighed at the same time-intervals at which the humidity values were recorded. The permeabilities of both the chamber and the bag can be calculated when the transmission rate of water vapour and the relative humidity values inside the chamber and the desiccator are known. The permeability, in the unit of $g_{H2O}$/(% RH s), is obtained when the slope of the weight increase is divided by the humidity gradient. Before the actual follow-up measurements the permeabilities were also defined individually for all the used bag and chamber materials gravimetrically.

## RESULTS AND DISCUSSION

The relative humidity inside the chamber along with its mass increase was followed for seven months. The measurements were made in duplicate and if not otherwise stated the results were identical. The combinations of the powder chamber and the salt solution bag utilized in the study are presented in Table 1 together with the predicted and the measured humidity values inside the powder chamber. Predicted values are calculated according to Eq. (1) and the pre-measured permeabilities of the chambers and the bags. The measured RH value is the value to which the internal humidity of the chamber stabilized. If the humidity inside the chamber did not reach any constant value, the value at the end of the measurement period is stated. When comparing the predicted and actually measured values, the individual differences in permeabilities of the chambers and bags need to be taken into account. However, the values correspond to each other quite well especially if the accuracy of the RH sensors is considered.

### Polycarbonate Chambers

For polycarbonate (PC) chambers the humidity values were also measured for empty chambers and the chambers with silica containers. Silica was enclosed in thin cotton bags, which did not form any barrier against moisture transfer. In such case the humidity inside the chamber does not settle down to any constant value, but rises until the internal humidity value is reached as was reported by Lehto and Lankinen (2004). In Figure 2 the mass increase and the humidity curves are presented for the empty chamber and the chamber containing silica. The amount of silica used was 2.3 g. When comparing the results with the results obtained using the salt solution bag (Figure 3), it is obvious that better resistivity against humidity is achieved when the desiccant bag contains salt solution. When the salt solution inside the bag is no longer saturated the humidity inside the chamber starts to rise. The solubility of $MgCl_2$ was determined as 230 g / 100 mL (22°C) for the salt used in the study. One must notice that the water needed to dissolve the salt crystals depends on the moisture pre-absorbed by the salt. Thus, $MgCl_2$ solution containing 2.5 mg salt would remain saturated until 0.9 mL (approx. 900 mg) water had permeated

TABLE 1
The Drug Chamber and Desiccant Bag Combinations Utilized in the Study and the Corresponding Permeability Values $P_{ch}$ and $P_{bag}$. The Last Two Columns Indicate the Predicted ($RH_{ch}$ Predicted) and Measured ($RH_{ch}$ Measured) Relative Humidity Values Inside the Drug Chambers

| # | Chamber Material | $P_{ch}$ (ng/(min% RH)) | Bag Material | $P_{bag}$ (ng/(min% RH)) | Salt in the Bag* | $RH_{ch}$ Predicted | $RH_{ch}$ Measured |
|---|---|---|---|---|---|---|---|
| 1 | Polycarbonate | 110 | PVC | 450 | $MgCl_2$ | 41% | 39% |
| 2 | Polycarbonate | 110 | Latex | 250 | $MgCl_2$ | 46% | 46% |
| 3 | Polycarbonate | 110 | Silicone | 1300 | $MgCl_2$ | 36% | 36% |
| 4 | Polycarbonate | 110 | Latex | 250 | NaCl | 62% | 65% |
| 5 | Polycarbonate | 110 | Silicone | 1300 | NaCl | 72% | 70% |
| 6 | LDPE | 10 | Latex | 250 | $MgCl_2$ | 34% | 34% |
| 7 | LDPE | 10 | Silicone | 1300 | $MgCl_2$ | 33% | 33% |
| 8 | LDPE | 10 | Latex | 250 | NaCl | 74% | 74% |
| 9 | LDPE | 10 | Silicone | 1300 | NaCl | 75% | 74% |
| 10 | HDPE (75 mL) | 5 | Silicone | 1300 | $MgCl_2$ | 33% | 32% |
| 11 | HDPE (40 mL) | 2 | Silicone | 1300 | $MgCl_2$ | 33% | 32% |
| 12 | HDPE (120 mL) | 3 | Silicone | 1300 | $MgCl_2$ | 33% | 32% |
| 13 | HDPE (200 mL) | 4.5 | Silicone | 1300 | $MgCl_2$ | 33% | 34% |
| 14 | Polypropene | 4.5 | PVC | 450 | MgCl2 | 33% | 38% |
| 15 | Polypropene | 4.5 | Latex | 250 | $MgCl_2$ | 34% | 37% |
| 16 | Polypropene | 4.5 | Silicone | 1300 | $MgCl_2$ | 33% | 33% |

*When $MgCl_2$ is used inside the salt solution bag NaCl is utilized in the desiccator. If NaCl solution is loaded in the bag then $MgCl_2$ is utilized to generate the environmental moisture condition in the desiccator.

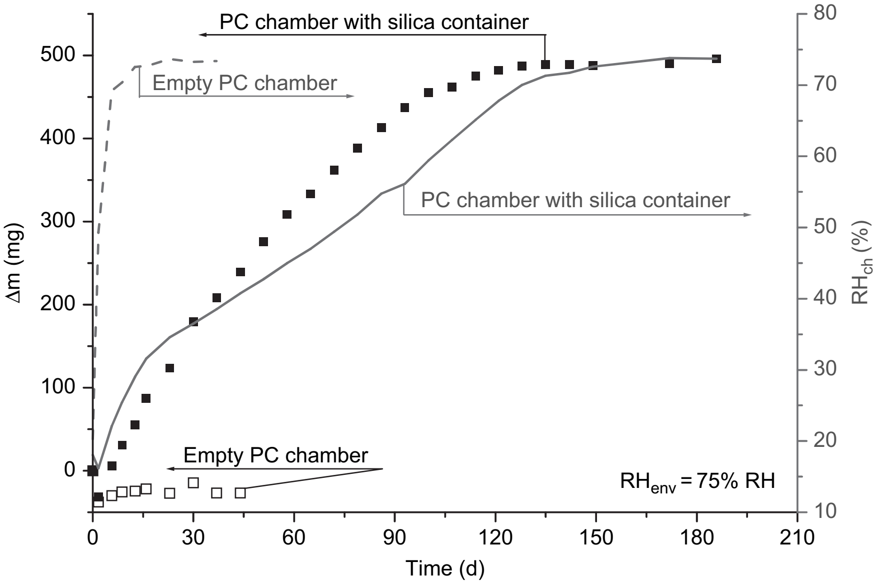

FIGURE 2. The mass increase (Δm) and the internal humidity of the drug chamber ($RH_{ch}$) as a function of storage time at 75% RH for the PC chambers as empty (open symbols for Δm and dashed line for $RH_{ch}$) or containing silica gel (solid symbols for Δm and solid line for $RH_{ch}$).

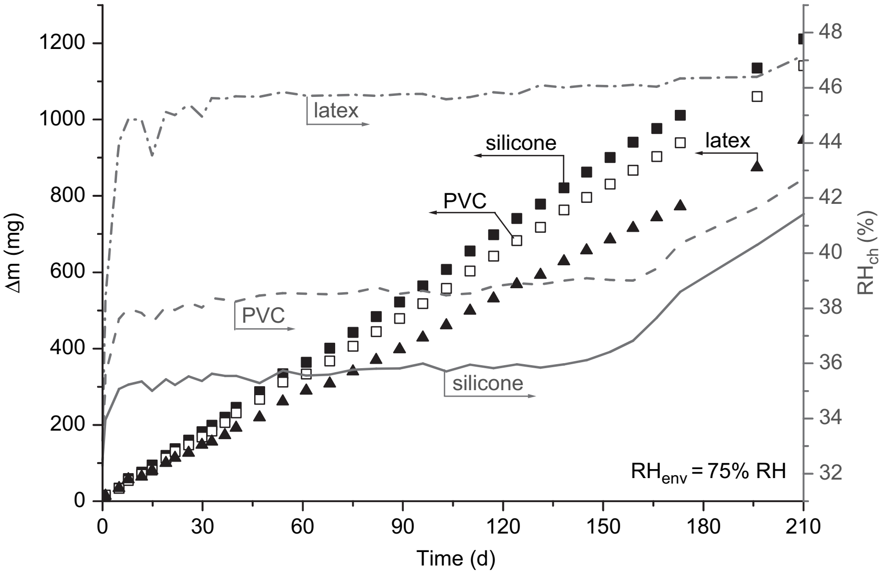

FIGURE 3. The mass increase (Δm) and the internal humidity ($RH_{ch}$) as a function of storage time at 75% RH for the PC chambers containing silicone (solid squares for Δm and solid line for $RH_{ch}$), PVC (open squares for Δm and dashed line for $RH_{ch}$) or latex (solid triangles for Δm and dotted line for $RH_{ch}$) bag loaded with $MgCl_2$ solution.

inside the bag. This point is reached after 150 days with the silicon bag and after 160 days with the PVC bag. As can be seen in Figure 3, the humidity values start to rise slowly after the calculated time point. The humidity values raise ca. 5% RH in two months, while the humidity inside the empty chamber reached the humidity of the environment in two weeks.

The barrier properties of the system were tested also in the reversed conditions. The goal was to maintain a high humidity value inside the chamber while the humidity outside the chamber being noticeably lower. The saturated NaCl solution was loaded inside the silicon and latex bags and the chambers were preserved in a desiccator of 33% RH. Now a mass decrease curve is obtained, since the direction of humidity gradient is changed. The humidity inside the chamber still reaches a constant value (Figure 4). The value will remain constant as long as there is water left inside the bag.

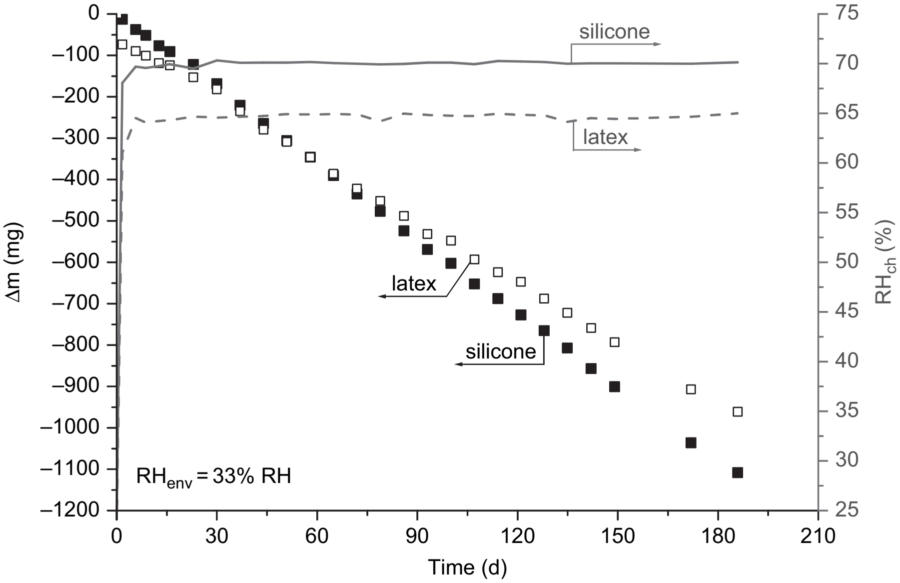

FIGURE 4. The mass increase (Δm) and the internal humidity (RH$_{ch}$) as a function of storage time at 33% RH for the PC chambers containing silicone (solid squares for Δm and solid line for RH$_{ch}$) or latex (open squares for Δm and dashed line for RH$_{ch}$) bag loaded with NaCl solution.

## Low- and High-Density Polyethene Chambers

The silicone and latex bags were placed inside the low-density polyethene (LDPE) chambers. Both salt solutions, $MgCl_2$ and NaCl, were used. Also with these four combinations, constant humidity values inside the chambers were achieved. Humidity inside the chambers settled very close to the predicted values calculated in Table 1 and remained constant for the requested time of six months. The monitoring of the humidity inside the chamber containing the latex bag filled with NaCl solution was interrupted by the broken humidity sensor. Results are presented in Figures 5 and 6.

The effect of different chamber sizes was tested with high-density polyethene (HDPE) chambers using 40, 75, 120, and 200 mL chambers. In principle the internal humidity of the larger chamber should reach higher humidity values if the specific permeabilities of the bag wall material are the same. This is because the effective permeability of the chamber is

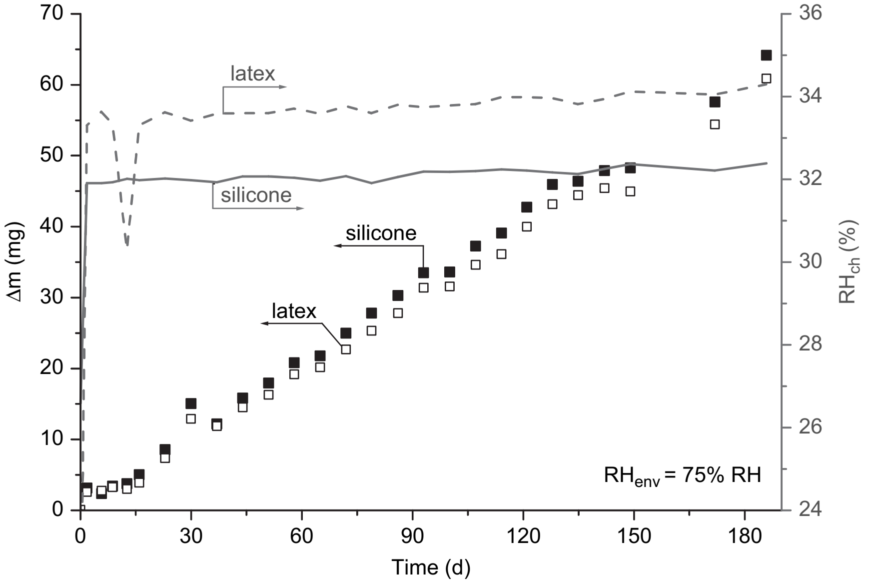

FIGURE 5. The mass increase (Δm) and the internal humidity (RH$_{ch}$) as a function of storage time at 75% RH for the LDPE chambers containing silicone (solid squares for Δm and solid line for RH$_{ch}$) or latex (open squares for Δm and dashed line for RH$_{ch}$) bag loaded with $MgCl_2$ solution.

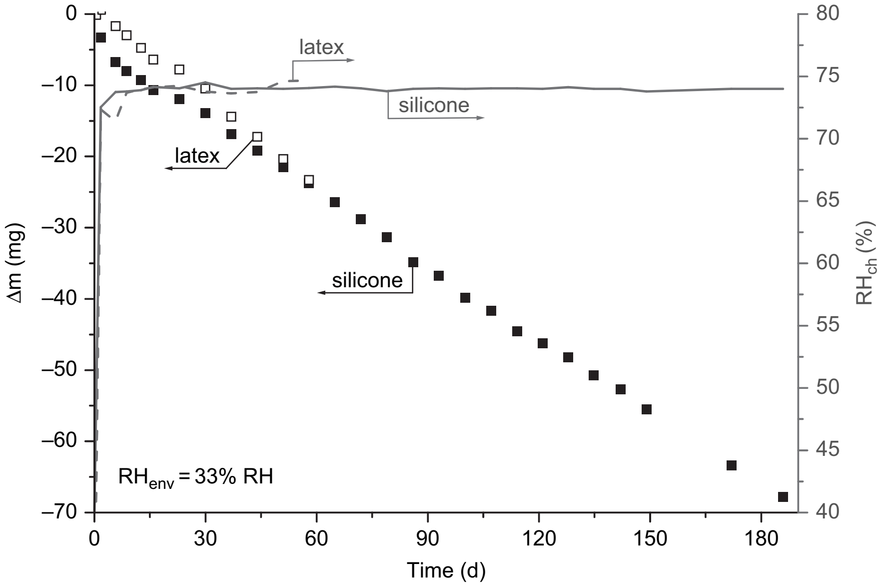

FIGURE 6. The mass increase (Δm) and the internal humidity ($RH_{ch}$) as a function of storage time at 33% RH for the LDPE chambers containing silicone (solid squares for Δm and solid line for $RH_{ch}$) or latex (open squares for Δm and dashed line for $RH_{ch}$) bag loaded with NaCl solution.

proportional to the surface area of the chamber. Also the humidity inside the smaller chamber should reach the constant value faster than the larger ones. Because the chambers were closed at the humidity near the balance value, differences in balancing times were not seen. The slope of the mass increase curve increased together with volume of chamber, as can be seen from Figure 7.

## Polypropene Chambers

The polypropene chambers were measured with the silicon, latex, and PVC bags in 75% RH (Figure 8). With the silicon bag the system behaved as predicted and the internal humidity reached the constant value of 33% RH. This value was also maintained for the 7 months of the measurement period. With latex and PVC bags the values did not reach any constant

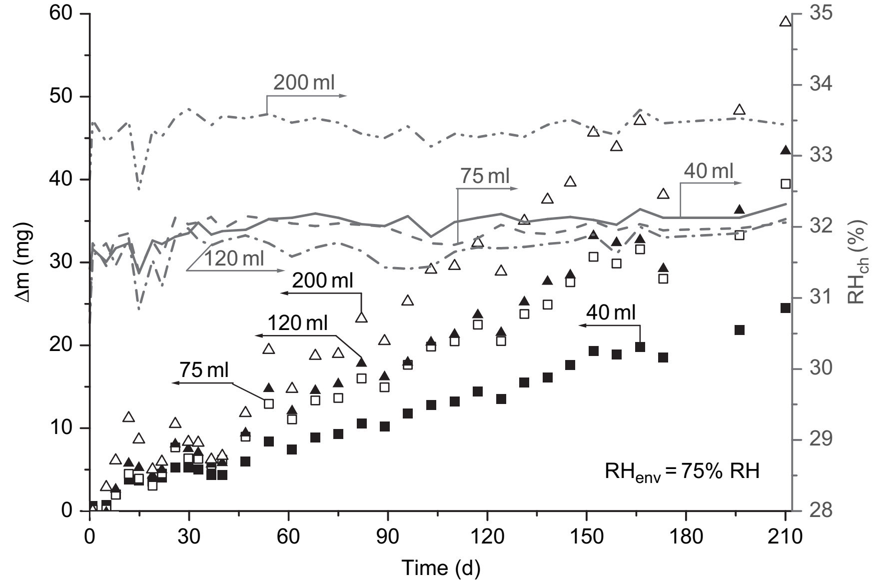

FIGURE 7. The mass increase (Δm) and the internal humidity ($RH_{ch}$) as a function of storage time at 75% RH for the HDPE chambers of different sizes containing the silicone bags loaded with $MgCl_2$ solution.

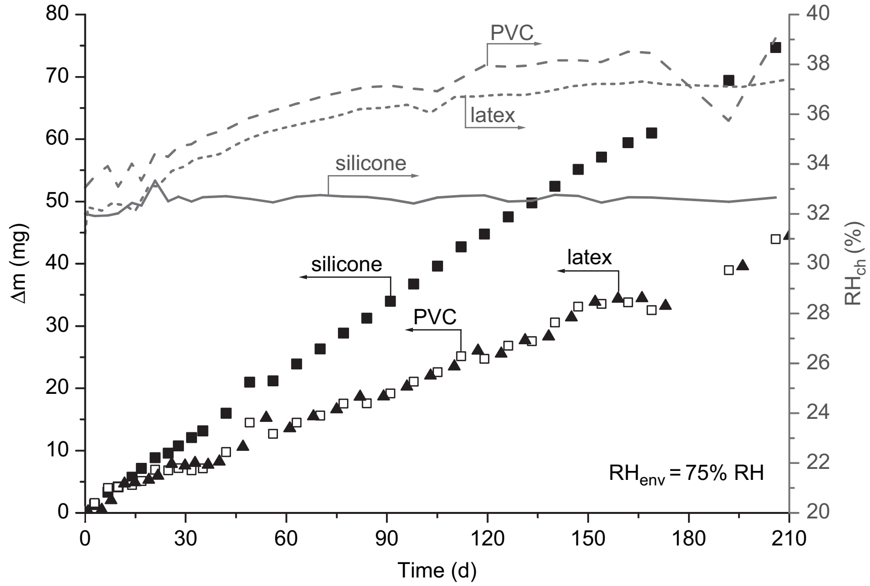

FIGURE 8. The mass increase (Δm) and the internal humidity ($RH_{ch}$) as a function of storage time at 75% RH for the PP chambers containing silicone (solid squares for Δm and solid line for $RH_{ch}$), PVC (open squares for Δm and dashed line for $RH_{ch}$) or latex (solid triangles for Δm and dotted line for $RH_{ch}$) bag loaded with $MgCl_2$ solution.

value, but kept rising slowly. However, the rising was not remarkable and can be explained with normal measurement errors. It is noticeable that even in these cases the predicted and measured $RH_{ch}$ values agreed quite well (Table 1).

## CONCLUSION

Utilization of the salt solution bags proved to be an efficient method for regulating the internal humidity of the drug chambers. The internal humidity was regulated between 33–74% RH by changing the salt solution and altering the permeabilities of the chambers and the bags. When taking into account the accuracy of the humidity sensors and the individual differences in the permeabilities of the chambers and the bags, the behavior of the system was well predicted. The humidity values also remained constant for prolonged times in the case where the chambers were very permeable to water. If the internal humidity value should be near the humidity generated by the salt solution, a bag with a large permeability coefficient should be chosen. When using a bag with a smaller permeability coefficient, the internal humidity will settle further from the value of the salt solution. In this case, the time for reaching the calculated humidity value will be longer. If the internal humidity changes, the balanced value also changes. To minimize this effect, the difference between the chamber and the bag permeabilities must be sufficiently large. When choosing the bag permeability to be ten times the permeability of the chamber, the balanced humidity value of the chamber will vary by a maximum of 10% RH while the humidity outside the chamber varies from 10 to 100% RH.

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