Application of Multivariate Methods to Evaluate the Functionality of Bovine- and Vegetable-Derived Magnesium Stearate

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ABSTRACT: This work distinguishes and quantifies the effects of bovine- and vegetable-derived magnesium stearate (MgSt) molecular and macroscopic properties on lubrication efficiency using multivariate analysis. Principal component analysis (PCA) and partial least-square regression (PLS) were used to evaluate and quantify the lubricant effectiveness on a model tablet formulation. PCA score and loading plots showed a separation of model formulations based on the MgSt sources, which indicated different bovine- and vegetable-derived MgSt lubrication potential. PLS quantified the MgSt molecular [enthalpy of dehydration (ΔHd), enthalpy of melting (ΔHm), percent crystallinity, and moisture content] and macroscopic [particle size (d_{50}), specific surface area (SSA-MgSt), and MgSt Hausner ratio (HF-MgSt)] properties, their interactions, and square effects on formulation powder flow and tableting properties relating to MgSt's lubrication effectiveness. For crystalline MgSt, moisture content, HF-MgSt, d_{50}, and SSA-MgSt showed a major influence on the lubrication efficiency compared with the other MgSt molecular properties (percent crystallinity, ΔHm, and ΔHd). Amorphous MgSt showed poor lubrication, and none of its molecular or macroscopic properties showed significant effects on lubrication efficiency. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:1466–1477, 2014

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INTRODUCTION

A critical step in the development of a "robust pharmaceutical manufacturing process" is to understand the material property attributes of all components of the formulation. This is because a small variation in the physical and chemical properties of the materials might have unpredictable effects on the resulting product properties. Thus, such in-hand knowledge of the material property attributes might enable a formulation scientist to gain formulation confidence about the new materials at an early development stage of the tablet manufacturing process, where a limited amount of the material is available. This material science knowledge can lead to material sparing product design strategies, decrease the risk of design failure, and increase the speed to market. Furthermore, establishing a fundamental understanding of the input material properties is consistent with the US Food and Drug Administration (FDA) and the International Conference on Harmonization Q8 "Process Analytical Technology" guidance that focuses on a "Quality-by-Design" rather than an end product quality control of pharmaceuticals.[1,2]

Magnesium stearate (MgSt) is a well-known lubricant used to reduce the die wall friction during the compression and ejection of the tablet, as well as to improve the flow properties of the tablet formulation.[3] MgSt forms an adsorbed lubricant film around the host particles during mixing. The MgSt lubricant film acts as a physical barrier that decreases the adhesive interactions between the powder particles and die wall leading to a decrease in the tablet ejection force (EF). This film also decreases the strong cohesive interactions between the host particles.[4] This phenomenon leads to an improved flow property of the formulation, reduction of the tablet crushing strength, increase in the tablet disintegration time, and decrease in the tablet dissolution rate.[3] From the literature, it is known that the lubrication effectiveness of the MgSt depends on MgSt concentration and macroscopic properties such as particle shape, particle size, and particle-specific surface area. It also depends on the moisture content, number of water molecules incorporated in the crystal lattice such as anhydrate, dihydrate or trihydrate, and varying degrees of molecular order associated with these pseudopolymorphs.[5–7]

In the present study, MgSt has been chosen as a model material to distinguish and quantify its material property attributes on the tablet manufacturing process and the tablet characteristics. MgSt is widely used as a lubricant in tableting and capsule filling processes.[8] In the past, the pharmaceutical industry used bovine-derived MgSt as the primary source of MgSt. Today, companies have switched to vegetable-derived MgSt because of reports of life-threatening bovine diseases such as mad cow and foot and mouth disease.

Not surprisingly, MgSt obtained from different sources show differences in their lubrication effectiveness.[9] This can cause changes in the quality attributes of the final product and may even lead to one or more processing problems such as poor formulation flowability, weaker tablet mechanical strength, tablet capping, and tablet lamination.[10,11] As a result, changes in the sources of MgSt have been considered as a major change by the FDA. This requires suitable studies to demonstrate equivalence between product formulated with bovine- and vegetable-derived MgSt (MgSt-V).[12]

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Thus, the aim of the present study was to employ multivariate analysis (MVA) methods such as principal component analysis (PCA) and partial least-square regression (PLS) to distinguish and quantify the MgSt lubrication effects of the different lots and sources of MgSt. The use of MVA can mine complex datasets and model hidden phenomena that can lead to unexpected results. Initially, molecular and macroscopic properties of different lots of bovine–derived MgSt (MgSt-B) and MgSt-V were analyzed and evaluated. The molecular properties included moisture content, enthalpy of melting, enthalpy of dehydration, and percent crystallinity. The macroscopic properties evaluated were particle size (d_{50}), particle morphology, specific surface area (SSA-MgSt), and Hausner ratio (HF-MgSt). The lubrication effects of these MgSt lots were assessed using a model acetaminophen tablet formulation. Finally, MVA methods such as PCA and PLS were used to distinguish and quantify the MgSt lubrication effects of the different lots and sources of MgSt.

MATERIALS

Two lots of MgSt-B [Lot no. K30W058 (MgSt-BL1) and Lot no. JO4X062 (MgSt-BL2)], and two lots of MgSt-V [Lot no. SZBA2930V (MgSt-VL1) and Lot no. SZBB1870 (MgSt-VL2)] were purchased from Alfa-Aesar (Ward Hill, Massachusetts), and Sigma–Aldrich (St. Louis, Missouri), respectively. Compap™ L, acetaminophen (90%) (Lot no. 099311V567) was purchased from Covidien Mallinckrodt (Raleigh, North Carolina), whereas Foremost® NF Lactose (lactose monohydrate, Lot no. 8509041961) was purchased from Foremost Farms (Baraboo, Wisconsin).

METHODS

Molecular and Macroscopic Characterization of MgSt-B and MgSt-V Powders

Dynamic Moisture Sorption–Desorption–Resorption Studies

Magnesium stearate powder was placed in a carbonized glass pan and moisture sorption–desorption–resorption studies were carried out in triplicate using the Q5000 Sorption Analyzer (TA instruments, New Castle, Delaware). Sorption is a term that includes both absorption and adsorption. Initially, the sample was equilibrated at 25°C and 40% relative humidity (% RH). Sorption studies were carried out by exposing MgSt powder from 40% RH to 90% RH. Desorption studies were carried out by lowering the % RH from 90% RH to 0% RH, whereas resorption studies were carried out by increasing the % RH from 0% RH to 60% RH. All sorption–desorption–resorption protocols increased the % RH in 10% RH increments.

Powder X-Ray Diffraction

The powder X-ray diffraction (PXRD) pattern for both lots of MgSt-B and MgSt-V was obtained using a Rigaku Ultima-IV X-ray powder diffractometer (Rigaku Americas, The Woodlands, Texas) equipped with a Bragg–Brentano geometry (θ/2θ) optical setup. The diffraction was monitored with a scintillation counter detector. Monochromatic CuKβ radiation ($\lambda = 1.5406$ Å) was used at an operating voltage and amperage of 40 mV and 44 mA, respectively. A MgSt powder sample was mounted evenly as a thin layer on a glass slide. Samples were scanned at 2.00° 2θ/min from 2° to 50° 2θ.

Determination of Percentage Crystallinity

The percentage crystallinity calculations of MgSt powder were based on the assumption that the experimentally measured crystalline and amorphous X-ray intensities were proportional to the crystalline and amorphous fractions of the sample. The percentage crystallinity of MgSt powder was estimated from Eq. (1).[13,14]

$$\text{Crystallinity}\,(\%) = \frac{100A_c}{A_c + A_a} \tag{1}$$

where A_c and A_a represent the respective area contributions from the crystalline and amorphous phases of MgSt powder to the diffractograms. The total area underneath the X-ray peaks ($A_c + A_a$) was calculated between 2° and 50° 2θ using the PDXL software version 1.8.03 (Rigaku Americas).

Differential Scanning Calorimetry/Thermogravimetric Analysis

Both lots of MgSt-B and MgSt-V were analyzed by differential scanning calorimetry/thermogravimetric analysis (DSC/TGA). DSC measurements were carried out using a DSC Q200 (TA instrument) with samples of approximately 5 mg weighed into nonhermetically sealed aluminum pans. Samples were heated at 10°C/min from 10°C to 270°C.

Thermogravimetric analysis measurements were carried out using a TGA Q500 (TA instrument) with samples of approximately 6 mg weighed into the platinum pan. Samples were heated at 10°C/min from 25°C to 350°C.

In both DSC and TGA, nitrogen was used as a purge gas. In DSC, nitrogen flow rate was 40 mL/min. In TGA, nitrogen flow rate was 60 mL/min through the furnace. Data analysis was performed using Universal Analysis software version 4.5A (TA instrument). All DSC and TGA measurements were performed in duplicate.

Particle Size

Dry powder laser diffraction analysis was performed in triplicate (Mastersizer® 3000 Malvern Instruments Limited, Worcestershire, UK).

Particle Morphology

Samples were mounted on an aluminum base with adhesive carbon tape. Prior to scanning electron microscopy (SEM) (JEOL JSM-6400F FESEM; Japan Electron Optics Laboratory, Ltd., Tokyo, Japan) examination, all samples were sputtered with 60% gold and 40% palladium under vacuum 10^{-4} Torr for approximately 300 s.

Brunauer–Emmett–Teller-Specific Surface Area Analysis

Brunauer–Emmett–Teller-specific surface area (m^2/g) was determined from N_2 adsorption isotherms measured at 77.30 K using a Micrometrics Tristar II 3020 V1.04 (Micromeritics Instrument Corporation, Norcross, Georgia). Specific surface area (SSA-MgSt) was calculated from Eq. (2) derived from BET theory.[15,16]

$$S = \frac{V_m N a}{m \times 22,400} \tag{2}$$