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Effect of Hydrophobic Excipients on the Properties of Fast Disintegrating Tablets

Seong Hoon Jeong[1†] and Kinam Park[2]

[1]*Wyeth Research, 401 N. Middletown Road, Pearl River, NY 10965, U.S.A*

[2]*Department of Pharmaceutics & Biomedical Engineering, Purdue University, West Lafayette, IN 47907, U.S.A*

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ABSTRACT – Highly hydrophobic lubricants including magnesium stearate may hinder water penetration into the tablet core resulting in delayed disintegration of fast disintegrating tablets. Alternative lubricants with equivalent lubricating properties may need to be incorporated into the tablet formulations. Sodium stearyl fumarate, glyceryl behenate and polyethylene glycol were evaluated regarding the tablet ejection energy, mechanical strength and disintegration time using Texture analyzer (TA). Resulting tablets were also compared with different particle sizes of granules and various compression forces. Among the tested lubricants, sodium stearyl fumarate was less sensitive to mixing time and also showed better or competitive tablet properties. During the experiments, TA was found to be very useful tool to investigate the tablet properties.

Key words – lubricant, texture analyzer, sodium stearyl fumarate, magnesium stearate, fast disintegrating tablet

Lubricants are one of the critical ingredients for the manufacturing of tablets. They can reduce the friction between the tablet and the die wall preventing adhesion to tablet punches. Lubricants-free would be ideal due to their unfavorable effects on tablet properties.[1)] However, few tablet formulations are self-lubricating. Tablet tooling finished with highly polished chrome to minimize friction and wear is not enough and only facilitates the lubrication.

Typical examples of lubricants with hydrophilic or hydrophobic ones are shown in Table I. Magnesium stearate, one of the most common lubricants, has been broadly used in tablet formulation but it still has some limitations on tablet properties including tablet strength, disintegration time, and dissolution rate.[2-5)] The negative effects were dependent on the lubricant concentration as well as other ingredients in the formulation.[6)] These effects were more pronounced with extended mixing,[4,8,9)] because lubricant film forms during the mixing process.[7,10)] The extent of film formation depends on the length and intensity of mixing. Magnesium stearate molecules are sheared off mechanically during the mixing process and the sheared particles adhere to the ingredients forming a film. This film interferes with both particle binding during compression and tablets' water uptake. A short mixing time resulted in poor distribution of magnesium stearate, which does not impair the efficiency of the lubricant. For this reason, short mixing time can be applied when magnesium stearate is mixed with other tablet ingredients.[11)]

As the production scale increases, mixing and shearing intensity also increase compared to the lab scale.[6,7)] When tablet ingredients are mixed with a lubricant, the formation of film proceeds faster in production-scale mixers than in lab-scale ones and will depend on the type of mixer used and its rotation speed. However, in the early stage of pharmaceutical product development, formulations in small scales occur quite often due to the limited resources. Monitoring the processing factors including tablet ejection energy may not be easy in such case so alternative methods such as using TA (Texture analyzer) will be a good tool to investigate the factors.

Recently, a new fast disintegrating tablet (FDT) technology was developed using conventional wet granulation and compression method.[12,13)] It is based on maximizing the porous structure of the tablet matrix with incorporating highly plastic granules to improve tablet mechanical strength. To ensure the tablet's fast disintegrating property, water must be absorbed quickly into the tablet matrix. However, hydrophobic ingredients such as lubricants and glidants may hinder the water penetration resulting in delayed disintegration.

When the compression force is high enough to make fragmentation, new solid bridges can be formed resulting in hardness increase. However, FDTs are usually compressed in low force, so the tablet properties including mechanical strength and lubricant effect might be different compared to high compression force. Due to the limitation of long wetting with highly hydrophobic lubricants, alternative lubricants with equivalent properties may need to be incorporated into the tablet formulations. Sodium stearyl fumarate, glyceryl behenate,

†본 논문에 관한 문의는 이 저자에게로
Tel : 042)866-2166, E-mail : ricjeong@hotmail.com

Table I–*Typical Examples of Hydrophobic and Hydrophilic Lubricants with Their Suggested Percentage in Tablet Formulations*

Lubricants	Suggested percentage
Hydrophobic (water insoluble)	
Magnesium stearate	0.5 - 2
Glyceryl behenate	0.5 - 4
Sodium stearyl fumarate	0.5 - 2
Mineral oil	1 - 3
Stearic acid	1 - 2
Talc	5 - 8
Hydrophilic (water soluble)	
Polyethylene glycols (4000, 6000)	2 - 8
Sodium acetate, benzoate, and chloride	5 - 8
DL-leucine	2 - 5
Sodium lauryl sulfate	1 - 3
Magnesium lauryl sulfate	1 - 3

and polyethylene glycol 4000 (PEG) were selected[14-16] and evaluated in respect of tablet ejection energy, strength, and disintegration time using the Texture analyzer.

Materials and Methods

Materials

Pruv® (sodium stearyl fumarate) and Compritol 888ATO (glyceryl behenate) were donated by JRS Pharma LP (Patterson, NY) and Gattefossé (Cedex, France), respectively. Polyethylene glycol (PEG) 4000 and Talc were from the Dow Chemical Company (Midland, MI) and Whittaker Clack and Daniels Inc. (South Plainfield, NJ), respectively. Maltrin QD® M580 (maltodextrin and corn syrup solids) was from Grain Processing Corporation (Muscatine, IA) and Mannogem™ EZ spray (mannitol) was from SPI Pharma (New Castle, DE). Sucrose was obtained from Mallinckrodt Baker, Inc. (Paris, Kentucky).

Methods

Preparation of granules and fast disintegrating tablets – The granulation process is similar to the ones described previously[12,13] and the procedure is shown in Table II. Granules were prepared using a high shear granulator (Diosna, Dierks & Söhne GmbH, Osnabrük, Germany) and a peristaltic pump (Masterflex®, Cole-Parmer Instrument Co., Chicago, IL) to supply a binder solution (50 w/v% sucrose).

The weighed ingredients were placed into a granulation bowl, and then dry-mixed for 1 min with a mixer speed of 400 rpm and chopper speed of 300 rpm. The binder solution was transferred and mixed for another 30 sec. The wet mass was sieved using US sieve #8.

The collected wet granules were spread evenly on trays and then placed on drying racks in a drying room set at 20°C and 17% RH. The moisture content was measured using a Karl Fischer titrator (Model 270, Denver Instrument, Arvada, CO). If the moisture content of the granules was 1.6 - 1.9%, then proceeded to sieving. Tablets (300 mg) were prepared on a single punch Carver Laboratory Press (Carver Inc., Wabash, IN) using plane-face punches with a diameter of 11 mm.

Tablet tensile strength, wetting time, and tablet porosity – Tablet crushing force was measured using a Texture analyzer (TA XT2", Texture Technologies Corp., Scarsdale, NY). The force that causes a breakage of a tablet in the radial direction was taken as the crushing load (F) for the tablet. The tablet tensile strength (T) can be calculated from the following equation:

$$T = \frac{2F}{\pi \times d \times t}$$

where d and t represent the diameter and thickness of the tablet, respectively.

For tablet wetting time measurement, a tablet was put on a pre-wetted filter paper with water and the time for complete wetting was measured using a stopwatch. In order to differentiate the time more easily, 0.2% of Coomassie Brillant Blue R-250 (Bio-Rad Laboratories, CA, USA) solution was used.

Tablet porosity, ε, can be calculated using the following equation:

$$\varepsilon = 1 - \frac{m}{\rho_t V}$$

where ρ_t is the true density, and m and V are the weight and

Table II–*Preparation of the Granules for the Fast Disinteg- rating Tablets*

Components	Amount	Granulation procedure
Maltrin QD 580	200 g	Mixing → Sieving No. 8 → Drying → Sieving No. 16
Mannogem EZ spray	800 g	
Sucrose solution (50% in 50% EtOH)	240 mL	

volume of the tablet, respectively. True density was measured using helium pycnometer (Accupyc 1330, Micromeritics, Norcross, GA).

Tablet ejection energy – To compare the effect of lubricants in reducing the friction between the tablet and the inner surface of die-wall, it was necessary to simulate the tablet compression so new tools were designed in-house and applied in the TA. Granules were put into the die and compressed with a probe of the TA, and then the ejection energy was measured from the compressed tablet. The experiment was run at least three times for each sample.

Disintegration time – The TA was also used to measure the disintegration time. A tablet was adhered to the bottom of a probe, which is attached to the load cell, with double-sided tape. The tablet under a constant force was moved to wetted filter paper in a defined volume of water. The time for the tablet to disintegrate was determined by measuring the distance the probe traveled into the tablet. Typical time-distance profiles generated by the TA software enabled the calculation of disintegration time. The instrument was programmed to apply a moderate force for up to 60 sec and to measure the penetration distance as the tablet was compressed while contacting the water. The probe distance would be steady, as the tablets remain cohesive. However, once the tablets disintegrate the compression distances increase, because the probe needs to keep the pressure constant.

Scanning electron microscopy – The morphologies of the raw materials were examined by scanning electron microscopy (SEM). Dried samples were attached to specimen stubs using double-sided tape and sputter coated with gold-palladium in the presence of argon gas using a Hummer I sputter coater (Anatech Ltd., Denver, NC). The samples were imaged with a JEOL JSM-840 scanning electron microscope (JEOL USA Inc., Peabody, MA) using a 5 kV accelerating voltage, a 18 mm working distance, a 70 μm objective aperture, and a probe current of 6×10^{-11} amps.

Results and Discussion

Effect of compression pressure on the tablet properties

Since granule properties are strongly dependent on moisture content, it was necessary to monitor the moisture content in every experiment. Sometimes moisture content was controlled using high humidity chamber to keep the level 1.5-2.0 w/w%. As already introduced,[13] it could be easily expected that as the compression pressure increases, tablet tensile strength increases while porosity decreases. While tablet tensile strength increased linearly, porosity decreased as a log scale (Fig. 1-A). When 300 lbs was applied, the porosity of the resulting tablets was about 30% and the tensile strength was 3.4 kg/cm^2.[13]

The tablet wetting time is closely related to the porosity as well as the hydrophilic properties of the excipients. If the porosity increases, the wetting time will decrease. However, there was an optimum compression pressure to have the shortest wetting time, which was around 300 lbs in the formulation (Fig. 1-B). When the pressure decreased less than 300 lbs, the wetting time did not go faster. The tablet wetting time can be used to predict disintegration or to differentiate formulations. In case of fast dispersible ibuprofen tablets, there was an opti-

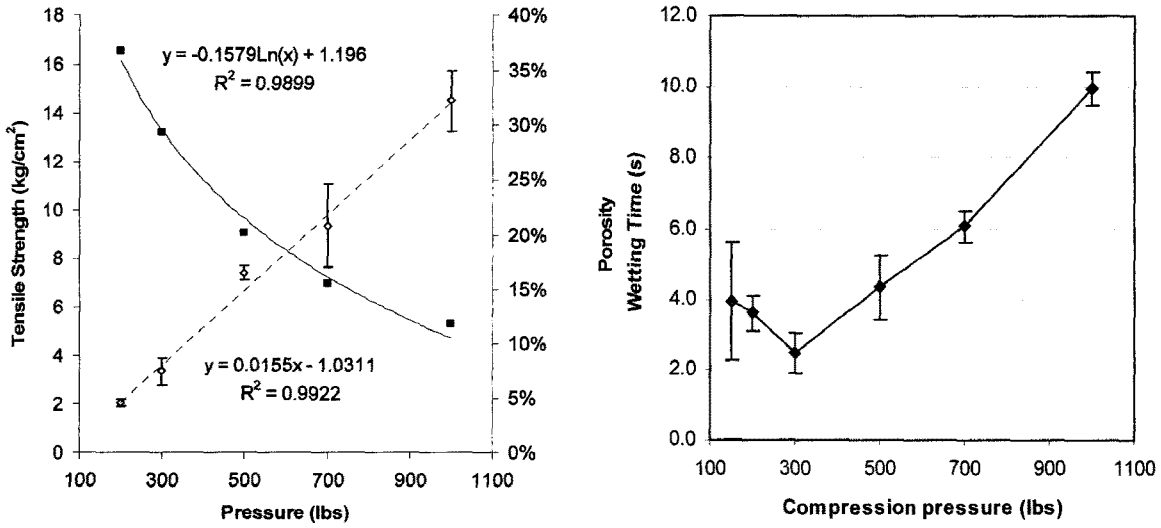

Figure 1–Effect of compression pressure on the tablet tensile strength and porosity (A)[13] and change of tablet wetting time (B) as a function of the compression pressure.

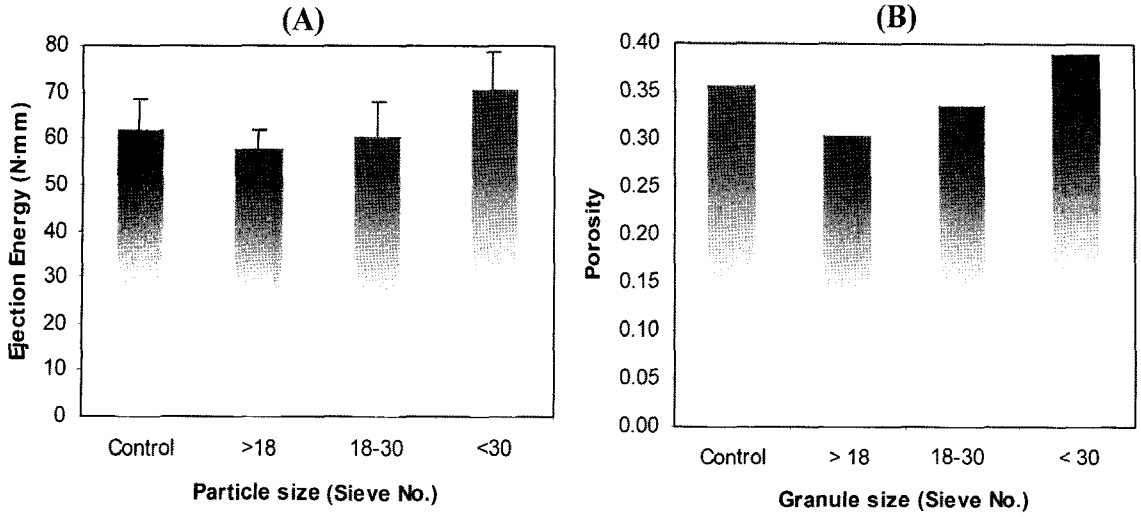

Figure 2–Tablet ejection energy (A) and tablet porosity (B) as a function of the particle size distribution.

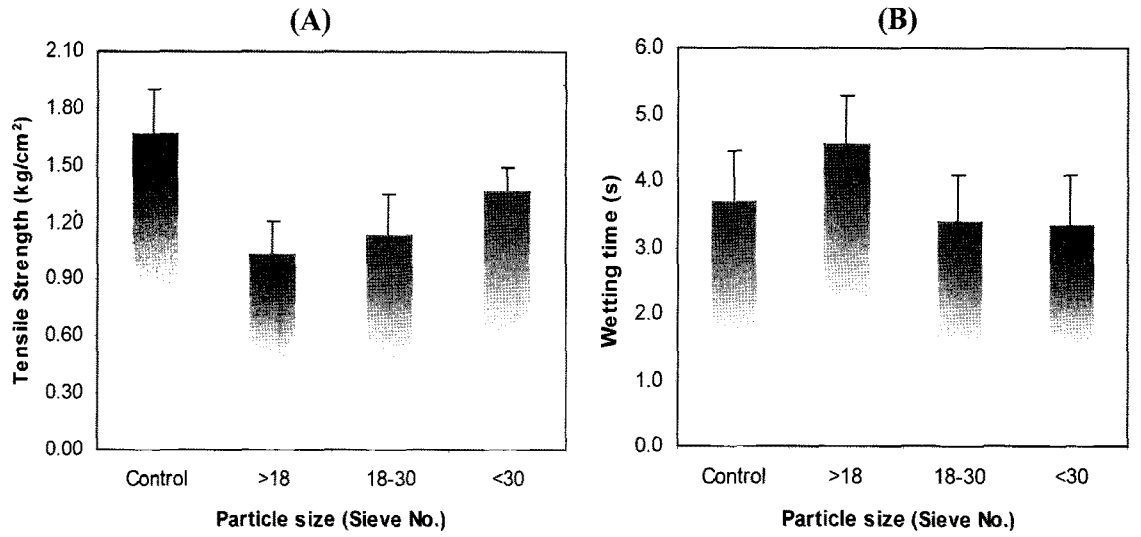

Figure 3–Tablet tensile strength (A) and tablet wetting time (B) as a function of the particle size distribution.

mum porosity to have the shortest disintegration time and it was 10-15%.[17]

Effects of particle size distribution on the tablet properties

After the high shear granulation process, the wet mass was passed through US standard test sieve and then dried. The dried mass was milled and the resulting granules were labeled as a control. The control was divided into three parts using #18 (1000 μm) and #30 (600 μm) sieves to investigate the effect of particle size distribution on the tablet properties. One part was >#18, another part was #18-#30, and the other part was <#30. More than 60 w/w% of granules were less than the size of sieve #30. Smaller particles gave smoother surface of the tablet than bigger particles. It was necessary to monitor particle size distribution to make the tablet properties consistent.

As the particle size of the granules decreased, the tablet ejection energy increased (Fig. 2-A). This might be due to the increased contact area between the compact and die-wall as the particle size decreased. On the other hand, tablet porosity increased as the particle size decreased (Fig. 2-B). The bigger granule can have more space between the particles than the smaller ones, so they might be easily deformed or fragmented into smaller particles to fill the void spaces. The thickness of the tablets from control, >18, 18-30, and <30 is 3.43, 3.37, 3.41 and 3.53 mm, respectively and this may support the assumption.

As the particle size of the granule decreased, the tablet tensile strength increased, even though the thickness increased (Fig. 3-A). The control tablet showed the highest tensile strength. Tablet wetting time is clearly related to the porosity

of a tablet, which can have strong effect on the capillary action, and also to the hydrophilicity of the tablet. Porosity of the granule >18 was the lowest, which was 0.3, and this showed the longest wetting time (Fig. 3-B). Based on the data, controlling granule size can be important to tablet performance and properties including tablet appearance, porosity, hardness and disintegration.

Different particle size of the same granules can have different initial packing densities. Smaller particles can have greater packing density and hence a greater number of contact points for interparticulate bonding. Therefore, as the particle size decreases, hardness will increase in the case of plastic deformation.

Application of lubricants for the fast disintegrating tablets

Magnesium stearate, sodium stearyl fumarate and PEG 4000 were initially selected to test the lubricating efficacy for the FDTs. PEG 4000 was milled to decrease particle size comparable to the others and particles less than 25 μm were used.

SEM observation showed magnesium stearate has the particle size ranging <1 μm and the aggregates of the fines (Fig. 4-A). Magnesium stearate molecules are assumed to be sheared off mechanically from the aggregates during the mixing process. The sheared particles would adhere to the granules forming the film and this may result in making the lubricating efficiency stronger and even adverse effects. Therefore, when magnesium stearate added, mixing time has to be controlled to get optimum effect. In case of sodium stearyl fumarate, the particles looked like disk-shaped ones and the size of them were less then 15 μm (Fig. 4-B). Even though there were still very small particles on their surface, they did not form aggregates. PEG 4000 molecules were sphere-shaped particles with broad size distribution (Fig. 4-C). After milling, the particle size was reduced to <25 μm and they did not form aggregates (Fig. 4-D).

Lubricants generally increase the elastic nature of powders by disrupting interparticulate bonds. Small particles of a lubricant can coat the larger granules, which interrupts interparticulate bonding.[18,19] When magnesium stearate was mixed with different sieved fractions of microcrystalline cellulose (Avicel PH 102), the disintegration time increased and the crushing strength decreased with increasing particle size of the Avicel fractions.[4] When lubricants were used with the same amount, they gave tablets different in hardness, disintegration, and dissolution depending on each lubricant. However, when they were used in such amount with equivalent lubricating areas, the final properties of the tablets were almost identical. A direct correlation was found between lubricating areas and ejection force.[20]

Tablet ejection energy and hardness

As the concentration of lubricants increased, the tablet ejection energy from the die-wall decreased and the energy required to push the tablets out is in the order of magnesium

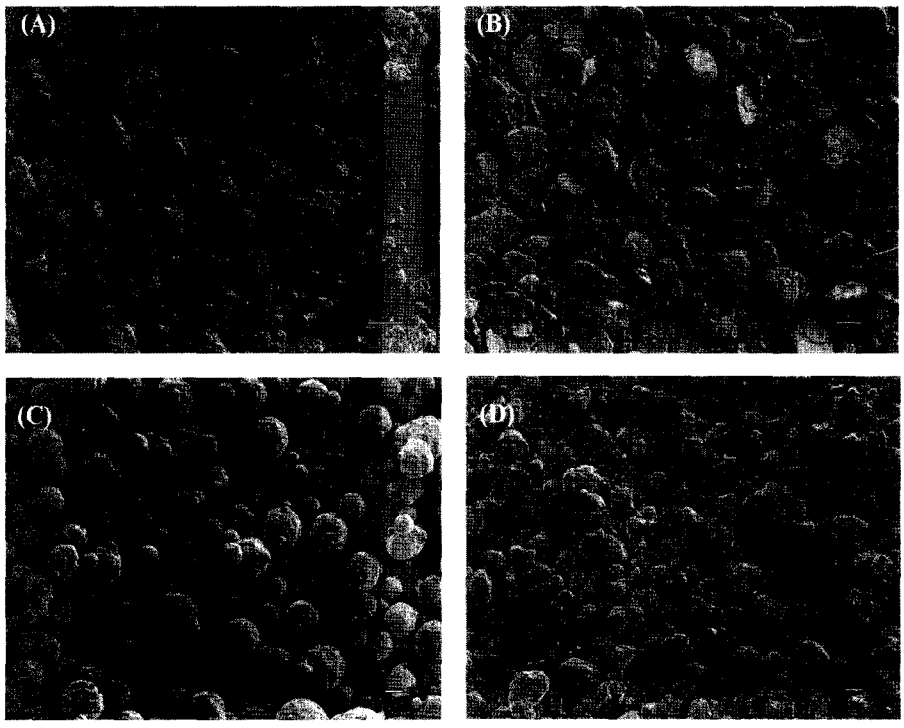

Figure 4–Scanning electron micrographs of magnesium stearate (A), sodium stearyl fumarate (B), PEG 4000 (C) and milled PEG 4000 (D).

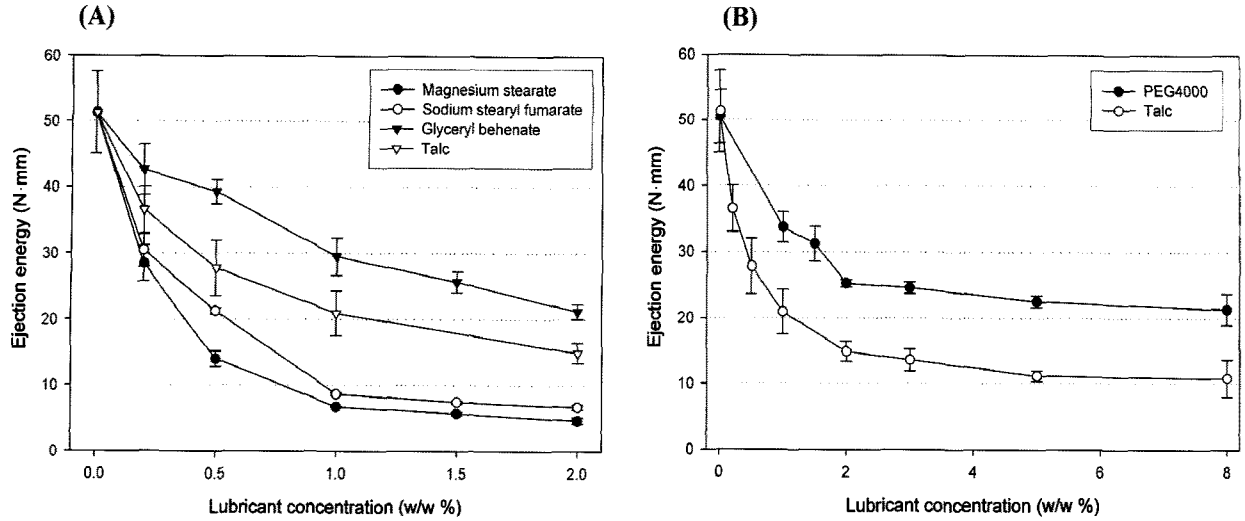

Figure 5—Tablet ejection energy from the die-wall with selected lubricants including magnesium stearate, sodium stearyl fumarate, glyceryl behenate and talc (A). The comparison of the tablet ejection energy between PEG 4000 and talc in higher concentration up to 8% (B).

stearate, sodium stearyl fumarate, talc and glyceryl behenate (Fig. 5-A). The difference between magnesium stearate and sodium stearyl fumarate was insignificant. If replacement of magnesium stearate is necessary due to any stability or performance issues, sodium stearyl fumarate will be an alternative one. Other properties such as hardness and disintegration should be considered together. Since the recommended amount of PEG 4000 and talc in tablet formulation is 2-8%, the test concentration was increased up to 8%. Talc showed better efficacy than PEG 4000 (Fig. 5-B). In higher concentrations starting around 2%, the effect of the both approached to a plateau.

Higher concentration of the lubricants decreased the tablet crushing strength (Fig. 6). Among the tested lubricants, glyceryl behenate decreased the crushing strength the least. The difference between magnesium stearate and sodium stearyl fumarate is not significant. The effect of lubricants on the tablet mechanical strength depends on the bonding mechanism.[21-24] Tablet strength is dependent on the area of intimate contact between the particles and the adhesive strength over this area. For excipients consolidating by predominantly plastic deformation, the tensile strength is reduced as the concentration of lubricant is increased.[25] This is also true for the axial and radial work of failure. However, for excipients having fragmentation consolidation, the tensile strength is not proportional to lubricant concentration.

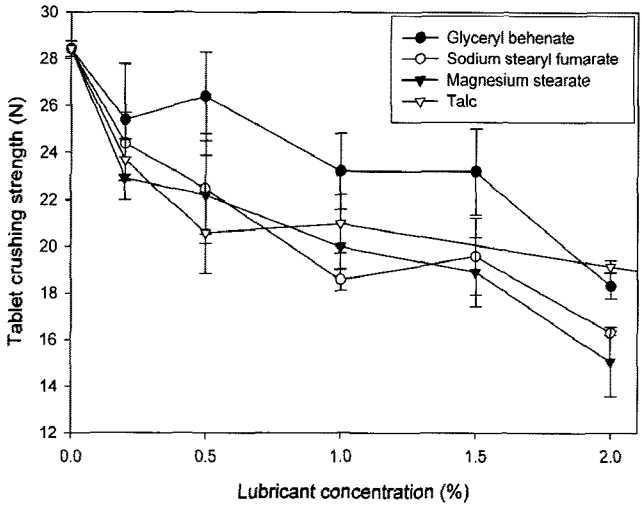

Figure 6—Tablet crushing strength with selected lubricants including magnesium stearate, sodium stearyl fumarate, glyceryl behenate and talc.

Tablet wetting and disintegration time

As the concentration of lubricants increased, the tablet wetting time also increased due to their hydrophobic properties. The time order was glyceryl behenate<talc<magnesium stearate<sodium stearyl fumarate (Fig.7-A). Glyceryl behenate showed the least increase. Since the tablet formulation had the good intrinsic wetting and disintegrating properties, even the high concentration up to 2% of glyceryl behenate showed only 10 sec of the wetting time. In the case of PEG 4000, it showed almost no change in the wetting time compared to the control (data not shown). It did not decrease hardness and had comparable ejection energy. However, during the tablet preparation, PEG 4000 showed sticking issue in the upper and lower punches. In case of tablet disintegration, tablets of magnesium stearate and sodium stearyl fumarate were compared. Even though magnesium stearate showed faster disintegration at 0.5%, the difference between the both was insignificant (Fig. 7-B).

When compared tablet wetting and disintegration, wetting

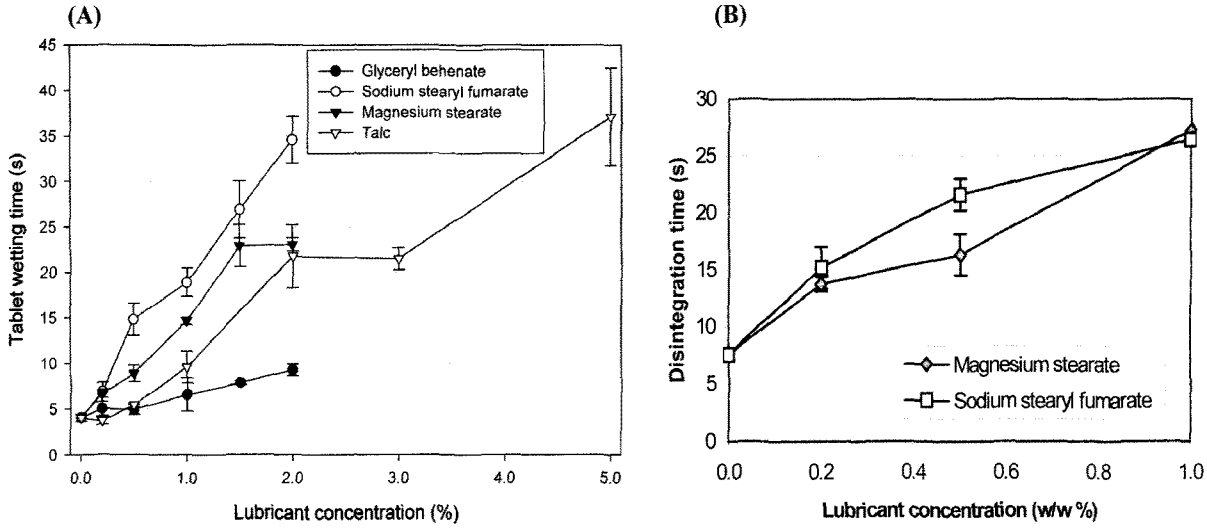

Figure 7–Tablet wetting (A) and disintegration time (B) as a function of the amount of selected lubricants.

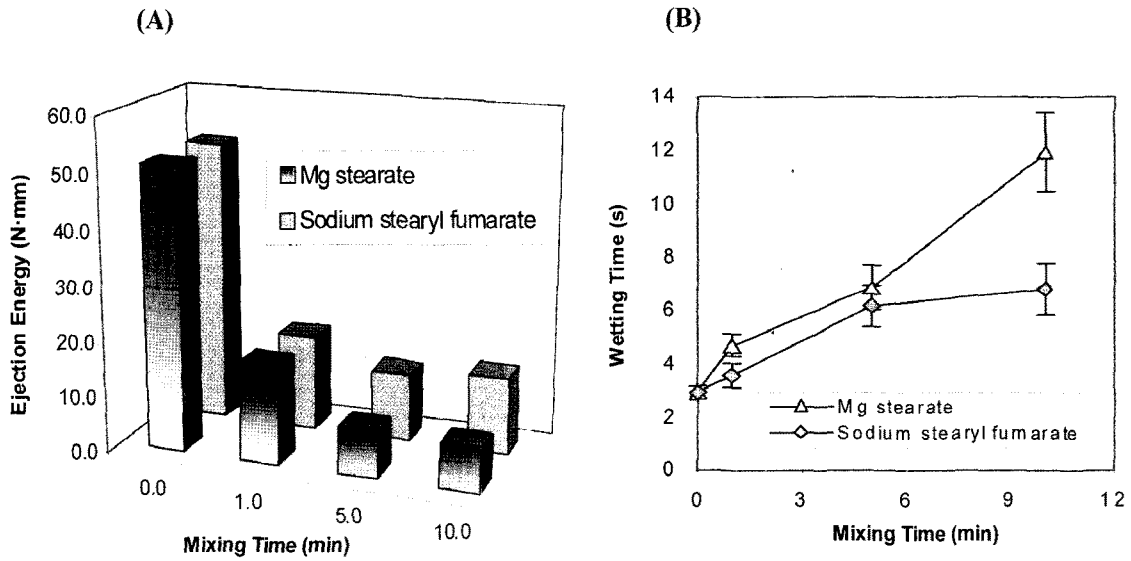

Figure 8–Tablet ejection energy from the die-wall (A) and tablet wetting time (B) as a function of the mixing time for magnesium stearate and sodium stearyl fumarate.

seemed to be faster than disintegration since wetting and disintegration can be considered as sequential processes. One issue when to add a lubricant in higher concentration was that tablets were not wetted thoroughly especially in hydrophobic lubricants. This might be due to the localized distribution of lubricants. Even though they are not fully wetted, the tablets can be disintegrated. One property of the prepared tablets was that the structural integrity was disrupted as soon as the tablets were wetted.

Effect of mixing time on tablet properties

As the mixing time increased, the tablet ejection energy and tablet tensile strength decreased. In case of magnesium stearate, the ejection energy decreased more than sodium stearyl fumarate and the magnesium stearate looked more shear-sensitive (Fig. 8-A). Tablet tensile strength also showed sodium stearyl fumarate was less sensitive to mixing time than magnesium stearate. As the mixing time increased, the tablet wetting time also increased. Unlikely to magnesium stearate, the time of sodium stearyl fumarate approached to a plateau region and showed little change (Fig. 8-B).

Since the content uniformity of active pharmaceutical ingredients is a concern for accurate dosing, mixing process is usually given carefully to the final formulation. However, other properties such as disintegration, dissolution, stability and physical integrity are also dependent on the nature and extent

of distribution of each excipient and the active ingredients. Mixing might affect interaction between lubricants and excipients, resulting in different tablet properties. Interaction between lubricants and excipients together with mixing effect is an important factor to be considered in tablet formulation.

Sodium stearyl fumarate looked less sensitive to mixing compared to magnesium stearate. However, the former one is still dependent on mixing time. The assumption is that when the mixing time is short, the particle cohesion energy of it is stronger than the shear force of mixer. However, after a certain point, the particle would be deaggregated and coat the granules, resulting in increased lubricating effect. Beyond the point it may not dependent on mixing time. More work will be necessary to support the assumption.

Conclusion

When FDTs are prepared with different compression forces, it was confirmed that tablet tensile strength increased, yet porosity decreased. As the particle size of the granules decreased, the tablet ejection energy increased. Moreover, the tablet wetting time is strongly dependent on the porosity. The selected lubricants were evaluated with tablet ejection energy, hardness and wetting & disintegration time. Among the tested lubricants, sodium stearyl fumarate looked less sensitive to mixing compared to magnesium stearate and also the former showed better or competitive tablet properties. The above information can be expanded when to incorporate active pharmaceutical ingredients (API) into the tablet formulations. Each API has different lipophilicity and it may have similar effect as the lubricants. During the experiments, Texture analyzer was found to be very useful tool to measure the tablet properties including tablet ejection energy, mechanical strength and disintegration, especially in a small scale.

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