



## **THE IMPORTANCE OF SAMPLE PREPARATION WHEN MEASURING SPECIFIC SURFACE AREA**

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### **ABSTRACT**

Specific surface area is a fundamental measurement in the field of fine particle characterization. Specific surface area measurements have numerous pharmaceutical manufacturing and quality applications. Compliance professionals should have a general understanding of the principles, procedures, and instrumentation associated with specific surface area testing, and be vigilant of potential situations that may impact the accuracy of test data. The conditions under which a sample is prepared for a specific surface area measurement can often influence test results. The first step when preparing a sample for specific surface area measurement is to clear the surface of all water and various contaminants. Discussed are the different types of water including surface adsorbed water, porosity and absorbed water, and water of hydration. When preparing a sample for analysis, the primary factor to be controlled is the temperature. The importance of thermal analysis is discussed in regards to specific surface area measurement. During heating, samples may undergo various changes, especially to their surfaces. These changes, including glass transitions, sintering, annealing, melting, and decomposition are discussed. Common materials are divided into groups, and general sample preparation conditions are provided for each group.

### **INTRODUCTION**

Since the introduction of quality by design and design space in ICH Q8<sup>i</sup>, it has been apparent that US Food and Drug Administration and the rest of the international regulatory community expect pharmaceutical dosage form developers to establish a thorough, science-based knowledge of its product and processes, and present this knowledge in its application.

Where the raw material is a solid, the specific surface area may be important, especially to solubility, dissolution, and bioavailability. The impact of this characteristic should be determined, and it may be appropriate that this characteristic be included as one dimension of the multi-dimensional design space.



Specific surface area is defined as the surface area per unit mass of sample. Most often, this is expressed in units of  $m^2/g$ . Specific surface area is a fundamental measurement in the field of fine particle characterization, and is covered by United States Pharmacopoeia (USP)<sup>ii</sup>, Japanese Pharmacopoeia (JP)<sup>iii</sup>, British Pharmacopoeia (BP)<sup>iv</sup>, European Pharmacopoeia (EP)<sup>v</sup>, and International Organization for Standardization (ISO) ISO-9277<sup>vi</sup>. It is also discussed in several texts<sup>vii</sup>.

The way the sample is prepared is most often critical in determining whether the specific surface area of a sample is measured by dynamic flow or by static pressure. This is also true regardless of the underlying theory applied (e.g., Langmuir theory<sup>viii</sup>, Brunauer-Emmett-Teller (BET) theory<sup>ix</sup>, etc.).

## **SPECIFIC SURFACE AREA MEASUREMENT**

The method of specific surface area measurement by static pressure follows six general steps:

1. The surface of a known mass of sample is cleared of all adsorbed gases and water by some combination of vacuum, heat, and purging with an inert gas. This step is often referred to as “outgassing”. The conditions in which a sample is outgassed can often dictate the results of the measurement and are the focus of this paper.
2. The sample is then cryogenically cooled, typically with liquid nitrogen (77 K), liquid oxygen (90 K), or liquid helium (4 K).
3. The adsorbate gas, which is typically either nitrogen or krypton, is then dosed into the system at a series of reduced pressures. Note the reduced pressure ( $p/p_0$ ), is the pressure,  $p$ , of the adsorbate gas divided by its saturation pressure,  $p_0$ .
4. The gas is then adsorbed and the system is allowed to equilibrate, after which time the resultant pressure over the sample is measured.
5. The amount of gas adsorbed by the sample at each reduced pressure point is then used to construct an isotherm.
6. The theory of choice is then applied to the raw data, which yields the specific surface area of the sample.



Similarly, the method of specific surface area measurement by dynamic flow follows nine general steps:

1. The sample is properly outgassed to clear away all adsorbed gases and water by some combination of vacuum, heat, and purging with an inert gas.
2. The sample is then cryogenically cooled, typically with liquid nitrogen (77 K), liquid oxygen (90 K), or liquid helium (4 K).
3. The adsorbate gas mixture, which is typically nitrogen and helium, is then allowed to flow over the sample at a given reduced pressure. Note the reduced pressure is set by the composition of the gas.
4. The gas is then adsorbed and the system is allowed to equilibrate. During the equilibration, the baseline signal of the system is measured.
5. The sample is removed from its cryogenic cooling bath and quickly warmed to ambient temperature.
6. The nitrogen adsorbed on the surface of the material is then desorbed. The quantity of nitrogen desorbed is registered as the difference in signal from that of the measured baseline at equilibrium.
7. Steps 2 to 6 are then repeated with a different gas ratio thus different reduced pressure.
8. The amount of gas adsorbed by the sample at each reduced pressure point is then used to construct an isotherm.
9. The theory of choice is then applied to the raw data, which yields the specific surface area of the sample.

## OUTGASSING

As previously mentioned, the goal of outgassing is to clear away all adsorbed and absorbed gases and water by some combination of vacuum, heat, and purging with an inert gas. Ideally, this should be done at the highest temperature possible in order to reduce the outgassing time. However, the temperature must not be so high that it changes the structure of the sample.



If the vacuum method is used, a nonporous, macroporous, or mesoporous sample is most likely outgassed sufficiently if a residual pressure of approximately 1 Pa (7.5 mTorr) is achieved<sup>vii</sup>. Likewise, for a microporous sample, a residual pressure of approximately 0.01 Pa (0.075 mTorr) may need to be achieved. In order to reach this pressure, a diffusion or turbo molecular pump may be required.

However, these levels may not be achievable because of the vacuum pump, the volume of plumbing between the pump and the sample, the quality of the vacuum seals, and other factors. Thus, it is common to determine the minimum vacuum pressure of a system with no sample and use this as the goal during outgassing. For example, if the minimum vacuum pressure of a system with no sample is found to be 3 Pa (22.5 mTorr), then no amount of heating or purge gas can make the residual pressure over a sample any lower. Thus, the working target pressure may be  $\leq 4$  Pa (30 mTorr).

## **FLOW VS. VACUUM**

There are two commonly used methods to remove the water and contaminating gases from a sample. They are by flow and by vacuum, both of which are often accompanied by the addition of thermal energy<sup>vii</sup>. In the case of flow, a very low flow of pure inert gas is released in or slightly above the sample. The gas then carries away the desorbed water and contaminants. This is a very simple way to outgas a sample and does not require a vacuum pump, extensive tubing, valves, or other components.

Outgassing a sample by vacuum is also used extensively, especially when a sample may be particularly hazardous. As the pressure in the system is decreased, the amount of heat required to outgas the sample may be lower than that in the flow system. However, the vacuum system is often hampered by sample elutriation. Powder exists in a state of elutriation when the particle fines are drawn into the vacuum system.

Which system is used is often a matter of personal choice or instrument availability. However, it is most common to use flow for samples that are restricted by diffusion. This includes samples that are of a high specific surface area but are relatively non-porous, and samples having a high bulk density. Examples of these may include fumed silica and iron oxide, respectively. By contrast, outgassing by vacuum is most often used for materials that are sensitive to heat (i.e., a low thermal decomposition temperature or a low glass transition temperature, or samples that are porous, especially microporous materials). Examples of these may include magnesium stearate and zeolites.



## ADSORBED SURFACE WATER

All common surface area theories assume that the starting surface is clean and clear of all gasses, water, and other contaminants. Furthermore, it is assumed that surface active sites are energetically homogeneous. No interaction between adsorbed gas molecules in the initial monolayer is assumed for both the Langmuir theory and BET theory as well<sup>8,9</sup>.

Two cases can be thought of to illustrate the effect of water left on the surface. In the first case, which is that of an ideal surface, the starting material is completely outgassed, leaving a homogeneous surface. By contrast, the second case can be thought of as a surface with some water molecules remaining. The second case represents one of the types of water known as surface water, sometimes called physisorbed water.

In the latter case, as nitrogen molecules approach the surface, the water molecule may present an issue in terms of steric hindrance and molecular packing fraction, (i.e., additional nitrogen molecules cannot physically get to the surface because the water molecule is blocking the way). The net effect is that water and other contaminants may decrease the amount of adsorbate gas molecules that form the surface monolayer. In fact, if the surface is not sufficiently outgassed, the resulting specific surface area measurement is often biased due to the unavailability of portions of the surface to the adsorbate gas.

Physisorbed water is characterized by weak bonding<sup>x</sup>, often of the Van der Waals type, on the order of perhaps 10 kJ/mole or less. In some instances, the bond may be a stronger hydrogen bond, on the order of approximately 20 kJ/mole. Physisorption is also characterized by little or no evidence to support the perturbation of the electronic states of the adsorbent or adsorbate. Thus, the amount of energy required to remove it from the surface is typically low. However, transport processes such as diffusion may hamper the rate of removal.

## ABSORBED WATER AND POROSITY

The subject of porosity is often closely associated with gas adsorption and the measurement of specific surface area<sup>xi</sup>. A full discussion of particle porosity measurement is outside the scope of this article, but it is important to mention the existence of absorbed water. Where adsorption is a surface process, absorption is a bulk process. Thus, when speaking of absorbed water, one must assume the particle of interest is porous to some extent. There are many theories in existence that are used to estimate the porosity of a particle, but they generally all make use of the Kelvin equation (Equation 1).

$$\ln \frac{p}{p_0} = \frac{-2\gamma V}{rRT}$$

Equation 1



Where  $p/p_0$  is the reduced pressure,  $\gamma$  is the surface tension of the condensed gas,  $V$  is the molar volume of the condensed gas contained in a pore of radius  $r$ ,  $R$  is the ideal gas constant (8.314 J/mol K), and  $T$  is the temperature in K. For example, if degassing under vacuum, the minimum applied pressure,  $p$ , that is achievable is 3 Pa (22.5 mTorr), and the saturation pressure of water is about 610 Pa (4577 mTorr), this suggests pores with a radius of approximately 2.5 nm should be eventually evacuated at the applied vacuum pressure

The Kelvin equation and most porosity theories assume the pores are smooth cylinders, the walls of which are energetically homogeneous. In reality, the pores of a sample are quite often non-cylindrical. Some common pore shapes include slits, cylinders, funnels, ink bottles, and wedges. Some samples such as coal and other carbonaceous materials have pore structures that are quite tortuous. Thus, though the thermodynamics may dictate the pores should completely outgas at this pressure, the pore shape and degree of tortuosity often determine the kinetic rate at which the absorbed water is released.

To help put the energetics into perspective in relationship to physisorbed water, the enthalpy of vaporization for water is about 40.7 kJ/mol. Therefore, approximately one-half to one-fourth the amount of energy per mole is required to break a hydrogen bond and release a physisorbed water molecule from the surface than to release a water molecule in the gaseous state from the water in the liquid state found in a pore.

## WATER OF HYDRATION

Water of hydration, sometimes called water of crystallinity, may be thought of as water found in a crystalline substance that is chemically bonded to the central molecule such as a metal ion, non-metal ion, protein, etc.<sup>xii</sup> Perhaps the most well known examples of crystals that contain water, known as hydrates, are metal salts. These often have a molecular formula of the form:  $M_xA_y \cdot (H_2O)_n$  where  $M$  is a metal cation,  $A$  is an anion, and  $x$ ,  $y$ , and  $n$  are set by the stoichiometry of the molecule. For instance,  $CrCl_3 \cdot (H_2O)_6$ ,  $MnBr_2 \cdot (H_2O)_4$ ,  $FeCl_2 \cdot (H_2O)_6$ ,  $CuSO_4 \cdot (H_2O)_5$ , etc.

Sometimes, the water of hydration may also be referred to as chemisorbed water. Chemisorbed water is characterized by a strong covalent bond on the order of perhaps 250 kJ/mole. As opposed to physisorption, there is evidence to support the perturbation of the electronic states of the adsorbent and adsorbate. Thus, the amount of energy required to remove it from the sample is comparatively high.



## IMPORTANCE OF THERMAL ANALYSIS

Frequently, very little information accompanies the sample submission of an investigational material. Information of particular use would include a glass transition temperature if applicable, melting point, and decomposition temperature. In some cases, these values can be referenced in various texts or handbooks, or they can be found online or on a material safety data sheet (MSDS). However, when the data are not available or if the identity of the sample is unknown, it is vital to know the conditions in which the sample should be outgassed prior to analysis.

At a minimum, it is suggested the melting point be known for the material of interest. There are several commercially available capillary melting temperature instruments that may be used to get a quick and convenient answer. This device is that is cannot account for decomposition or a glass transition if one does occur. Alternatively, a more accurate and informative set of analyses would include thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC)<sup>xiii</sup>. Both TGA and DSC require minimal sample quantities (typically less than 10 mg).

The TGA records the mass of a sample as a function of temperature as the sample is heated, sometimes to 1000°C or higher. As water or other decomposition products are lost, the change in mass is recorded. Furthermore, if a material is prone to decomposition, the temperature at which this begins can be determined, as well as the amount of mass lost in the decomposition process. A common material used to check the performance of a TGA is calcium oxalate monohydrate. Shown below in Figure 1 is a typical TGA of calcium oxalate monohydrate.

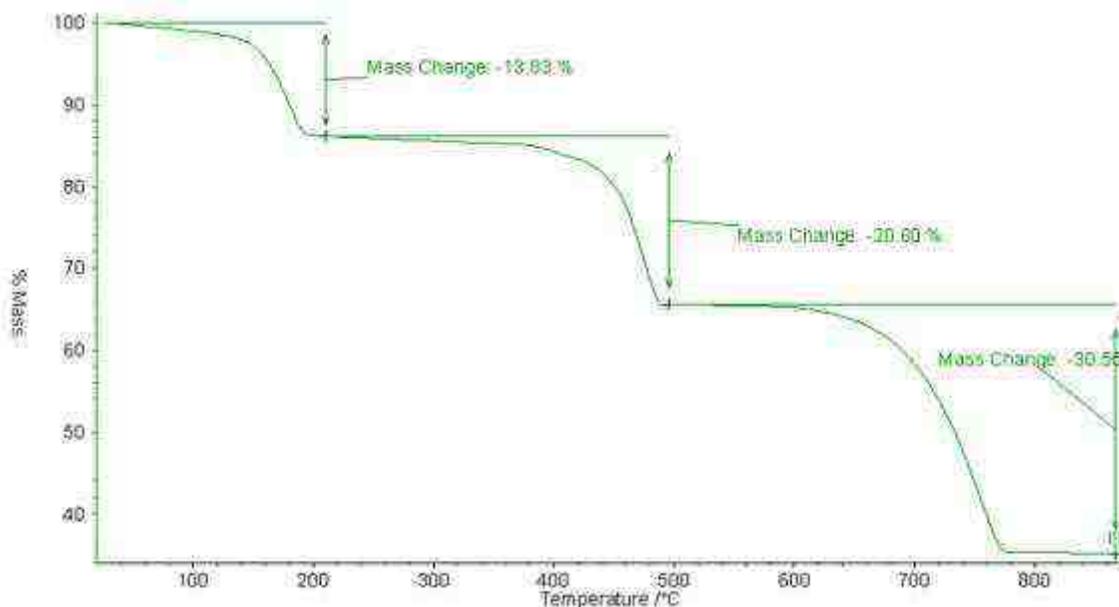
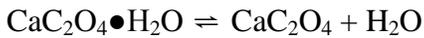


Figure 1 - TGA of calcium oxalate monohydrate



Calcium oxalate monohydrate undergoes three typical mass loss steps. The first is attributed to the loss of water of crystallization at about 190°C by the following equation:



This, in theory, accounts for a mass loss of 12%. The second mass loss is attributed to the loss of carbon monoxide at approximately 500°C by the following equation:



This, in theory, accounts for a mass loss of 19%. The final mass loss is attributed to the loss of carbon dioxide at about 780°C by the following equation:



This, in theory, accounts for a mass loss of 30%. TGA, however, is only a portion of the thermal data that may be necessary to make an appropriate decision regarding the proper outgassing temperature of an unknown or uncharacterized material.

The other thermal analysis technique that may prove useful is DSC. The DSC records the heat flow of a sample as a function temperature as it is heated to perhaps 500°C or higher. When the sample experiences either an exothermic or an endothermic event, this is indicated as a deflection in the DSC output. The most common endothermic events observed are glass transitions and melting. A common material used to check the performance of a DSC is Indium. Shown below in Figure 2 is a typical DSC of Indium.

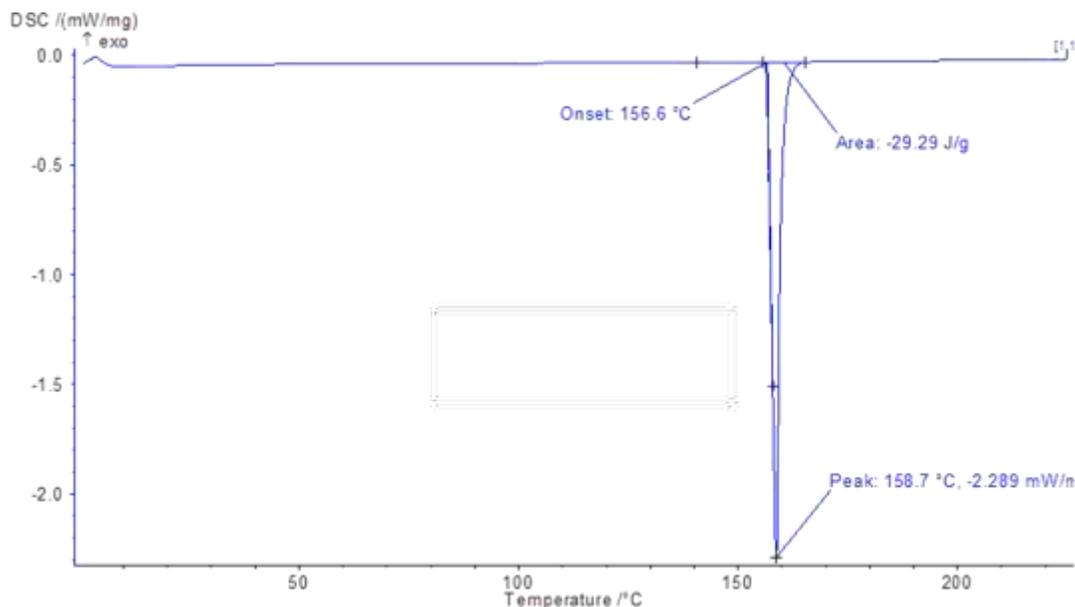


Figure 2 - DSC of Indium



As shown in Figure 2, endotherms or endothermic events are indicated as negative deflections or troughs. If there had been an exotherm or exothermic event, it would have been indicated as a positive deflection or peak. The endotherm shown in Figure 2 is attributed to the melting point of pure Indium with an onset of 156.6°C and a peak melting temperature of 158.7°C. This is in perfect agreement with the textbook melting point of 156.6°C.

## **SURFACE EFFECTS**

There are three characteristics of a particle that contribute to the specific surface area: size, porosity, and roughness. As expected, the smaller the size, the greater the porosity, and the greater the roughness, the larger the specific surface area. There are a variety of mechanisms which may affect a material during heating, some of which include sintering, melting, sublimation, and decomposition<sup>xiv</sup>. When outgassing a sample, it is vital the temperature be kept low enough to avoid melting, sublimation, and decomposition. Sintering, the less often considered mechanism must also be avoided in degassing because of its potential impact on the specific surface area.

Sintering may be defined as a process based on the atomic diffusion of solids in which at elevated temperatures, atoms may diffuse between two particles, fusing the two particles together. Sintering can even occur between surfaces of the same particle, for instance, within the pores of a particle. Sintering can affect the particle size, porosity, and roughness and is observed very frequently in materials that have a low  $T_g$  or a low melting point. A glass transition temperature is of great importance in the polymer industry and is commonly known as the temperature range over which a substance begins to act less like a hard solid and more pliable like rubber.

As an example, consider two hard, solid, porous samples with considerable surface roughness. As the temperature of the sample is increased and the  $T_g$  is exceeded, the solid may become pliable and the surface somewhat tacky. Thus, the probability of two or more particles sticking together is greatly increased. As more particles stick together, the surface area would decrease. In addition, the pores within the sample may begin to collapse or deform, again, decreasing the specific surface area. Finally, elevated temperatures often allow surface annealing. Annealing is as a process by which the surface rearranges itself in a manner to reduce the surface tension and surface energy. This is often accompanied by a smoothing of the surface or a decrease in surface roughness, which also decreases the specific surface area.

## **GENERAL CLASSES OF SAMPLES**

Although there are exceptions, most samples for which specific surface area is measured fall into one of seven groups. Each one of these groups will be discussed and suggestions will be made on how to outgas samples in each respective group. These groups include active pharmaceutical ingredients, materials that chemisorb or are microporous, magnesium stearate, excipients, amorphous nonmetal oxides, metal oxides, and ionic salts and crystalline nonmetal compounds.



## ACTIVE PHARMACEUTICAL INGREDIENTS (API)

The category of active pharmaceutical ingredients is obviously quite broad. The majority of API samples are crystalline, but some are also amorphous. Likewise, some are free bases while others are salt forms, e.g., •HCl, •succinate, or hydrates, e.g., •H<sub>2</sub>O, •2H<sub>2</sub>O. There are also the issues of stereoscopic purity, polymorphic forms, and stability to consider. All this complexity necessitates a very conservative approach. Unless data about the stability, T<sub>g</sub> (if applicable), melting point, and decomposition temperature are known *a priori*, it is suggested to outgas the material at 40°C or less for 2 hours or more until completed. This approach may not yield the fastest or most efficient method, but almost all API samples should be sufficiently stable when exposed to these conditions.

Another common practice is to outgas API materials at ½ the melting point. This practice works well for some compounds, but can sometimes lead to erroneous results, especially if a material has a glass transition temperature or if multiple polymorphic forms exist. This technique, while useful and possibly more efficient, should only be employed when sufficient sample information is available.

## ACTIVATED CARBON, ZEOLITES, CATALYSTS

Materials such as activated carbon, graphite, carbon black, zeolites, molecular sieves, metal catalysts, and certain ceramics are often best characterized by a Type I isotherm, which is associated with the Langmuir model. These materials generally exhibit a very high specific surface area (often in excess of 250 m<sup>2</sup>/g) and are frequently microporous.

In the case of some carbonaceous samples, it is suggested the outgas procedure follow two steps. The first step is to heat the sample at about 90°C for an hour under vacuum to remove the majority of oxygen from the sample and sample cell. In certain samples, there may also be residual solvent that is removed during the initial heating and evacuation step. After the first step, the temperature is typically increased to approximately 300°C for about 3 hours. The purpose of the first, milder step is to decrease the amount of oxygen available to the surface, thus decreasing the chance of forming oxidation products once heated to a higher temperature during the second step.

Zeolites in particular exhibit another mechanism, sometimes called steaming<sup>vii</sup>. This occurs because most zeolites exhibit a great deal of microporosity and tend to have a moderate amount of adsorbed and absorbed moisture. If the zeolite is heated too quickly, the absorbed water can be turned to steam inside the pores. This allows for the possibility of vaporization and recondensation within the pores, which can cause structural damage to the particle. In order to minimize the probability of steaming, like in carbonaceous samples, it is suggested the outgas procedure follow the aforementioned two-step process.



## MAGNESIUM STEARATE

Magnesium stearate, calcium stearate, and similar materials form a class by themselves due to increased difficulty in relation to outgassing and analysis. Magnesium stearate is a waxy, lamellar solid that exists in amorphous, anhydrous, mono-, di-, and tri-hydrate forms. Two of the prominent specific surface area instrument manufacturers, Quantachrome and Micromeritics, have written white papers about the difficulties of magnesium stearate analysis<sup>xv</sup>.

Most commercial grades of magnesium stearate also contain a distribution of fatty acids, (e.g., palmitic acid ( $\text{CH}_3(\text{CH}_2)_{14}\text{COOH}$ ), stearic acid ( $\text{CH}_3(\text{CH}_2)_{16}\text{COOH}$ ), arachidic acid ( $\text{CH}_3(\text{CH}_2)_{18}\text{COOH}$ ), etc.) and some contain cations other than magnesium, (e.g., calcium, sodium, potassium, etc.). Each of these combinations of metal cations and fatty acid esters has its own melting point, polymorphic forms, hydrate forms, glass transition temperature ranges, etc. Thus, defining a single glass transition temperature and melting point for this material is quite challenging. Depending on the source, grade, purity, etc., the glass transition temperature can be as low as perhaps  $40^\circ\text{C}$  to as high as perhaps  $60^\circ\text{C}$ . Likewise, the melting point can be as low as approximately  $75^\circ\text{C}$  to as high as about  $125^\circ\text{C}$ .

With a potential  $T_g$  as low as  $40^\circ\text{C}$  and a melting temperature as low as  $75^\circ\text{C}$ , the temperature at which the sample is outgassed is critical as shown in Figure 3. It is for this reason the suggested preparation conditions are  $40^\circ\text{C}$  or less for 2 hrs under vacuum. This is in agreement with the USP monograph for magnesium stearate<sup>xvi</sup>.

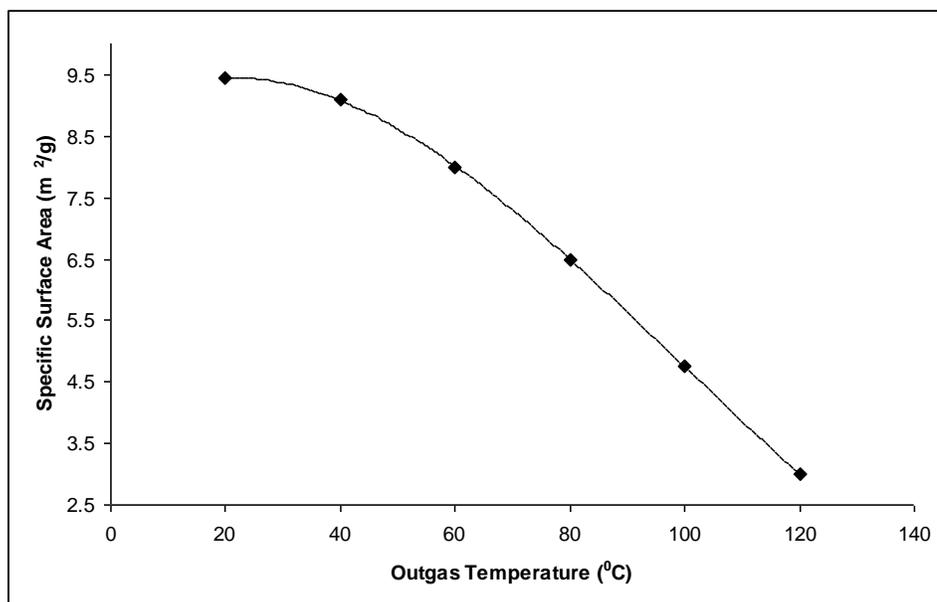


Figure 3 - Effect of outgas temperature on the specific surface area of magnesium stearate



## **EXCIPIENTS -- STARCHES, CELLULOSES, SUGARS, POLYMERS**

This is an extremely broad group of materials, especially if there are no criteria to narrow the group. In fact, any one of these sample types is actually a broad group in itself. However, if the broad group is streamlined by only including those of interest in the pharmaceutical business, the number of sample types is dramatically narrowed to those typically used as excipients or FDA approved additives. Some of the more common materials include waxy and dent starches; alkyl, hydroxyalkyl, and carboxyalkyl cellulose ethers; monosaccharides and disaccharides; and various polymers such as polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), and polymethyl methacrylate (PMMA)<sup>xvii</sup>.

In general, they are polymeric (except monosaccharides) and contain or are prone to hydrogen bonding. Some of them have glass transitions, and most of them begin to thermally decompose near their melting points. Because these materials are used so frequently, there is a wealth of readily available published information. For the less-used samples, TGA and DSC analyses are strongly encouraged.

As a rule, these materials need to be outgassed at a temperature that is typically about 10 to 20°C lower than the onset of their glass transition temperature or if one does not exist, at approximately ½ the melting point.

One note concerning these types of materials is the tendency to adsorb moderate amounts of surface water and the formation of hydrates. As is common with many polymeric materials, water can act as a plasticizer and can reduce the onset of the glass transition and melting temperatures. Thus, the amount of starting moisture in these materials can be very important when establishing an outgassing temperature.

## **AMORPHOUS OXIDES -- SILICA, ALUMINA**

This group includes all forms of silica, (e.g., fumed silica, precipitated silica, xerogels, aerogels, etc.). It also includes amorphous alumina (Al<sub>2</sub>O<sub>3</sub>) and titania or titanium dioxide (TiO<sub>2</sub>). Potentially other amorphous oxides such as germania (GeO<sub>2</sub>), zirconia (ZrO<sub>2</sub>), and ceria (CeO<sub>2</sub>) may also be put in this category, but far less data exist for these compounds than on silica and alumina.

The range of specific surface area for siliceous materials is quite broad. For instance, some precipitated silicas have a relatively low specific surface area (50 to 100 m<sup>2</sup>/g), while some aerogels have extremely high specific surface areas (>1000 m<sup>2</sup>/g). However, both materials are amorphous and their surfaces are populated with varying types and degrees of hydroxyl groups. The hydroxyl groups on a silica surface, Si-OH, are analogous to a carbon-based alcohol functional group, and are called silanols. Similarly, -OH groups exist in various forms on the surfaces of amorphous alumina, titania, germania, zirconia, and ceria, but they are typically just referred to as hydroxyl groups.



There are three types of silanols: isolated, vicinal, and geminal. Isolated silanols are as they sound – isolated from other surface silanol groups. Vicinal silanols are two or more silanols that are close enough the hydrogen atom of one silanol can hydrogen bond with the oxygen atom of an adjacent silanol. Geminal silanols are rare, but exist when two silanols extend from the same silicon atom. See Figure 4 below for an illustration of the silanol types. Note the horizontal line that connects all the silicon atoms is intended to represent the surface of the particle. It does not suggest there are Si-Si bonds present nor are any of the bond lengths drawn to scale.

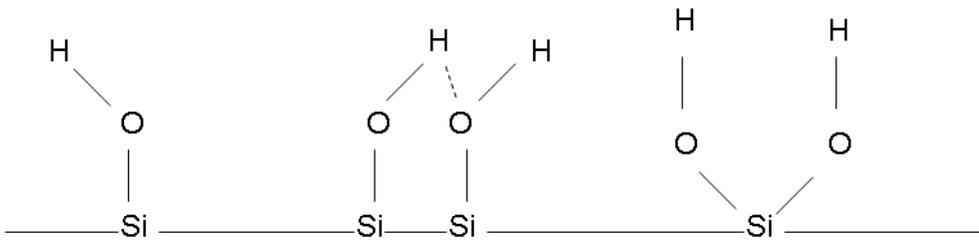


Figure 4 - Types of surface silanol groups: isolated (left), vicinal (middle), geminal (right)

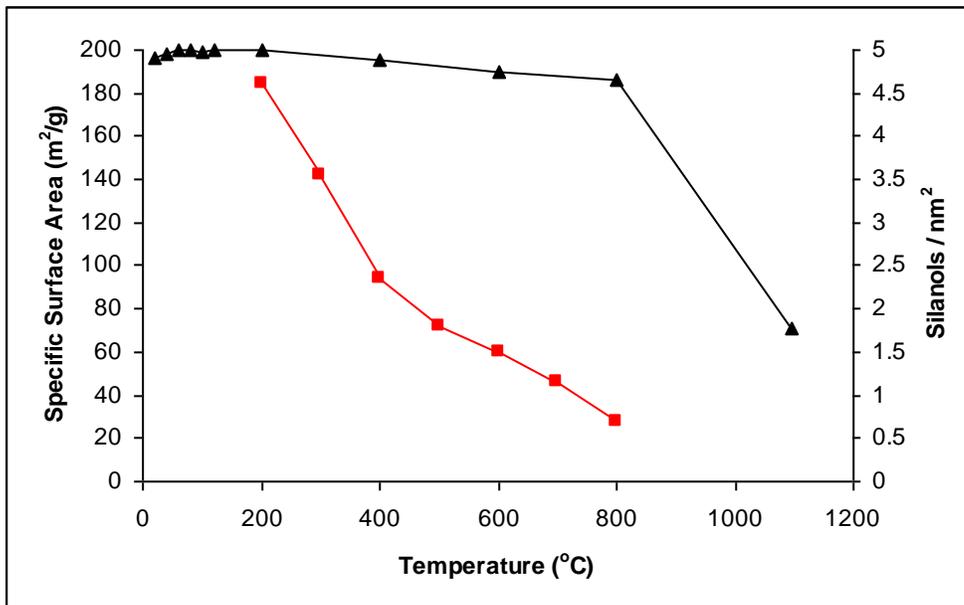


Figure 5 - Effect of outgas temperature on the specific surface area (black) and silanol concentration (red) of fumed silica

The reason why amorphous oxides are in a class by themselves is because they undergo similar mechanisms upon heating. In general, they can adsorb considerable amounts of surface water, which can be outgassed under reasonable conditions (100 to 200°C, < 2 hrs, by either flow or vacuum). There are data available to suggest surface annealing and considerable sintering may occur at temperatures above 800°C as shown in Figure 5.



What are not obvious from the specific surface area data alone are the changes to the surface chemistry through dehydroxylation over the range from about 200°C to approximately 650°C, which are supported by a wealth of FT-IR and <sup>29</sup>Si NMR data. The result of the dehydroxylation over the outgassing range from about 200°C to approximately 650°C is a decrease in the silanol population as demonstrated in Figure 5<sup>xviii</sup>. It is not until the sintering mechanism begins that the specific surface area is drastically reduced. The surface of a sample outgassed at 100°C cannot be considered energetically equivalent to the surface of a sample outgassed at 650°C, thus, these types of materials should not be outgassed above about 200°C.

### **METAL OXIDES -- TITANIUM DIOXIDE, ZINC OXIDE, IRON OXIDE, NICKEL OXIDE**

This group of materials is widely used in many applications other than pharmaceuticals and cosmetics, but among those regulated products, they are commonly used as pigments or sun blocking agents. They are generally crystalline materials with a relatively high density. They also have relatively high melting points as shown in Table I. It is also common for them to be found in multiple crystalline forms and for them to decompose after melting. As shown, the metals are generally transition metals and as such, can sometimes be found as oxides of two or more oxidation states, (e.g., Fe (II) oxide and Fe (III) oxide<sup>xix</sup>).

**Table I - Melting points of various metal oxides**

Material	M.P. (°C)
Cu <sub>2</sub> O	1235
CuO	1326
FeO	1377
WO <sub>3</sub>	1473
Fe <sub>2</sub> O <sub>3</sub>	1566
TiO <sub>2</sub>	1843
CoO	1933
NiO	1955
ZnO	1975
Cr <sub>2</sub> O <sub>3</sub>	2435
ZrO <sub>2</sub>	2715

By far, the largest majority of these materials can be outgassed at relatively high temperatures (250 to 300°C) until complete. Outgassing may require several hours, depending on the mass of sample, the initial moisture level, and the crystalline form of the material. Because of their high densities, it is common to outgas this class of materials using the flow method, rather than vacuum.



## IONIC SALTS & CRYSTALLINE NONMETALS

This group is primarily comprised of ionic salts, (i.e., those composed of a metal cation such as Li, Na, K, Mg, or Ca, and a nonmetal anion such as carbonate, sulfate, phosphate, hydroxide, chloride, nitrate, etc.). Also in this group are crystalline nonmetals such as quartz, talc, various clays, and alumino-silicates.

Though this would appear to be a group of miscellaneous materials, they do have several properties in common. The first commonality is that they are all crystalline, though their crystalline forms widely vary. They are generally inorganic materials with the exception of those that contain carbonates, citrates, cyanates, etc. Most of these materials, with the exception of some of the clays and alumino-silicates, are non-porous. The materials that are porous tend to have meso or macropores. They generally have a moderate density, though normally less than the metal oxides. It is also common for them to decompose after melting. Some of them have very high melting points, while others are somewhat low as shown in Tables II<sup>xix</sup> and III<sup>xx</sup>. In general, they do not have a glass transition temperature.

**Table II - Melting points of various ionic salts**

Material	M.P. (°C)	Material	M.P. (°C)
Li <sub>2</sub> CO <sub>2</sub>	723	KOH	360
Li <sub>3</sub> PO <sub>4</sub>	837	KCl	770
LiOH	450	KNO <sub>3</sub>	334
LiCl	605	MgCO <sub>3</sub>	350
LiNO <sub>3</sub>	264	MgSO <sub>4</sub>	1124
Na <sub>2</sub> CO <sub>3</sub>	851	MgCl <sub>2</sub>	714
Na <sub>3</sub> PO <sub>4</sub>	100	Mg(OH) <sub>2</sub>	350
NaOH	318	CaCO <sub>3</sub>	1339
NaCl	801	CaSO <sub>4</sub>	1460
NaNO <sub>3</sub>	307	CaCl <sub>2</sub>	782

**Table III - Melting points of various minerals**

Material	M.P. (°C)
Quartz	1715
Talc	1050
Kaolin	1750
Corundum	2035
Bentonite	1250



Because these materials do not have a glass transition temperature, melting and decomposition that often occurs immediately following melting must be avoided. It is suggested these materials be outgassed at a maximum temperature of  $\frac{1}{2}$  their respective melting points. Typically, the choice of vacuum or flow outgassing does not matter.

## **IMPLICATIONS OF SURFACE AREA TESTING FOR COMPLIANCE PERSONNEL**

Compliance personnel should have a general understanding of the principles, methods and instrumentation associated with specific surface area methodology. This testing is widely used in pharmaceutical manufacturing to control incoming materials and as an in-process control test. Recommended test methods for several categories of widely used pharmaceutical materials are discussed above. Compliance personnel should be vigilant in the following, any of which may potentially affect the accuracy of specific surface area determinations:

- Testing instrumentation: Test instruments must be qualified and appropriately maintained. Testing parameters must use calibrated standards where possible to assure reproducible instrument performance.
- Test methods: Development of test methods must be technically based, considering physiochemical properties of the materials of interest. Test method development must be thoroughly and accurately documented for future reference. Test methods should include instrument specific parameters such as the number and range of reduced pressure points, as well as the theory applied to the data (i.e., BET or Langmuir theory, etc.). Test methods should also include sample preparation and outgassing conditions.
- Personnel training: Personnel operating equipment must be appropriately trained. When multiple personnel perform tests on materials over an extended time period such as material stability testing, variation in test results due to analyst performance must be considered.
- Change control: Changes must always be recognized. Changes with potential for effects on data include materials from new vendors, new personnel conducting testing, testing conducted by new laboratories (outsourcing), changes in test methodology, and other potential changes.

Specific surface area testing is a well-established and reliable testing methodology. However, like any testing, the potential for variable or erroneous test results is present when details of methods, instruments, performance, or other factors are not adequately controlled.

## **CONCLUSIONS**

When measuring specific surface area, the conditions in which a sample is prepared often dictate the results. The goal of outgassing is to clear away all adsorbed and absorbed gases and water by some combination of vacuum, heat, and purging with an inert gas. When doing so, the temperature must not be so high the material passes through a glass transition temperature, sinters, anneals, melts, sublimates, or decomposes. An attempt is made to divide common samples into groups. A summary of these recommendations is given in Table IV.



**Table IV - Summary of outgassing conditions by material type**

<b>Material Type</b>	<b>Flow or Vacuum</b>	<b>Temp. (°C)</b>	<b>Duration (hr)</b>
Active pharmaceutical ingredients	Either	40 or ½ melting point	≥ 2
Activated carbon, zeolites, catalysts	Vacuum	90 then 300	1 then ≥ 3
Magnesium Stearate	Vacuum	40	2
Excipients, e.g. starches, celluloses, sugars, polymers	Either	20° < Tg or ½ melting point	≥ 2
Amorphous oxides, e.g. silica, alumina	Either	100 to 200	≥ ½
Metal oxide, e.g. titanium dioxide, zinc oxide, iron oxide, nickel oxide	Flow	300	≥ 2
Ionic salts & crystalline nonmetals	Either	300 or ½ melting point	≥ 2



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