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Water-solid interactions: I. A technique for studying moisture sorption/desorption

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Abstract

Moisture sorption and desorption have been characterized for active (naproxen and paracetamol) and inactive pharmaceutical solids by using a climatic test chamber. The relative humidity (RH) of the climatic test chamber was varied in the range from 15 to 90%. Equilibrium moisture content was achieved within a period of 2 h for slightly hygroscopic and moderately hygroscopic substances. For very hygroscopic substances equilibrium was reached within 2 h at low RH ($< 60\%$), whereas more than 24 h were needed at high RH ($> 60\%$). Moisture sorption isotherms were characterized by using the climatic test chamber and were found to be identical with moisture sorption isotherms characterized by desiccators.

Keywords: Equilibrium moisture content; Climatic test chamber; Desiccator; Moisture sorption/desorption isotherm; Moisture sorption kinetics; Hygroscopicity

1. Introduction

Water associated with solids may greatly influence both chemical, physical and mechanical properties of active and inactive pharmaceutical substances. A profound knowledge about the amount of moisture associated with solids and its state of association is therefore of the utmost importance during the development of an optimal composition of solid dosage forms as well as during upscaling and trouble-shooting.

In order to optimize the moisture content and control its effects, it is important to have a fast and robust technique which is able to control the equlibrium moisture content, EMC, or water activity, A_w, and which could be used for conditioning of powder samples and for characterization of moisture sorption isotherms.

Moisture sorption/desorption isotherms describe interactions between moisture and solid substances. They relate the total water content of a material to the relative humidity in which the material is treated (Konty, 1988), and are one of the most commonly used terms for establishing the quantitative relationship between solids and moisture. Such an isotherm may be used as a part of quality control specifications (Handbook of Pharmaceutical Excipients, 1986a). Moreover, it

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might serve as a tool for investigating batch-to-batch variations.

Different techniques are available for the characterization of moisture sorption. The 'desiccator method' as described by several authors (Scott et al., 1963; Callahan et al., 1982) is still widely used due to its simplicity. However, it is time-consuming with equilibirum periods for achieving EMC of 1 week or more. Alternatives based on automated systems are described in the literature. Rasmussen and Akinc (1983) and Astill (1987) propose complex vacuum systems which evacuate the atmosphere surrounding the sample. Teng et al. (1991) and Bergren (1994) put forward controlled atmosphere microbalance systems which are constructed for dynamic analysis of moisture sorption. Commercial analytical techniques based on automated analysis of moisture sorption are also available, such as DVS 1 (Dynamic vapour sorption 1, SurfaceMeasurments Systems Ltd, Bucks, U.K.).

The aim of the present study was to develop a fast and robust technique, compared to the widely used desiccator method, by using a climatic test chamber for investigating the moisture sorption and desorption of pharmaceutical materials. A further aim was to investigate the time for achieving EMC or constant A_w for the samples.

2. Materials and methods

2.1. Materials

Moisture sorption/desorption was characterized for the following substances: monohydrous lactose (DMV), anhydrous lactose (Pharmatose DC21, DMV), microcrystalline cellulose (Emcocel, Mendell), sodium starch glycolate (Primojel, Avebe), maltodextrin (Lycatab DSH, Roquette), polyvinyl pyrrolidone (Plasdone K-25, GAF), potato starch (Lyckeby,Sweden), naproxen (Syntex), and paracetamol (Rhône-Poulenc).

2.2. Climatic test chamber

A climatic test chamber (Hereaus Vötsch HC 4055, Germany) in which the relative humidity (RH) can be varied within the range of 10–98%, and the temperature from 10 to 70°C, was used in the studies.

To determine whether a homogeneous distribution of the set relative humidity and temperature is obtained throughout the climatic test chamber during the test period, a qualification was performed by controlling the relative humidity and temperature at defined positions according to a set program. The set climate is evenly distributed all over the climatic test chamber within the specifications, i.e., precision, ±3% and accuracy, ±1% regarding humidity, and within ±1°C regarding temperature. A high rate of air convection (2 m/s) inside the test chamber ensures this even distribution of moisture and temperature controlled air throughout the test space. Signals from a humidity sensor placed in connection with the samples were recorded every other minute during the investigations of the moisture sorption/desorption to assess whether the humidity was within the specifications as defined above.

A balance was placed inside the climatic test chamber in such a way that the gravimetric analysis could be carried out within the controlled environment.

2.3. Validation of the gravimetric analysis

The accuracy of the gravimetric analysis, determined by measuring the weight variations of non-water absorbable substances (lactose monohydrate, naproxen and paracetamol) at 20, 40, 60 and 80% relative humidity, was found to be within ±0.2% of the total sample weight (400 mg).

The high air velocity in the climatic test chamber may, however, also involve the risk of losing particles of the solid materials from the open glass petri dishes. To ensure that no material is lost during the characterization of the moisture sorption, samples of microcrystalline cellulose, potato starch and sodium starch glycolate were studied for 24 h at a relative humidity corresponding to the water activity, A_w, under ambient conditions. The weight variations were found to be in the same order as the accuracy of the weighings (±0.2%), showing that no substance was lost due to the high rate of air circulation.

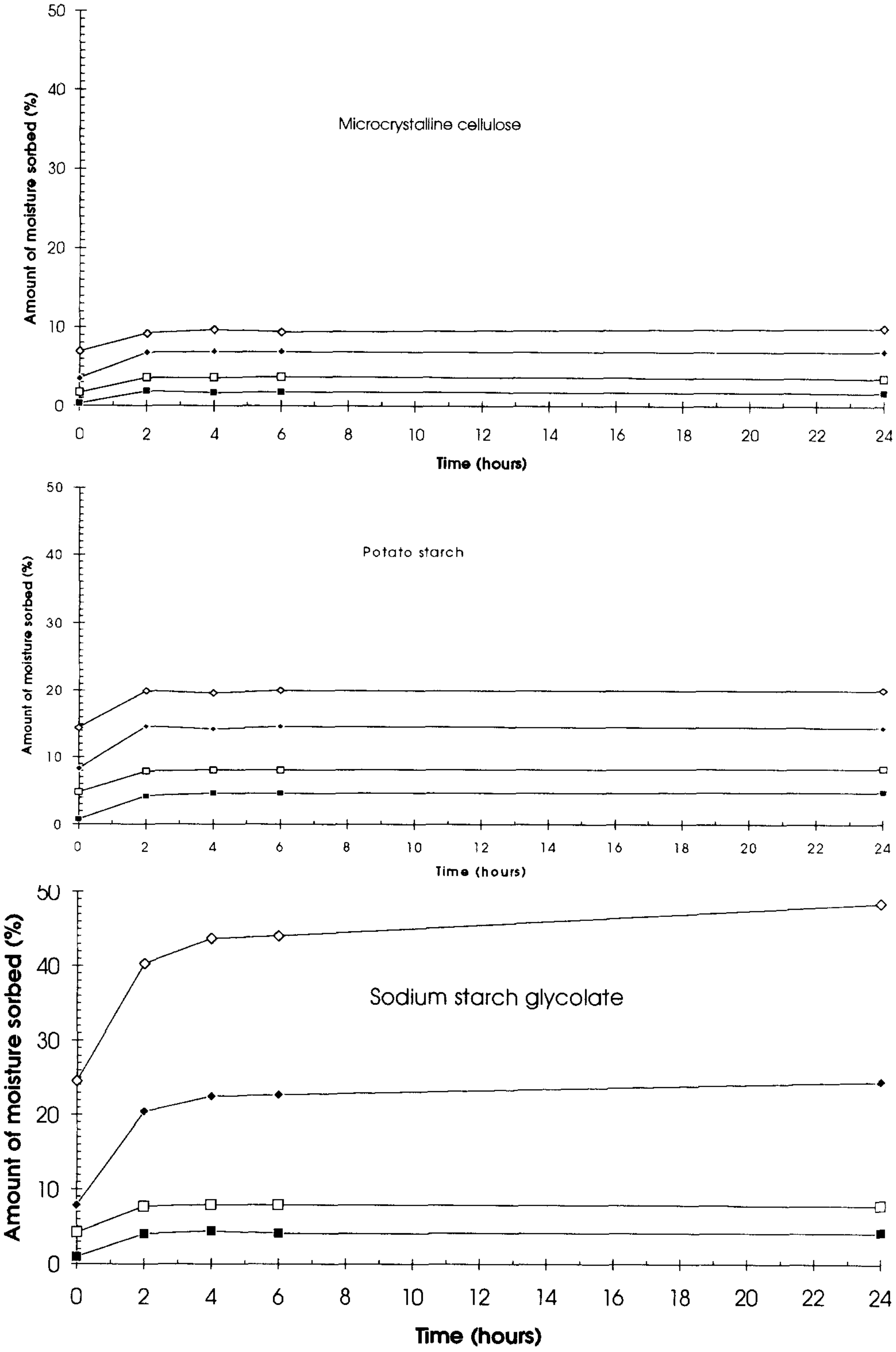

Fig. 1. Moisture sorption for microcrystalline celluose (top), potato starch (middle) and sodium starch glycolate (bottom) as a function of time when successively changing the relative humidity in the climatic test chamber from 20 to 40% (■), 40 to 60% (□), 60 to 80% (♦) and 80 to 90% (◇) RH.

2.4. Moisture sorption / desorption

Prior to the sorption studies (for the desiccator as well as climatic test chamber studies) the substances were dried in the climatic test chamber at 15% RH and 30°C for 24 h. The drying procedure was carried out in order to attain an initial water content of the materials that was less than the EMC at the first relative humidity studied. The terms equilibrium and EMC value are based upon a plateau in moisture content between 2 and 24 h. We define the plateau as a weight change from the previous weighing of less than 0.5% of the total sample weight provided that the time between the two weighings is at least 2 h.

Equilibrium moisture content (EMC) and time to achieve equilibrium were gravimetrically determined inside the climatic test chamber by weighing the samples in open glass petri dishes to the nearest 0.1 mg. The size of the dishes ranged from 4 to 10 cm in diameter. Sample sizes between 400 and 1500 mg were studied. The number of samples for each study varied from 1 to 10. After a drying procedure the weight of the dried substance was registered. The relative humidity and temperature were changed to 20% RH and 22°C, respectively, and the weight gain of the substances was determined at 2, 4, 6 and 24 h. The humidity was then successively changed to 40, 60, 80 and 90% after studying the sorption for 24 h at each relative humidity.

Before commencing the studies of the time to reach a state of equilibrium for the desorption process, the substances were first dried at 15% RH and 30°C as described above, and then directly exposed to 80% RH at 22°C, 24 h before the desorption study started. The weight loss of the substances was determined at 2, 4 and 24 h after each change of humidity, successively to 60, 40 and 20%.

2.5. Water assay

The aim of the water assay was to determine the total amount of water in the samples in order to describe the level of the sorption isotherms. The total amount of water in the samples, for the studies of moisture sorption isotherms, was determined after equilibration at 40% RH for the climatic test chamber method and at 35% RH for the desiccator method. These humidities were chosen to minimize sorption/desorption of water vapour from/to the environment during the open exposure in connection with the analysis. The substances were first dried as described above and then equilibrated at 40 and 35% RH, respectively.

The water assay was performed by Karl Fisher titration (Karl Fisher, Mettler DL35). The solutions used were Karl Fisher solution, one component system, and dry methanol (Merck, Germany). The solubility of the substances was found to be sufficient in methanol to allow the determinations.

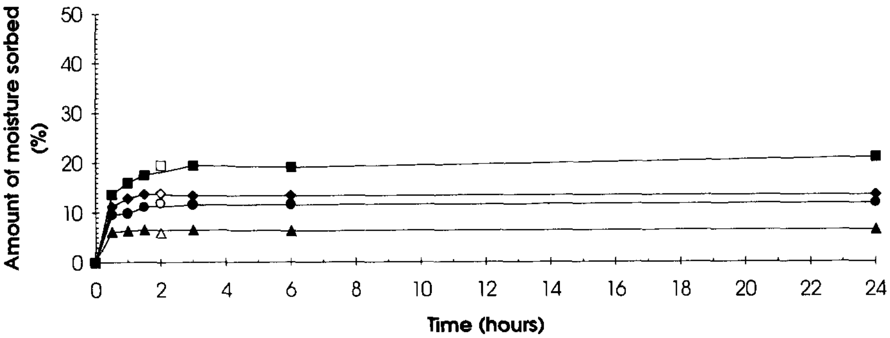

Fig. 2. Moisture sorption for potato starch, maltodextrin, microcrystalline cellulose and sodium starch glycolate as a function of time when changing the relative humidity in the climatic test chamber from 20–80% (closed symbols). Values obtained when changing the relative humidity step by step are included as references (open symbols): (●,○) potato starch, (♦,◇) maltodextrin, (▲,△) microcrystalline cellulose, (■,□) sodium starch glycolate.

2.6. Desiccators

Seven glass desiccators, approx. 22 cm in diameter and 18 cm in height, were used to determine sorption isotherms by the traditional desiccator method. Saturated salt solutions at 22°C were prepared from analytical grade salts and purified water. The salts used were lithium chloride, potassium acetate, chromium trioxide, sodium bromide, sodium chloride, potassium bromide and potassium nitrate (Nyqvist, 1983). The EMC was determined gravimetrically, according to Callahan et al. (1982), using 400 mg samples of potato starch, microcrystalline cellulose and sodim starch glycolate. The samples were kept in open plastic petri dishes at room temperature (22 ± 2°C) for 1 week at each of the humidities described, and weighed to the nearest 0.1 mg outside the desiccators.

3. Results

3.1. Sorption / desorption kinetics - climatic test chamber

Fig. 1 and 2 demonstrate the sorption kinetics for microcrystalline cellulose, potato starch and sodium starch glycolate, studied by moisture sorption in the climatic test chamber. Fig. 3 shows the desorption kinetics for sodium starch glycolate and microcrystalline cellulose, investigated by moisture desorption. The moisture content at zero time for each relative humidity studied is the same as that after 24 h for the previous relative humidity. The moisture sorption kinetics was found to be independent of the sample size or sample layer thickness studied.

For potato starch and microcrystalline cellulose as well as for maltodextrin (not shown) the EMC was already reached after 2 h.

Sodium starch glycolate behaves similarly when changing the humidity from 20 to 40% and from 40 to 60%. However, the time for attaining equilibrium is successively prolonged and at 90% RH equilibrium is not reached within 24 h. Similar behaviour was observed for polyvinyl pyrrolidone.

No moisture sorption could be observed for monohydrous lactose, paracetamol and naproxen. Anhydrous lactose adsorbed 0.5% moisture within the first 2 h at 90% RH. No further sorption was seen for the next 22 h at 90% RH.

Fig. 2 shows the moisture sorption for potato starch, maltodextrin, microcrystalline cellulose and sodium starch glycolate when changing the relative humidity directly from 20 to 80% RH.

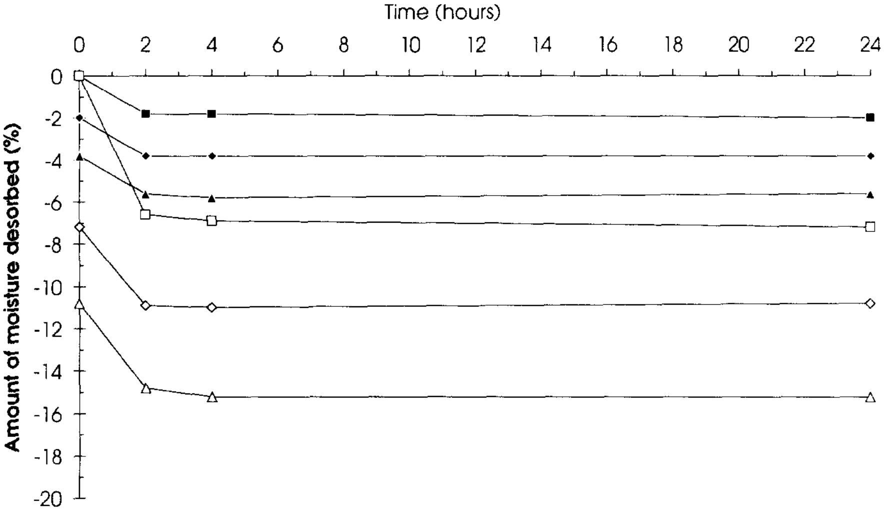

Fig. 3. Moisture desorption for microcrystalline cellulose (mcc) and sodium starch glycolate (ssg) as a function of time when successively reducing the relative humidity in the climatic test chamber: (■) mcc 80-60%, (□) ssg 80-60%, (◆) mcc 60-40%, (◇) ssg 60-40%, (▲) mcc 40-20%, (△) ssg 40-20%.

Even in this case an equilibrium could be attained within a period of 2 h except for sodium starch glycolate. The values, after an equilibrium period of 2 h at 80%, found after changing the relative humidity step by step are included as references. Corresponding results were obtained when changing directly from 20 to 60% RH.

The desorption kinetics for microcrystalline cellulose and sodium starch glycolate are depicted in Fig. 3. It is shown that equilibrium is achieved within 2–4 h for changes of relative humidities from 80 to 60%, from 60 to 40% and from 40 to 20%. Similar results were obtained for potato starch and maltodextrin (not shown), and for potato starch for the change of the relative humidity directly form 80 to 20% RH.

3.2. Reproducibility – moisture sorption / desorption

To investigate the reproducibility of the moisture sorption three or four replicates of each substance were studied. The standard deviations of amount of moisture sorbed were found to be less than 1.5% for all the humidities and time intervals. The reproducibility of the moisture desorption was studied in the same way for the substances potato starch, sodium starch glycolate, microcrystalline cellulose and maltodextrin. The standard deviations of three replicates were found to be less than 1.0%.

3.3. Characterization of moisture sorption isotherms by the Climatic test chamber method

Fig. 4 shows the sorption isotherms for all the materials characterized by the climatic test chamber method. The weight gain profiles for the materials vary. Polymers with a high degree of amorphous structure have a high capacity for moisture sorption as can be seen for potato starch, sodium starch glycolate, polyvinyl pyrrolidone and maltodextrin. Crystalline, relatively hydrophobic substances, such as paracetamol and naproxen, have a low capacity for moisture sorption as well as the crystalline, hydrophilic substances anhydrous lactose and monohydrous lactose. For anhydrous lactose no moisture sorption is seen until the relative humidity exceeds 80%. At higher relative humidities anhydrous lactose incorporates crystal water (Handbook of Pharmaceutical Excipients, 1986b). Microcrystalline cellulose,

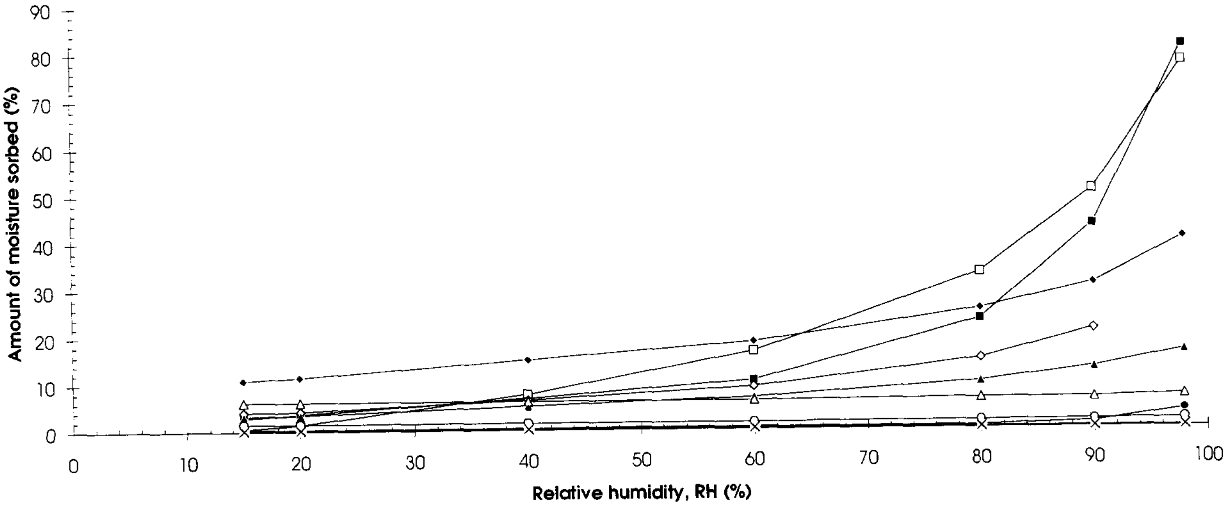

Fig. 4. Moisture sorption isotherms characterized by the climatic test chamber method for (◆) potato starch, (●) anhydrous lactose, (■) sodium starch glycolate, (▲) microcrystalline cellulose, (□) polyvinyl pyrrolidone, (○) paracetamol, (△) monohydrous lactose, (×) naproxen and (◇) maltodextrin.

containing partially crystalline and partially amorphous regions (Nakai et al. 1977), is intermediate between the two.

3.4. Moisture sorption isotherms – the climatic test chamber method *vs* the desiccator method

Fig. 5 shows moisture sorption isotherms for microcrystalline cellulose and sodium starch glycolate characterized by the desiccator method and by the climatic test chamber after a sorption time of 2 and 24 h. The total content of moisture was determined by the Karl Fisher method. The three isotherms for microcrystalline cellulose demonstrate very similar profiles and weight gains. Even after a test period of only 2 h in the climatic test chamber the same weight gain was reached as after 1 week in desiccators. For sodium starch glycolate, a very hygroscopic substance as classified by Callahan et al. (1982), the sorption isotherms show similar profiles for all the test conditions studied. However, it could be observed that the total amount of weight gain at 2 h in the climatic test chamber at relative humidities above 60% is significantly lower than after 24 h in the climatic test chamber and after 1 week in desiccators. This indicates that a test period of only 2 h is not sufficient to attain equilibrium for very hygroscopic substances at higher relative humidities.

4. Discussion

4.1. Drying of the substances

The experimental history, i.e., previous desorption, resorption and resulting water content, is likely to influence the moisture sorption isotherms and the total amount of moisture sorbed at a given relative humidity as described by Slade and Levine (1991). Van den Berg (1986) has pointed out that this history along with physical pretreatments of samples can have unpredictable effects on the reproduciblility and accuracy of moisture sorption isotherms. This variation in sample history, before the initial drying, may also account for the variations we have seen in the reproducibility (< 1.5%). Furthermore, variation in the physical structure, such as surface area, particle size and amount of noncrystalline structure of the samples due to the sampling procedure, may also influence moisture sorption.

Different procedures for drying of solid substances prior to determining sorption isotherms have been described. Callahan et al. (1982) describe a method where the substances are dried for 2 h at 105°C. Malamataris et al. (1991) use phosphorus pentoxide to achieve 0% RH for drying of the substances and Oksanen and Zografi (1990) dry the substances under vacuum at 90°C for 12 h. There might be a risk of influencing the

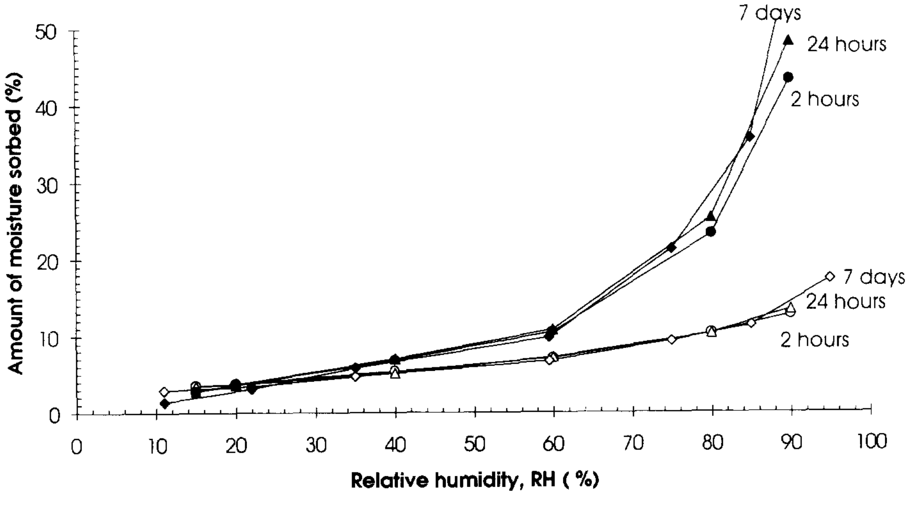

Fig. 5. Moisture sorption isotherms for sodium starch glycolate (closed symbols) and microcrystalline cellulose (open symbols) characterized in the climatic test chamber during a test period of 2 and 24 h and in desiccators for 7 days.

solid-state characteristics and hence the sorption characteristics of the solids by the drying procedure. To minimize this risk the materials in this study were dried as carefully as possible with the aim of obtaining materials with a lower water content than the EMC under the first sorption condition studied.

4.2. Desorption / sorption kinetics

Practically all materials capable of sorbing moisture show some degree of hysteresis (Johnston and Duckworth 1985), i.e., a separation of moisture sorption and desorption isotherms. We also found hysteresis when studying the sorption/desorption isotherms by the climatic test chamber method. However, this phenomenon did not influence the kinetics of moisture sorption or desorption processes as equlibrium was attained within 2 h for both the sorption and desorption studies. Nevertheless, it should be pointed out that the kinetics within the first 2 h of the sorption/desorption were not investigated in this study.

Fig. 1 and 2 show that the EMC values for moisture sorption determined by the climatic test chamber method could be achieved after a period of only 2 h. Thus, relative to the period of 1 week or more for the widely used desiccator method, this is a clear improvement, and may be explained by the rapid convection (2 m/s) of the air in the climatic test chamber.

As can be seen in Fig. 3, desorption equilibrium can also be attained within 2 h, characterized by the climatic test chamber method. Relative to the desorption kinetics for compressible sugar of about 20 days, as described by Tabibi and Hollenbeck (1984) for the desiccator method, this is a fast process.

4.3. Hygroscopicity

Callahan et al. (1982) classify microcrystalline cellulose as a slightly hygroscopic material, based on thermodynamical considerations, whereas sodium starch glycolate and polyvinyl pyrrolidone are classified as very hygroscopic materials. Our data show that potato starch and maltodextrin could be classified as moderately hygroscopic materials. The results in the present study thus indicate that for slightly hygroscopic and moderately hygroscopic materials, an EMC value could be reached after an equilibration period of only 2 h by the climatic test chamber method at all the humidities. For very hygroscopic substances, an equilibration period of 2 h is sufficient for humidities below 60%. At relative humidities above 80% even 24 h could be too short a period to attain EMC values by the climatic chamber method. However, Fig. 5 does show that a test period of only 2 h seems to be sufficient for classifying the hygroscopicity characteristics, even for very hygroscopic substances such as sodium starch glycolate, as demonstrated by the similar profiles for the moisture sorption isotherms, at 2 and 24 h.

4.4. Comparison of techniques

Heidemann and Jarosz (1991) have published data where moisture sorption kinetics were studied for various materials in a 'walk-in chamber' at 30°C and 60% RH during a period of 320 min for undried materials and materials dried for 3 h at 105°C. The gravimetric analyses were performed within the chamber on an analytical balance that had fully equilibrated to the surroundings. They observed an equilibrium, defined as no change in weight gain, for two qualities of microcrystalline cellulose within 60–120 min whereas for pregelatinized starch and the antacid magaldrate a period of more than 320 min seemed to be necessary. The amorphous structure of the starch provides a high capacity for moisture sorption, giving moderately hygroscopic characteristics, and hence a longer equilibrium period. However, the moisture sorption kinetics were not studied under other conditions.

Schepky (1982) used a specially constructed apparatus, consisting of a hygrostat and a balance giving continuous reading of the weight without removing the sample from the test conditions, for moisture sorption characterization. Using the above method he showed that the EMC for Esma-spreng, a formaldehyde casein classified as a very hygroscopic substance, could be obtained after 6–8 h (Schepky 1989).

The traditional way of characterizing sorption isotherms by the desiccator method is time consuming. Radosta et al. (1989) have shown that a test time of about 6 days is needed for potato starch and maltodextrin to reach equilibrium at 98% RH. According to generally accepted methods, the samples are equilibrated for 1 week or more before the EMC is determined (Callahan et al., 1982; Ahlneck and Alderborn, 1989; Vidgren et al., 1989; Malamataris et al., 1991).

The desiccator method involves weighing of the sample outside the controlled humidity. During this weighing procedure the sample may sorb or desorb moisture to its environment, depending on the surrounding relative humidity. Thus, an under- or overestimation of the moisture content may arise. However, when using the described climatic test chamber method this problem is avoided as the balance is placed inside the climatic test chamber and all of the gravimetrical analyses are carried out at the same relative humidity as the sorption/desorption studies.

On-line automated gravimetrical systems based upon dynamic sorption methods are described in the literature. Most of them rely upon a vacuum system (Rasmussen and Akinc, 1983; Astill, 1987) to evacuate the atmosphere around the samples. The moisture sorption is measured directly as a function of the pressure in the system. These methods may involve risks of changing the solid-state characteristics of the pharmaceutical solids.

Bergren (1994) has described an automated controlled atmosphere microbalance for measurement of moisture sorption as an alternative to the vacuum systems. In this the humidity can be regulated between 1 and 98% RH. The temperature range is restricted to 20–25°C. This system is favourable for small volume samples, typical sample masses of 10 mg, where isotherms can be obtained in less than 1 day. However, the time needed for obtaining the isotherm for microcrystalline cellulose was extended to 8 days.

Commercial techniques are available for determining moisture sorption isotherms, such as the DVS1/2 (Dynamic Vapour Sorption 1/2, Surface Measurements Systems Ltd, Bucks, U.K.). These techniques are based upon automated gravimetrical systems for continuous measurement. Along with the technique described by Bergren (1994) these techniques seem to be very well suited for analytical studies of moisture sorption of solids. The number of samples at a time is, however, restricted to one or two.

The climatic chamber described in this paper presents a larger space of controlled relative humidity compared to the commercially available techniques. It can therefore be used for comparative studies of a large number of samples simultaneously (10–20). In addition, the climatic test chamber method provides the opportunity for effective conditioning of sufficient amounts of material for studies of the effect of moisture content on solid state characteristics such as compressibility and compactability.

5. Conclusions

Sorption isotherms determined by the described climatic test chamber method can be obtained after an equilibration period of only 2 h for most substances. Commercial techniques are available for such analysis of moisture sorption isotherms. However, these are rather expensive, and the number of samples is restricted to one or two.

The present technique is proposed to replace the more time-consuming desiccator method. A wider use of sorption isotherms and studies on water-solid interactions in pharmaceutical preformulation, formulation and trouble-shooting work is thus possible.

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References

Ahlneck, C. and Alderborn, G., Effect of adsorbed moisture on volume reduction behaviour and tablet strength for two crystalline materials. *5th Int. Congr. Int. Technol. Pharm.*, 2 (1989) 161-170.

Astill, D.M., Hall, P.L. and MacConnel, J.D.C., An automated vacuum microbalance for measurement of adsorption isotherms. *J. Phys. E: Sci. Instrum.*, 20 (1987) 19-21.

Bergren, M.S., An automated controlled atmosphere for the measurement of moisture sorption. *Int. J. Pharm.*, 103 (1994) 103-114.

Callahan, J.C., Cleary, G.W., Elefant, M., Kaplan, G., Kensler, T. and Nash, R.A., Equilibrium moisture content of pharmaceutical excipients. *Drug Dev. Ind. Pharm.*, 8 (1982) 355-369.

Handbook of Pharmaceutical Excipients, American Pharmaceutical Association, Washington, DC, and The Pharmaceutical Society of Great Britain, London, 1986a, p. 138.

Handbook of Pharmaceutical Excipients, American Pharmaceutical Association, Washington, DC, and The Pharmaceutical Society of Great Britain, London, 1986b, p. 155.

Heidemann, D.R. and Jarosz, P.J., Preformulation studies involving moisture uptake in solid dosage forms. *Pharm. Res.*, 8 (1991) 292-297.

Johnston, K.A. and Duckworth, R.B., The influence of soluble components on water sorption hysteresis. In Simatos, D. and Multon, J.L. (Eds), *Properties of Water in Foods*, Martinus Nijhoff, Dordrecht, The Netherlands, 1985, pp. 65-88.

Konty, J., Distribution of water in solid pharmaceutical systems. *Drug Dev. Ind. Pharm.*, 14 (1988) 1991-2027.

Malamataris, S., Goidas, P. and Dimitriou, A., Moisture sorption and tensilestrength of som tabletted direct compression excipients. *Int. J. Pharm.*, 68 (1991) 51-60.

Nakai, Y., Fukuoka, E., Nakajima, S. and Hasegawa, J., Crystallinity and physical characteristics of microcrystalline cellulose. *Chem. Pharm. Bull.*, 15 (1977) 96-101.

Nyqvist, H., Saturated salt solutions for maintaining specified relative humidities. *Int. J. Pharm. Technol. Prod. Manuf.*, 4 (1983) 47-48.

Oksanen, C.A. and Zografi, G., The relationship between the glass transition temperature and water vapor absorption of polyvinylpyrrolidone. *Pharm. Res.*, 7 (1990) 654-657.

Radosta, S., Schierbaum, F., Reuther, F. and Anger, H., Polymer-water interaction of maltodextrins: I. Water vapour sorption and desorption of maltodextrin powders. *Stärke,* 41 (1989) 395-401.

Slade, L. and Levine, H., Beyond water activity: Recent advances based on an alternative approach to the assessment of food quality and safety. *Crit. Rev. Food Sci. Nutr.*, 30 (1991) 115-360.

Schepky, G., Ein hygrostat mit enfacher und störungsarmer Probenauswaage. *Acta Pharm. Technol.*, 28 (1982) 87-88.

Schepky, G,. Preformulation - the role of moisture in solid dosage forms. *Drug. Dev. Ind. Pharm.*, 15 (1989) 1715-1741.

Scott, M.W., Leberman, H.A. and Chow, F.S., Pharmaceutical application of the concept of equilibrium moisture content. *J. Pharm. Sci.*, 52 (1963) 994-998.

Tabibi, S.E. and Hollenbeck, R.G., Interaction of water vapor and compressible sugar. *Int. J. Pharm.*, 18 (1984) 169-183

Teng, D.C., Zarrintan, M.H. and Groves, M.J., Water vapor adsorption an desorption isotherms of biologically active proteins. *Pharm. Res.*, 8 (1991) 191-195.

Vidgren, P., Vidgren, M. and Petteri, P., Physical stability and inhalation behaviour of mechanically micronized and spray dried disodium cromoglycate in different humidities. *Acta Pharm. Fenn.*, 98 (1989) 71-78.

Van den Berg, C., Water activity. In MacCarthy, D. (Ed.), *Concentration and Drying of Foods*, Elsevier, London, 1986, p. 11.