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*RESEARCH ARTICLES*

# Mechanism of Surface Lubrication: Influence of Duration of Lubricant–Excipient Mixing on Processing Characteristics of Powders and Properties of Compressed Tablets

**A. C. SHAH ˣ and A. R. MLODOZENIEC**

**Abstract** □ A mathematical expression for tablet hardness was related to lubricant mixing by considering increases in the surface coverage with prolonged mixing time. The duration of lubricant mixing significantly changed the apparent bulk volume of the mix, ejection force during tableting, hardness, and disintegration and dissolution properties of tablets. These findings may provide some rationale for the changes in processing characteristics and properties of finished drug products often encountered in the scale-up of solid dosage formulations. Several lubrication mechanisms are discussed in connection with the duration of mixing effects and scanning microscopy studies.

**Keyphrases** □ Tablets, compressed—effect of duration of lubricant–excipient mixing on physical properties □ Powders—effect of duration of lubricant–excipient mixing on processing characteristics □ Lubrication, surface—effect of duration of lubricant–excipient mixing on physical properties of tablets and processing characteristics of powders □ Dosage forms—tablets compressed, effect of duration of lubricant–excipient mixing on physical properties

The formulation of a solid dosage form often requires precise processing control of the powder mixture to ensure a volumetric delivery of a homogeneous aliquot. Thus, various adjuvants are gravimetrically added to form the bulk mix to achieve uniform mixing and flow of the powders as in capsule or tablet die filling.

In tablet formulation, a lubricant usually permits resolution of several production problems related to compression. As an essential unit operation in the production of a compressed tablet, lubrication facilitates glidancy of the powders during material flow, eliminates binding of the compact to the die, and minimizes sticking and picking by the punch face surfaces in contact with the compressed tablet. Lubrication, in general, involves adding small quantities of an antifriction agent to powders or granules and mixing them for a specified time.

## BACKGROUND

Many studies evaluated different types of lubricants (1–5), the influence of lubricant concentration (6, 7), the relationship between lubricant effects and tablet properties (hardness and disintegration) (8, 9), and changes in physical properties of powder mixes as a function of lubrication (10–15). Few of these studies, however, concerned the influence of mixing time on the processing characteristics of the powder and, especially, the performance properties of the compressed tablet.

Properties of the compact critical to its performance include the ejection force, tablet hardness, disintegration, and dissolution. It is generally recognized that a lubricant modifies these properties. However, the duration of mixing in the lubricant component may not only affect the properties of the compact but also the properties of the blended mixture by altering the apparent bulk volume, the compression force required to make a prescribed compact, and the hydrophobic character of the mixture. The research studies described in this report concerned the interdependency of these physical properties for several model systems designed to test the effects of mixing time.

Previous mixing studies dealt with the homogeneity of the mixture (16–20), evaluations of mixing equipment (21–23), and segregation kinetics associated with model systems (24–27). This work emphasized the importance of solid–solid mixing related to drug distribution and homogeneity of the mix. Since content uniformity of the active ingredient is a primary control for accurately dosing a patient with a unit dosage form, emphasis is always given to the final composition of the assayed tablet or other dose form. Nonetheless, the release characteristics and performance criteria (such as physical integrity and stability) also rely on the nature and extent of distribution of inert excipients as well as the active ingredient. Of significance is the lubricant–excipient interaction and the manner in which these materials are affected by mixing. Possibly, mixing times can modify the intended role of these adjuvants, in some cases altering or diminishing their primary function.

The present work investigated the mixing of direct compaction excipients such as lactose and microcrystalline cellulose with various commonly used lubricants. Furthermore, the occasional nonpredicted increased disintegration time of a compressed tablet associated with a decreased hardness or crushing force requirement prompted an investigation of the effects of lubricants (*e.g.*, stearates) and mixing duration on the physical properties of a blended mixture and compact.

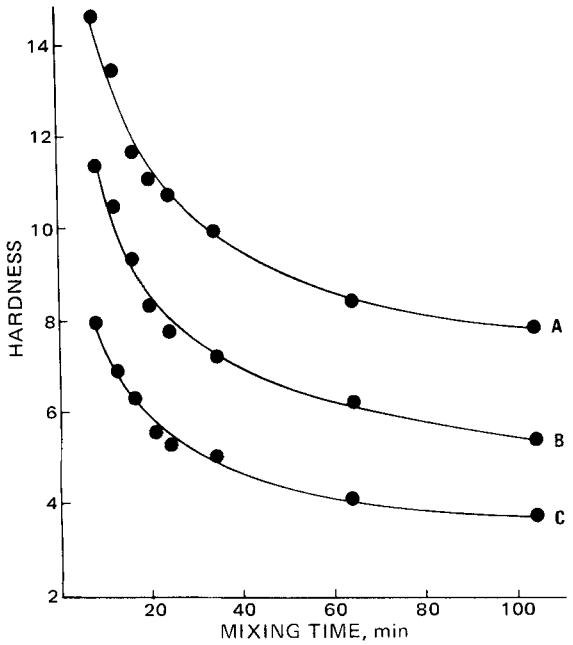


**Figure 1**—*Strong–Cobb hardness of lactose–1% magnesium stearate tablets (average of 10 tablets) plotted as a function of mixing time. Tablets were compressed at 1620 (A), 1300 (B), and 970 (C) kg.*

It has not been generally known that the mechanism of lubricant action can affect the bulk volume of the mix. Previous studies (10–15) showed that the bulk volume decreases by admixing the lubricant. The present studies demonstrate the effect of mixing time on processing characteristics and tablet performance properties. A mechanism for the role of lubricant materials as a function of mixing time was explored.

## THEORY

The change of particle distribution with time caused by mixing has been described as three-dimensional shuffling (28). In such a case, the surface of separation (defined as the separation plane between dissimilar particles) can be used as a measure of the degree of mixing. Thus, for a pharmaceutical powder blend, the maximum surface of separation would correspond to a perfect mix. This qualitative variable can be employed to measure the effect of mixing time on the rate and extent of lubricity when the theory of lubrication assumes a surface coverage of lubricant adsorbed on a particle substrate. This model was applied to extend mixing theory to pharmaceutical powder lubrication. Several effects of different lubricating materials can be explained in this way.

Lubricancy in solid particles improves the fluidity and packing characteristics of a blended mix and permits a homogeneous mix to be transferred compositionally intact to a target volume such as a compressing die. Agents that reduce such interparticulate friction also alter the particle packing characteristics by modifying the particle size and shape factors and have been termed glidants. The degree and extent of surface coverage of a substrate particle by such agents can be described theoretically for pharmaceutical mixtures by invoking at least three different mechanisms: (*a*) adsorption or surface contact adhesions; (*b*) diffusion or solids penetration, which includes mechanical interlocking; and (*c*) delamination or deagglomeration of the lubricating agent to form a film coating (usually discontinuous) on the substrate particles. Whichever mechanisms may be involved, the effect of mixing time should modify both glidant and lubricant roles of the agent.

The true lubricant role of these antifriction agents in pharmaceutical mixes occurs during and after the primary compaction process in tablet manufacturing. While facilitating consolidation of particles in the die cavity, these agents prevent adhesion of the tablet surface to the dies and punches during compression. During ejection, the agents act as boundary lubricants by reducing the frictional force needed to overcome the shear strength at the die wall.

The nature and extent of surface coverage of the lubricant achieved by mixing often predetermine the strength or weakness of the consolidating forces. Ultimately, of course, the bonding forces must be designed to fail in cohesion and/or adhesion when the tablet performs, *i.e.*, disintegrates and dissolves. The duration of mixing exerts not only a statistical effect on randomizing the location of the lubricant within the compact but also affects surface characteristics of the powder and interparticular bond strength in the compact.

Hydrophobic surfaces are those granule or tablet surfaces on which water will not spread. Ganderton (9) described the effect of lubricant distribution on the penetration of a tablet by water. The degree of mixing, both in duration and shearing energy, may affect the porosity, air permeability, and liquid penetration rate of a tablet. Magnesium stearate is a widely used lubricant and is strongly hydrophobic. In general, it is not desirable to render a dosage form hydrophobic inasmuch as the poor wetting of a tablet or other solid dosage form can retard dissolution and drug release.

Thus, the hydrophobicity or water repellancy of a surface, when measured by contact angle (9), affects the capillary action involved in pore penetration. Even if the pores of a surface are hydrophobic, water vapor can pass through them if a sufficient hydrostatic pressure is imposed. The presence of hydrophilic sites, which are almost always present even on hydrophobic solids, also facilitates the interaction of water on a granule or tablet. Thus, it can be assumed that the nature of a hydrophobic surface coverage on a tablet or other solid dosage form enhances or retards the interaction rate but does not inhibit the primary intermolecular attractions at work during disintegration and dissolution.

The adsorption of a lubricant and its distribution on the substrate surface during mixing determines the hydrophobic matrix. The duration of mixing should be related to the clustering around specific sites on the solid surface, which will affect the polarity of the localized surface and create sufficient large or small areas of hydrophilic character; these areas can affect glidancy, consolidation, ejection, dissolution, and other tablet processing variables. The extent and effect on hydrophobicity due to lubricant coverage as modified by mixing are determined by the primary mechanism of action, which physically dominates at the granule or tablet surface. Each of the three general mechanisms previously described operates *via* different pathways in the various unit operations employed.

Mixing theory has generally been employed to help describe those operations in which some energy is applied to a given mass of material for the purpose of changing the initial particle arrangement into a more desirable one. By using kinetics and assuming that mixing is essentially a three-dimensional shuffling operation, Brothman *et al.* (28) derived an expression:

$$S_t = S_m(1 - e^{ct}) \qquad \text{(Eq. 1)}$$

where $S_t$ is the instantaneous magnitude of a surface of separation, $t$ is the time of mixing, $S_m$ is the maximum theoretically possible surface of separation, and $c$ is a constant depending on the substances to be mixed and the mixing equipment. Thus, the function of a V-shelled blender or other mixing device is to enlarge the initial plane of separation between ingredients such as excipients and lubricants. The degree of mixing can then be measured by the extent of the surface of separation at different mixing times. This approach allows the evaluation of the amount of surface enlargement that would occur in a given period of time as proportional to the difference between $S_t$, the instantaneous magnitude of the surface, and its greatest possible value, $S_m$.

According to the mechanisms of boundary lubrication put forward by Strickland *et al.* (3), solid lubricants such as magnesium stearate are adsorbed on the granule surface. These lubricants form a uniform surface-adsorbed film in a manner similar to a Langmuir-type adsorption. If it is assumed that during the mixing process lubricant particles first adsorb on the surface and then, upon continued mixing, distribute uniformly upon the granule surface, the breaking of these lubricant particles by delamination or deagglomeration may take place. Such processes would result in greater coverage of the granule surface by the lubricant, thereby producing a greater interfacial surface between the lubricant and the excipient granule, *i.e.*, surface of separation. The mixing process described by Eq. 1 should then relate an exponential relationship for mixing time and any surface coverage-oriented mixing parameter.

The extension of this mixing theory, based on the concept of the surface of separation, can be utilized to relate the interfacial strength of the boundaries of granules initiated through mixing and residing in a formed dosage unit such as a compressed tablet. Hardness, $H$, is related to the intergranular or interfacial bonds formed within a tablet. Shotton and Lewis (8) described the effect of a lubricant on tablet hardness. In this work, the surface of separation related by mixing time was interpreted to derive an expression for hardness as a function of mixing time:

$$H_t = H_m(1 - e^{-ct}) \qquad \text{(Eq. 2)}$$

where $H_t$ and $H_m$ represent instantaneous hardness at time $t$ and theoretical maximum hardness, respectively. Predicting such an exponential

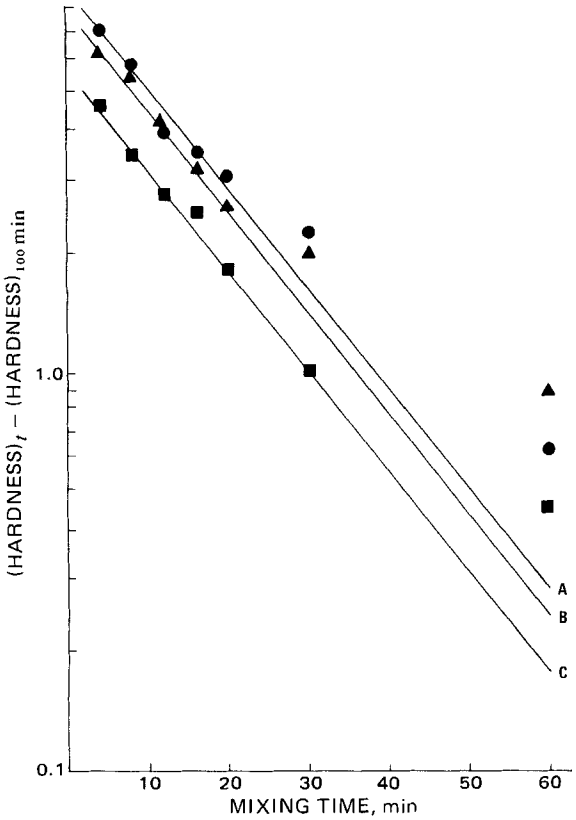


**Figure 2**—*Semilogarithmic relationship of tablet hardness data shown in Fig. 1.*

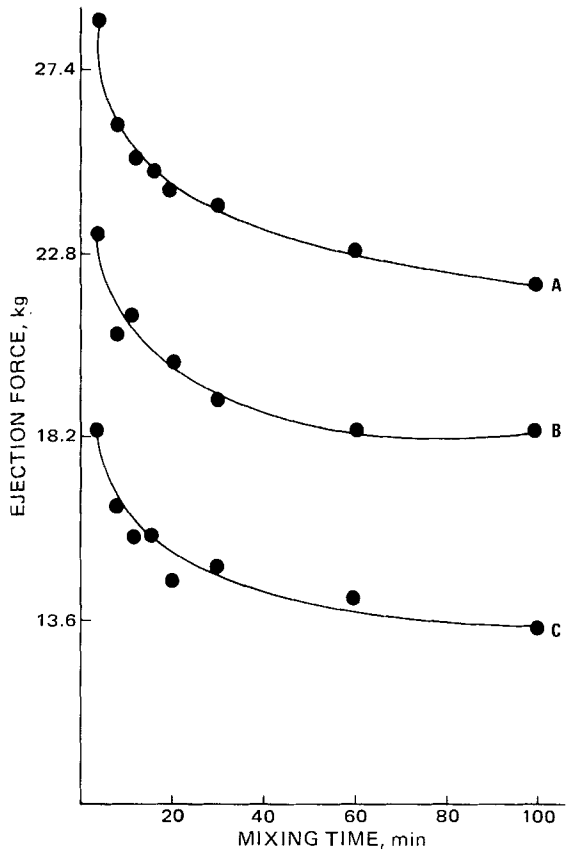


**Figure 3**—*Ejection force of lactose–1% magnesium stearate tablets as a function of mixing time. Tablets were compressed at 1620 (A), 1300 (B), and 970 (C) kg.*

relationship for hardness implies a direct mechanism whereby the surface of separation affected by mixing is controlling the lubricant–excipient interaction and, ultimately, the tablet crushing strength. The experimental results show that this approach provides some convenient guidelines for predicting lubricant action.

The systems involving magnesium stearate and excipients could be described by such a mechanism of time effects. However, it need not be the only explanation for lubricant action. Miyake *et al.* (15) postulated a diffusion mechanism for lubricant action. All such results seem to apply for magnesium stearate but not necessarily for all other pharmaceutical lubricants. Until more comparisons are made, one can only speculate on how lubricant action is altered by time effects. Nevertheless, there is ample evidence now that delamination is at least a primary mechanism for magnesium stearate.

The extension of mixing theory to lubricant–excipient interactions can be fully exploited if the surface of separation meets other criteria of physical models useful to pharmaceutical operations. Thus, glidancy, lubricancy, frictional flow, and compression (due to plastic deformation and flow) all can rely on the qualitative measure of degree of mixing described by three-dimensional shuffling and a surface of separation. Moreover, within the compact, the hydrophobicity (affecting disintegration and dissolution) as well as hardness (measured only as crushing strength) are equally extrapolatable to the time effects of mixing. Such concepts must be refined in controlled studies, however, since the $c$ value, assumed to be a constant, could be a variant for the changing shear effects in a blender or the changes in particle character of materials.

## EXPERIMENTAL

Materials used in the mixing study were spray-dried lactose USP, microcrystalline cellulose (medium powder) NF, magnesium stearate USP, talc (bolted) USP, stearic acid USP, colloidal silicon dioxide NF, calcium stearate NF, and salicylic acid USP. Throughout the study, a single lot of each material was used to eliminate the possibility of lot-to-lot variability.

Mixing operations were performed in a 3.8-liter stainless steel twin-shell V-shape mixer[1]. Unless specified otherwise, 1 kg of spray-dried lactose or 475 g of microcrystalline cellulose was employed in all studies. To prepare an excipient–lubricant mixture, a weighed amount of lubricant was screened through a 40-mesh screen over the bed of excipient; the mixture was then transferred into the mixer and allowed to blend at 22 rpm for a specified period. A series of mixtures blended for different time intervals was prepared similarly.

Tablets were compressed on an instrumented single-punch[2] machine, equipped with 1.9-cm diameter half-oval punches, at a machine speed

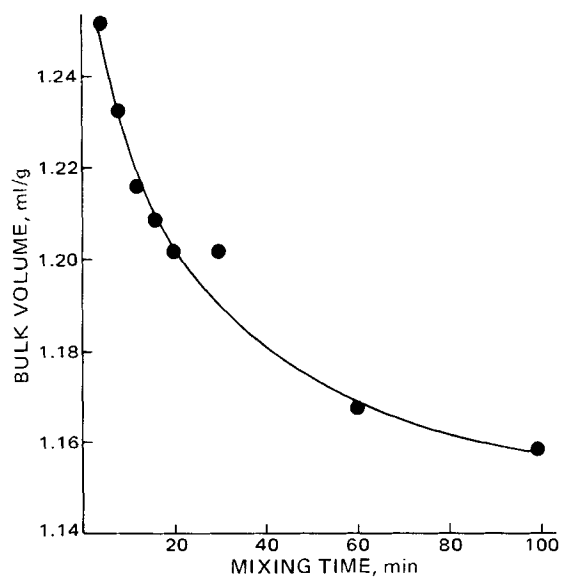


**Figure 4**—*Apparent bulk volume of lactose–1% magnesium stearate mixtures as a function of mixing time.*

[1] Patterson-Kelley Co., East Stroudsburg, Pa.

[2] Key Industries, Farmingdale, NJ 07727.

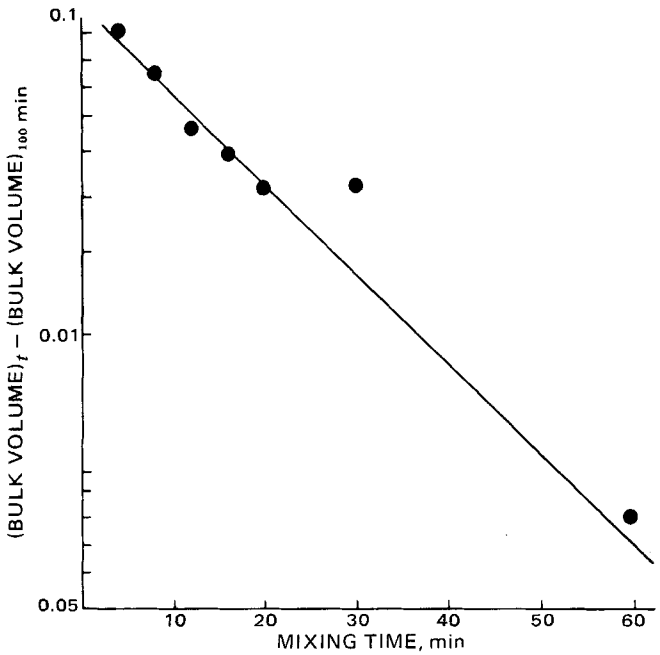


**Figure 5**—*Semilogarithmic relationship of apparent bulk volume data shown in Fig. 4.*

of 56 tablets/min. A tablet weight of 550 mg for the lactose tablets and of 372 mg for microcrystalline cellulose tablets was maintained. Compression and ejection forces were recorded by photographing the signals transmitted by strain gauges to an oscilloscope.

The apparent bulk volume of the powder mixture was determined by volumetric measurement of the mixture in a 500-ml conical flask. The mixture was transferred into the flask at a uniform rate of about 100 g/min by a mechanical conveyor. From the fill weight and volume of the flask, the apparent bulk volume of the mixture was calculated. During the filling operation, care was taken to avoid any vibration of the flask. Repeated measurements by this procedure showed less than 5% variation in the bulk volume values.

The dissolution rate of salicylic acid from an *in situ* constant-surface pellet was determined by the Levy and Hayes (29) beaker method with the pellet suspended 3 cm above the bottom of the beaker. The test conditions employed were 1000 ml of pH 7.5 phosphate buffer, 37°, and a 300-rpm stirring speed. The amount of salicylic acid dissolved was measured by automated spectrophotometric analysis of the dissolution medium.

## RESULTS AND DISCUSSION

Spray-dried lactose and microcrystalline cellulose, typical direct compaction adjuvants, were selected as the major inert excipients.

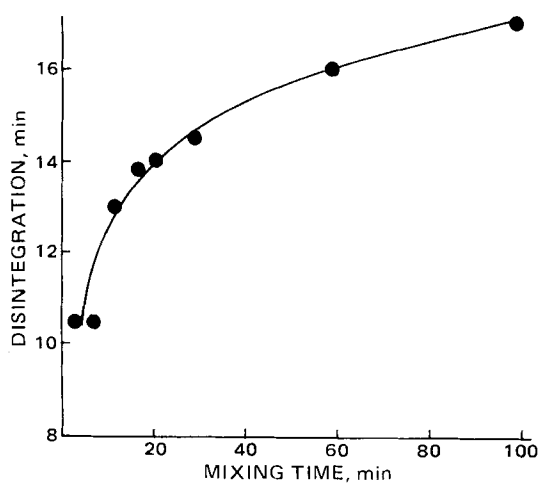


**Figure 6**—*Disintegration time (USP) of lactose–1% magnesium stearate tablets plotted as a function of mixing time. Tablets were compressed at 1300 kg.*

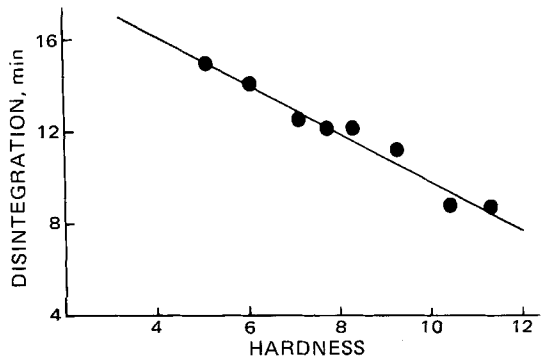


**Figure 7**—*Correlation between disintegration time and hardness of lactose–1% magnesium stearate tablets (r = 0.9544).*

Magnesium stearate was the common lubricating agent added. Among the properties of the excipient–lubricant mixtures evaluated as a function of mixing time were apparent bulk volume, surface morphology, ejection force during tablet compression, tablet hardness, and tablet disintegration.

**Lactose–Magnesium Stearate Mixing Studies**—Figure 1 shows the effect of mixing time upon tablet hardness for the lactose–1% magnesium stearate blends compressed at three different compression forces. The hardness continued to decrease and reached a constant value with the increased mixing time. A plot of log [(hardness at time $t$) − (hardness at 100 min)] *versus* mixing time (Fig. 2) suggests an apparent first-order rate of change in tablet hardness. These results correlate with Eq. 2, which predicts an exponential change in tablet hardness as a function of mixing time.

The effect of mixing time on the ejection force recorded during tablet compression is shown in Fig. 3. The decrease in the ejection force upon mixing would reflect increased lubrication efficiency of magnesium stearate as a result of greater surface coverage by the lubricant. The ratio of compression to ejection force at 100 min was about 31 kg for the three compression forces employed. This ratio may be considered as the optimum lubricant efficiency of magnesium stearate in this system. Similar results were also obtained with 0.5% magnesium stearate, but the lubrication efficiency ratio after 100 min of mixing was about half of that for the 1% magnesium stearate–lactose system.

During tablet compression, the die-fill weight tended to increase with a longer mixing time. To maintain constant weight, it was necessary to reduce the fill volume by adjusting the lower punch settings. This observation prompted a study of the effect of mixing time upon the apparent

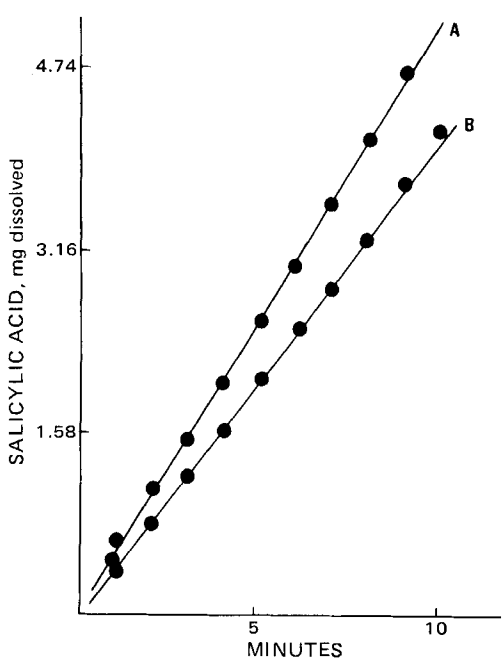


**Figure 8**—*Dissolution of salicylic acid from constant-surface pellets containing lactose and magnesium stearate. Lubricant mixing time was 10 (A) and 100 (B) min.*

**Table I—Magnesium Stearate Concentration of Lactose Tablets Determined by Atomic Absorption Analysis**

| Mixing Time, min | Magnesium Stearate in Tablet, % | | | | | | |
|---|---|---|---|---|---|---|---|
| | Tablet 1 | Tablet 2 | Tablet 3 | Tablet 4 | Tablet 5 | Average | *SD* |
| 4 | 102.9 | 86.1 | 104.8 | 106.6 | 102.9 | 100.7 | 8.23 |
| 100 | 104.8 | 111.3 | 106.6 | 97.3 | 107.6 | 105.5 | 5.17 |

bulk volume of the mixture samples. Figure 4 shows a decrease in the apparent bulk volume of lactose–1% magnesium stearate mixture with the longer mixing time. A log exponential relationship of [(bulk volume at time $t$) − (bulk volume at 100 min)] *versus* mixing time is shown in Fig. 5. These results suggest that, like tablet hardness, apparent bulk volume also changes by an apparent first-order rate with respect to mixing time. Furthermore, the first-order rate constant value of $4.33 \times 10^{-2}$ min$^{-1}$ for the tablet hardness estimated from Fig. 2 seems quite comparable with $5.54 \times 10^{-2}$ min$^{-1}$ for the apparent bulk volume, suggesting that the influence of mixing time upon both properties is probably a manifestation of the enlarged surface of separation or greater surface coverage by the lubricant upon mixing.

The duration of mixing had major effects upon the tablet disintegration. Figure 6 shows the USP disintegration time of lactose–1% magnesium stearate tablets plotted as a function of mixing time. The mixtures blended for a longer time yielded tablets with a slow disintegration. The observed effect upon tablet disintegration may be attributed to the formation of a hydrophobic surface by the lubricant upon mixing. A correlation of disintegration time with tablet hardness (Fig. 7) represents a unique case, where disintegration time is inversely proportional to tablet hardness (*i.e.*, the harder the tablet, the faster it disintegrates). This result is due to the decline in tablet hardness and prolongation of disintegration time as a result of the lubricant covering over the surface of lactose particles upon mixing.

In an effort to demonstrate the influence of mixing time upon drug dissolution, a well-mixed sample of lactose–1% salicylic acid was subjected to further mixing with 1% magnesium stearate for 10 and 100 min. Dissolution rates of salicylic acid were determined from constant-surface pellets of the two mixtures. The pellet prepared from the 10-min mixed sample dissolved at a relatively faster rate (0.53 mg/ml) compared to the 100-min mixed sample (0.40 mg/ml) (Fig. 8). This effect of lubricant upon the dissolution rate is attributed to the increased hydrophobicity of the compact with a prolonged mixing time.

The magnesium stearate content in the lactose tablets was examined to confirm the distribution of lubricant in each tablet during the continued mixing process. Atomic absorption analysis of tablet samples made at 4- and 100-min mixing intervals for the 1.0% magnesium stearate–lactose system is shown in Table I. The elemental analysis was reasonably uniform even after only 4 min of mixing.

Particle-size analysis of sieving also independently confirmed that the essential size distribution of each mixture was not altered during any of the lactose–stearate mixing studies.

**Microcrystalline Cellulose–Lubricant Mixing Studies**—These studies were performed similarly to the lactose studies. In these studies, 475 g of microcrystalline cellulose was used because the apparent bulk volume of this amount of microcrystalline cellulose is equivalent to 1.0 kg of spray-dried lactose. This amount kept the bulk volume essentially constant for mixing in a similar size mixer.

The effect of mixing time on tablet hardness is shown in Fig. 9 for microcrystalline cellulose–1% magnesium stearate tablets. These results show the same surface coverage-oriented mixing dependency of Eq. 2 as was found previously for lactose. This result again may be interpreted

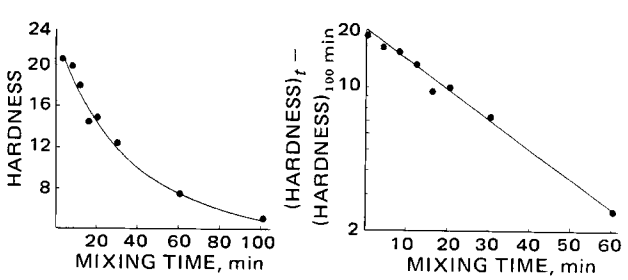


**Figure 9**—*Strong–Cobb tablet hardness of microcrystalline cellulose–1% magnesium stearate tablets plotted on a linear (left) and semilogarithmic (right) scale as a function of mixing time.*

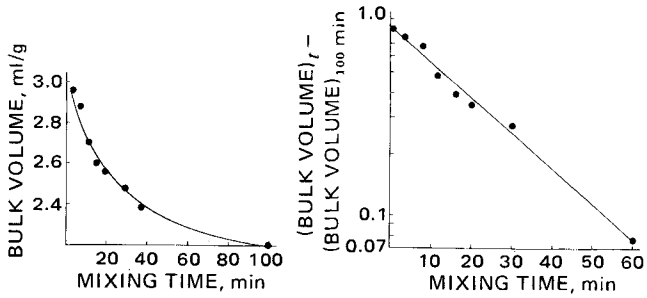


**Figure 10**—*Apparent bulk volume of a microcrystalline cellulose–1% magnesium stearate mix plotted on a linear (left) and semilogarithmic (right) scale as a function of mixing time.*

as the kinetics of a three-dimensional shuffling operation in which the surface of separation is enlarged upon mixing.

As in the lactose studies, the apparent bulk volume of the microcrystalline cellulose–1% magnesium stearate mixture decreased with mixing time (Fig. 10). The rate constant for the change in the bulk volume, $k = 4.07 \times 10^{-2}$ min$^{-1}$, is quite comparable to the $k = 3.46 \times 10^{-2}$ min$^{-1}$ obtained for the hardness change (Fig. 9), suggesting that both properties are related to the extent of lubricant surface coverage.

The influence of mixing microcrystalline cellulose with various lubricants upon apparent bulk volume was examined. Mixing of microcrystalline cellulose alone, without lubricant, showed no apparent change in the bulk volume (Fig. 11). Stearic acid also produced no significant change. A rapid initial change observed with talc and colloidal silicon dioxide may be attributed to their action as glidants rather than as lubricants. Magnesium stearate and calcium stearate showed essentially a similar change in the bulk volume as a function of mixing time.

Scanning electron microscopy studies were performed on both lactose and microcrystalline cellulose systems lubricated with 1.0% magnesium stearate. The spray-dried lactose is relatively equidimensional in shape, characteristic of powders prepared in this manner. The morphology of microcrystalline cellulose is such that the powder can be assumed to be composed of microfibers with elongation ratios (length to width) typically in the 3.0–5.0 range. Magnesium stearate occurs as a lamellar solid, stacked in plate-like sheets resembling a deck of cards.

Magnesium stearate particles adhered to the surface of spray-dried lactose granules could be identified by scanning electron microscopic observations. However, they could not be identified on microcrystalline cellulose because of the similar morphology of the fine particle debris of microcrystalline cellulose itself. Figure 12 shows photomicrographs of lactose–magnesium stearate samples blended for 8 and 100 min. These photographs suggest that magnesium stearate adsorbs on the surface of lactose during the initial mixing time. As mixing proceeds at 100 min, the

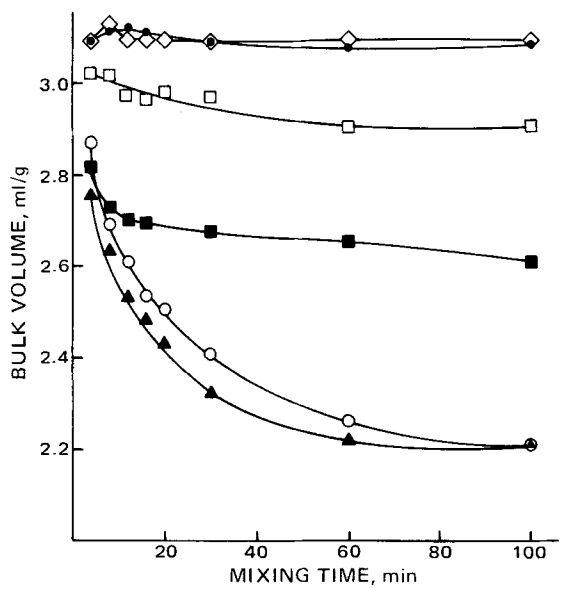


**Figure 11**—*Apparent bulk volume of microcrystalline cellulose–lubricant mixtures plotted as a function of mixing time. Key: ●, no lubricant; ◇, 1% stearic acid; □, 3% talc; ■, 0.3% colloidal silicon dioxide; ○, 1% magnesium stearate; and ▲, 1% calcium stearate.*

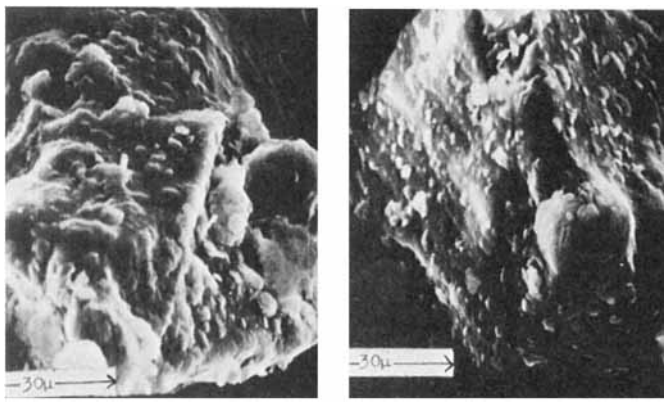

**Figure 12**—*Scanning electron microscopic photomicrographs of lactose–1% magnesium stearate 8- (left) and 100- (right) min mixes.*

population of individual magnesium particles increases by a delamination process, and a greater surface coverage of lactose particles by magnesium stearate results.

The mechanism of lubrication envisioned for magnesium stearate involves surface coverage due to adsorption upon initial mixing. As mixing continues, the shear effects induce delamination or deagglomeration of the lubricant to harness more stearate particles that slide or adhere on the excipient granule surface. The adhered particles, once they delaminate to individual "cards," no longer spread over the excipient surface during mixing. This process accounts for the leveling in the bulk volume and, perhaps, the hardness plots after long mixing times. This mechanism is called delamination or the "stack of cards" theory because the shear-induced effects of continued mixing are arrested at a given time in the mixing cycle.

Diffusion or solids penetration plays a minor role in the lubricant spreading, since mixing occurs as a function of time. Moreover, a continuous coating of lubricant does not completely occur during mixing, but surface contact adhesion (action of a boundary lubricant) may occur only after compression. Under compression, however, a mechanism of a lubricant may undergo diffusion adhesion or surface contact adhesion. This mixed mechanism of lubricant action may help to explain the changes in bulk specific volume and tablet hardness affected by mixing time.

The surface coverage-oriented parameters affected by mixing time include glidancy, frictional flow, hydrophobicity, and lubricancy as predicted by Eq. 1. The derived expression for hardness shown as Eq. 2 also appears to be related to a surface or separation phenomenon. This mixing effect would be expected to influence not only tablet hardness but tablet compression and hydrophobicity within the compact as well. Thus, it may help to explain the mixing time effects noted in the physical properties more important to drug release and bioavailability, such as disintegration and dissolution.

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