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# THE EFFECT OF THE VARIABILITY IN THE PHYSICAL AND CHEMICAL PROPERTIES OF MAGNESIUM STEARATE ON THE PROPERTIES OF COMPRESSED TABLETS

Richard Dansereau and Garnet E. Peck

Department of Industrial and Physical Pharmacy
School of Pharmacy and Pharmacal Sciences
Purdue University
West Lafayette, IN 47907



## ABSTRACT

A series of magnesium stearate samples, supplied by foreign and domestic manufacturers, were characterized by their physical and chemical properties. The results indicated that the samples differed significantly with respect to chemical purity, particle size and surface area. The properties of magnesium stearate lots, manufactured by the same company, were very similar. Whatever variation that was seen was principally due to different suppliers.

Microcrystalline cellulose tablet formulations were prepared and evaluated using samples of magnesium stearate obtained from 16 sources. Differences in tablet quality were observed in regard to bulk volume of the blends, tablet tensile strength, and tablet friability. The data revealed that the

smaller particle sized magnesium stearate samples (2.4 - 7.0 μm), with a large surface area (10.6 - 14.8 $m^2/g$), had the most detrimental effects on the physical properties of microcrystalline cellulose tablets. Regression analysis and modeling was used to define, quantitate, and predict the effects of magnesium stearate source variation on the physical properties of microcrystalline cellulose blends and compressed tablets.

## INTRODUCTION

One of the most important components of compressed tablets, used to deliver various medicinal agents, is the material employed to lubricate the system. Magnesium stearate appears to be the most efficient lubricant employed to decrease the frictional forces operative during tablet formation and ejection. Magnesium stearate is an ideal processing agent which fcilitates the smooth operation of a tablet press. However, the incorporation of magnesium stearate into the tablet matrix may introduce several undesirable quality features to the compressed dosage form. These characteristics may include: (a) a decreased compressibility of the granulation or direct compression mixture (1,2), (b) a decreased wettability of the formulation (3), and (c) prolonged tablet disintegration and dissolution time profiles (4,5). A tablet formulator may be faced with competing ojectives. A

sufficient quantity of magnesium stearate must be added to facilitate tablet ejection, but if an excess of magnesium stearate is added, which is termed overlubrication, the physical properties of the tablet mixture will not be satisfactory to produce tablets of acceptable quality.

An additional factor must be considered when deciding upon the amount of magnesium stearate to be incorporated into a tablet formulation. This is the fact that magnesium stearate is synthesized from naturally occurring fatty acids by a number of different manufacturers. When dealing with products derived from natural origin, it is anticipated that variation in the physical and chemical properties may exist among manufacturers (6). Current standards which evaluate the primary physical and chemical properties are not sufficiently defined to predict and quantitate this effect of raw materials variation on compressed tablet characteristics. This situation has placed additional responsibilities on the product development group and the quality control section to look for a better definition of magnesium stearate.

In most reported investigations of magnesium stearate, little or no information is presented which is related to the physical and chemical properties of the grade of material used. The role of magnesium stearate as a tablet lubricant may be influenced by the quality of the material. Appropriate quantification techniques, which could predict lubricant

performance prior to tableting, would obviate the costly process of tablet reworking caused by an inferior grade of magnesium stearate. Raw material quantification techniques, indicative of magnesium stearate's quality, are mandatory to assure the safety, efficacy, reliability, and reproducibility of all batches of a manufactured product.

## MATERIALS AND METHODS

Twenty samples of magnesium stearate were supplied by a pharmaceutical firm which represents samples used in their worldwide operation. A single lot of microcrystalline cellulose[1] was used to reduce the possibility of lot to lot variation. The first step of the study was to characterize and define the magnesium stearate samples by standard physical and chemical tests. The following chemical tests were performed on each lubricant sample:

(A) U.S.P. Assay - The U.S.P. assay is a back titration procedure which determines the equivalent amount of MgO in a given sample (7). The reaction also converts the salts to their corresponding fatty acids.

(B) Analysis of the U.S.P. Assay Residue by Gas Chromatography - The free fatty acids, obtained from the U.S.P. assay were analyzed using a gas chromatograph[2] equipped with a flame ionization detector. The free fatty acids were derivitized to the corresponding methylesters and assayed on a column packed with 2% OV-101 on chromasorb W-HP, 100-200 mesh.

(C) Free Fatty Acids - The free fatty acids content (expressed as stearic acid) was determined by titration with sodium hydroxide.

(D) Ash Content - The inorganic matter present as impurities was determined in a muffle[3] furnace.

(E) Reduction in the Surface Tension of Distilled Water by the Water Soluble Extractables in Magnesium Stearate - A sample of magnesium stearate was agitated in a bottle of distilled water for six hours. The surface tension of the filtrate was then determined on a Fisher autotensiomat.[4]

(G) Loss on Drying - A moisture balance[5] was used to determine the loss on drying of the samples.

The following physical tests were performed on the lubricant sample:

(A) X-Ray Powder Diffraction - The crystal lattice sparings were determined on a Peiker Nuclear x-ray powder diffraction camera.[6]

(B) Melting Points - Sample melting point ranges were determined on a Hot Stage Microscope.[7]

(C) True Density - The true density of the samples were determined using a Beckman Air Comparison Pycnometer.[8]

(D) Bulk Density - The bulk density was determined in a graduated cylinder. The bulk volume was determined after 1500 taps to ensure a maximum packing arrangement. The porosity of the packed mass was then calculated.

(E) Particle Size Measurement - Lubricant particle size was determined using a Model B Coulter Counter.[9] Samples were sonified with .004% sodium lauryl sulfate in an isotonic saline solution prior to counting.

(F) Surface Area Measurements - Lubricant surface area was determined on a Micromeritics ace-US-orb instrument. The surface areas were then calculated using the BET equation.

The second part of the study examined the effects of magnesium stearate concentration, mixing time and source variation on the physical properties of microcrystalline cellulose blends and tablets. The independent variables were: (a) magnesium stearate concentration - .25, .75, 1.25%, (b) magnesium stearate - microcrystalline cellulose mixing time - 10, 20, 30 minutes, and (c) the particular magnesium stearate sample. The following procedure was used for sample preparation:

(1) The appropriate amount of magnesium stearate was screened through a 60 mesh screen over a bed of microcrystalline cellulose.

(2) The mixtures (500 g) were transfered to a 2.5 liter V-blender[10] and mixed for the specified time 32 rpm.

(3) Tablets were compressed on a Carner press[11] using a one-half inch, flat-faced punch and die set. A constant rat compressional force was applied up to a miximum value of 1000 pounds for all formulations. Tablet weight was maintained at 425 mg + 10 mg.

The bulk volume of a 20 gram sample was determined in a 100 ml graduated cylinder. The cylinder was dropped 100 times through a distance of 5 cm. Tablet tensile strength was determined on an apparatus adapted for the evaluation of cylindrical shaped tablets (8). The friability of six tablets was determined after 100 revolutions on a Eureka Friabillator.[12]

## RESULTS AND DISCUSSION

### Chemical Testing of Magnesium Stearate

(A) U.S.P. Assay - The U.S.P. sttes that all samples must contain the equivalent of 6.8 - 8.0% MgO. Based solely on this criterion, over one-half of the samples listed in Table 1 failed the test.

(B) Stearic Acid Content - The U.S.P. claims that stearic acid, the starting mateial in the synthesis of magnesium stearate, must contain at least 40% stearic acid and at least 40% palmitic acid. All samples in Table 1 conformed to this purity specificaiton. However, it is interesting to note that the stearic acid content ranged from 43.6% - 77.9%, indicating the influence of magnesium stearate source variation on sample purity.

(C) Free Fatty Acids - This value is indicative of the conversion ratio of the fatty acids into their corresponding salts during the synthesis of magnesium stearate. The free

Table 1. Summary of the Chemical Properties of the Magnesium Stearate Samples Supplies by Manufacturers Throughout the World

| Lubricant Sample | U.S.P Assay (%) | Stearic Acid[a] Content of | Free Fatty Acids (%) | Ash Content | Surface Tension of the Water Soluble Extractables | Loss on Drying (%) |
|---|---|---|---|---|---|---|
| Argentina A | 8.3 | 62.9 | 1.1 | 8.0 | 61.0 | 0.2 |
| Argentina B | 7.6 | 61.6 | 1.4 | 8.7 | 57.0 | 0.5 |
| Canada | 8.1 | 68.0 | 1.1 | 7.2 | 68.6 | 0.3 |
| Columbia A | 8.6 | 65.6 | 0.5 | 7.8 | 64.7 | 0.3 |
| Columbia B | 8.0 | 59.4 | 1.4 | 8.7 | 66.3 | 0.3 |
| England | 8.3 | 52.4 | 1.1 | 7.1 | 68.6 | 0.7 |
| France A | 8.2 | 43.6 | 1.1 | 7.3 | 63.5 | 0.8 |
| France B | 8.0 | 58.1 | 1.8 | 6.5 | 60.9 | 0.7 |
| Italy A | 8.1 | 64.1 | 3.0 | 7.0 | 61.5 | 0.2 |
| Italy B | 8.1 | 46.4 | 1.2 | 8.0 | 57.0 | 0.5 |
| Italy C | 8.3 | 66.5 | 2.3 | 7.5 | 68.8 | 0.3 |
| Italy D | 8.4 | 65.5 | 3.3 | 7.5 | 66.0 | 0.3 |
| Japan A | 7.8 | 60.7 | 0.8 | 7.2 | 64.7 | 0.1 |
| Japan B | 8.0 | 77.3 | 0.6 | 7.1 | 61.5 | 0.7 |
| Japan C | 7.7 | 64.6 | 1.5 | 8.0 | 62.3 | 0.8 |
| Mexico | 8.2 | 58.9 | 1.1 | 7.5 | 67.8 | 0.5 |
| Spain | 8.2 | 64.1 | 1.0 | 7.5 | 72.0 | 0.2 |
| Thailand | 8.1 | 53.5 | 1.1 | 8.1 | 68.4 | 0.5 |
| United States | 7.8 | 77.9 | 0.7 | 7.1 | 70.9 | 0.5 |
| Venezuela | 8.0 | 61.7 | 1.1 | 6.7 | 63.0 | 0.3 |

[a]The stearic acid content of the fatty acid sample used in the synthesis of magensium stearate

fatty acids content ranged from 0.5 - 3.3% indicating an incomplete synthesis reaction.

(D) Ash Content - The inorganic residue, primarily MgO, ranged between 6.5 - 8.7%.

(E) Reduction in the Surface Tension of Distilled Water by Water Soluble Extractables in Magnesium Stearate - The surface tension of all samples were between 57.0 - 72.0 dynes/cm. These values indicate that the water soluble impurities are dependent on the source of the magnesium stearate.

(F) Loss on Drying - The U.S.P. states that magnesium stearate may contain up to 4.0% moisture. All samples tested conformed to this specification.

Physical Testing of Magnesium Stearate

(A) X-Ray Powder Diffraction - The diffraction patterns are not shown, but 10 polymorphic forms of magnesium stearate were detected. This indicates that the crystal structure of the lubricant does vary from manufacturer to manufacturer.

(B) Melting Points - The melting points ranged from 117° - 150°C indicating the varying ratio of the constituent fatty acids. The melting point data did correlate with the stearic acid content. The greater the stearic acid content, the greater the melting point.

(C) Density Measurements - The true density values ranged from 0.89 - 1.16 g/ml. The bulk density of all samples were

between 0.26 and 0.57 g/ml. These values are indicative of differences in lubricant particle size distributions, particle shape, and the cohesive nature of the particles.

(D) Particle Size Measurements - Lubricant particle sizes ranged from 02.4 - 10.6 μm. These differences are attributed to the manufacturing techniques employed by the various manufacturers.

(E) Surface Area Measurements - The surface area of several selected samples ranged from 05.2 - 14.8 $m^2/g$. As anticipated, the smaller particle sized lubricants had larger surface areas. These data are summarized in Table 2.

These tests clearly demonstrate that the physical and chemical properties of pharmaceutical grade magnesium stearate is dependent upon the source of the material. Samples coded Columbia A and United States were both manufctured by Mallinckrodt and samples Italy C and Italy D were both manufactured by Eigermann-Veronelli. Table 3 shows the intrasource variation of magnesium stearate. The table shows the similarity of the physical and chemical properties of lots manufactured by the same company. Thus, it appears that this raw material variation problem might be minimized by procuring magnesium stearate lots from a single manufacturer.

The second step of the project was to determine the physical and/or chemical properties of magnesium stearate that influence the physical properties of microcrystalline cellulose

Table 2. Summary of the Physical Properties of Magnesium Stearate Supplied by Manufacturers Throughout the World

| Lubricant Sample | Melting Point Range C° | True Density g/ml | Bulk Density g/ml | Porosity % | Average Particle Size (um) | Surface Area (m2/g) |
|---|---|---|---|---|---|---|
| Argentina A | 137.5-142.0 | 1.06 | 0.34 | 0.66 | 5.8 | - |
| Argentina B | 117.0-120.0 | 1.05 | 0.30 | 0.71 | 5.9 | - |
| Canada | 138.0-142.0 | 0.96 | 0.29 | 0.70 | 6.5 | - |
| Columbia A | 144.0-149.0 | 0.98 | 0.28 | 0.72 | 5.6 | 07.4 |
| Columbia B | 141.5-148.0 | 0.91 | 0.34 | 0.63 | 4.2 | 10.6 |
| England | 144.5-147.0 | 0.98 | 0.34 | 0.75 | 2.4 | 14.8 |
| France A | 135.0-141.0 | 0.92 | 0.35 | 0.62 | 6.0 | - |
| France B | 122.5-127.0 | 0.89 | 0.35 | 0.61 | 6.0 | - |
| Italy A | 136.0-138.0 | 0.97 | 0.38 | 0.61 | 6.1 | - |
| Italy B | 120.0-122.5 | 1.16 | 0.57 | 0.51 | 6.8 | - |
| Italy C | 142.5-146.0 | 1.00 | 0.37 | 0.63 | 5.8 | - |
| Italy D | 141.0-146.0 | 0.90 | 0.37 | 0.59 | 6.6 | - |
| Japan A | 125.0-133.0 | 0.93 | 0.43 | 0.54 | 10.2 | 05.2 |
| Japan B | 135.0-140.0 | 1.05 | 0.29 | 0.72 | 5.4 | 07.4 |
| Japan C | 117.0-120.0 | 0.99 | 0.33 | 0.67 | 7.0 | 06.0 |
| Mexico | 132.0-137.5 | 0.92 | 0.29 | 0.69 | 3.5 | 08.3 |
| Spain | 142.0-146.0 | 1.00 | 0.30 | 0.71 | 5.2 | 10.0 |
| Thailand | 127.5-132.5 | 1.05 | 0.36 | 0.66 | 7.6 | - |
| United States | 145.0-150.0 | 1.14 | 0.26 | 0.76 | 6.3 | 06.5 |
| Venezuela | 127.0-131.5 | 0.89 | 0.43 | 0.52 | 6.4 | - |

Table 3. Comparison of the Physical and Chemical Properties of Magnesium Stearate Samples, Representing Intra-manufacturer Variation

| Sample | MgO (%) | Stearic Acid (%) | Ash Content (%) | Free Fatty Acids (%) | Moisture Content (%) | Surface Tension (dynes/am) | Water Soluble Salts (%) | Lubricant Melting Point (Co) | True Density (g/ml) | Bulk Density (g/ml) | Particle Size (µm) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Columbia[a] | 8.60 | 65.60 | 7.80 | 0.50 | 0.30 | 64.70 | .17 | 144-149 | 0.98 | .28 | 5.60 |
| United States[a] | 7.80 | 77.90 | 7.10 | 0.70 | 0.50 | 70.90 | .10 | 145-149 | 1.14 | .26 | 6.30 |
| Italy[b] | 8.30 | 66.50 | 7.50 | 2.30 | 0.30 | 68.80 | .10 | 142.5-146 | 1.00 | .37 | 5.80 |
| Italy[b] | 8.50 | 65.60 | 7.50 | 3.30 | 0.30 | 66.00 | .15 | 141-146 | 0.90 | .37 | 5.60 |

[a] Mallinckrodt

[b] Eigermann-Veronelli

(MCC) blends and compressed tablets. A statistical evaluation concluded that the two variables having the greatest influence on the properties of MCC were magnesium stearate particle size and surface area. Two regression models were run in conjunction with the dependent variables of maximum tensile stress, friability and bulk volume. The second order regression models were based upon the following independent variables:

Model A - 1) magnesium stearate concentration
2) magnesium stearate - MCC mixing time
3) magnesium stearate particle size

Model B - 1) magnesium stearate concentration
2) magnesium stearate - MCC mixing time
3) magnesium stearate surface area

When evaluating the fit and predictive merit of a regression model, the key factors to examine are the $r^2$ value and the coefficient of variability.

The summary of the second order regression models are listed in Table 4.

Based on the $r^2$ values and the coefficient of variability, it appears that either magnesium stearate particle size or surface area can be used to define and predict a specific lubricants performance characteristics in MCC.

Figures 1 and 2 show the effects of magnesium stearate particle size and surface area, respectively, on the bulk

Table 4. Summary of the Second Order Regression Models for the MCC - Magnesium Stearate Study

| | Tensile Strength | | Friability | | Bulk Volume | |
|---|---|---|---|---|---|---|
| | $r^2$ | C.V.[a] | $r^2$ | C.V. | $r^2$ | C.V. |
| Model A | .9870 | 7.1 | .9504 | 15.5 | .9737 | 1.4 |
| Model B | .9942 | 5.3 | .9647 | 14.4 | .8896 | 3.0 |

[a]Coefficient of Variability

volume of MCC at selected treatment combinations. As indicated by the data, the following conclusions were made: (a) As the concentration of magnesium stearate increased from 0.25 - 1.25%, the bulk volume decreased, (b) as the mixing time increased from 10-30 minutes, the bulk volume decreased, and (c) as the particle size of the lubricant increased or the surface area decreased, the bulk volume increased. The greater the amount of magnesium stearate in the mixture, the greater the percentage of the void space that are filled up, which results in blends with a lower porosity. The effect of mixing is probably due to the fact that as the mixing time increases, the lubricant particles are subjected to deagglomeration and delamination induced by the shearing action of the mixer. This results in a spreading of the lubricant over the excipient particles. This spreading facilitates a greater packing arrangement resulting in a lower bulk volume. More interesting

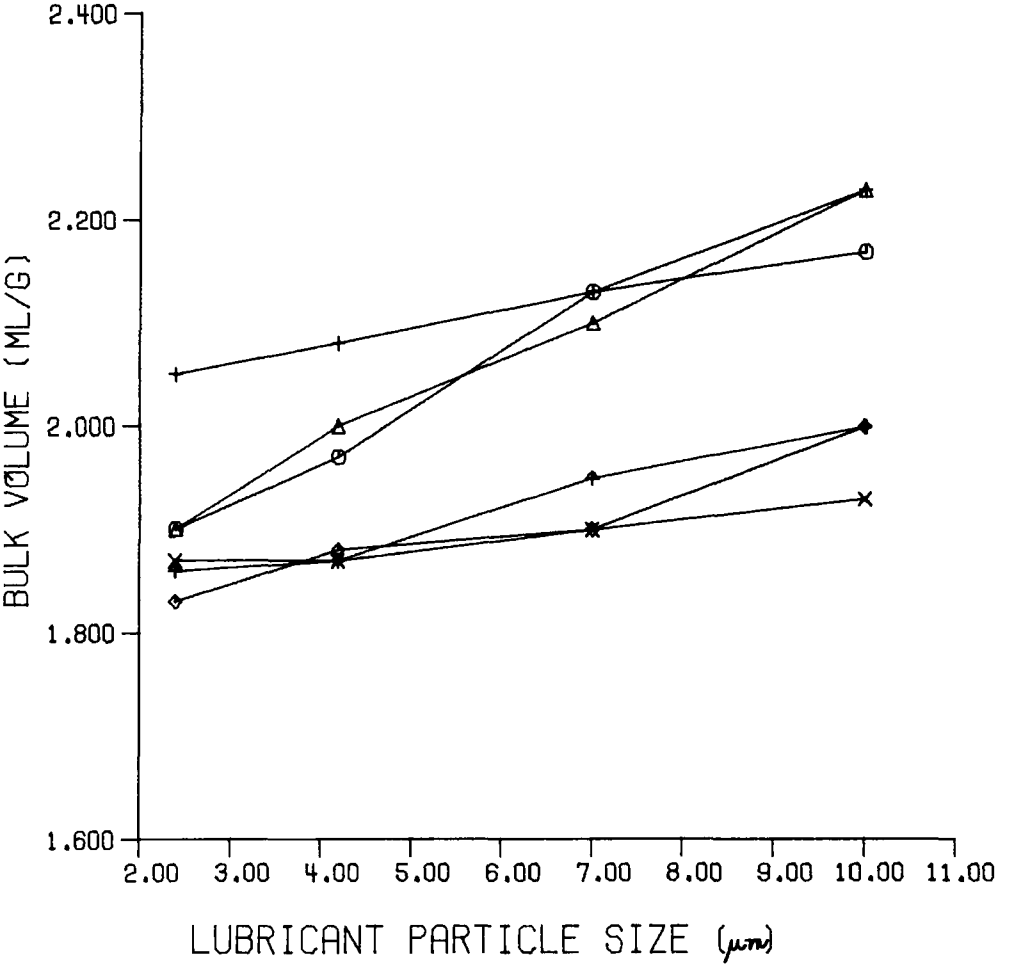


FIGURE 1

The effect of magnesium stearate particle size on the bulk volume of MCC blends at selected lubricant concentrations and mixing times. Key: 0.25% - 10 minutes, +; 0.75% - 10 minutes, o; 1.25% - 10 minutes, Δ; 0.25% - 30 minutes, ◇; 0.75% - 30 minutes, 4; 1.25% - 30 minutes, x.

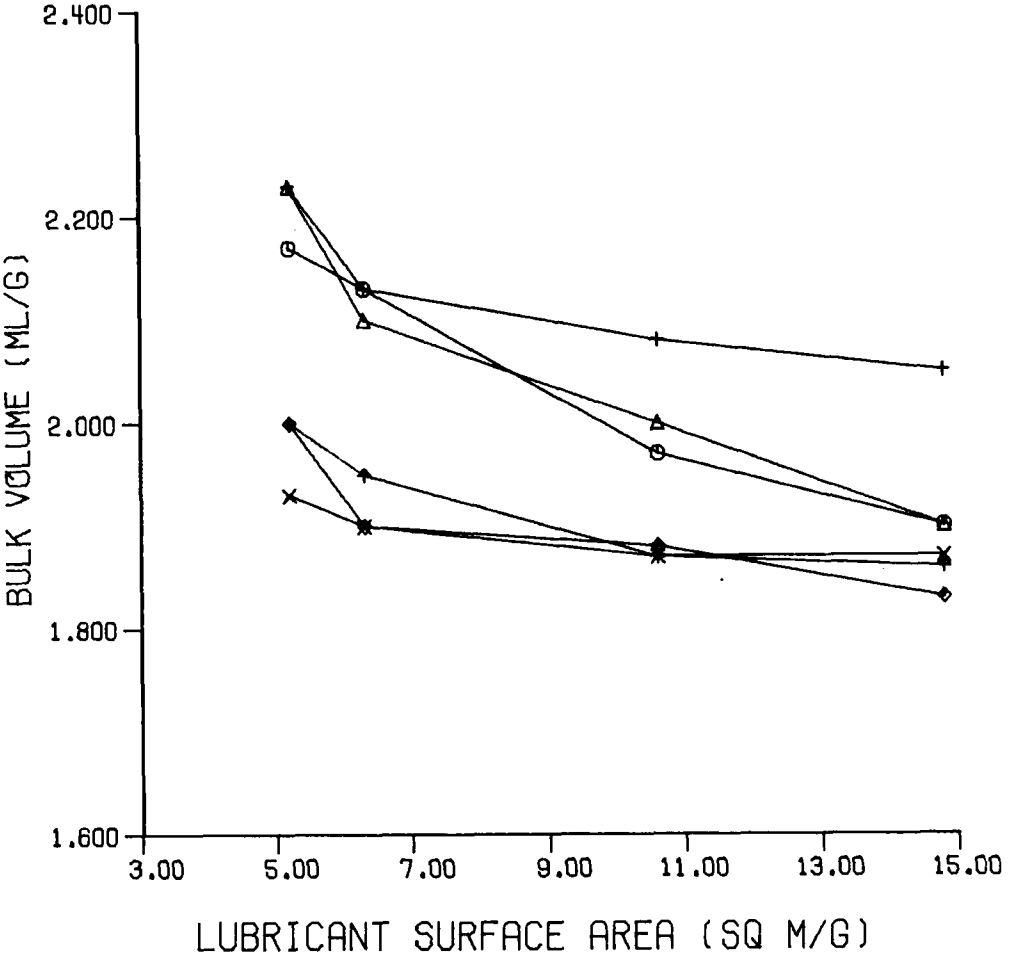


FIGURE 2

The effect of magnesium stearate surface area on the bulk volume of MCC blends at selected lubricant concentrations and mixing times. Key: 0.25% - 10 minutes, +; 0.75% - 10 minutes, o; 1.25% - 10 minutes, Δ; 0.25% - 30 minutes, ◆; 0.75% - 30 minutes, ⍋; 1.25% - 30 minutes.

is the effect of magnesium stearate particle size and surfce area on the bulk volume of the mixtures. The smaller particle sized stearates having a greater number of particles per unit weight, fill in a greater percentage of the void space, resulting in more densely packed cakes.

The effects of lubricant concentration and mixing time on the crushing strength and friability of compressed tablets has been previously reported (2). Figures 3 and 4 demonstrate the effect of lubricant particle size and surface area on the maximum tensile stress of MCC tablets. Based on the data, several conclusions may be made: (a) Tablets compressed with the smaller particle sized stearates having a large surface area consistently produced tablets with a greater tensile strength, and (b) there appears to be a leveling off in all of the hardness profiles at approximately 7 μm or 11 $m^2/g$. The theory being that the greater the surface area and the smaller the particle size of the lubricant, the more MCC bonds that are disrupted, and the weaker the tensile strength of the tablet.

Figures 5 and 6 show the relationship between MCC tablet friability and magnesium stearate particle size and surface area, respectively. Several observations became apparent, as indicated by the graphical representation of the data: (a) As the magnesium stearate particle size increased and the surface area decreased, the friability of the tablets decreased, and (b) the greatest variation in tablet friability was observed

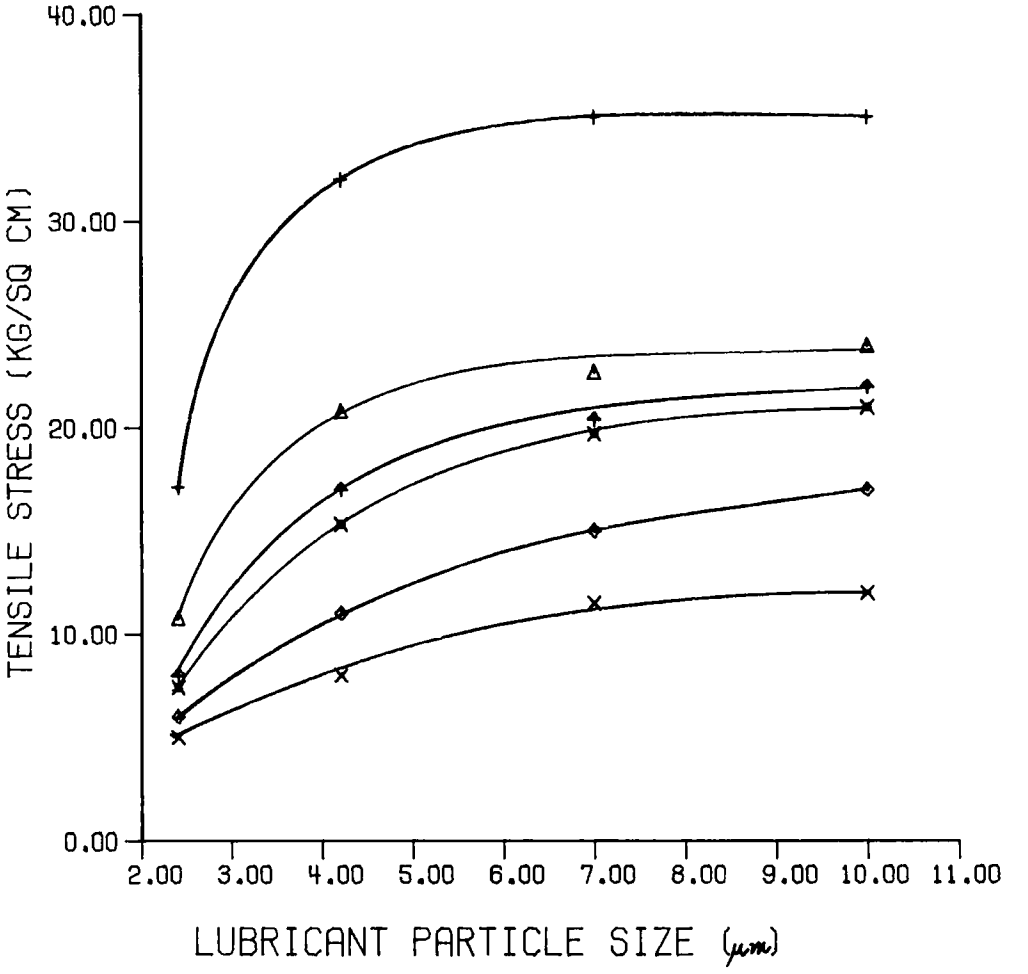


FIGURE 3

The effect of magnesium stearate particle size on the maximum tensile stress of MCC tablets at selected lubricant concentrations and mixing times. Key: 0.25% - 10 minutes, +; 0.75% - 10 minutes, △; 1.25% - 10 minutes, ⍋; 0.25% - 30 minutes, ⌑; 0.75% - 30 minutes, ◇; 1.25% - 30 minutes, x.

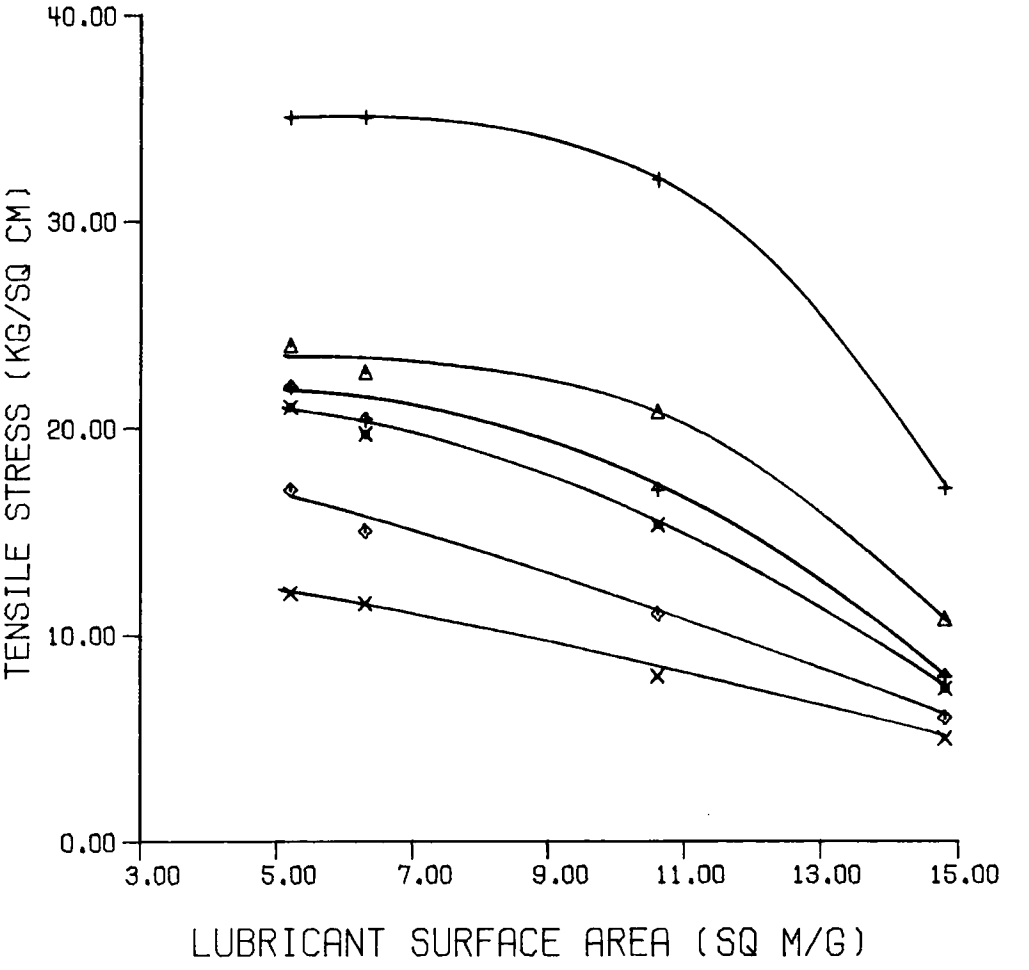


FIGURE 4

The effect of magnesium stearate surface area on the maximum tensile stress of MCC tablets at selected lubricant concentrations and mixing times. Key: 0.25% - 10 minutes, +; 0.75% - 10 minutes, △; 1.25% - 10 minutes, ⍋; 0.25% - 30 minutes, ⧖; 0.75% - 30 minutes, ◇; 1.25% - 30 minutes, x.

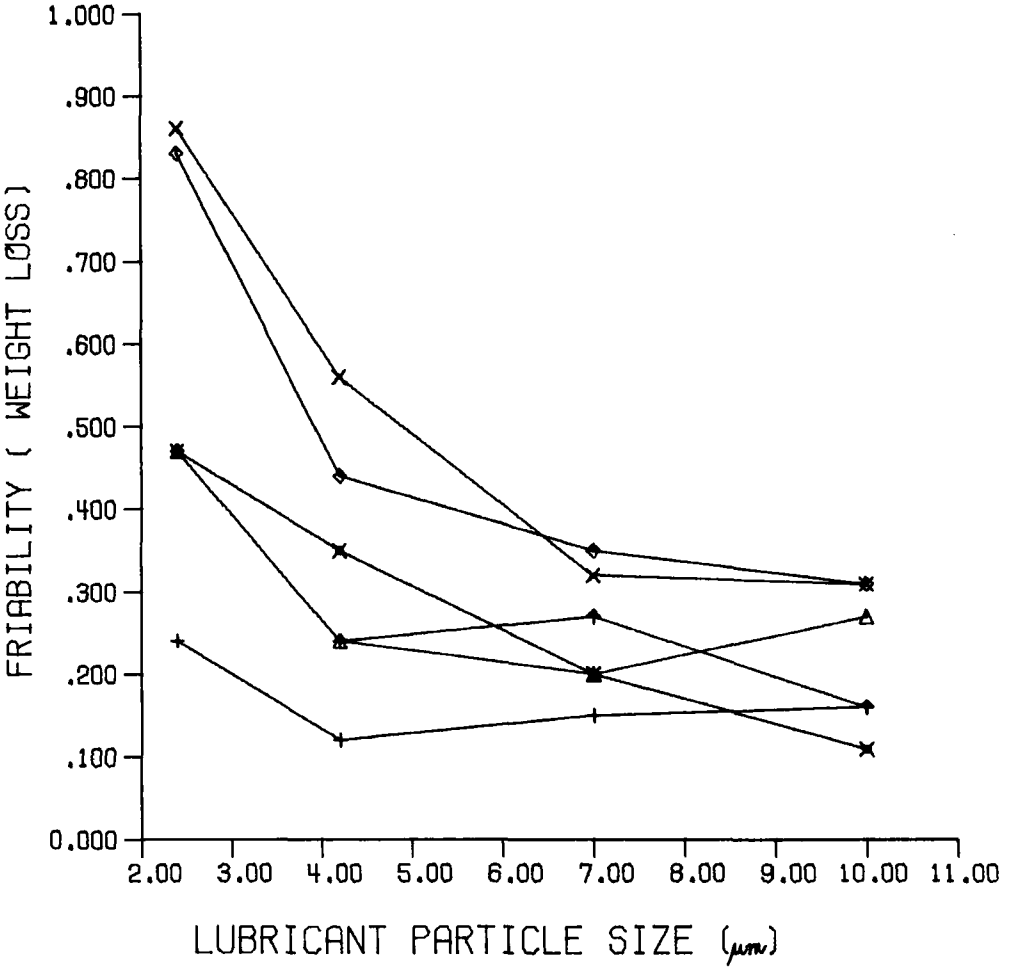


FIGURE 5

The effect of magnesium stearate particle size on the friability of MCC tablets at selected lubricant concentrations and mixing times. Key: 1.25% - 10 minutes, ↑; 0.75% - 10 minutes, △; 0.25% - 10 minutes, +; 1.25% - 30 minutes, x; 0.75% - 30 minutes, ◇; 0.25% - 30 minutes, ⌘.

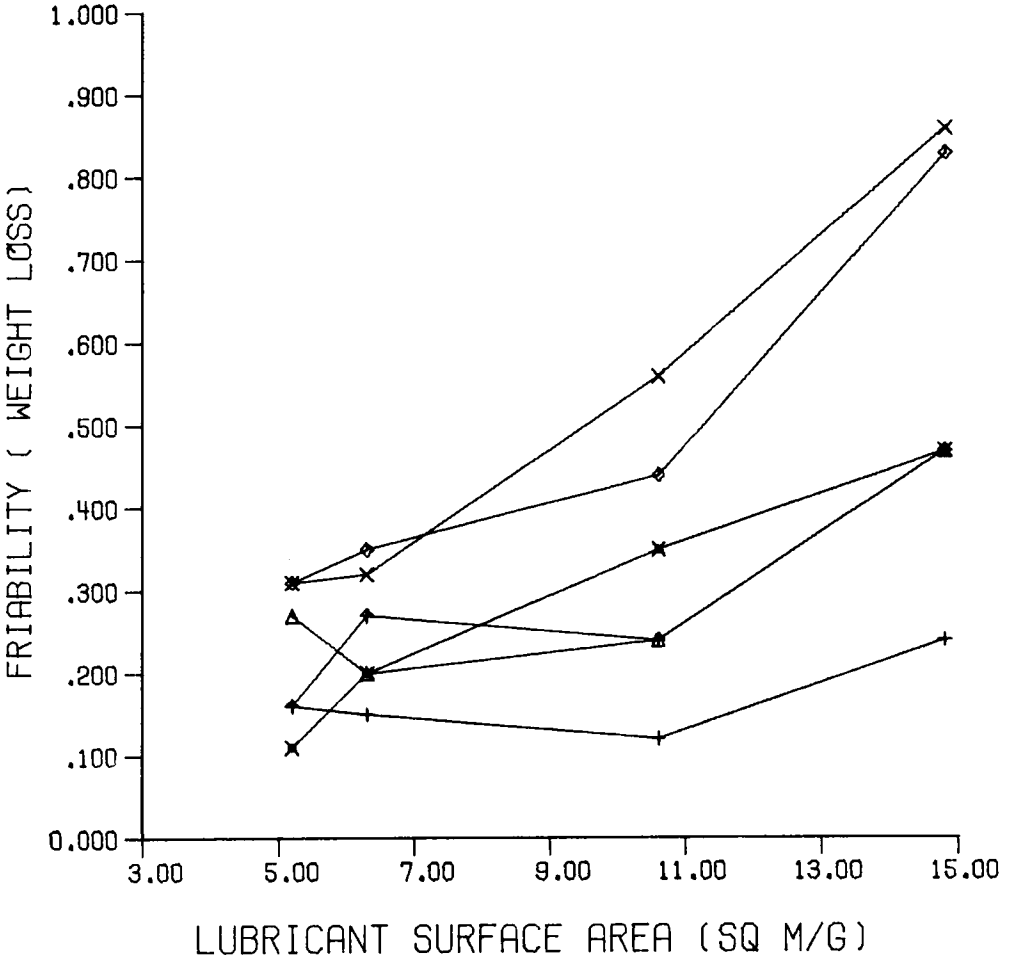


FIGURE 6

The effect of magnesium stearate surface area on the friability of MCC tablets at selected lubricant concentrations and mixing times. Key: 1.25% - 10 minutes, ♠; 0.75% - 10 minutes, Δ; 0.25% - 10 minutes, +; 1.25% - 30 minutes, x; 0.75% - 30 minutes, ◇; 0.25% - 30 minutes, ⌘.

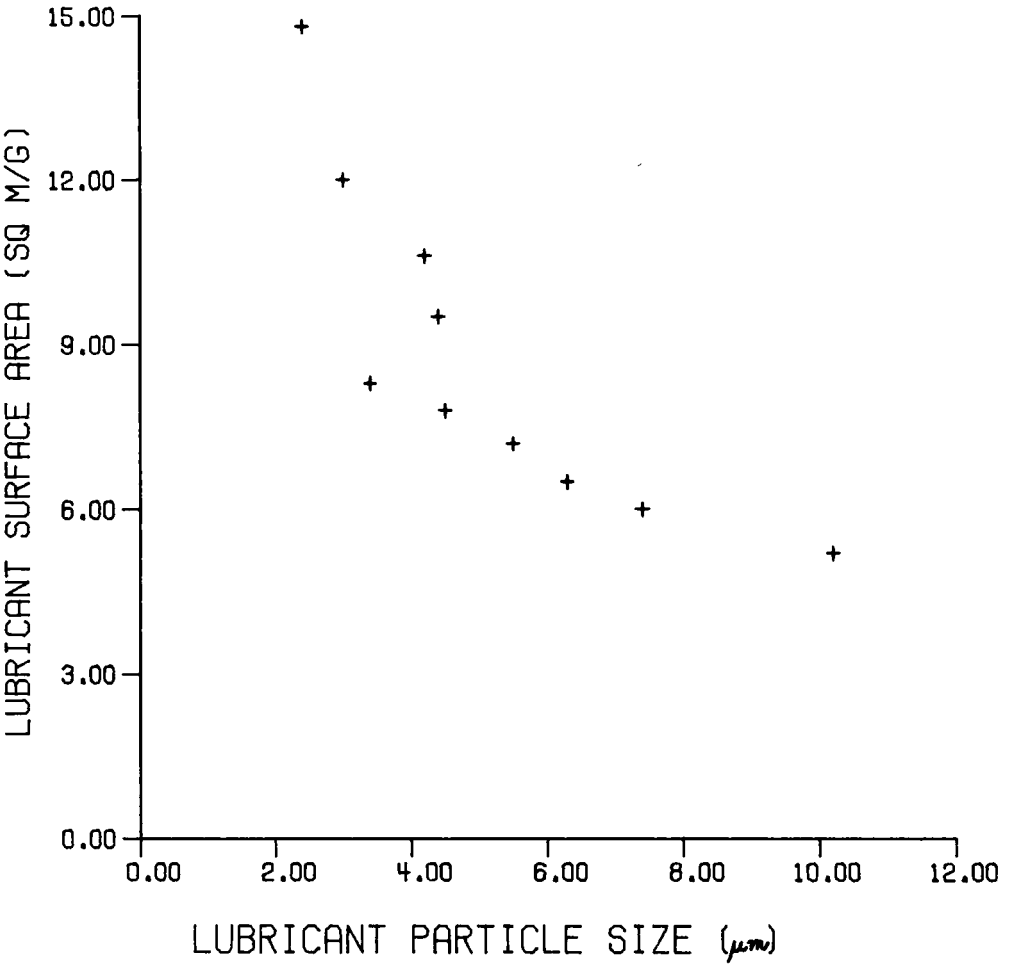


FIGURE 7

The relationship between magnesium stearate particle size and surface area.

with the lubricants having a particle size below approximately 7.0 μm and with a surface area greater than 11 $m^2/g$. Recall that the variation in tablet tensile strength was most pronounced with the fine particle sized lubricants. This phenomenon may be explained by examining the relationship

between magnesium stearate particle size and surface area. Figure 7 shows that the greatest fluctuation in magnesium stearate surface area is below approximately 6-7 μm. Thus, it appears that the greatest source variation problem is encountered with all samples having a fine initial particle size and relatively large surface areas.

## CONCLUSIONS

The data reveals that although the chemical and physical properties of magnesium stearate differ significantly from supplier to supplier, the key factors governing magnesium stearate performance rating is its particle size and surface area. The source variation problem may be minimized by procuring magnesium stearate from a single supplier.

The techniques presented here may be rapid screening tests used to indicate a lubricant's effect on the bulk volume, hardness and friability of compressed tablets. Discriminating tests of this nature may detect poor quality stearates prior to release from the quality control laboratory. The second order regression models represent a workable solution to the lubricant source variation problem.

## ACKNOWLEDGMENT

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## NOTES

1 Avicel PH-101, H.F., FMC Corp., Philadelphia, PA.

2 Hewlett-Packard Model 5710, Avondale, PA.

3 Thermalyne Furnace, Model F-A1740, Sybron Corp.

4 Model 215, Fisher Scientific co., Fair Lawn, NJ.

5 Ohaus Moisture Balance, Model 6010, Ohaus Schole Co., Union, NJ.

6 Picker Instruments, Cleveland, OH.

7 Mettler Instrument Co., Heghtstown, NJ.

8 Beckman Model 930, Beckman Instruments, Fullerton, CA.

9 Coulter Electronics, Hialea, FL.

10 Patterson-Kelly, East Stroudsberg, PA.

11 Model 2157, Carver, Inc., Summit, NJ.

12 Type TA3, Offenbach Main, W. Germany.

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