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COMMUNICATION

Consolidation Behavior of an Experimental, Cross-Linked Polyalkyl Ammonium Polymer

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ABSTRACT

The effect of various factors (i.e., particle size, lubricant, moisture, and excipients) on the tableting properties of DMP 504 powder, an experimental, cross-linked polyalkyl ammonium polymer, was studied using an instrumented single-punch tablet press. The results indicate that plastic deformation is the primary consolidation mechanism for DMP 504. Lubrication of DMP 504 with magnesium stearate resulted in negative interaction in compactibility. The increase in tablet hardness with increase in water content of DMP 504 (up to 2.5%) could be attributed to the lubricating effect of water. Increasing the water content above the optimum moisture range (i.e., 2.5% to 4.0%) caused a drastic reduction in tablet crushing strength due to the hydrodynamic resistance. A mixture of DMP 504 with microcrystalline cellulose or starch led to a positive interaction with respect to compactibility. A deviation in tablet strength from the linear interpolated value did not correspond to a deviation in tablet thickness. The improved compactibility for the mixture of DMP 504 and microcrystalline cellulose or starch is not related directly to the facilitated densification.

INTRODUCTION

The position of tablets as the mainstay of the pharmaceutical industry is indisputable. There are several reasons for their acceptance by both consumers and manufacturers, including relative ease of manufacturing, generally good chemical and physical stability, and convenience of administration. Especially for large doses of active ingredient, another reason for their success is the ability of the compaction process to reduce the volume

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to an acceptable size for swallowing. DMP 504 is a strong basic anion-exchange polymer. The polymer contains randomly distributed primary, secondary, tertiary, and quaternary amine groups in their hydrochloride salt form. The alkylammonium groups that comprise this polymer form a random network containing a high level of branching and a low level of cross-linking (1,2). DMP 504 binds bile acids in the intestine, forming a complex that is excreted in the feces; it is intended for oral use as a systemic cholesterol-lowering agent. The dose required to reduce the plasma level of low-density lipoprotein (LDL)–cholesterol is 4 to 6 g per day. Therefore, DMP 504 in a tablet form is the most feasible dosage form to ensure patient compliance. It is important for tablet dosage form development to understand the effects of various factors (i.e., lubricant, moisture, and excipients) on compressibility (i.e., the ability of a powdered material to decrease in volume under pressure) and compactibility (i.e., the ability of a powdered material to increase mechanical strength of a tablet formed under pressure) of DMP 504 powder. This need for basic information led to the investigation of consolidation behavior of DMP 504.

EXPERIMENTAL

Materials

DMP 504 was synthesized from 1,6-dibromodecane and hexane diamine and was prepared by the Chemical Processing Division of the DuPont Pharmaceutical Company (Wilmington, DE) (1,2). The physicochemical properties of DMP 504 have been reported previously (3). Other excipients, such as microcrystalline cellulose (Avicel PH-102, FMC Corp., Philadelphia, PA), lactose (Fast Flo Lactose, Foremost Ingredient Group, Baraboo, WI), starch (Starch 1500, Colorcon, Inc., West Point, PA), and magnesium stearate (Mallinckrodt, Inc., Chesterfield, MO) were used as received. Physical properties for DMP 504 powder, lactose, starch, and microcrystalline cellulose are summarized in Table 1.

Methods

Sieve fractions of DMP 504 (>125 μm and 75–125 μm) were separated using U.S. standard sieves. The powder from these two sieve fractions was lubricated with 1% magnesium stearate in a Turbular Mixer (Glenmills, Inc., Maywood, NJ) at 30 rpm for 3 min. In the lubricant studies, DMP 504 powder was screened through U.S. 20-mesh screen, and the screened DMP 504 powder was lubricated with magnesium stearate (prescreened through a 30-mesh screen) at different levels (0%, 0.5%, 1%, and 2%) in a Turbular Mixer at 30 rpm for 3 min. For the moisture effect study, the moisture content of the DMP 504 powder was decreased by drying in an oven at 50°C overnight or increased by spraying a calculated quantity of water to attain the desired moisture content. After the drying period or the spraying process, the powders were transferred to dry glass bottles with tight-sealing screw caps and were equilibrated for at least 24 hr before determining the exact moisture content. The moisture content was determined by a loss-on-drying method (Computrac, model Max 50, Arizona Instrument Corp., Phoenix, AZ). Prior to the compression, the DMP 504 powder with the desired moisture content was blended with 1% magnesium stearate. In the excipient study, the excipient and the DMP 504 powder were prescreened through a U.S. 20-mesh sieve, and mixtures of different ratios were blended in a Turbular Mixer. The powder

Table 1

Physical Properties for DMP 504 Powder, Lactose, Starch, and Microcrystalline Cellulose

Ingredient	True Density (g/cc)	Bulk Density (g/cc)	Tapped Density (g/cc)	Loss on Drying (%)	Mean Particle Size (μm)
DMP 504	1.06	0.36	0.50	2.0	67
Lactose	1.50	0.64	0.71	4.8	140
Starch	1.48	0.62	0.82	6.3	80
Microcrystalline cellulose	1.55	0.33	0.42	3.8	105

True density was measured by using an air comparison pycnometer (Accypyc1330, Micromeritics).
Tapped density was measured using a Tap-Pak Volumeter (Vankel Industries, model 50-1200).
The particle size was measured using a Malvern laser particle size analyzer (Malvern Instruments, model 2600).

blends were subsequently lubricated with 1% magnesium stearate.

Tablets (250 mg tablet weight) were compressed on an instrumented Manesty model F-3 single-punch tablet press (Thomas Engineering, Inc., Hoffman Estate, IL) with 11/32-inch standard concave punches at five compression forces (250 kg, 500 kg, 750 kg, 1000 kg, and 1500 kg). Tablet weight of 20 randomly selected tablets was measured using a Mettler AC 100 analytical balance (Mettler-Toledo, Inc., Highstown, NJ). Tablet thickness was determined with a micrometer ($n = 10$), and tablet hardness was measured with an Erweka TBS-28 hardness tester (Erweka Instruments, Inc., Milford, CT) ($n = 10$).

RESULTS AND DISCUSSION

Figure 1 shows the tablet hardness–compression force profiles for two sieve fractions of DMP 504. Approximately parallel curves were observed with the smaller particle size fraction forming harder tablets. Figure 2 shows the Heckel plots for two sieve fractions of DMP 504 powder. Results illustrate that the curves are initially steep at the low compression force end and become gradually flatter as compression force increases. The Heckel plots of particle size fractions of DMP 504 exhibit type A behavior, which suggests that the plastic deformation is the predominant consolidation mechanism (4). In addition, a multicompression cycle approach, described in a previous paper (5), was used to characterize further the consolidation mechanism of DMP 504. DMP 504 powders have similar compression cycle profiles for the first and subsequent compression cycles, indicating that DMP 504 is a plastic material under current experimental conditions.

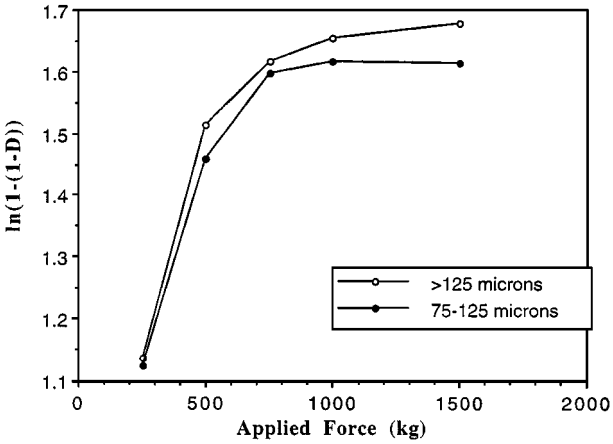

Figure 2. Heckel plots for two sieve fractions of DMP 504 powder.

Figure 3 is a plot of tablet hardness as a function of compression force at three magnesium stearate concentrations. The deleterious effect of DMP 504 on magnesium stearate lubrication was noted, and tablets made from DMP 504 powder without magnesium stearate had excellent mechanical strength.

DMP 504 is a hygroscopic granular powder, and the equilibrium water uptake ranged from 4.4% at 11% relative humidity (RH) to 66.8% at 100% humidity. The data reported previously suggest that DMP 504 has a tendency to gain or lose moisture with ease (3). An investigation

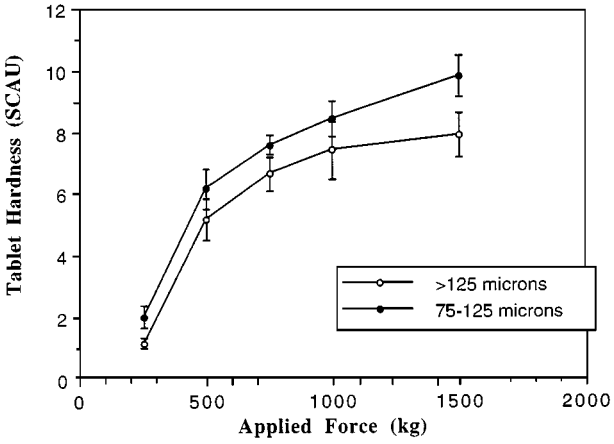

Figure 1. Tablet hardness–compression force profiles for two sieve fractions of DMP 504 powder.

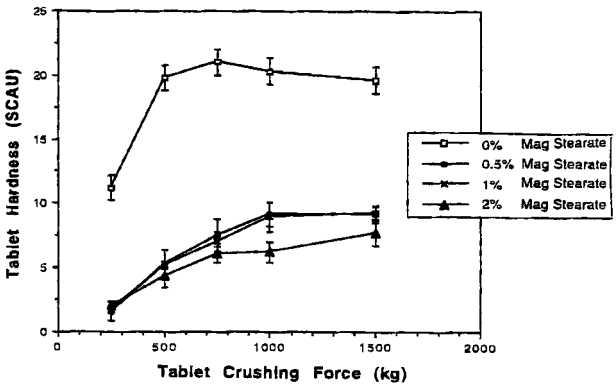

Figure 3. Compression force–tablet hardness relationships for powder blends containing various amounts of magnesium stearate.

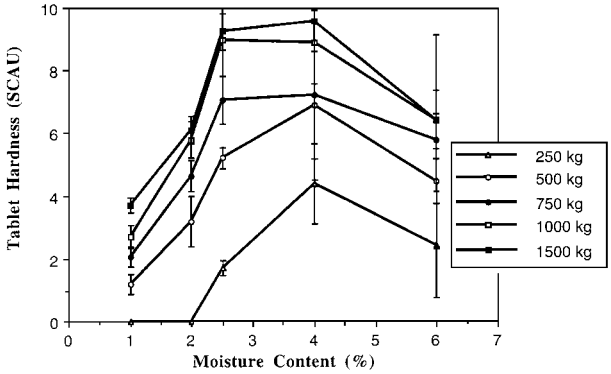

Figure 4. Effect of varying concentration of moisture on the crushing strength of DMP 504 tablets prepared at five different compaction forces.

into the moisture effect on compression properties of DMP 504 is warranted to be a factor of importance with respect to the DMP 504 tablet development. The effect of varying concentrations of moisture on the crushing strength of DMP 504 tablets prepared at five different compaction forces is shown in Fig. 4. The increase in hardness with increase in water content of DMP 504 (up to 2.5%) could be attributed to the lubricating effect of water. This lubricating effect facilitates the densification process, which can be substantiated by the thickness of the tablets. In addition, water assisted the adhesion between particles by gelling some of the DMP 504 powder. On subsequent release of the pressure, the moist compacts produced relatively strong compacts owing to the formation of solid bridges from the gel bridges. Figure 4

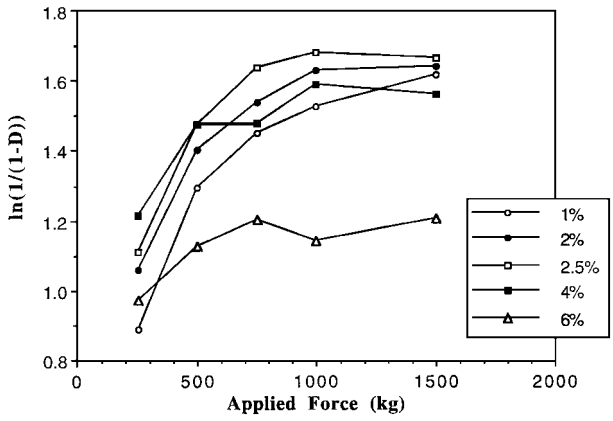

Figure 5. Heckel plots for DMP 504 powder with various amounts of moisture.

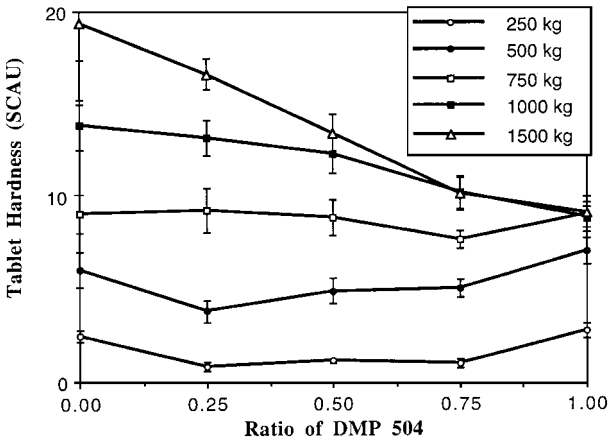

Figure 6. Relationship between tablet crushing strength of tablets prepared at different compaction forces and mixture compositions of DMP 504 and lactose.

also shows that the optimum moisture content is between 2.5% to 4.0%. Increasing the water concentration above the optimum range causes a drastic reduction in the tablet crushing strength. At higher water content, there is an appreciable hydrodynamic pressure under load within the interstitial liquid; it resists compaction and prevents intimate contact between the particles of the compressed material. In addition, DMP 504 has excellent water uptake and swell properties. At higher water content, DMP 504 swells significantly, which leads to an increase of elastic properties and a decrease of compactibility of the mate-

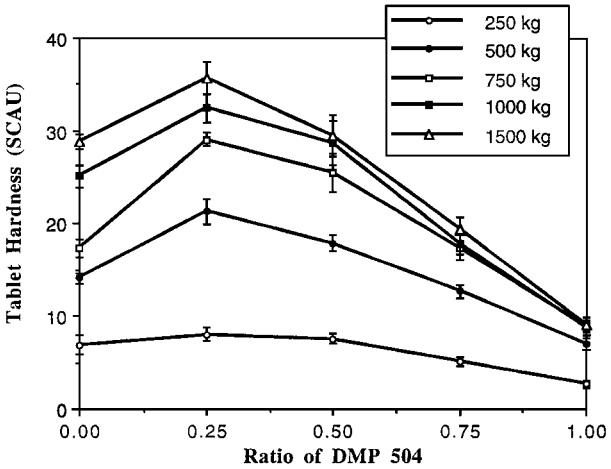

Figure 7. Relationship between tablet crushing strength of tablets prepared at different compaction forces and mixture compositions of DMP 504 and microcrystalline cellulose.

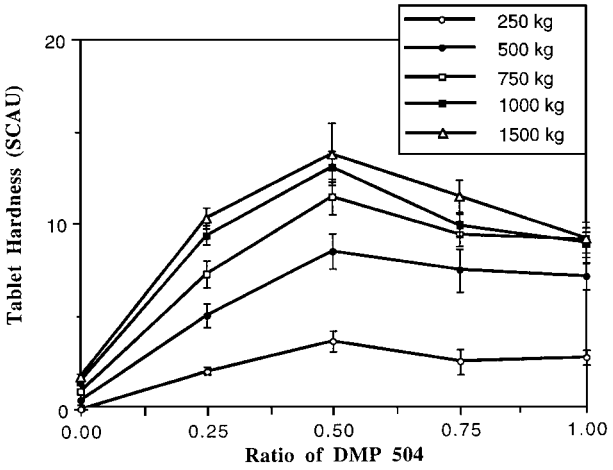

Figure 8. Relationship between tablet crushing strength of tablets prepared at different compaction forces and mixture compositions of DMP 504 and starch.

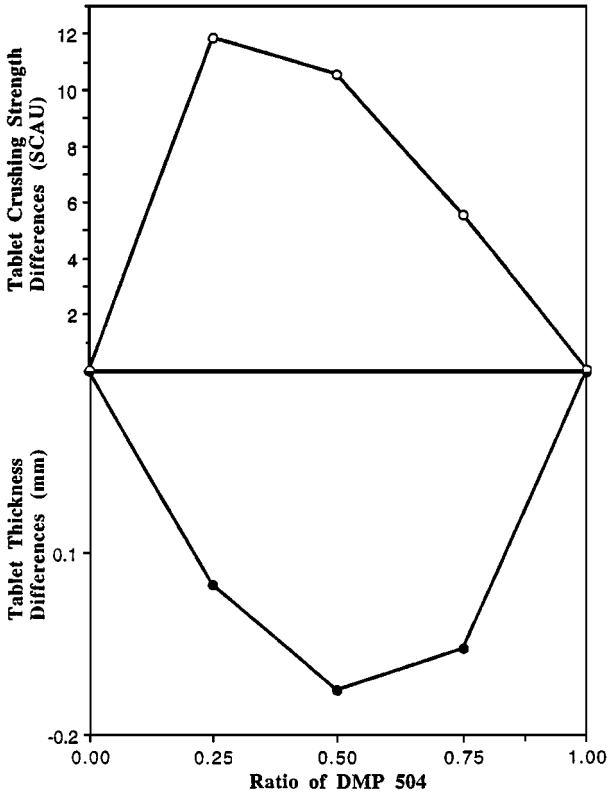

Figure 9. Plot of the differences between the measured and calculated values for both tablet hardness and thickness for the DMP 504–microcrystalline cellulose mixture system. The calculated values were obtained by intrapolation based on the measured values for two extreme DMP 504 ratios (i.e., 0 and 1).

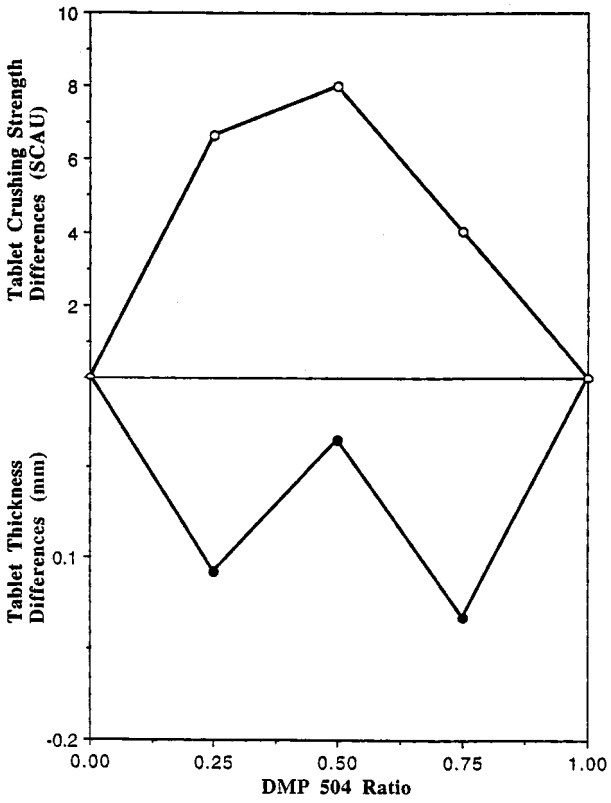

Figure 10. Plot of the differences between the measured and calculated values for both tablet hardness and thickness for the DMP 504–starch mixture system. The calculated values were obtained by intrapolation based on the measured values for two extreme DMP 504 ratios (i.e., 0 and 1).

rial. DMP 504 with 9% water lost its compressibility and compactibility. Even at a 1500-kg compression force, the tablet crushing strength was extremely low (i.e., 1.22 SCAU [Strong Cobb Armstrong units]), and tablet thickness was relatively large (i.e., 7 mm).

Figure 5 shows the Heckel plots for DMP 504 powder with various amounts of moisture. The movement of the plots of the DMP 504 powder containing 1% to 2.5% moisture can be attributed to the facilitated densification or lubricating effect of water. For DMP 504 with 4% moisture, the densification facilitated by water can still be noticed at low compression forces; at higher compression forces, the significant resistance to densification of DMP 504 is due to moisture-activated swelling of DMP 504 powder. However, the moisture at the 4% level also improves the bonding between DMP 504 particles. A further increase in moisture level decreases the material's compressibility and compactibility.

The mechanical strength of tablets prepared from mixtures of different materials was not always a simple additive function of the strength of the tablets made from the individual components (6–10). In designing a tablet formulation, it is ideal to select an excipient that has a strong positive interaction with the drug substance to produce tablets of greater mechanical strength. Figures 6–8 show the relationship between tablet crushing strength of tablets prepared at different compaction forces and mixture composition of DMP 504 and three selected excipients. For lactose, the crushing strength of tablets prepared from the mixture exhibited a simple additive property at higher compression forces and a minimum at the lower compression forces (Fig. 6). For both microcrystalline cellulose and starch (Figs. 7 and 8, respectively), the crushing strength of tablets prepared from the mixture shows a maximum, indicating strong positive interaction between DMP 504 and these two excipients. Figures 9 and 10 are the plots of the differences between the measured and calculated values for both tablet hardness and thickness. It is apparent that the increased tablet hardness is not just related to the facilitated densification. This provided evidence for the positive interaction between DMP 504 powder and starch or microcrystalline cellulose.

CONCLUSIONS

Under the experimental conditions studied here, the primary consolidation mechanism for DMP 504 is plastic deformation, which can be substantiated by the type A Heckel plot, similar compression cycle profiles for the first and subsequent compression cycles, and the sensitivity of DMP 504 tablet crushing strength to particle size and magnesium stearate. There is an optimum range for moisture content of the DMP 504 (2.5–4%) with respect to the tablet crushing strength. The mixture of lactose–DMP 504 exhibited an additive property at higher compression forces and a minimum at lower compression forces. For the mixtures of starch–DMP 504 and microcrystalline cellulose–DMP 504, unexpectedly higher tablet crushing strength was noted that cannot be attributed to the facilitated densification alone.

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