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Research Article

Difference in the Lubrication Efficiency of Bovine and Vegetable-Derived Magnesium Stearate During Tabletting

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Abstract. The purpose of this work was to evaluate and compare the functionality of bovine fatty acids-derived (MgSt-B) and vegetable fatty acids-derived (MgSt-V) magnesium stearate powders when used for the lubrication of granules prepared by high-shear (HSG) and fluid bed (FBG) wet granulation methods. The work included evaluation of tablet compression and ejection forces during tabletting and dissolution testing of the compressed tablets. Granules prepared by both granulation methods required significantly lower ejection force ($p<0.01$) when lubricated with the MgSt-V powder as compared to those lubricated with the MgSt-B powder. Granules prepared by the HSG method and lubricated with the MgSt-V powder also required significantly lower compression force ($p<0.01$) to produce tablets of similar weight and hardness as compared to those lubricated with the MgSt-B powder. The dissolution profiles were not affected by these differences and were the same for tablets prepared by same granulation method and lubricated with either magnesium stearate powder. The results indicate significant differences ($p<0.01$) between lubrication efficiency of the MgSt-B and the MgSt-V powders and emphasize the importance of functionality testing of the MgSt powders to understand the impact of these differences.

KEY WORDS: characterization; fluid bed granulation; functionality testing; high-shear granulation; lubricant efficiency; magnesium stearate.

INTRODUCTION

Magnesium stearate (MgSt) is a widely used lubricant in the pharmaceutical industry for the manufacturing of tablet dosage form. The recent increase in the life-threatening bovine diseases, e.g., mad cow disease, foot and mouth disease, etc., has resulted in MgSt manufacturers switching over from the bovine-derived fatty acids to the vegetable-derived fatty acids as the starting material to synthesize MgSt powder. This difference in the starting fatty acids results in a change in the technical grade of the MgSt powder. A change in the technical grade of this excipient is considered as a major change by the United States Food and Drug Administration and requires studies to demonstrate equivalence between the products formulated before and after implementing this change (1,2). The primary function of MgSt powder is to lubricate the die walls and assist in the ejection of the compressed tablet from the die. Therefore, determination of the functional equivalency of the MgSt as an efficient die wall lubricant for powders derived from these two fatty acid sources also becomes crucial. The authors have earlier reported differences in the lubrication efficiency of the bovine and vegetable-derived magnesium stearate powders when used to lubricate dry granulated products (3). Granules prepared using different granulation methods may not always show differences in lubrication efficiency between the two grades of magnesium stearate powder; additional studies are warranted to examine the effect of this variation on the wet granulated product. Additional, non-compendial analytical techniques were also used to identify potential differences between these two grades of MgSt powder.

Previous studies have indicated that pharmaceutical product quality is sensitive to differences in the MgSt powders, and the product quality may be compromised if it does not perform as expected, leading to processing problems, e.g., poor tablet hardness, chipping, lamination, etc. or change in the drug product release profile (4–6). Due to this reason, for some formulations, a switch from the bovine fatty acids-derived MgSt powder (MgSt-B) to the vegetable-derived MgSt powder (MgSt-V) may also necessitate a change in the concentration of MgSt powder to obtain equivalent lubrication efficiency with the new formulation. As demonstrated in this paper, such determination can easily be performed on an instrumented tablet press by comparing

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the compression and ejection forces during tabletting from granules lubricated with either grade of MgSt powder at different MgSt concentrations. The information gained could then be used to change the MgSt concentration in the formulation, if needed, and submitted to the agency as part of the application documents.

MATERIALS AND METHODS

Material

Two MgSt powders with similar specifications but derived from different fatty acid sources, namely, bovine (MgSt-B) and vegetable (MgSt-V), were obtained from Mallinckrodt (Hazelwood, MO, USA). A test formulation containing ibuprofen (IBU, Albemarle, Orangeburg, SC, USA), microcrystalline cellulose (MCC, Emcocel®, JRS Rettenmaier & Soehne, Rosenburg, Germany), and lactose monohydrate (LMH, Foremost, Rothschild, WI, USA) in a 1:1:2 ratio was used to prepare granules for tablet compression. Hypromellose, 2.4% [dry weight basis; hydroxypropyl methylcellulose (HPMC), E15 Methocel™ LV, Dow Chemical, Midland, MI, USA] was used as the binder. All materials were used "as received" after passing through standard US no. 20 (850 μm) sieve, unless otherwise noted.

Characterization of Magnesium Stearate Powders

The MgSt-B and MgSt-V powders were found to be equivalent based on the certificate of analysis provided by the manufacturer and complied with the USP30-NF25 requirements for the MgSt powder. Non-compendial tests were therefore used to identify potential differences between the two grades. A 2920 CE differential scanning calorimeter (DSC; TA Instruments, New Castle DE, USA) and a 2950 thermogravimetric analyzer (TGA) (TA Instruments) were used for the thermal analysis from room temperature to 300°C at 20°C/min heating rate under constant flow of dry nitrogen. A symmetrical gravimetric analyzer (model SGA-100, VTI Corporation, Hialeah, FL, USA) was used for determining the equilibrium moisture content at different relative humidity (RH) conditions between 5% and 95% RH.

Preparation of Granules

High-Shear Granulation

Appropriate quantities of IBU, MCC, and LMH were weighed and blended together in a high-shear granulator followed by the addition of a 10% (*w*/*w*) aqueous HPMC solution over 5 min. The granules were wet-massed for an additional 5 min and hand screening though a standard US no. 8 (2.36 mm) sieve. The resulting granules were air-dried overnight to a moisture content of less than 1.5% (*w*/*w*). The dry granules were screened though a standard US no. 20 sieve.

Fluid Bed Granulation

Appropriate quantities of IBU, MCC, and LMH were weighed, blended, and transferred to a fluid bed granulator. Five percent (*w*/*w*) aqueous HPMC solution was sprayed on the fluidized powder blend, followed by drying to a moisture content of less than 1.5% (*w*/*w*). The dry granules were screened though a standard US no. 20 sieve.

Lubrication

Granules prepared by both granulation methods were lubricated at 0.25%, 0.50%, 1.00%, and 1.50% (*w*/*w*) MgSt concentration in a 2.0-L V-blender for 5 min at 30 rpm.

Tablet Compression and Characterization

The lubricated granules were compressed on a ten-station, instrumented tablet press (MiniPress-I, Globe-Pharma, New Brunswick, NJ, USA) fitted with load cells to measure the tablet compression and ejection forces. Only one set of 12-mm flat-faced, beveled-edged, round punches and cylindrical die was used to minimize variation arising from the use of multiple punch–die sets. The press speed was kept constant at 20 rpm. Tablets were compressed starting with the granules lubricated at 0.25% MgSt, followed by 0.50%, 1.00%, and 1.50% MgSt. The granules lubricated with the MgSt-B powder were compressed first, followed by those lubricated with the MgSt-V powder. Tablet weight and hardness were kept constant for all tablets. The die and punch on the tablet press were cleaned using methanol after each compression run. One hundred compression and ejection force profiles were collected on each lubricated granules.

All tablets were characterized for weight variation, hardness, and dissolution. Ten tablets randomly selected from each batch were weighed on an analytical balance followed by measurement of the diametral crushing strength using a tablet hardness tester (VK-200 Varian, Cary, NC, USA). In accordance with the dissolution test for the ibuprofen tablets from USP30, the USP II paddle method was used with paddles rotating at 50 rpm (7). Dissolution profiles were collected for tablets by monitoring the absorbance of the dissolution medium at 266 nm.

RESULTS

The two grades of MgSt showed no difference in the DSC and TGA profiles (Fig. 1), and the profiles were in agreement with those reported in the literature for the MgSt powder (8,9). No difference in the equilibrium moisture content was observed between the two grades of MgSt powders below 60% RH (Fig. 2). However, above 60% RH, a significantly higher moisture uptake was observed with the MgSt-B powder.

The specifications for tablets are typically based on the tablet weight and hardness, with the target values determining the compression and ejection forces on the tablet press. Hence, the weight and hardness of the tablets were maintained at constant values for all tablets (Fig. 3). At constant tablet weight and hardness, an increase in the MgSt concentration resulted in an increase in the tablet compression force for tablets prepared by the HSG method (Fig. 4a). This increase, however, did not lead to an increase in the tablet ejection force, which remained constant. Among the two grades, significantly higher compression and ejection forces

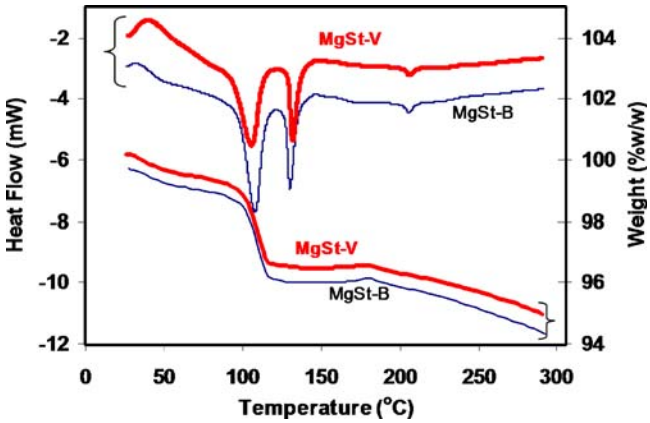

Fig. 1. DSC and TGA plots for the MgSt-B and MgSt-V powders

($p<0.01$) were needed for tablets compressed from the HSG granules lubricated with the MgSt-B powder as compared to those lubricated with the MgSt-V powder. The tablets prepared by the HSG method and lubricated with either 0.5% MgSt-B or 0.5% MgSt-V powder were compressed to similar weights and under similar compression force (Fig. 4a). However, a significantly greater force ($p<0.01$) was needed to eject tablets lubricated with 0.5% MgSt-B powder, yet resulted in tablets with significantly lower hardness values ($p<0.01$) as compared to those lubricated with 0.5% MgSt-V powder (Figs. 3a and 4a).

The tablets prepared by the FBG method also showed a significantly lower ejection force ($p<0.01$) for the granules lubricated with the MgSt-V powder at all MgSt concentrations (Fig. 4b). Similar compression force was required to compress the FBG granules lubricated with either grade of MgSt powder at 0.25% and 0.5% concentrations. However, for both grades, a lower ejection force was observed for the granules lubricated with 0.5% MgSt. Above this concentration, an increase in the MgSt concentration resulted in an increase in the tablet compression and ejection forces for both grades. The ejection forces, although, remained lower

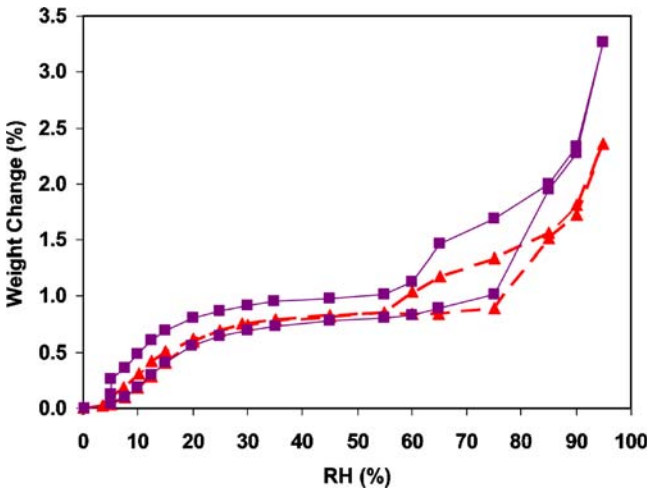

Fig. 2. Moisture sorption/desorption profiles of the MgSt-B (*square*) and MgSt-V (*triangle*) powders

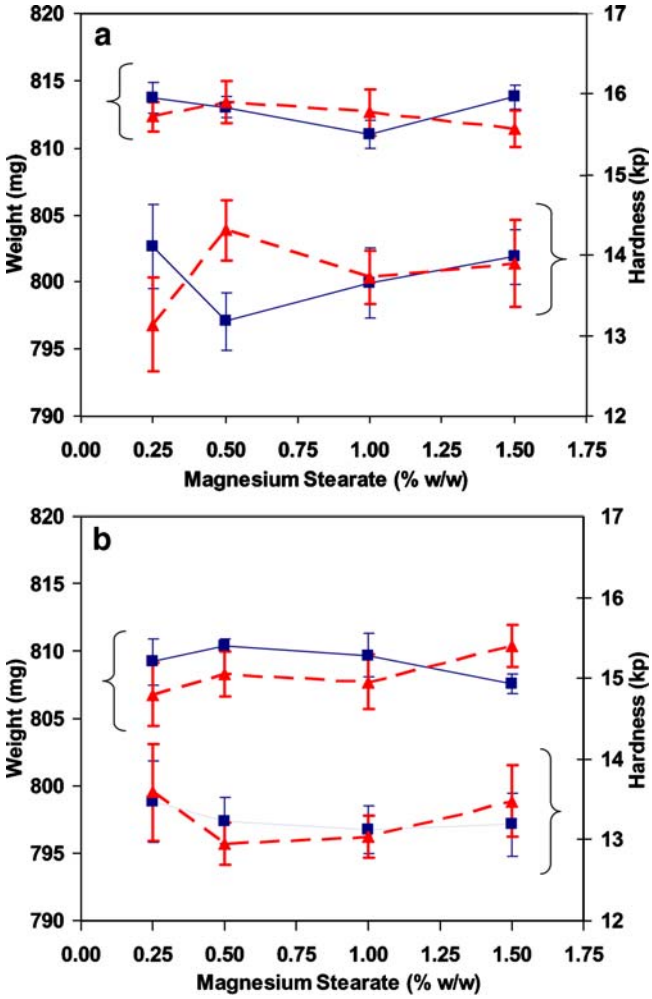

Fig. 3. Weight and hardness data for tablets lubricated with the MgSt-B (*square*) and MgSt-V (*triangle*) powders. **a** Tablets prepared by the HSG method. **b** Tablets prepared by the FBG method

for the MgSt-V-lubricated tablets as compared to the MgSt-B-lubricated tablets.

Tablets prepared by the two granulation methods showed different dissolution profiles. However, dissolution profiles of the tablets prepared by the same granulation method but lubricated with either grade of the MgSt powder showed no difference (Fig. 5). Dissolution profiles of tablets lubricated at different concentration of MgSt also showed no difference.

DISCUSSION

A significant difference was observed in the lubrication efficiency of the MgSt-B and the MgSt-V powders when tested on granules prepared by the high-shear and fluid bed wet granulation methods. When compressed to similar hardness and weight, granules lubricated with the MgSt-V powder required lower ejection force on the tablet press as compared to the granules lubricated with the MgSt-B powder. Difference was also observed in the moisture sorption profiles of the two grades, suggesting higher affinity for moisture as well as the presence of some amorphous material in the MgSt-B powder (10). None of these differences, however,

resulted in significant differences in the release profiles of tablets lubricated with either MgSt powder.

The variation in lubrication efficiency of different MgSt may be formulation-dependent. The results of this study are based on a single formulation containing ibuprofen [a high-permeability and low-solubility (BCS class II) compound] as the active pharmaceutical ingredient and granulated using two wet granulation techniques. Formulations prepared with different active ingredients, excipients, and/or using different manufacturing processes may show different results. The tablet press used in this study was operated at a relatively slow speed of 15 rpm. On tablet presses running at high speed, which is normally the case in the production environment, this small difference in lubrication efficiency may also lead to problems, e.g., capping, lamination, chipping, sticking, etc. Hence, it is important to study and understand the effect of any such change before switching between the two grades of MgSt powders.

CONCLUSIONS

This study highlights the importance of the functionality testing of MgSt powders, in addition to testing for the compendial requirements, for a comprehensive comparison of MgSt powders derived from different starting materials prior to making the source change. It also demonstrates that the switch in the MgSt powder derived from different source may need adjustment in the manufacturing and processing parameters to meet the establish product specifications, e.g., hardness, dissolution, stability, etc.

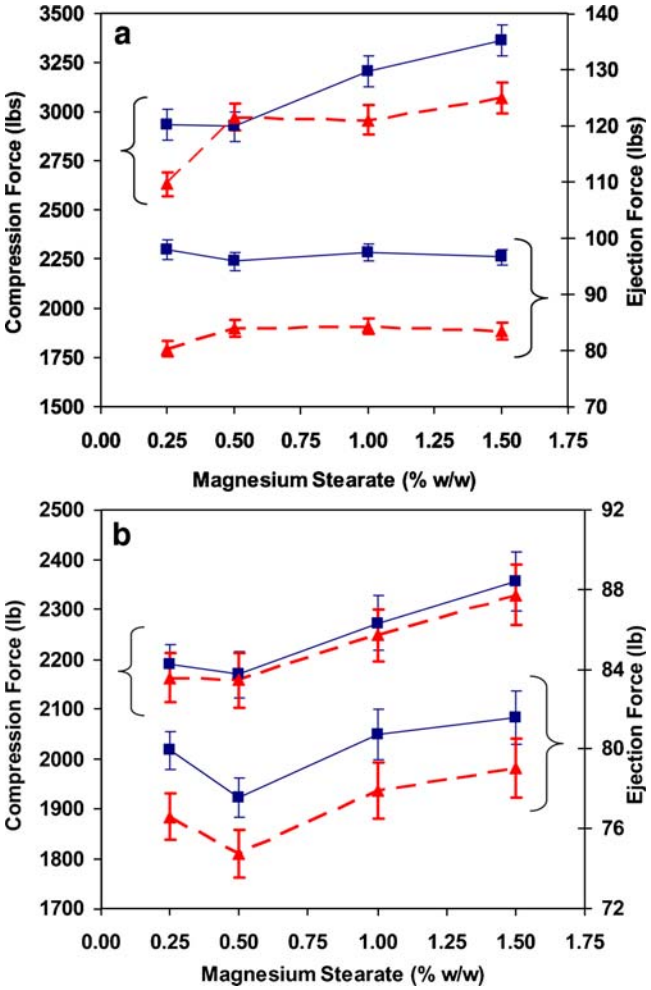

Fig. 4. Compression force and ejection force data for tablets lubricated with the MgSt-B (*square*) and MgSt-V (*triangle*) powders. **a** Tablets prepared by the HSG method. **b** Tablets prepared by the FBG method

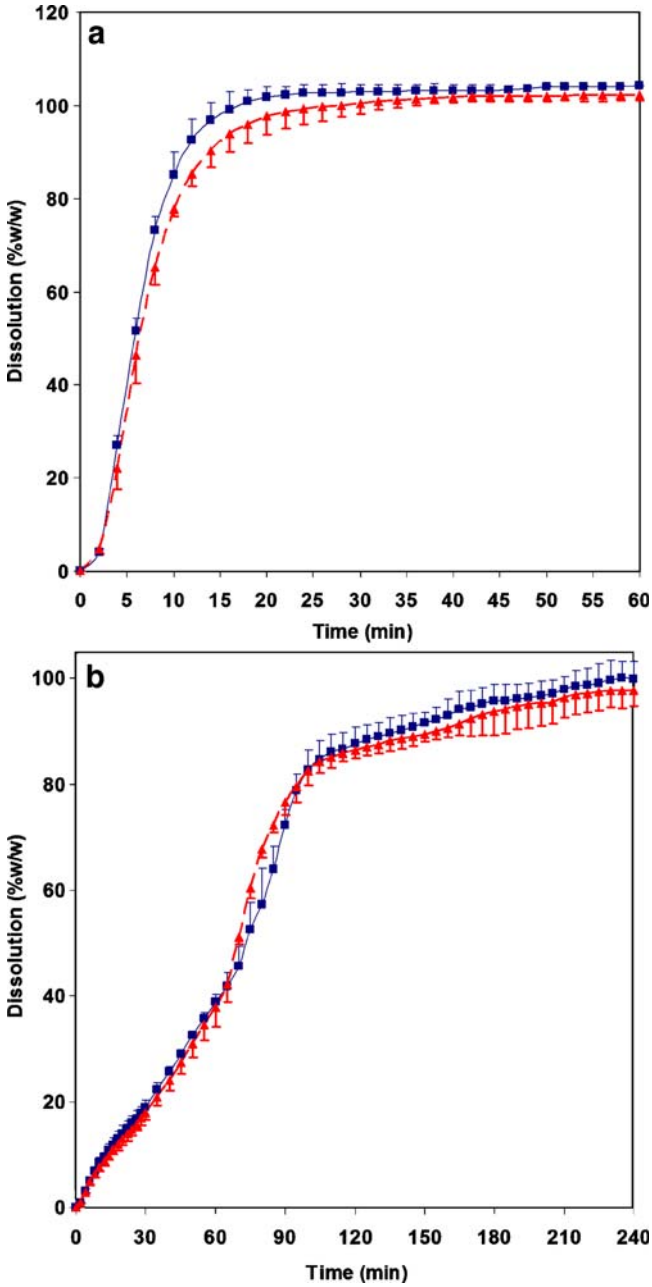

Fig. 5. Dissolution profiles of tablets lubricated with 0.5% MgSt-B (*square*) and MgSt-V (*triangle*) powders. **a** Tablets prepared by the HSG method. **b** Tablets prepared by the FBG method

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