# 1.1 Determination of the adsorption and desorption of moisture in pharmaceutical substances

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The behavior of substances with regard to drying, moisture uptake, and moisture content has become a topic of major importance because moisture can very often have adverse effects on the properties of materials and products.
The new TGA Sorption Analyzer System is a very convenient method to study such problems. The advantages of the technique are illustrated in the following article using amiloride hydrochloride dihydrate as an example.

### 1.1.1 Introduction

Recent surveys among TA users have confirmed that one of the current trends in modern thermal analysis is to control the gas atmosphere surrounding the sample. This can involve the use of reactive gases, the application of vacuum or pressure, or setting different levels of relative humidity (RH).
In particular, investigations at defined relative humidity are becoming more and more important. This article describes the application of the new TGA Sorption Analyzer System to study a pharmaceutically active substance. An application study from the aroma/foodstuffs industry was published in UserCom 17 in 2003 [1].
Humidity influences the processibility, storage stability and usability of many materials such as pharmaceutical products (active ingredients, and fillers like lactose), plastics (nylon), construction materials (cement), metals (iron/rust formation), explosives (dynamite) and foodstuffs (potato chips). This makes it important to investigate material properties at defined levels of relative humidity or to measure the humidity dependence of the material.
A sample exposed to high relative humidity at room temperature tends to take up moisture. Products stored in contact with the open air may take up or lose moisture, depending on the relative humidity. Among other effects, the uptake of moisture can also influence mechanical properties, as anyone who has left potato chips in the open for a few days knows. In this case, moisture acts as a plasticizer and shifts the glass transition of the potato chips to below room temperature; the chips are then soft and no longer crisp [2].
The study of the behavior of materials as a function of relative humidity is particularly important with pharmaceutical preparations. This begins early on in the processing stage. A spray-dried powder can, for example, cause immense problems if it becomes moist and blocks the supply lines and dispensing devices thus leading to a shutdown of production. And if the finished medication takes up moisture due to inadequate packaging while in stock in the drug store, the shelf life of the product is obviously reduced.
Furthermore, increased moisture content can also lead to major changes in the structural properties of the drug and reduce its bioavailability and therapeutic effect. One possible reason for such a change resulting from the uptake of moisture is due to the recrystallization of the active substance. This phenomenon is referred to as pseudopolymorphism, and the term pseudopolymorph refers to the compounds formed, which are known as hydrates or solvates. These are produced when the crystalline form changes due to the incorporation of water or solvent molecules into the crystal lattice. Hydrates (mono-, di-, tri-hydrates, etc.) are very often stable compounds in which the water is strongly bound as so-called water of crystallization. In contrast, moisture can also be merely adsorbed on the surface, in which case the water is only weakly bound.
Hydrates and anhydrates (i.e. the anhydrous form that does not contain any water of crystallization) behave differently and can have different therapeutic effects. It is important to identify and characterize pseudopolymorphs because they can be separately patented just like polymorphs [3]. This matter is usually investigated early on in the development phase.

### 1.1.2 Experimental details

TGA is a quantitative method and is therefore ideally suited to study the drying or moisture uptake of a substance, or to determine its moisture content. To reliably set up a defined relative humidity in the furnace chamber requires an instrument system consisting of a computer-controlled humidity generator, a heated transfer line to maintain the humidified air flow at a defined temperature, an interface on the TGA instrument, and if necessary, an optional humidity sensor inside the furnace chamber. The present study was carried out using a VTI RH-200 humidity generator and a Rotronic HygroClip SC04 humidity sensor with the TGA/SDTA851$^e$ (large furnace).
The system was used to investigate the influence of relative humidity on pure (> 98%) amiloride hydrochloride dihydrate, the hydrochloride derivative of the diuretic drug amiloride, whose structure is shown in Figure 1.

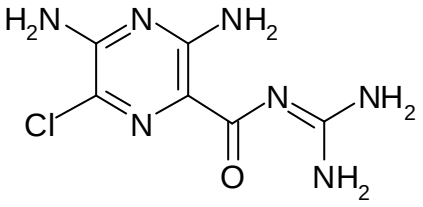


Figure 1. Chemical structure of anhydrous amiloride (N-amidino-3,5-diamino-6-chloropyrazine- carboxamide)

Diuretics are drugs that help to remove excess water from the body by increasing the amount that is excreted as urine. Diuretic drugs are used in the treatment of a variety of disorders including hypertension (high blood pressure) and conditions in which there is excessive accumulation of fluid in the body or body tissues (ascites, edema).

Amiloride hydrochloride dihydrate (approx. 14 mg of fine yellow powder) was weighed into a 150-µl platinum crucible and inserted into the TGA instrument at 25 °C. The sample was heated to 125 °C at 5 K/min, held at this temperature for 30 minutes and then cooled down to 25 °C again at 5 K/min. A relative humidity (RH) of 5% was maintained during this phase of the experiment. The sample was then held isothermally at 25 °C and exposed to increasing levels of RH, from 5 to 95% in steps of 10% with first and final steps of 5%. Afterward, the RH was successively decreased stepwise down to 10% RH. The measurements were performed using a gas flow of 100 mL/min.

### 1.1.3 Results

Different standard procedures are available to characterize the loss on drying depending on the method described in the particular pharmacopeia. Figure 2 shows the mass loss curve of the test substance performed according to USP 26 guidelines (United States Pharmacopeia) [4]. In this method, a sample of approximately 10 mg is heated from room temperature at a heating rate of 10 K/min. The mass loss between room temperature and 200 °C must not be less than 11.0% and must not be greater than 13%. Responsible for mass loss is the initial evaporation of a very small amount of weakly bound water up to about 80 °C followed by the elimination of both molecules of water of crystallization between 80 and 140 °C. The dehydration can be clearly seen in the SDTA curve as a two-step endothermic effect. Evaluation of the TGA curve yielded a mass loss of 11.8%. From about 280 °C onward, the substance melts with simultaneous decomposition. The melting point of the anhydrate was 292 °C (onset), which is about 1.5 K less than the value given for the anhydrate in the Merck Index [5]. This is no doubt due to the formation of decomposition products that contaminate the substance and hence lower the observed melting point

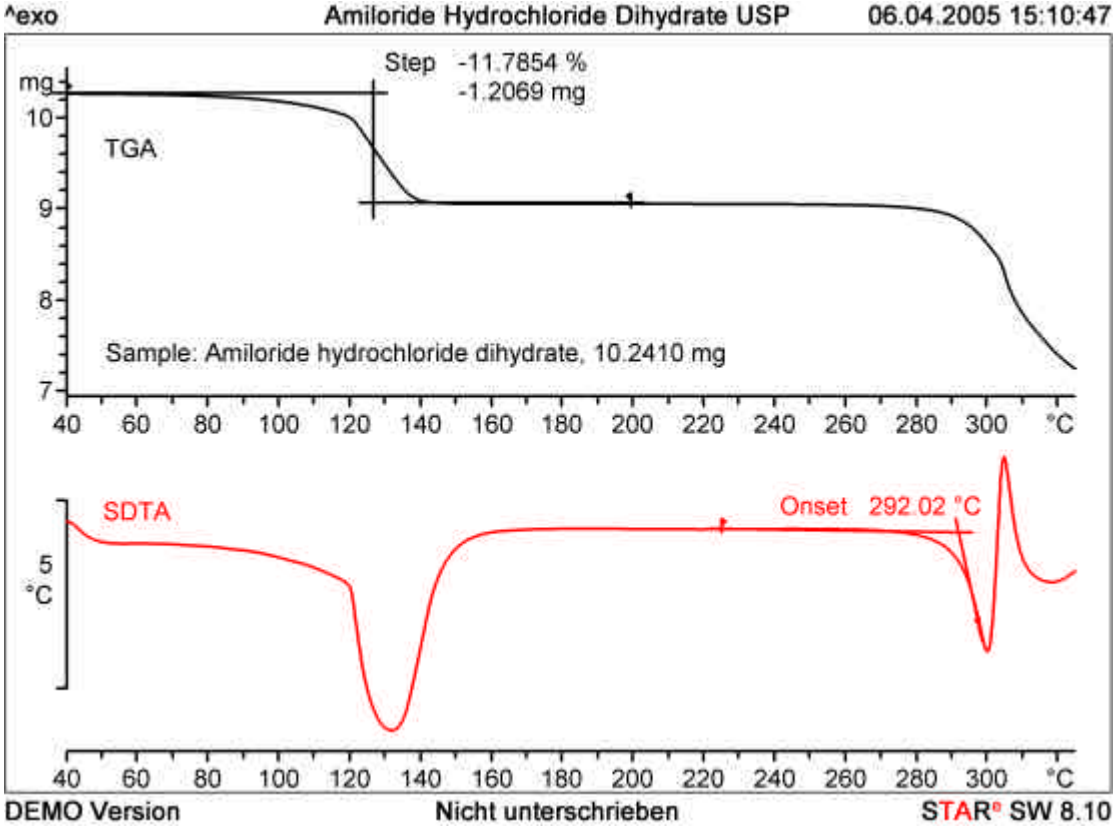


Figure 2. The TGA and simultaneously recorded SDTA curves of amiloride hydrochloride dihydrate. In the upper diagram, the loss on drying is evaluated according to USP 26 [4].

The curves in Figure 3 show the initial dehydration at 125 °C, the rehydration, and moisture adsorption and desorption at 25 °C. The dotted curve depicts the temperature program, the red stepped curve the changes in relative humidity, and the continuous black curve the change in mass of the sample.
The sample (initial mass 14.5870 mg) was first heated to 125 °C, held at this temperature for 30 minutes and then cooled back down to 25 °C. At the end of this period, the recorded mass was constant and the sample has lost approximately 1.7 mg or 11.5% mass. The relative humidity in the sample chamber was then increased in a series of steps of 5 and 10% over a period of 800 minutes. Sufficient time was allowed for the sample mass to equilibrate and stabilize each time. The first small step in the mass curve corresponds to uptake of moisture at 5% RH. The mass curve shows the increase in sample mass for each increase in relative humidity. The original mass of the sample is reached at about 50% RH, that is, rehydration is complete. Each further increase in sample mass now corresponds to the uptake of weakly bound water, that is, to the adsorption of moisture on the surface of the sample.
Following this, the RH was then decreased in steps; a corresponding stepwise change (decrease) in mass was again observed. This experiment is recorded in the right part of Figure 3 and on an expanded scale in Figure 4. With adsorbed moisture, the mass attained at each value with decreasing RH corresponds to the value obtained at the same RH with increasing RH. The dihydrate however can only be converted to the anhydrate at a higher temperature in a dry atmosphere.

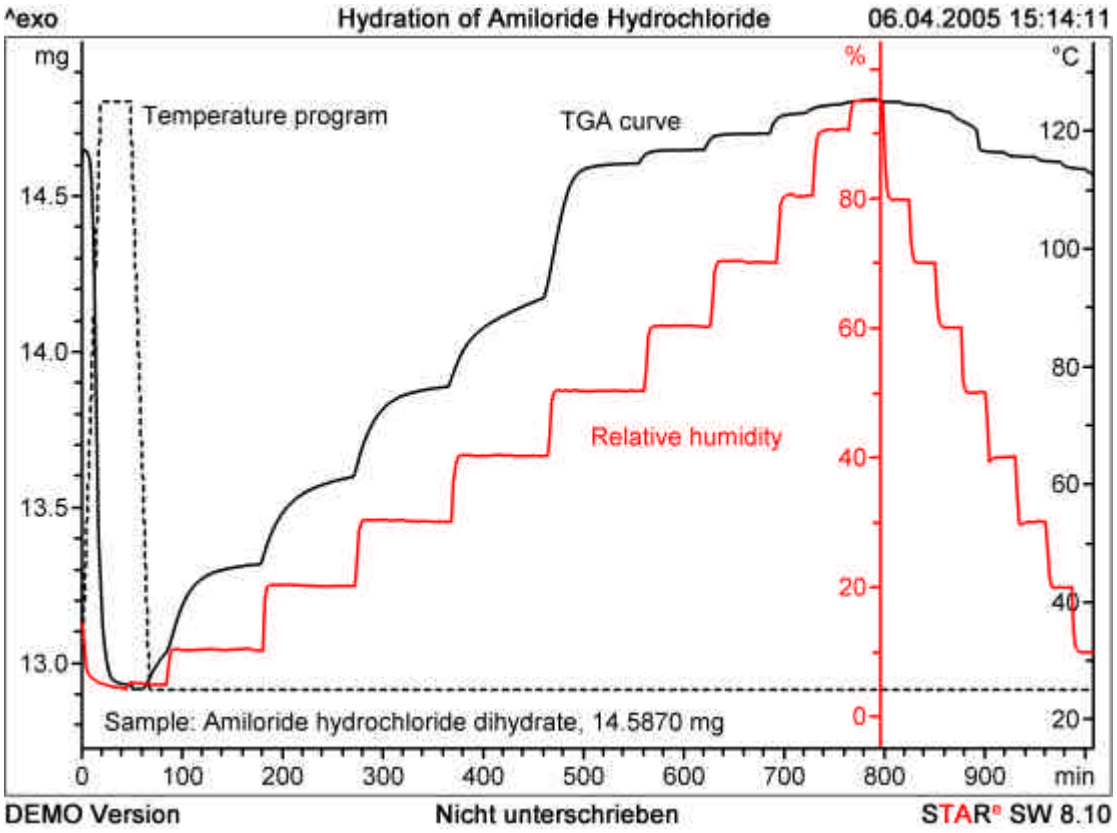


Figure 3. Uptake and release of moisture measured using a sample of amiloride hydrochloride dihydrate. The dihydrate can only be converted to the anhydrate at a higher temperature in a dry atmosphere.

The period in which the RH was decreased is displayed on an expanded scale in Figure 4. In particular, one should note the excellent stability of the balance signal, which allows the very small mass loss steps to be accurately measured.

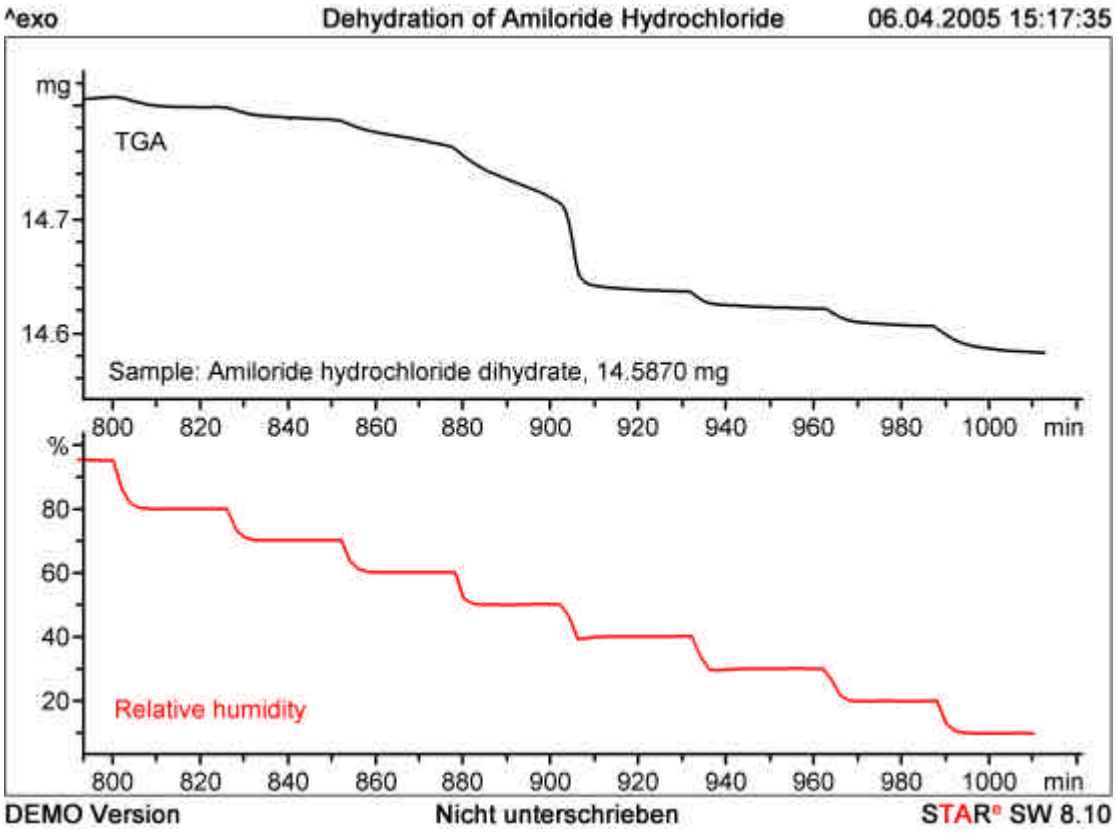


Figure 4. Release of adsorbed (weakly bound) water from amiloride hydrochloride hydrate (expanded section of the curve in Fig. 3)

### 1.1.4 Summary

The results clearly demonstrate that the TGA Sorption Analyzer System is able to reliably measure the drying process, the adsorption of strongly bound and weakly bound water, and desorption of weakly bound water from a pharmaceutical active substance such as amiloride hydrochloride dihydrate.
The equipment including the heated transfer line and the optional humidity sensor enabled well-defined humidity conditions to be set up in the TGA furnace chamber. This coupled with the high sensitivity and stability of the TGA balance allowed even the smallest mass losses to be resolved.
In conclusion, the new TGA Sorption Analyzer System is a reliable and sensitive instrument that can be used to accurately determine the adsorption and desorption behavior of many different types of substances.

### 1.1.5 Literature

[1] M. Schudel, J.B. Ubbink, Ch. Quellet, Measurement of dynamic water vapor sorption processes by modified TGA, METTLER TOLEDO TA UserCom 17, 1/2003, pp 7-9

[2] Y.H. Roos, Thermal Analysis, State Transitions and Food Quality, Thermal Analysis Seminar Presentation, Cork (Ireland), 2004

[3] J. Bernstein, Polymorphism in Molecular Crystals, Clarendon Press, Oxford 2002, Chapter 10

[4] United States Pharmacopeia, Vol. 26, 2003, p 114

[5] The Merck Index, 10$^{th}$ edition, 1983, p 60 (No. 406)