Surface Area of Magnesium Stearate Using the Volumetric Method

Relevant for: Dietary supplements, pharmaceutical researchers and manufacturers, excipients, formulation tablets and capsules.

Magnesium stearate, a waxy, lamellar (platy) solid, is a widely used excipient in pharmaceutical technology. Primarily, magnesium stearate is added to a formulation in order to modify compaction behavior and reduce ejection forces from tablet dies and is available in a range of grades having similar or different surface area. The NOVAtouch is ideal for specific surface area measurements according to USP <846> Method II (volumetric method) and the well-known BET [1] calculation described therein.

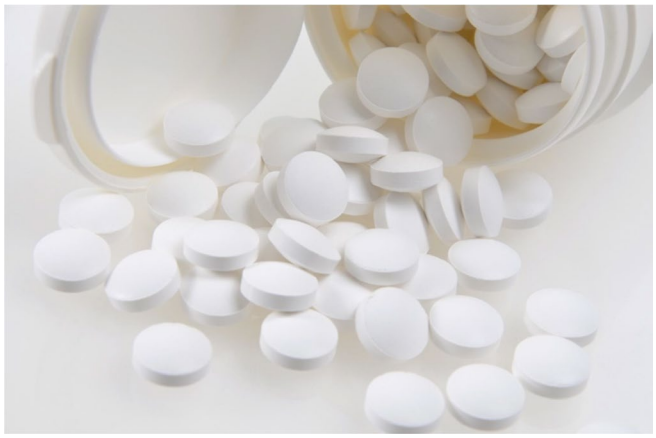

Figure 1: Magnesium Stearate commonly used in pharmaceuticals and dietary supplements.

1 Why measure the surface area of magnesium stearate?

The specific surface area of any solid relates to its particle morphology including porosity, aspect ratio, and fineness, and can be indicative of its manufacturing and thermal history and its suitability in a specific application. The preferred physical form of magnesium stearate has a lamellar structure that has a low shearing force, thereby imparting a means of dry lubrication between a compacted powder and the walls of a tablet die, when properly blended with the active pharmaceutical ingredient and other excipients.

It is also largely hydrophobic, however, and can impart undesirable effects to the dissolution profile of a solid dosage form. Pharmaceutical formulations are optimized with respect to both effective lubrication and desirable Bio-availability, which can be mutually counter-productive.

The surface area of pharmaceutical grade magnesium stearate is formally recognized as an important characteristic and its analysis is formalized in the USP Monograph "*Magnesium Stearate*." The analytical method is described in USP chapter <846> [2] together with conditions specific to magnesium stearate stated in the aforementioned monograph.

2 Which instrument is used?

For this analysis, conforming to USP<846> Method II, the **NOVAtouch** gas sorption analyzer is recommended. This instrument has integrated sample preparation stations for degassing the sample to prepare the surface for analysis, as described in the aforementioned methodology. Analysis on one set of samples can proceed while degassing the next set of samples.

The **NOVAtouch** is available with 21 CFR Part 11-compatible software to ensure the integrity of the analytical data and comply with the food and drug regulations of many countries.

3 Which samples are tested?

Commercial samples of magnesium stearate having unknown surface areas have been analyzed to determine the appropriate linear P/P0 range and whether in fact it falls within the requirements of the USP method. Not all grades of magnesium stearate and certainly not all brands of the material behave in an identical manner in this regard. The two samples used for this robustness evaluation were from the same manufacturer and represented two lots of the same material.

4 Measuring the samples

The monograph indicates that data points in the range 0.05 to 0.15 P/P0 should be used; however if the resulting BET plot is not sufficiently linear, then a different range can be taken but should be clearly stated when reporting the results. In this study, eleven data points were programmed to be measured over the nominal range 0.05 to 0.30 P/P0, since the exact behavior of these samples was not known in advance. Three specific ranges of P/P0 could then be extracted to evaluate the robustness of the method.

4.1 Sample preparation

According to the USP monograph samples were degassed at 40°C under vacuum, for 2 hours in a pre-weighed sample cell that will also be used for the measurement. The filler rod is not inserted into the cell during degassing, only for the actual measurement step. After degassing, the sample cell is backfilled with nitrogen and cooled to room temperature while capped. The dry sample weight is determined by difference from the empty "*tare*" weight of the sample cell recorded earlier.

4.2 Sample analysis

The **NOVAtouch** can operate with pre-calibrated sample cells thereby avoiding the use of helium gas, or can operate in classical helium void volume mode. In this case, helium mode was chosen to help understand the samples' susceptibility to morphological change. Indeed, there are a number of additional factors that can influence the end result according to the susceptibility of any given magnesium stearate sample to its time being cooled to liquid nitrogen temperature. These are discussed in Section 6.

Parameter	Used	Comments
Sample cell type	9mm large bulb with filler rod	9 mm or 12 mm stem to facilitate sample loading
Sample mass	~1.35 g dry weight	Typically 0.5 g to 1.5 g
Outgassing mode	Vacuum mode	Alternatively dry purge can be used
Operating mode	Helium mode	Normally NOVA mode would be preferred
Thermal delay	120 seconds	Depends on sample size
Equilibrium pressure tolerance	0.05	Typical
Equilibration time	200	To understand the samples' susceptibility to morphological change
Equilibration timeout	400 seconds	Typically twice the Equilibration time
P_0 type	"P_0 calculate"	To reduce time in liquid nitrogen
Cross-over pressure	38 torr	Lower pressures for more powdery samples

Figure 1. Analysis parameters for magnesium stearate.

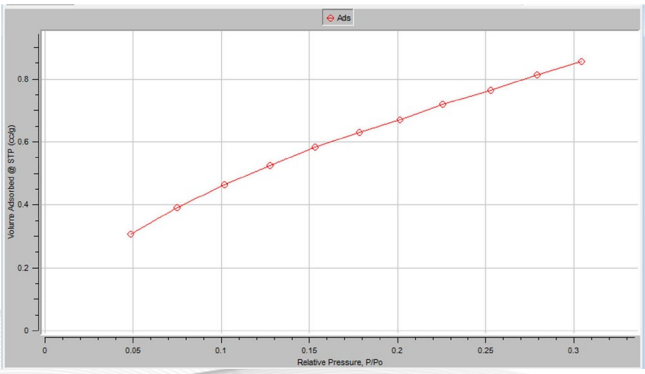

Figure 2. Eleven point isotherm of Magnesium Stearate, Sample 1.

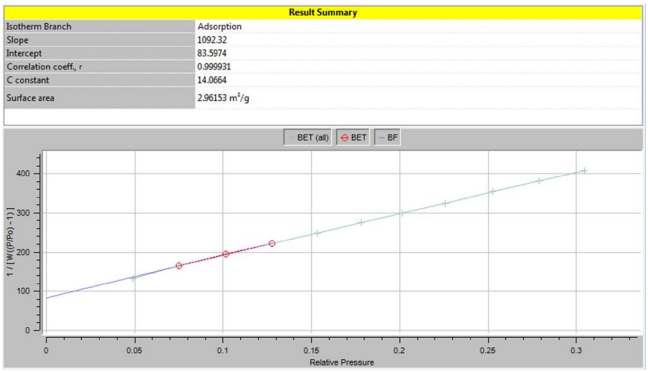

Figure 3. Corresponding three point BET plot.

5 Results

For both samples the BET specific surface area (SSA) was calculated using (i) the entire range of P/P_0 values measured, (ii) the nominal range indicated by the USP monograph and (iii) an automatic software method based on the uppermost extent of linearity in the BET plot [2]. The linearity in each range (correlation coefficient, r) plus the BET "*C*" constant were also evaluated by the software automatically as part of the BET calculation and report. These are shown in the tables below.

Sample	SSA(i) 11 points m2g-1	SSA (ii) 3 points m2g-1	SSA (iii) 7 points m2g-1
1	3.032	2.962	3.067
2	2.824	2.786	2.843

Table 2: BET specific surface area of the two samples calculated using points in the three ranges described in the text.

Sample	r (i) 11 points	r (ii) 3 points	r (iii) 7 points
1	0.999856	0.999931	0.999915
2	0.999971	0.999994	0.999968

Table 3: BET correlation coefficient of the two samples calculated using points in the three ranges described in the text.

Sample	"*C*" (i) 11 points	"*C*" (ii) 3 points	"*C*" (iii) 7 points
1	13.5	14.1	12.8
2	14.0	14.4	13.6

Table 4: BET "*C*" constant of the two samples calculated using points in the three ranges described in the text.

In both cases the BET results for all three computed ranges show remarkable stability across the range of experimental values used in the calculation. In all cases the correlation coefficient satisfies the USP <846> minimum requirement of 0.9975 which denotes a suitable liner correlation in the BET plot. Nevertheless, the nominal range indicated by the magnesium stearate monograph shows slightly increased linearity (notwithstanding the small number of points used – which is still in accordance with USP<846>). The usual value of "C" for magnesium stearate is 14, and again the closest agreement with that comes from data within the nominal range, even though all results show remarkably good agreement within expectation.

It should be noted that this study not only determined the BET specific surface area of two closely related samples, but demonstrated that their morphologies were strikingly resistant to change when exposed to the extreme temperature of liquid nitrogen. This is consistent with the quite low surface areas which itself suggests a rather stable form of the material.

6 Effect of Experimental Parameters

Many experimental parameters and conditions can be adjusted to improve the quality of the data and still remain within the guidelines of USP<846>. Some of these are discussed here to provide guidance for the user.

Sample cell type: For ease of loading and emptying sample into and from the cell, a 9 mm or 12 mm stem cell should be used and of the "*large bulb*" type to enhance rapid cooling and equilibration of the sample. The sample should be distributed around the walls of the bulb simply by turning the cell, especially immediately prior to starting the measurement step. This ensures the best thermal contact of the material with the cell, hence fastest cooling in liquid nitrogen.

Sample mass: The monograph does not indicate a specific sample mass to be used, but typically 0.5 g to 1.5 g are taken according to the anticipated specific surface area. If possible, it is preferred that there be 2–5 m^2 of total surface area in the cell. Unnecessarily large sample masses lead to excessive analysis times, which might lead to temperature/time related changes in the magnesium stearate morphology, and therefore its surface area.

Outgassing mode: It is acceptable to prepare the sample under a flow of dry inert purge gas (such as nitrogen or helium) or by evacuation for the requisite time.

Operating mode: Using pre-calibrated cells (NOVA mode [4]) reduces the time for which the sample is immersed into the liquid nitrogen. Therefore, for susceptible samples, this mode should be chosen, in which case the operator should know the true density of the sample and enter it when prompted, or select "*measure volume*" as the method for correcting the empty cell calibration. Using helium eliminates the need for both cell calibration and knowing the sample density.

Thermal delay: The time that the sample is precooled before the actual measurement phase begins is adjustable. Longer times ensure full thermal equilibrium and highest quality results but reduce sample throughput. Furthermore, this time can increase the chance of morphological change. Shorter times avoid the negative effect of too long a time in liquid nitrogen, but can lead to temperature gradients in the sample and non-linearity in the BET data. A reasonable compromise is to enter the combined time based on 30 seconds per gram per sample, with no less than 60 seconds total. For example, 3 samples, each 0.5 g can be analyzed with reasonable confidence if a time of 60 seconds is used. However, 3 samples of 1.5 g each require no less than 135 seconds.

Equilibrium pressure tolerance: Sufficiently tight tolerance should be set for equilibrated data without causing undue delay. A value of 0.05 torr is reasonable in most cases.

Equilibration time: Since equilibrium is detected by the instrument as when the pressure change over the "*equilibration time*" is less than the "*equilibrium pressure tolerance*", this time determines the rate at which the pressure is changing. Too long a time will unnecessarily lengthen the total analysis time and, in the case of some samples, promote the morphological change. 0.1 torr in 60 seconds is the same rate as 0.05 torr in 30 seconds, but the latter condition is actually met sooner, but more susceptible to noisy signal.

Equilibration timeout: If the sample is changing during the analysis, it tends to increase in surface area, and can cause equilibration to take even longer than normal. This timeout curtails the process and causes the analysis to proceed at a more reasonable rate. The timeout value is typically twice the equilibration time value.

P_0 type: P_0, the saturation pressure of the analysis gas at the analysis temperature, is required to calculate surface area as it relies on the relationship between the amount of gas adsorbed and P/P0, the relative pressure of the gas. The BET method is very tolerant of small uncertainties in the P0 value, so a very precise determination of it is not needed. Rather than having the NOVAtouch measure P0 while the sample is in liquid nitrogen, the "*P0 Calculate*" or "*P0 Entered*" modes are recommended.

Cross-over pressure: The overall rate at which the NOVA evacuates the sample(s) is determined by the crossover pressure from fine (slow) to coarse (fast) evacuation. Most magnesium stearates are somewhat "*sticky*" and do not usually presents an elutriation problem.

7 Conclusion

The NOVAtouch LX4 is perfectly suited for measuring the surface area of pharmaceutical grade magnesium stearate according to the strict requirements of USP <846> (a harmonized standard), and the USP Monograph, when used within the guidelines set out in this report. It is also possible to determine a given sample's morphological stability which can be useful when selecting a certain grade of material for a particular functionality on formulation and tableting.

8 References

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2. USP 34 / NF 29 Specific Surface Area / Physical Tests.

3. Rouquerol, J., Llewellyn, P., & Rouquerol, F. (2007). Is the BET equation applicable to micro porous adsorbents? Studies in surface science and catalysis, 49–56.

4. Lowell, S. (1994). U.S. Patent No. 5,360,743. Washington, DC: U.S. Patent and Trademark Office.

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