

1 *NOTE ON THE GENERAL CHAPTER*

2 *This chapter represents the stage 3 draft proposal according to the International*  
3 *Harmonisation Procedure. The Ph. Eur. is the coordinating pharmacopoeia.*

4 *The scope of the text has been enlarged compared to the initial intention, since it had*  
5 *been decided to prepare a text on Gravimetric Water Sorption only. This draft is largely*  
6 *based on chapter <1241> Water-Solid interactions in Pharmaceutical Systems from*  
7 *the USP.*

8 *According to the revised procedure of International Harmonisation, a stage 3 text need*  
9 *not be published in the forums. Since no text exists in the Ph. Eur. at the moment*  
10 *(prospective harmonisation) it was decided to ask for comments, awaiting further*  
11 *progress in the PDG.*

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15 **2.9.39. WATER-SOLID INTERACTIONS - SORPTION**  
16 **ISOTHERMS, WATER ACTIVITY**  
17

18 INTRODUCTION

19 Pharmaceutical solids as raw materials or as dosage forms most often come in contact  
20 with water during processing and storage. This may occur (a) during crystallization,  
21 lyophilization, wet granulation, or spray drying; and (b) because of exposure upon  
22 handling and storage to an atmosphere containing water vapour or exposure to other  
23 materials in a dosage form that contains water capable of distributing to other ingredients.  
24 Some properties known to be altered by the association of solids with water include rates  
25 of chemical degradation in the "solid-state", crystal growth and dissolution, dispersibility  
26 and wetting, powder flow, lubricity, powder compactibility, compact hardness and  
27 microbial contamination.

28 Although precautions can be taken when water is perceived to be a problem, i.e.  
29 eliminating all moisture, reducing contact with the atmosphere, or controlling the relative  
30 humidity of the atmosphere, such precautions generally add expense to the process  
31 with no guarantee that during the life of the product further problems associated with  
32 moisture will be avoided. It is also important to recognise that there are many situations  
33 where a certain level of water in a solid is required for proper performance, e.g. powder  
34 compaction. It is essential for both reasons, therefore, that as much as possible is known  
35 about the effects of moisture on solids before strategies are developed for their handling,  
36 storage and use.

37 Some of the more critical pieces of required information concerning water-solid  
38 interactions are:

- 39  
40 – total amount of water present;  
41 – the extent to which adsorption and absorption occur;  
42 – whether or not crystal hydrates form;  
43 – specific surface area of the solid, as well as such properties as degree of crystallinity,  
44 degree of porosity, and glass transition and melting temperature;  
45 – site of water interaction, the extent of binding, and the degree of molecular mobility;  
46 – effects of temperature and relative humidity;  
47

- 1 – various factors that might influence the rate at which water vapour can be taken up  
2 by a solid;  
3 – for water-soluble solids capable of being solubilised by the sorbed water, under which  
4 conditions dissolution will take place.  
5

#### 6 PHYSICAL STATES OF SORBED WATER

7 Water can associate with solids in 2 ways. It can interact only at the surface (adsorption)  
8 or it can penetrate the bulk solid structure (absorption). When both adsorption and  
9 absorption occur, the term sorption is often used. Adsorption is particularly critical in  
10 affecting the properties of solids when the specific surface area is large. Large values  
11 of specific surface area are seen with solids having very small particles, as well as with  
12 solids having a high degree of intraparticle porosity. Absorption is characterized by  
13 an association of water per gramme of solid that is much greater than that which can  
14 form a monomolecular layer on the available surface, and an amount that is generally  
15 independent of the specific surface area.  
16

17 Most crystalline solids will not absorb water into their bulk structures because of the  
18 close packing and high degree of order of the crystal lattice. Indeed, it has been shown  
19 that the degree of absorption into solids exhibiting partial crystallinity and partial  
20 amorphous structure is often inversely proportional to the degree of crystallinity. With  
21 some crystalline solids, however, crystal hydrates may form. These hydrates may exhibit a  
22 stoichiometric relationship, in terms of water molecules bound per solid molecule, or they  
23 may be non-stoichiometric. Upon dehydration, crystal hydrates may either retain their  
24 original crystal structure, lose their crystallinity and become amorphous, or transform  
25 into a new anhydrous or less-hydrated crystal form.

26 Amorphous or partially amorphous solids are capable of taking up significant amounts of  
27 water when there is sufficient molecular disorder in the solid to permit penetration and  
28 dissolution of the water molecule. Such behaviour is observed with most amorphous  
29 polymers and with small-molecular-mass solids rendered amorphous during preparation,  
30 e.g. by lyophilization, or after milling. The introduction of defects into highly crystalline  
31 solids will also produce this behaviour. The greater the chemical affinity of water for  
32 the solid, the greater the total amount that can be absorbed. When water is absorbed  
33 by amorphous solids, the bulk properties of the solid can be significantly altered. It is  
34 well established, for example, that amorphous solids, depending on the temperature, can  
35 exist in at least one of 2 states, “glassy” or “fluid”; the temperature at which one state  
36 transforms into the other is the glass transition temperature,  $T_g$ .

37 x

38 Water absorbed into the bulk solid structure, by virtue of its effect on the free volume of  
39 the solid, can act as an efficient plasticizer and reduce the value of  $T_g$ . Since the rheological  
40 properties of “fluid” and “glassy” states are quite different, i.e. the “fluid” state exhibits  
41 much less viscosity as one goes increasingly above the glass transition temperature, it is  
42 not surprising that a number of important bulk properties dependent on the rheology of  
43 the solid are affected by moisture content. Since amorphous solids are metastable relative  
44 to the crystalline form of the material, with small-molecular-mass materials, it is possible  
45 for absorbed moisture to initiate reversion of the solid to the crystalline form, particularly  
46 if the solid is transformed by the sorbed water to a fluid state. This is the basis of “cake  
47 collapse” often observed during the lyophilization process. An additional phenomenon

1 noted specifically with water-soluble solids is their tendency to deliquesce, i.e. to dissolve  
2 in their own sorbed water, at relative humidities,  $RH_i$ , in excess of the relative humidity  
3 of a saturated solution of the solid,  $RH_0$ . Deliquescence arises because of the high water  
4 solubility of the solid and the significant effect it has on the colligative properties of water.  
5 It is a dynamic process that continues to occur as long as  $RH_i$  is greater than  $RH_0$ .

6  
7 The key to understanding the effects water can have on the properties of solids, and vice  
8 versa, rests with an understanding of the location of the water molecule and its physical  
9 state. More specifically, water associated with solids can exist in a highly immobile  
10 state, as well as in a state of mobility approaching that of bulk water. This difference in  
11 mobility has been observed through such measurements as heats of sorption, freezing  
12 point, nuclear magnetic resonance, dielectric properties and diffusion. Such changes in  
13 mobility have been interpreted as arising because of changes in the thermodynamic state  
14 of water as more and more water is sorbed. Thus, water bound directly to a solid is often  
15 thought of as "tightly" bound and unavailable to affect the properties of the solid, whereas  
16 larger amounts of sorbed water tend to become more clustered and form water more like  
17 that exhibiting solvent properties. In the case of crystal hydrates, the combination of  
18 intermolecular forces (hydrogen bonding) and crystal packing can produce very strong  
19 water-solid interactions. However, there are reported situations where hydration and  
20 dehydration of crystals occur quite easily at low temperatures. More recently, the concept  
21 of "tightly" bound water in amorphous systems has been questioned. Recognizing that  
22 the presence of water in an amorphous solid can affect the glass transition temperature  
23 and hence the physical state of the solid, it is argued, that at low levels of water, most  
24 polar amorphous solids are in a highly viscous glassy state because of their high values  
25 of  $T_g$ . Hence, water is "frozen" into the solid structure and is rendered immobile by the  
26 high viscosity, e.g.  $10^{14}$  poise. As the amount of water sorbed increases and  $T_g$  decreases,  
27 approaching ambient temperatures, the glassy state approaches that of a "fluid" state  
28 and water mobility along with the mobility of the solid itself increases significantly. At  
29 high  $RH$ , the degree of water plasticization of the solid can be sufficiently high so that  
30 water and the solid can now assume significant amounts of mobility. In general, therefore,  
31 this picture of the nature of sorbed water helps to explain the rather significant effect  
32 moisture can have on a number of bulk properties of solids such as chemical reactivity  
33 and mechanical deformation. It suggests strongly that methods of evaluating chemical  
34 and physical stability of solids and solid dosage forms take into account the effects water  
35 can have on the solid when it is sorbed, particularly when it enters the solid structure  
36 and acts as a plasticizer.

37 **Rates of water uptake.** The rate at which solids exposed to the atmosphere might either  
38 sorb or desorb water vapour can be a critical factor in the handling of solids. Even the  
39 simple act of weighing out samples of solid on an analytical balance and the exposure,  
40 therefore, of a thin layer of powder to the atmosphere for a few minutes can lead to  
41 significant error in, for example, the estimation of loss on drying values. It is well  
42 established that water-soluble solids exposed to relative humidities above that exhibited  
43 by a saturated solution of that solid will spontaneously dissolve via deliquescence and  
44 continue to dissolve over a long time period. The rate of water uptake in general depends  
45 on a number of parameters not found to be critical in equilibrium measurements because  
46 rates of sorption are primarily mass-transfer controlled with some contributions from  
47 heat-transfer mechanisms. Thus, factors such as vapour diffusion coefficients in air and

1 in the solid, convective airflow, and the surface area and geometry of the solid bed and  
 2 surrounding environment, can play an important role. Indeed, the method used to make  
 3 measurements can often be the rate-determining factor because of these environmental  
 4 and geometric factors.

#### 6 DETERMINATION OF SORPTION-DESORPTION ISOTHERMS

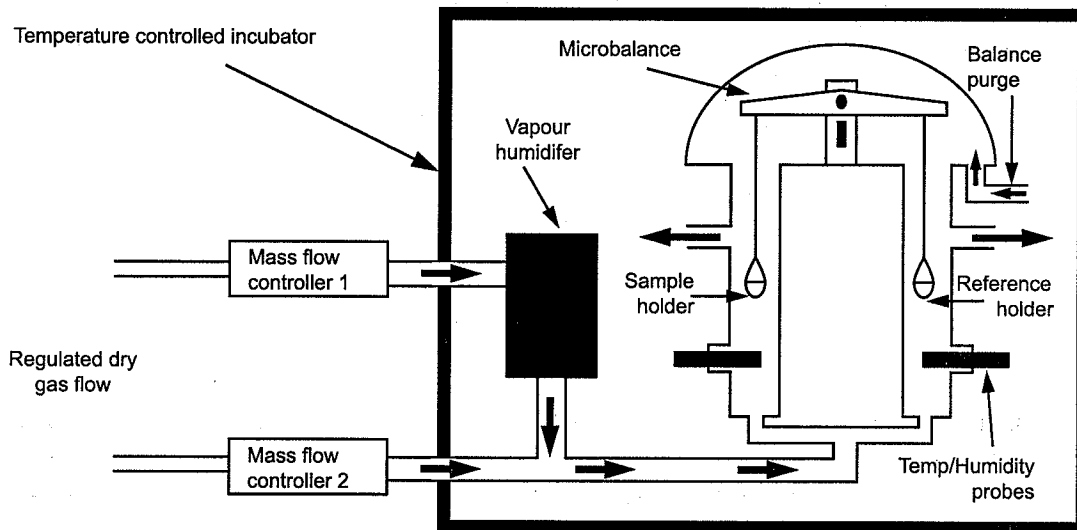
7 **Principle.** The tendency to take up water vapour is best assessed by measuring sorption  
 8 or desorption as a function of relative humidity, at constant temperature, and under  
 9 conditions where sorption or desorption is essentially occurring independently of time, i.e.  
 10 equilibrium. Relative humidity,  $RH$ , is defined by the following equation:

$$RH = \frac{P_c}{P_0} \times 100$$

15  $P_c$  = pressure of water vapour in the system;

17  $P_0$  = vapour pressure of pure water under the same conditions.

18 The ratio  $P_c/P_0$  is referred to as the relative pressure. Sorption or water uptake is best  
 19 assessed starting with dried samples and subjecting them to a known relative humidity.  
 20 Desorption is studied by beginning with a system already containing sorbed water  
 21 and reducing the relative humidity. As the name indicates, the sorption-desorption  
 22 isotherm is valid only for the reference temperature, hence a special isotherm exists for  
 23 each temperature. Ordinarily, if we are at equilibrium, moisture content at a particular  
 24 relative humidity must be the same, whether determined from sorption or desorption  
 25 measurements. However, it is common to see sorption-desorption hysteresis.



41 Figure 2.9.39.-1 – Example of an apparatus for the determination of the water sorption  
 42 (other design are possible)

43 **Methods.** Storing samples in chambers at various relative humidities and removing them  
 44 to measure mass gained or lost can be carried out. The major advantage of this method  
 45 is convenience, while the major disadvantages are the slow rate of reaching constant  
 46 mass, particularly at high relative humidities, and the error introduced in opening and  
 47 closing the chamber for weighing. Dynamic gravimetric water sorption systems allow

1 the on-line weighting of a sample in a controlled system to assess the interaction of the  
2 material with moisture at various programmable levels of relative humidity at a constant  
3 temperature. The major benefit of a controlled system is that isothermal conditions can  
4 be more reliably established and that the dynamic response of the sample to changing  
5 conditions can be monitored. Data points for the determination of the sorption isotherm  
6 (e.g. from 0 per cent to approximately 95 per cent *RH*, non condensing) are only taken  
7 after a sufficiently constant signal indicates that the sample has reached equilibrium at  
8 a given level of humidity. In some cases (e.g. deliquescence), the maximum time may be  
9 restricted although the equilibrium level is not reached. The apparatus must adequately  
10 control the temperature to ensure a good baseline stability as well as accurate control of  
11 the relative humidity generation. The required relative humidities can be generated, e.g.  
12 by accurately mixing dry and saturated vapour gas with flow controllers. The electrostatic  
13 behaviour of the powder must also be considered. The verification of the temperature  
14 and the relative humidity (controlled with, for example, a certified hygrometer, certified  
15 salt solutions or deliquescence points of certified salts over an adequate range), must be  
16 consistent with the instrument specification. The balance must provide a sufficient mass  
17 resolution and long term stability.

18 It is also possible to measure amounts of water uptake not detectable gravimetrically  
19 using volumetric techniques. In some cases, direct analysis of water content by different  
20 methods such as those described in chapters 2.2.12. *Boiling point*, 2.2.13. *Determination*  
21 *of water by distillation* and 2.2.32. *Loss on drying* or 2.2.28. *Gas chromatography* may  
22 be advantageous. In the case of adsorption, to improve sensitivity, one can increase the  
23 specific surface area of the sample by reducing particle size or by using larger samples  
24 to increase the total area. It is important, however, that such comminution of the solid  
25 does not alter the surface structure of the solid or render it more amorphous or otherwise  
26 less ordered in crystallinity. For absorption, where water uptake is independent of specific  
27 surface area, only increasing sample size will help. Increasing sample size, however, will  
28 increase the time to establish some type of equilibrium. To establish accurate values, it is  
29 important to get desolvation of the sample as thoroughly as possible. Higher temperatures  
30 and lower pressures (vacuum) facilitate this process; however, one must be aware of any  
31 adverse effects this might have on the solid such as dehydration, chemical degradation or  
32 sublimation. Using higher temperatures to induce desorption, as in a thermogravimetric  
33 apparatus, likewise must be carefully carried out with these possible pitfalls in mind.

34  
35 **Report and interpretation of the data.** Sorption data are usually reported as a graph  
36 of the apparent mass change in per cent of the mass of the dry sample as a function of  
37 relative humidity or time. Sorption isotherms are reported both in tabular form and as a  
38 graph. The measurement method must be traceable with the data.

39 Adsorption-desorption hysteresis can be interpreted, for example, in terms of the porosity  
40 of the sample, its state of agglomeration (capillary condensation), the formation of  
41 hydrates, polymorphic change, or liquefying of the sample. Certain types of systems,  
42 particularly those with microporous solids and amorphous solids, are capable of sorbing  
43 large amounts of water vapour. Here, the amount of water associated with the solid as  
44 relative humidity is decreased, is greater than the amount that originally sorbed as the  
45 relative humidity was increased. For microporous solids, vapour adsorption-desorption  
46 hysteresis is an equilibrium phenomenon associated with the process of capillary  
47 condensation. This takes place because of the high degree of irregular curvature of the

1 micropores and the fact that they “fill” (adsorption) and “empty” (desorption) under  
2 different equilibrium conditions. For non-porous solids capable of absorbing water,  
3 hysteresis occurs because of a change in the degree of vapour-solid interaction due to  
4 a change in the equilibrium state of the solid, e.g. conformation of polymer chains, or  
5 because the time scale for structural equilibrium is longer than the time scale for water  
6 desorption. In measuring sorption-desorption isotherms, it is therefore important to  
7 establish that something close to an equilibrium state has been reached. Particularly with  
8 hydrophilic polymers at high relative humidities, the establishment of water sorption or  
9 desorption values independent of time is quite difficult, since one is usually dealing with a  
10 polymer plasticized into its “fluid” state, where the solid is undergoing significant change.

11 In most cases, the shape of the curve obtained resembles that normally seen for gas  
12 adsorption fitted to the Langmuir or Brunauer, Emmett, and Teller equations. In the case  
13 of crystal hydrate formation, the plot of water uptake versus pressure or relative humidity  
14 will in these cases exhibit a sharp increase in uptake at a particular pressure and the  
15 amount of water taken up will usually exhibit a stoichiometric mole:mole ratio of water to  
16 solid. In some cases, however, crystal hydrates will not appear to undergo a phase change  
17 or the anhydrous form will appear amorphous. Consequently, water sorption or desorption  
18 may appear more like that seen with adsorption processes. X-ray crystallographic analysis  
19 and thermal analysis are particularly useful for the study of such systems.

20  
21 For situations where water vapour adsorption occurs predominantly, it is very helpful to  
22 measure the specific surface area of the solid by an independent method and to express  
23 adsorption as mass of water sorbed per unit area of solid surface. This can be very useful  
24 in assessing the possible importance of water sorption in affecting solid properties.

25 For example, 0.5 per cent  $m/m$  uptake of water could hardly cover the bare surface of  
26  $100 \text{ m}^2/\text{g}$ , while for  $1.0 \text{ m}^2/\text{g}$  this amounts to 100 times more surface coverage. In the  
27 case of pharmaceutical solids which have a specific surface area in the range of  $0.01 \text{ m}^2/\text{g}$   
28 to  $10 \text{ m}^2/\text{g}$ , what appears to be low water content could represent a significant amount of  
29 water for the available surface. Since the “dry surface area” is not a factor in absorption,  
30 sorption of water with amorphous or partially amorphous solids can be expressed on  
31 the basis of unit mass corrected for crystallinity, when the crystal form does not sorb  
32 significant amounts of water relative to the amorphous regions.

### 33 DETERMINATION OF THE WATER ACTIVITY

34  
35 **Principle.** Water activity,  $A_w$ , is the ratio of vapour pressure of water in product ( $P$ ) to  
36 vapour pressure of pure water ( $P_0$ ) at the same temperature. It is numerically equal to  
37  $1/100$  of the relative humidity ( $RH$ ) generated by the product in a closed system.  $RH$  can  
38 be calculated from direct measurements of partial vapour pressure or dew point, or from  
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1 indirect measurement by sensors whose physical or electric characteristics are altered by  
2 the *RH* to which they are exposed. The relationship between  $A_w$  and equilibrium relative  
3 humidity (*ERH*) are represented by the following equations:  
4

$$5 \quad A_w = \frac{P}{P_0}$$

$$8 \quad ERH \text{ (per cent)} = A_w \times 100$$

10 **Method.** For the determination of the water activity, it is necessary to place the sample  
11 in a small airtight cup inside which the equilibrium between the water in the solid and  
12 the headspace can be established. The volume of the headspace must be small in relation  
13 to the sample volume in order not to change the sorption state of sample during the  
14 test. The equilibration as a thermodynamic process takes time but may be accelerated by  
15 forced circulation within the cell. The acquired water activity value is only valid for the  
16 simultaneously determined temperature. This requires a precise temperature-measuring  
17 device as part of the equipment. Furthermore, the probe must be thermally insulated  
18 to guarantee a constant temperature during the test. The key sensor of the equipment  
19 is the one for humidity of the headspace air above the sample. Theoretically, all types of  
20 hygrometers can be used, but for analytical purposes miniaturisation and robustness are  
21 a precondition. The  $A_w$  measurement may be conducted using the dew point/chilled  
22 mirror method<sup>(1)</sup>. A polished, chilled mirror is used as a condensing surface. The cooling  
23 system is electronically linked to a photoelectric cell into which light is reflected from the  
24 condensing mirror. An air stream, in equilibrium with the test sample, is directed at the  
25 mirror which cools until condensation occurs on the mirror. The temperature at which this  
26 condensation begins is the dew point from which the *ERH* is determined. Commercially  
27 available instruments using the dew point/chilled mirror method or other technologies  
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(1) AOAC International Official Method 978.18.

1 need to be evaluated for suitability, validated, and calibrated when used to make water  
 2 activity determinations. These instruments are typically calibrated over an adequate range  
 3 using some saturated salt solutions at 25 °C as listed in Table 2.9.39-1.  
 4

5 Table 2.9.39-1 – *Standard saturated salt solutions*

| Saturated salts solutions<br>at 25 °C                     | <i>ERH</i><br>(per cent) | <i>A<sub>w</sub></i> |
|---|--------------------------|----------------------|
| Potassium sulphate<br>(K <sub>2</sub> SO <sub>4</sub> )   | 97.3                     | 0.973                |
| Barium chloride<br>(BaCl <sub>2</sub> )                   | 90.2                     | 0.902                |
| Sodium chloride<br>(NaCl)                                 | 75.3                     | 0.753                |
| Magnesium nitrate<br>(Mg(NO <sub>3</sub> ) <sub>2</sub> ) | 52.9                     | 0.529                |
| Magnesium chloride<br>(MgCl <sub>2</sub> )                | 32.8                     | 0.328                |
| Lithium chloride<br>(LiCl <sub>2</sub> )                  | 11.2                     | 0.112                |