Magnesium Lauryl Sulfate in Tableting: Effect on Ejection Force and Compressibility

A. M. SALPEKAR and L. L. AUGSBURGER[x]

Abstract □ The effect of magnesium lauryl sulfate on tablet ejection force and filler compressibility was evaluated and compared to magnesium stearate in four direct compression fillers (microcrystalline cellulose, compressible starch, spray-dried lactose, and direct compression sucrose) and a typical wet granulation (terra alba) using a rotary tablet press instrumented to monitor ejection and compression forces. Generally, higher concentrations of magnesium lauryl sulfate were required to produce ejection forces similar to those obtained with magnesium stearate. However, batches employing magnesium stearate were generally less compressible than batches employing magnesium lauryl sulfate at levels sufficient to produce similar or lower ejection forces.

Keyphrases □ Magnesium lauryl sulfate—effect on ejection force and compressibility of four direct compression fillers and a wet granulation, compared to magnesium stearate □ Tableting—effect of magnesium lauryl sulfate on ejection force and compressibility of four direct compression fillers and a wet granulation, compared to magnesium stearate □ Compressibility of tablet formulations—effect of magnesium lauryl sulfate, compared to magnesium stearate □ Lubricant effect of magnesium lauryl sulfate in tableting—ejection force and compressibility parameters, compared to magnesium stearate

Lubricants are agents added in small quantities to tablet formulations to improve certain processing characteristics of direct compression powder blends and granulations. In this regard, three activities have been identified (1) with the use of the term "lubricant." These are: (*a*) preventing sticking to punch faces and the die wall (antiadherent activity), (*b*) improving flow properties of the granulation (glidant activity), and (*c*) reducing friction at the tablet–die wall interface during tablet formation and ejection (true lubricant activity). While a given lubricant may provide one or more of these actions to varying degrees, the primary function of lubricants in tableting is that of true lubricants (1, 2). Therefore, it is not surprising that hydrophobic materials are more effective than hydrophilic ones. Although such an agent would only be needed at the interface of the tablet and the die wall, it must be distributed throughout the tablet, thereby tending to make the tablet matrix hydrophobic. Because of this, lubricants as a class are known to retard moisture penetration, disintegration times, and dissolution rates (3–5).

In a search for a water-soluble lubricant, water-soluble magnesium lauryl sulfate and the most widely used lubricant, magnesium stearate, were compared (6) in four tablet and capsule formulations. The data were reported to indicate that magnesium lauryl sulfate has the lubricating activity of magnesium stearate but not its waterproofing effect. Although it was noted whether or not the formulations would run, conclusions were based on weight variation data. These data provide information on the glidant properties of these materials but give no indication of true lubricant action. Tablet weight variation was used (7) to evaluate several silica-type glidants. Most true lubricants are poor glidants and may actually retard flow properties (1). Indeed, formulators often include both true lubricants and glidants in tablet formulations.

In an earlier study (8), the true lubricant effect of magnesium lauryl sulfate (as one of 70 different compounds) in a sulfathiazole granulation was evaluated on the basis of the R value (ratio of maximum lower to maximum upper punch force) and ejection force. According to the theory, R would approach 1 with perfect lubrication. Thus, the more closely R approaches 1, the better the lubricant and the lower ejection force should be. The tabulated data indicated that magnesium stearate was the most effective true lubricant of the compounds tested and somewhat more efficient than magnesium lauryl sulfate (magnesium stearate: $R = 0.95$, ejection force = 8 kg; magnesium lauryl sulfate: $R = 0.88$, ejection force = 24 kg; unlubricated control: $R = 0.67$, ejection force = 110–170 kg). Since these data were based on a single compression force and lubricant concentration (2%), they give no indication of the effect of compression pressure or lubricant concentration on lubricant efficiency. Both R values and ejection force are known to vary with compression pressure (8, 9). The fact that these data were generated on a single-punch, eccentric-type machine may limit their applicability because the rotary tablet press is more representative of the type of press used in the industry. Furthermore, no studies were conducted on the newer, direct compression filler systems.

The present study was designed to provide a more definitive evaluation of the true lubricant effect of magnesium lauryl sulfate in tableting, particularly in direct compression systems. Since lubricants such as magnesium stearate are known to interfere with interparticulate bonding in tablets and thereby reduce compressibility, one objective of this study was to evaluate the effect of magnesium lauryl sulfate on compressibility.

EXPERIMENTAL

Instrumentation—All studies were carried out on a rotary tablet press[1] instrumented to measure compression force and ejection force after the manner of Wray *et al.* (10, 11). Compression force is monitored from a remote site using a pair of metal foil resistance strain gauges[2] (in parallel circuit) bonded to either side of

[1] Stokes model RB2.
[2] Type SR-4, BLH Electronics, Waltham, Mass.

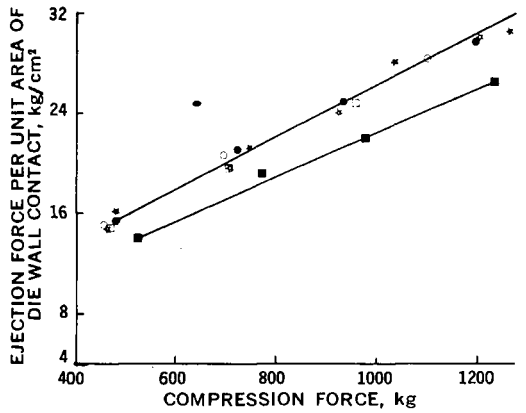

Figure 1—*Effect of magnesium lauryl sulfate (□, 2%; ○, 3%; ☆, 5%) and magnesium stearate (★, 0.5%; ●, 1%; ■, 2%) on the ejection force of spray-dried lactose tablets.*

the eye-bolt connecting the overload spring with the lower compression roller. These gauges form two active arms of a Wheatstone bridge. On tablet compression the eye-bolt is compressed, thereby changing the resistance in the gauges and unbalancing the bridge circuit. This force sensed at the eye-bolt is proportional to the tablet compression force and is monitored by measuring the bridge unbalance voltage using a carrier preamplifier[3], which also serves to activate the bridge. Ejection forces are monitored in a somewhat similar manner by replacing a portion of the ejection cam with a tool-steel cantilever beam. Metal foil resistance gauges are bonded to either side of the beam (in series) to form two active arms of a Wheatstone bridge. As the lower punch travels up the ejection cam, the force of ejection produces a deflection in the cantilever beam, thereby unbalancing the bridge.

Both the compression and ejection events were continuously recorded on an oscillographic recorder[4]. Responses were read directly in microstrains, which were converted to kilograms of force.

Preparation of Tablets—Because of its widespread use and recognized high efficiency as a true lubricant, magnesium stearate[5] was used throughout this study as a control for evaluating magnesium lauryl sulfate[6] in representative types of direct compression fillers and a typical granulation.

To promote good blending and uniform dispersion, both materials were passed through an 80-mesh screen before blending with the direct compression fillers or granulation. No other additives or active ingredients were included in these formulations.

The fillers used in the direct compression studies were microcrystalline cellulose[7], compressible starch[8], spray-dried lactose[9], and a direct compression sucrose[10]. All direct compression batches were mixed[11] for 10 min without the intensifier bar and then for 2 min with the intensifier bar running.

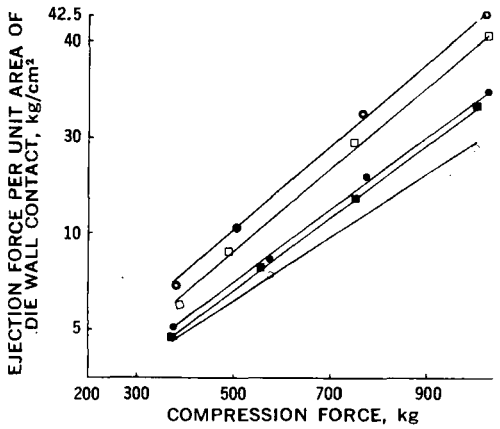

Figure 2—*Effect of magnesium lauryl sulfate (●, 3%; ○, 5%) and magnesium stearate (◘, 0.5%; □, 1%; ■, 2%) on the ejection force of direct compression sucrose tablets.*

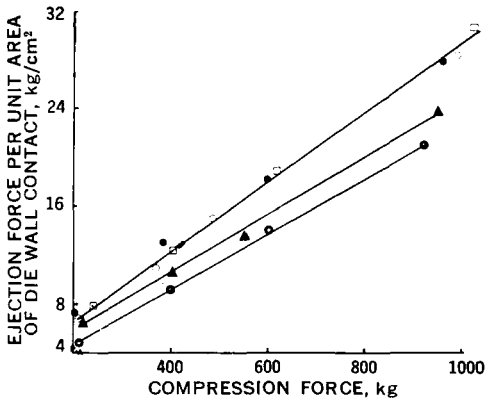

Figure 3—*Effect of magnesium lauryl sulfate (▲, 1%; ◘, 2%) and magnesium stearate (○, 0.25%; □, 0.5%; ●, 1%) on the ejection force of terra alba granulation tablets.*

For the granulation studies, a terra alba granulation was prepared using a 15% aqueous acacia solution as the binder. The wet mass was passed through a #34 plate on a laboratory wet granulating unit[12], dried 48 hr at 55°, and then passed through a 20-mesh screen by hand. All batches were blended in the mixer for 15 min. The intensifier bar was not used with these batches to avoid creating excessive fines.

The batches were of 500 g with the exception of the microcrystalline cellulose blends, which were 350 g.

All tablets were compressed using a single set of 1.11-cm (0.43-in.) flat-faced punches and die at a machine speed of 28 rpm. Tablets were compressed in a controlled humidity area (30 ± 10% relative humidity) where temperature was maintained at 26 ± 1°.

Ejection Force Study—Ejection forces were monitored at each of four compression forces to provide data over a wide range of tableting conditions. After evaluating each sample, the punches and die were thoroughly cleaned with acetone before running the next sample.

Magnesium lauryl sulfate was evaluated at the lowest concentration at which the batches appeared to run and at least one higher concentration. Magnesium stearate was evaluated at one lower concentration (usually 0.5%), at a concentration equal to the lowest effective concentration of magnesium lauryl sulfate as determined previously, and at one higher concentration, except as otherwise noted. In all cases, ejection forces were monitored for 10 min to ensure constancy of readings. To minimize variations in tablet thickness that might bias ejection force data, it was necessary to adjust tablet weight to account for the differences in density among the fillers. Thus, tablet weights were adjusted to about 500 mg for all fillers except microcrystalline cellulose and the terra alba granulation where the tablet weights were adjusted to about 350 and 750 mg, respectively. Nevertheless, small variations in tablet thickness (0.35–0.40 cm) were observed due to the various compression forces used. Although these variations were small relative to overall tablet thicknesses, ejection forces were reported in terms of kilograms force per unit apparent area of tablet-die wall contact (*i.e.*, kilograms per square centimeter) to ensure further that there would be no bias due to differences in tablet thickness. The data reported represent the means of at least 10 readings.

Compressibility—Compressibility, defined as the ease with which hard tablets are produced, was assessed by determining tablet hardness at each compression force. The mean hardness of

[3] Sanborn model 35-1100B, Hewlett-Packard Co., Palo Alto, Calif.
[4] Sanborn model 964, Hewlett-Packard Co., Palo Alto, Calif.
[5] Ruger Chemical Co., Inc., New York, N. Y.
[6] Courtesy of Alcolac Chemical Corp., Baltimore, Md.
[7] Avicel PH 101, F.M.C. Corp., American Viscose Div., Newark, Del.
[8] Sta-R 1500 starch, A. E. Staley Manufacturing Co., Decatur, Ill.
[9] Lactose USP, spray dried, Foremost Dairies, Inc., San Francisco, Calif.
[10] DiPac, a cocrystallization of 97% sucrose and 3% modified dextrins, Amstar Corp., New York, N.Y.
[11] Patterson Kelly V-mixer.
[12] Eureka.

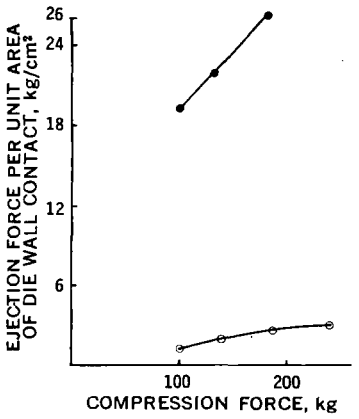

Figure 4—*Effect of magnesium lauryl sulfate on ejection forces of microcrystalline cellulose tablets. Key: ●, control (no lubricant); and ○, 0.25% magnesium lauryl sulfate.*

at least 10 tablets at each compression force was determined in Strong-Cobb units using a motorized tablet hardness tester[13].

RESULTS AND DISCUSSION

The ejection force data for the spray-dried lactose batches are summarized in Fig. 1. Although the use of 2% magnesium lauryl sulfate resulted in ejection forces comparable to the 1% magnesium stearate batch at compression forces up to 950 kg, an attempt to run this batch at a compression force of 1200 kg (average hardness of 21.4 Strong-Cobb units) was unsuccessful. Continuous monitoring showed that ejection force increased with each tablet ejection, going from 27.8 to 46.8 kg/cm² after only 300 tablets had been produced. There was no indication that an equilibrium value had been reached, and the run was terminated to prevent possible damage to the cantilever beam mechanism. Visual examination of these tablets revealed scoring of the tablet sides, and there was evidence of sticking to the die wall. This effect was not observed when magnesium lauryl sulfate was added at concentrations of 3 or 5%, but ejection forces were no lower. Increasing magnesium stearate to 2% measurably lowered ejection forces at all compression force levels. There was no evidence of sticking to the die wall in any of the magnesium stearate runs.

The ejection force results for the direct compression sucrose appear in Fig. 2. Ejection force was clearly reduced as magnesium stearate was increased to 2%. Closely similar ejection forces were observed with 3% magnesium lauryl sulfate; however, 5% of this compound resulted in ejection forces lower than any of the batches in this series, especially at the higher compression forces. There was noticeable sticking to the die wall when magnesium lauryl sulfate was employed at concentrations below 3%.

No significant differences in ejection force were noted when magnesium stearate was increased from 0.25 to 1% in the terra alba granulation, but ejection forces were higher at all compression force levels than when 1% magnesium lauryl sulfate was the

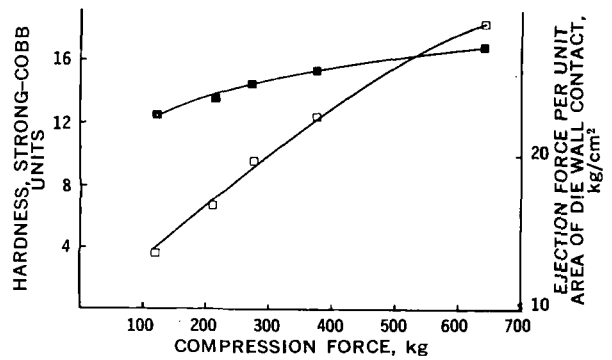

Figure 5—*Compressibility and ejection forces with unlubricated compressible starch. Key: ■, effect on ejection force; and □, effect on hardness.*

[13] Heberlein model 2E/106, Key Industries, Farmingdale, N.J.

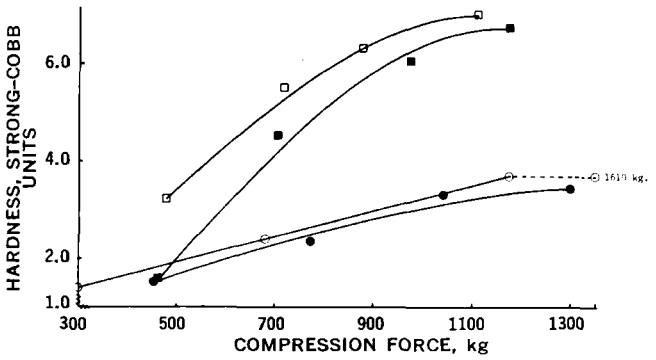

Figure 6—*Effect of magnesium lauryl sulfate (□, 0.3%; ■, 0.5%; ●, 1%) and magnesium stearate (○, 0.2%) on the compressibility of compressible starch.*

lubricant (Fig. 3). A further reduction in ejection force was noted when magnesium lauryl sulfate concentration was increased to 2%. Although these data suggest that concentrations of magnesium lauryl sulfate below 1% may still produce ejection forces below those observed here with magnesium stearate, it was not possible to compress such tablets successfully. At concentrations ranging from 0.25 to 0.75%, sticking to both the die wall and punch faces was observed. Apparently, magnesium lauryl sulfate was more efficient than magnesium stearate as a true lubricant in this system but less efficient as an antiadherent. The magnesium stearate data suggest that there would be no advantage in terms of ejection force to adding more than 0.25% of the lubricant in this system. Such a distinction could never be made in studies based on a single lubricant concentration. Similar results were reported by Wray *et al.* (10), who found no significant differences in ejection force at all compression forces tested between batches of a stock granulation using concentrations of magnesium stearate ranging between 0.1 and 1%. However, lower ejection forces were noted at the highest compression forces when 2% of the lubricant was added.

Adding 0.25% magnesium lauryl sulfate to microcrystalline cellulose dramatically reduced ejection forces to barely measurable levels (Fig. 4). At higher magnesium lauryl sulfate levels, ejection forces were too low to be measured and could not be plotted. Ejection forces were also too low to be measured when microcrystalline cellulose was lubricated with 0.25% or higher concentrations of magnesium stearate. Similarly, ejection forces too low to be measured were noted when 0.25% or greater concentrations of either magnesium lauryl sulfate or magnesium stearate were added to the compressible starch. These results were not unexpected because these fillers, by themselves, are known to be self-lubricating (12, 13). Ejection forces observed with the unlubricated compressible starch tablets (Fig. 5) were lower than those observed with the microcrystalline cellulose tablets and appeared to be less dependent on the compression force. More important than the ejection force data for these fillers are the compressibility data, particularly in the case of compressible starch. The deleterious ef-

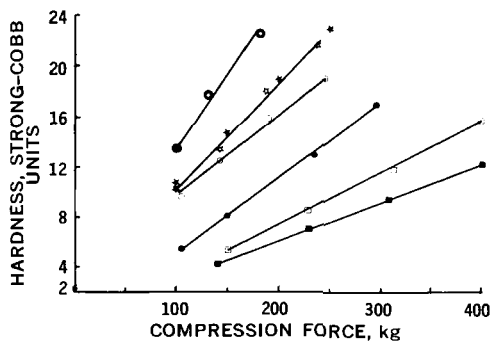

Figure 7—*Effect of magnesium lauryl sulfate (☆, 0.25%; ★, 0.5%; ○, 1.0%) and magnesium stearate (●, 0.25%; □, 0.5%; ■, 0.75%) on the compressibility of microcrystalline cellulose tablets. ✪: control (no lubricant).*

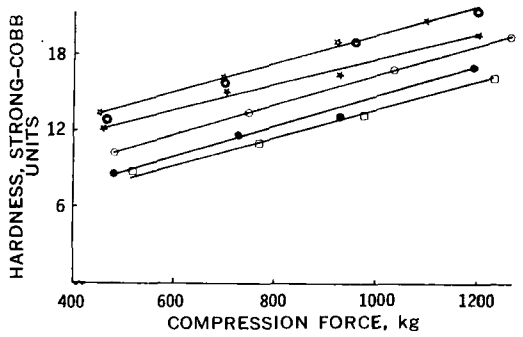

Figure 8—*Effect of magnesium lauryl sulfate* (◘, *2%*; ☆, *3%*; ★, *5%*) *and magnesium stearate* (○, *0.5%*; ●, *1%*; □, *2%*) *on the compressibility of spray-dried lactose.*

fect of magnesium stearate on the compressibility of these two fillers was previously reported (13, 14) and is confirmed here in plots of hardness *versus* compression force (Figs. 5–7).

As can be seen, the compressibility of the starch filler is dramatically reduced when only 0.2% of magnesium stearate is added. The maximum hardness that could be obtained with this formulation was 3.7 Strong-Cobb units at a compression force of 1175 kg; increasing the compression force to 1610 kg did not increase hardness. When 0.3 or 0.5% magnesium lauryl sulfate was the lubricant, compressibility was significantly greater than that observed with the magnesium stearate batch. For instance, with 0.3% magnesium lauryl sulfate, only about 550 kg compression force was required to produce tablets with a mean hardness of 3.7 Strong-Cobb units, and hardness could be increased to 7 units by increasing compression force to about 1100 kg. Compressibility was poorer than that observed with the magnesium stearate batch when 1% magnesium lauryl sulfate was used.

The compressibility of microcrystalline cellulose was also dramatically reduced with magnesium stearate (Fig. 7). However, this filler is inherently so compressible as to not negate its usefulness at the levels tested. Compressibility was also reduced when magnesium lauryl sulfate was the lubricant but to a much lesser extent. Although compressibility continued to decrease as the concentration was increased to 1%, even the 1% magnesium lauryl sulfate batches were significantly more easily compressed than the 0.25% magnesium stearate batches.

To assess the effect of these lubricants on the compressibility of spray-dried lactose, the direct compression sucrose, and the terra alba granulation, it would have been useful to first determine the compressibilities in the absence of lubricants. Although it was not possible to compress these substances without a lubricant, it may be seen in Figs. 8–10 that for a given filler the batches employing magnesium stearate are generally less compressible than the batches employing magnesium lauryl sulfate at the higher levels needed to yield similar or lower ejection forces. Although magnesium lauryl sulfate appears to have less effect on the compressibility of these fillers than magnesium stearate, both agents exert a more drastic effect on the compressibility of microcrystalline cellulose and the compressible starch than on the other three fillers. Similar results were reported (14) with magnesium stearate. A possible explanation for this phenomenon is that fracture and the

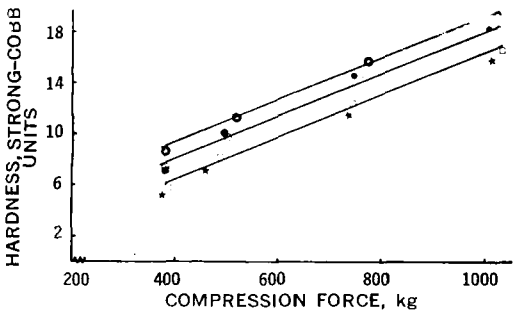

Figure 9—*Effect of magnesium lauryl sulfate* (◘, *3%*; ●, *5%*) *and magnesium stearate* (○, *0.5%*; □, *1%*; ★, *2%*) *on the compressibility of direct compression sucrose.*

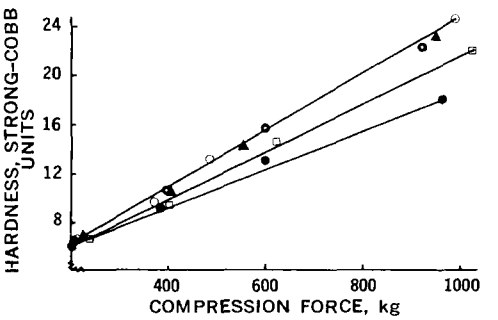

Figure 10—*Effect of magnesium lauryl sulfate* (▲, *1%*; ◘, *2%*) *and magnesium stearate* (○, *0.25%*; □, *0.5%*; ●, *1%*) *on the compressibility of terra alba granulation.*

creation of new surfaces under compression may not be major factors in the bonding of microcrystalline cellulose or starch tablets but may be important in the bonding of the other three fillers. Thus, the presence of lubricant at particle surfaces may exert a greater role in weakening the interparticulate bonds in compressible starch or microcrystalline cellulose tablets. With the granulation, it is recognized that the binder plays a major role in holding the tablet together. However, the granulation might be less sensitive to the presence of the lubricant because the granules may be expected to fracture under compression and expose fresh tablet matrix that would not be coated with lubricant.

SUMMARY AND CONCLUSIONS

The true lubricant properties of magnesium lauryl sulfate were evaluated and compared with magnesium stearate in microcrystalline cellulose, compressible starch, spray-dried lactose, direct compression sucrose, and a terra alba granulation using an instrumental rotary tablet press. With the exception of the terra alba granulation, generally higher concentrations of magnesium lauryl sulfate were required to produce similar ejection forces, and there was evidence of sticking to the punches and die at lower concentrations in the spray-dried lactose and compressible sucrose batches. In the case of the terra alba granulation, magnesium lauryl sulfate appeared to be more efficient than magnesium stearate in lowering ejection force but less efficient as an antiadherent.

There was no evidence of sticking to the punch faces or die wall in any batch employing magnesium stearate.

The effect of magnesium lauryl sulfate on the compressibility of these fillers was also studied. The results indicate that magnesium lauryl sulfate reduces compressibility to a lesser extent than magnesium stearate. These data also indicate that the compressibility of the sugars, spray-dried lactose, and direct compression sucrose, as well as that of the terra alba granulation, is affected less by lubricants than microcrystalline cellulose or compressible starch, thereby suggesting differences in the bonding mechanisms of these substances.

Because of the limited batch sizes, these results must be regarded as preliminary; the ultimate test of any lubricant would be its performance in a full-scale production run. Nevertheless, these results do clearly point up the potential of magnesium lauryl sulfate as a soluble lubricant. Furthermore, the fact that magnesium lauryl sulfate did not reduce compressibility to the same extent as magnesium stearate suggests that its use would enhance the usefulness of direct compression fillers. This was particularly evident in the compressible starch runs.

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The technology used relating to the measurement of ejection forces is protected under U.S. Patent 3,388,434, assigned to Lederle Laboratories. The authors are grateful to Lederle Laboratories for granting permission to publish research, part of which makes use of this technology.

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NOTES

Metabolism of 1-Methyl-5-nitro-2-(2′-pyrimidyl)imidazole

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Abstract □ 5-Acetamido-1-methyl-2-(2′-pyrimidyl)imidazole is shown to be one metabolite of 1-methyl-5-nitro-2-(2′-pyrimidyl)-imidazole in both rats and humans. Characterization was carried out by mass spectroscopy, NMR, and IR and by synthesis of the metabolite. This first example of a metabolite reduction product of the nitro group of an imidazole is discussed in relation to previous studies.

Keyphrases □ 1-Methyl-5-nitro-2-(2′-pyrimidyl)imidazole—metabolism, identification of 5-acetamido-1-methyl-2-(2′-pyrimidyl)imidazole as metabolite □ 5-Acetamido-1-methyl-2-(2′-pyrimidyl)imidazole—identified as metabolite of 1-methyl-5-nitro-2-(2′-pyrimidyl)imidazole □ Metabolism—1-methyl-5-nitro-2-(2′-pyrimidyl)imidazole

The drug 1-methyl-5-nitro-2-(2′-pyrimidyl)imidazole (I) was recently synthesized according to Scheme I (1). The drug I shows antitrichomonal properties both *in vitro* and *in vivo* against *Trichomonas vaginalis* in mice. During studies on the absorption, excretion, and metabolism of the drug, one major metabolite of I was noticed in the urine of both rats and humans. This paper presents data on the isolation, identification, and synthesis of this metabolite and shows it to be a product of reduction of the nitro group, with the structure 5-acetamido-1-methyl-2-(2′-pyrimidyl)imidazole.

Previous work on the metabolism of the nitroimidazole class of drugs (2, 3) showed that amines may be formed as metabolic reduction products of the nitro group, but they have never been isolated due to the extreme instability of 5-aminoimidazole derivatives. Work on the nitrofurfuraldehyde derivative class of drugs has shown (4, 5) that acetylated amine derivatives can be found as metabolites, and the first example of such a metabolite from the 5-nitroimidazole series is presented here.

EXPERIMENTAL[1]

1-Methyl-5-nitro-2-(2′-pyrimidyl)imidazole (I)—This com-

[1] Melting points were determined with a Büchi capillary apparatus and are uncorrected. IR spectra were obtained on a Hilger-Watts spectrophotometer, and UV spectra were obtained on a Beckman DB-GT spectrophotometer with a Sargent-Welch SRG recorder. NMR spectra were determined with a Perkin-Elmer R12-B spectrometer using tetramethylsilane as the internal reference. Mass spectra were obtained on an LKB 9000 instrument equipped with a gas chromatograph and a 3% SE-30 column (2 m long), operating at 250°. The ion beam energy was 70 ev, the ion source temperature was 290°, the accelerating voltage was 3.5 kv, and the trap current was 60 μamp. GLC was carried out on a Carlo Erba Fractovap GI chromatograph equipped with a flame-ionization detector using a 3% SE-30 glass column (2 m long). The operating conditions were: injection port temperature, 270°; oven temperature, 250°; nitrogen (carrier gas) flow rate, 30 ml/min; hydrogen flow rate, 100 ml/min; and air flow rate, 280 ml/min. TLC was carried out on Merck F_{254} silica gel plates, and column chromatography was carried out on Florisil, 100–200 mesh (British Drug Houses).