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EVALUATION OF TWO NEW TABLET LUBRICANTS - SODIUM STEARYL FUMARATE AND GLYCERYL BEHENATE. MEASUREMENT OF PHYSICAL PARAMETERS (COMPACTION, EJECTION AND RESIDUAL FORCES) IN THE TABLETING PROCESS AND THE EFFECT ON THE DISSOLUTION RATE

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ABSTRACT

A comparison of two new tablet lubricants, sodium stearyl fumarate and glyceryl behenate, was made with magnesium stearate. Physical parameters such as compaction force, ejection force and residual force were investigated and quantified. The effect of these lubricants on a biopharmaceutical parameter such as dissolution rate was also evaluated. The results indicate that where magnesium stearate cannot be used due to problems of compaction, lubrication, stability or for biopharmaceutical reasons, sodium stearyl fumarate should be used as the tablet lubricant of choice, followed by glyceryl behenate as the next alternative.

INTRODUCTION

Lubricants are used in tableting to reduce friction between the tablet and die wall and to prevent adhesion of the tablet material to the punches or

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die wall. When lubricants are added to the tablet granulation, they form a coating around individual granules which remains more or less intact during the process of tablet compression. Magnesium stearate and calcium stearate are good lubricants but are hydrophobic and may have a negative influence on the biopharmaceutical properties of the final product (1).

The effect of a tablet lubricant on mechanical strength depends on the bonding mechanism. The strength of a tablet results from the area of intimate contact between the particles and the adhesive strength over this area. For a material which undergoes plastic and/or elastic deformation, the addition of a lubricant interferes in this process by acting as a physical barrier between the particles (2).

Sodium stearyl fumarate and glyceryl behenate have recently been proposed as suitable lubricants for use in tableting. The purpose of this study was to evaluate their effect on the forces acting during the tableting process, e.g., compaction (tablet strength), ejection and residual forces (friction and adhesion) as well as on the dissolution rate of the active and inert ingredients from the tablet.

EXPERIMENTAL

Materials and Equipment.

Materials: Salicylic acid[1], corn starch[2], magnesium stearate[3], pregelatinized corn starch[4], sodium stearyl fumarate[5], glyceryl behenate[6].

1. Aldrich Chemical Co., Milwaukee, WI
2. National Starch, Bridgewater, NJ
3. Mallinckrodt Corporation, Chicago, IL
4. National Starch, Bridgewater, NJ
5. Syntex Nutritional & Chemical Corp., Springfield, MA
6. Gattefosse Corp., Hawthorne, NY

Equipment: Instrumented Stoke's single station tablet press[7], hardness tester[8], U.S.P disintegration apparatus[9], U.S.P. dissolution apparatus[10], spectrophotometer[11], microscope[12].

Particle Size Specifications:

All the lubricants were sieved through a #100 mesh sieve prior to use. The particle size analysis for each of the lubricants was determined microscopically. The results are shown in Table I.

Tablet Preparation:

Salicylic Acid Tablets: Salicylic acid (60-80 mesh powder) was granulated with 5% pregelatinized starch and the granulation was dried overnight at 45°C to a moisture content of 1% ± 0.2%. To the dried granulation which was sieved through a 16 mesh screen, corn starch (dry) was added and mixed for 10 minutes. The lubricant, at a concentration of 1-3%, was then added and was mixed for 5 minutes. The composition of the tablet formulation is given in Table II.

Lactose Tablets: Lubricant, at a concentration of 1-3%, was added to direct compression grade lactose and mixed for 5 minutes. The composition of the tablet formulation is given in Table II.

Measurement of Forces Acting During the Tableting Process. The value of instrumenting a tablet press to measure the forces acting during the compaction process has been recognized since the 1950's. A detailed com-

7. Hoffmann-La Roche, Inc., Nutley, NJ
8. Cherry Burrell Corp., Cedar Rapids, IA
9. Scientific Glass Co., Bloomfield, NJ
10. Van Kel Industries, Chatham, NJ
11. Beckman Instrument Corp., Fullerton, CA
12. Carl Zeiss, Germany

TABLE I

Particle Size Specifications for Lubricants

Lubricant	Particle Size μm	Specific Surface Area m^2/g
Magnesium Stearate	1-20	1.8
Sodium Stearyl Fumarate	5-25	1.0
Glyceryl Behenate	5-50	0.65

TABLE II

Composition of the Tablet Formulations

Salicylic Acid Tablets	mg/tablet Formulation # A	B
Salicylic Acid (60-80 mesh)	300	300
Pregelatinized Corn Starch	30	30
Corn Starch (dry)	15	15
Lubricant	3	9
TOTAL WEIGHT	348 mg	354 mg
Lactose Tablets		
Lactose Anhydrous	300	300
Lubricant	3	9
TOTAL WEIGHT	303 mg	309 mg

prehensive study presenting experimental data on the measurement of forces required to remove the tablet from the tablet press was authored by Mitrevej et al (3). The instrument developed at Hoffmann-La Roche for the measurement of these forces, "The Rostar V", was used in this investigation. A single piezoelectric force transducer was installed in the lower punch holder. The transducer consists of a piezoelectric crystal element and unity gain amplifier hermetically sealed inside a stainless steel enclosure. Power and signal voltages

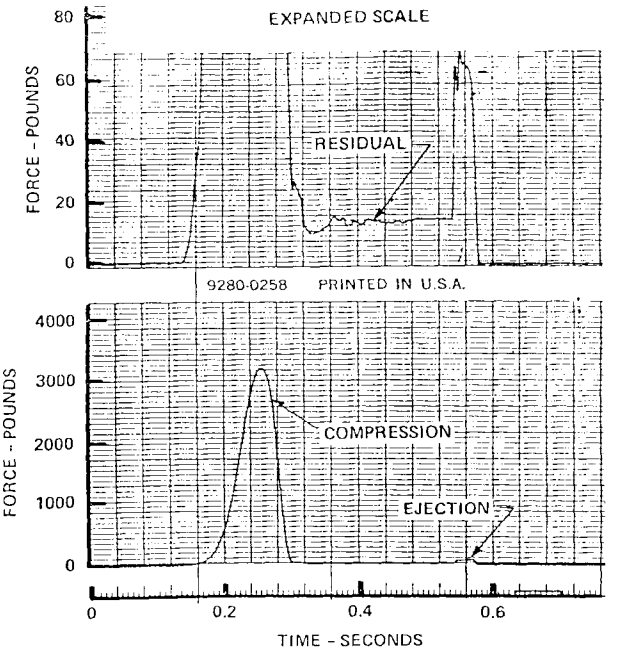

FIGURE 1. Analog Recoding from an Instrumented Single-Station Tablet Press

are transmitted through a single cable located on the side of the transducer case. A typical analogue signal from a load cell installed in a single station tablet press is shown in Figure 1. A more complete discussion of this instrumented press is described by J. Williams and D. Stiel (4). The data generated yields valuable information on tablet strength as well as frictional and adhesive forces which occur during tablet compaction.

Dissolution Rate Measurement:

Salicylic Acid Tablets: Dissolution was measured in 0.1 N HCl at 37°C ± 0.5°C using an automated dissolution apparatus at a wavelength of 300 nm. U.S.P. dissolution method I (Basket) was used at 100 rpm. The detailed procedure is described by Johnson et al (5).

Lactose Tablets: Dissolution of the lactose tablets was performed using a U.S.P. disintegration apparatus in water at 37°C ± 0.5°C. Since the lactose

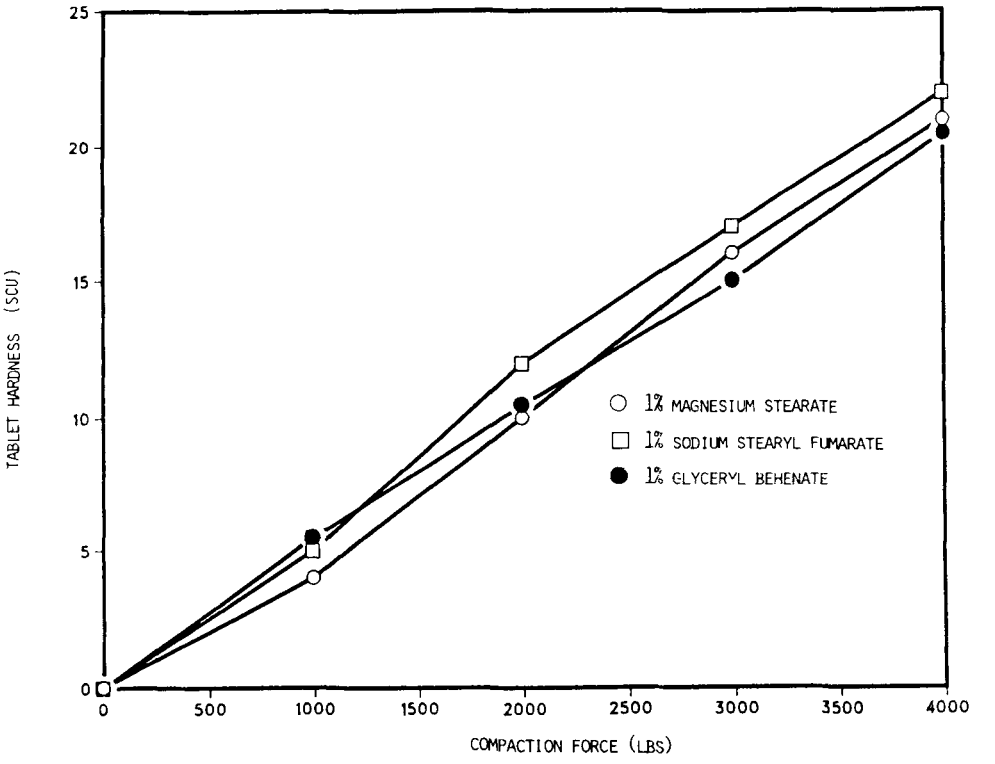

FIGURE 2. Effect of Lubricant Type on Compressibility of Lactose Tablets

tablets slowly erode, the non-eroded portions of the tablets were used as a measure of dissolution. At various time intervals, the non-eroded portions were removed from the disintegration apparatus, dried overnight at 50°C and weighed. Each data point represents an average of six tablets. The only disadvantage with this method is that a different set of tablets has to be used for each time point.

The tablet hardness was in the desired range of 14-16 Strong Cobb Units for the particular tablet size. The effect of different hardnesses with respect to lubricant type on the dissolution rate of lactose tablets was also evaluated.

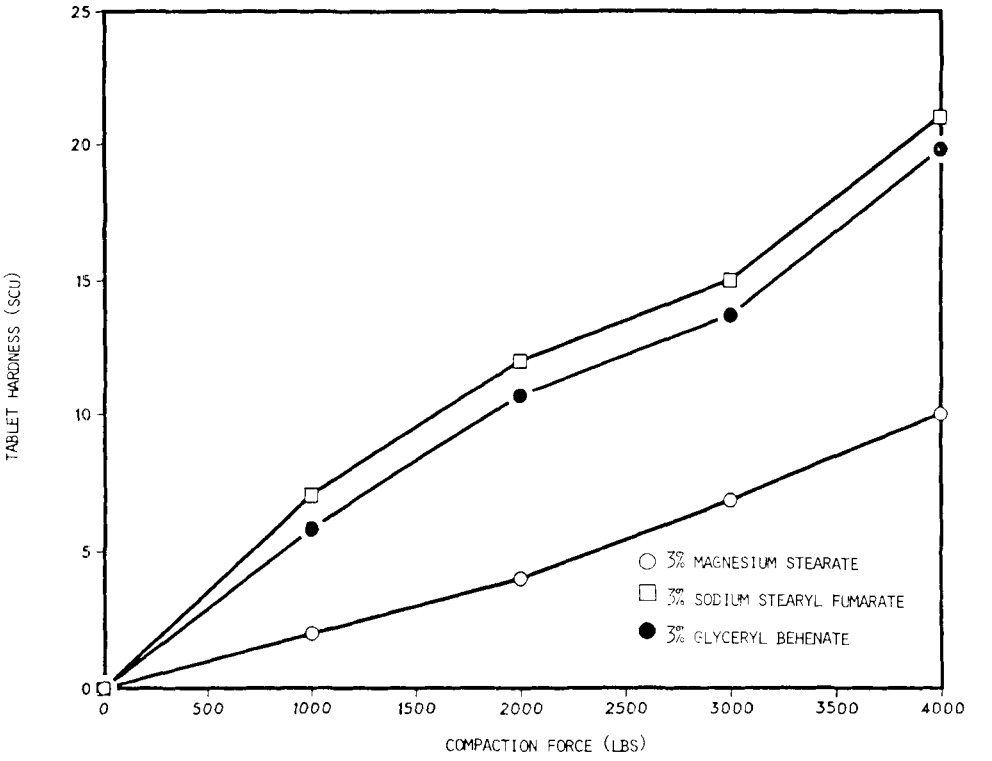

FIGURE 3. Effect of Lubricant Type on Compressibility of Lactose Tablets

Results and Discussion:

Compressibility

The strength of a tablet is related to its compaction behavior during tablet compression. Relative compressibility can be determined by comparing compaction force to tablet hardness.

In the lactose tablet at 1% lubricant concentration (Figure 2), sodium stearyl fumarate and glyceryl behenate showed slightly superior compressibility compared to magnesium stearate. But at 3% lubricant concentration (Figure 3), the compressibility of these two lubricants was twice that of magnesium stearate.

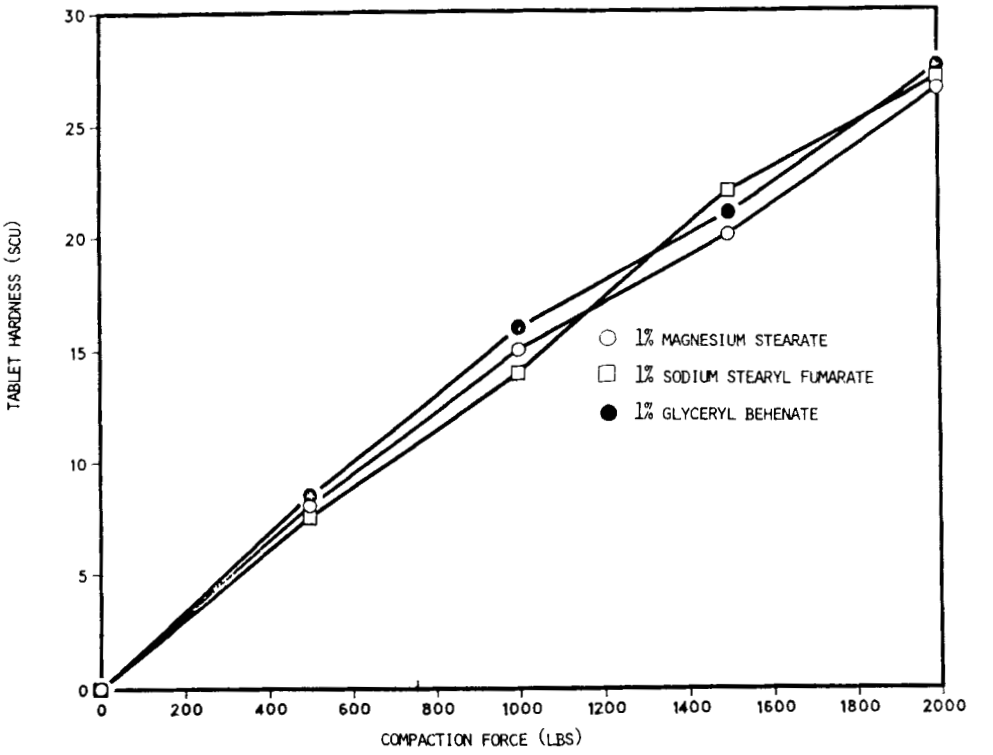

FIGURE 4. Effect of Lubricant Type on Compressibility of Salicylic Acid Tablets

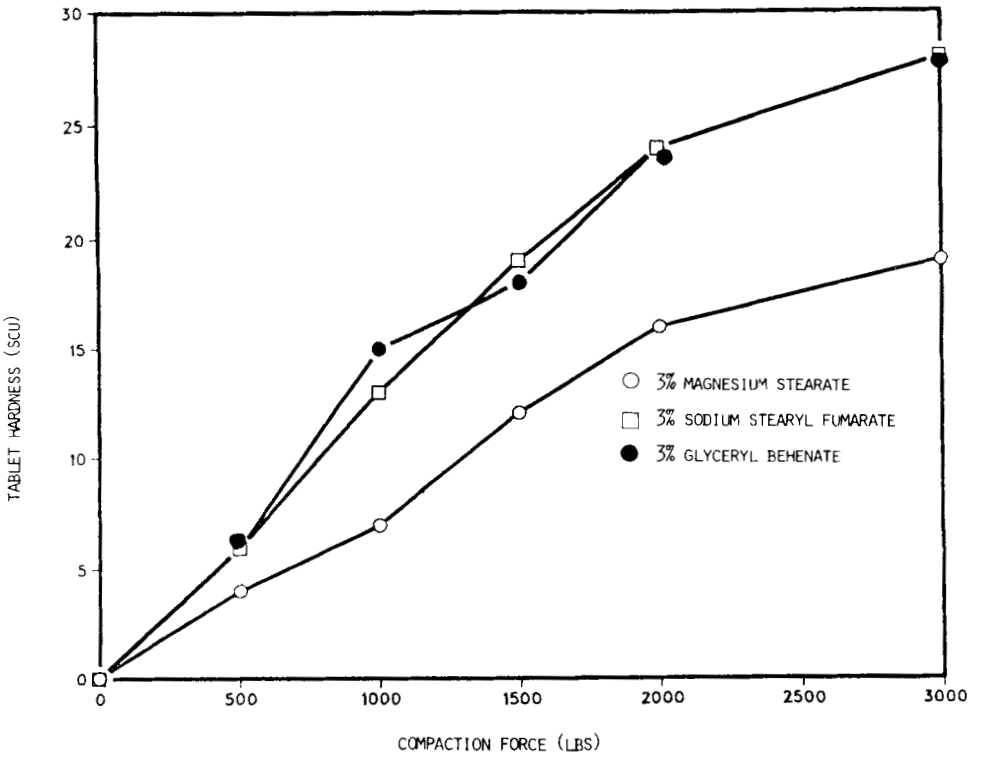

FIGURE 5. Effect of Lubricant Type on Compressibility of Salicylic Acid Tablets

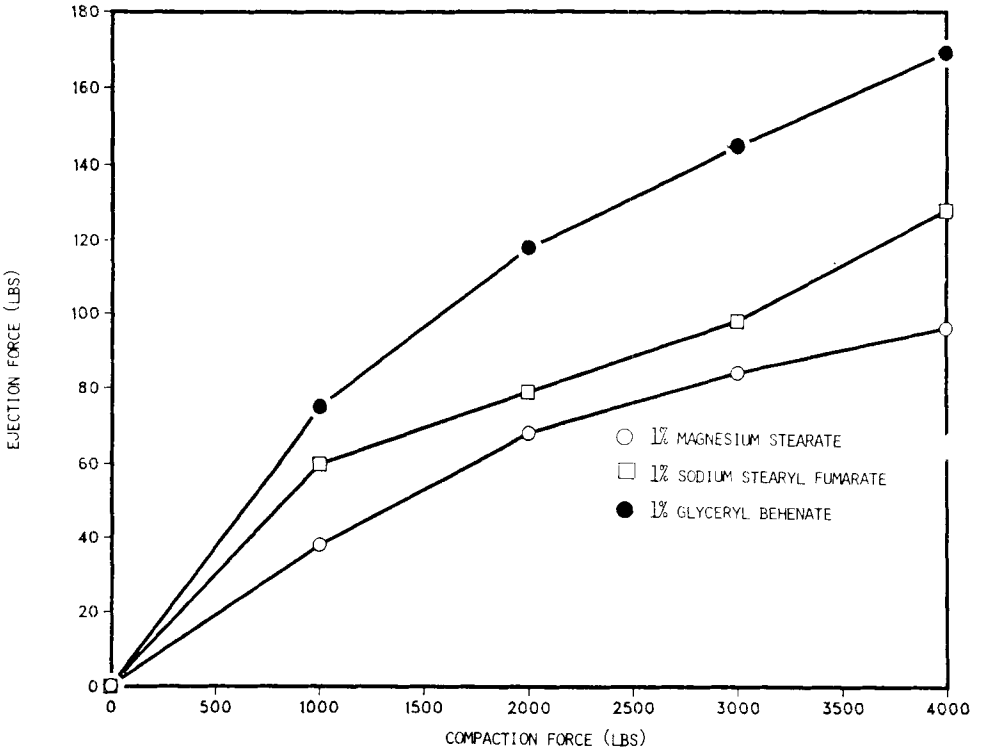

FIGURE 6. Effect of Lubricant Type on Ejection Profile of Lactose Tablets

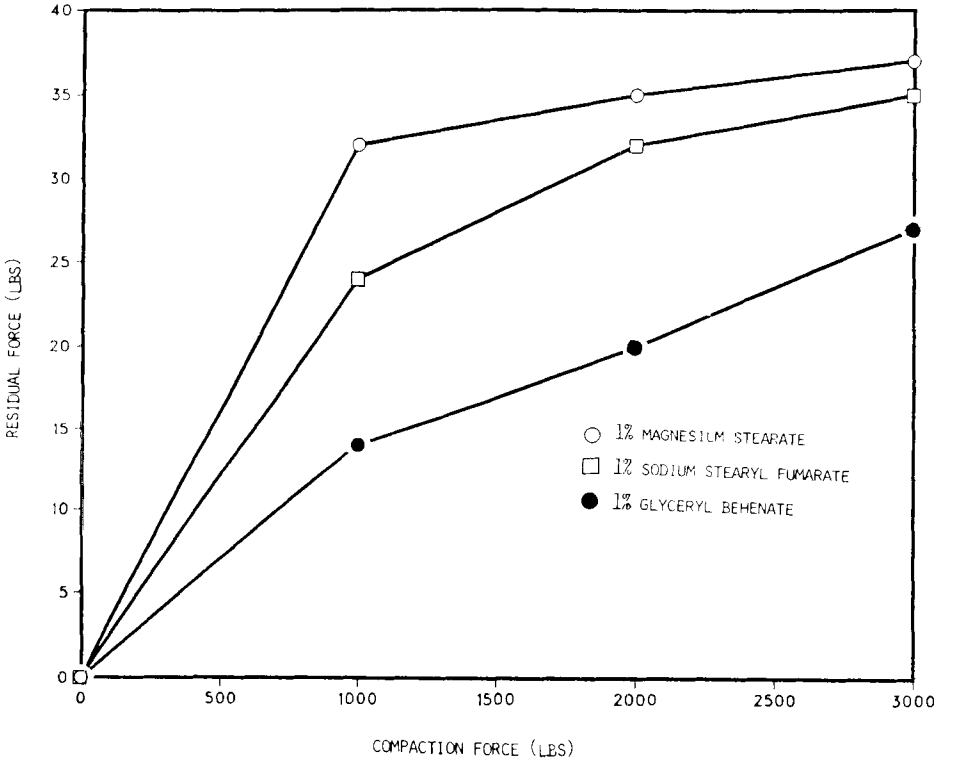

FIGURE 7. Effect of Lubricant Type on Adhesive Properties of Lactose Tablets

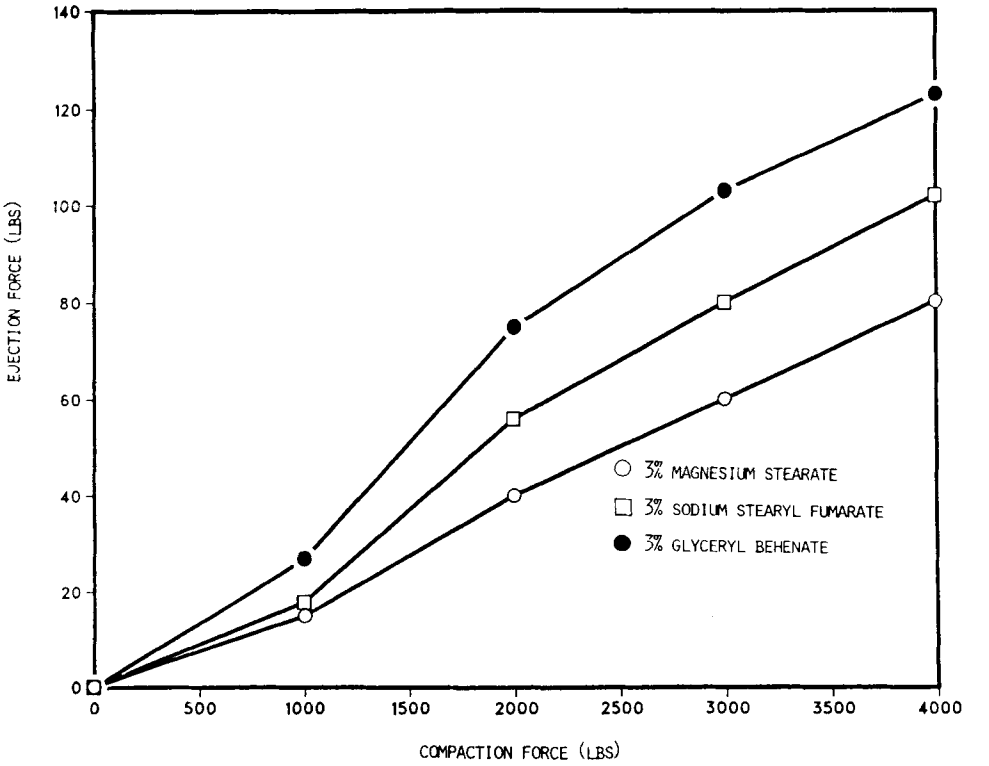

FIGURE 8. Effect of Lubricant Type on Ejection Profile of Lactose Tablets

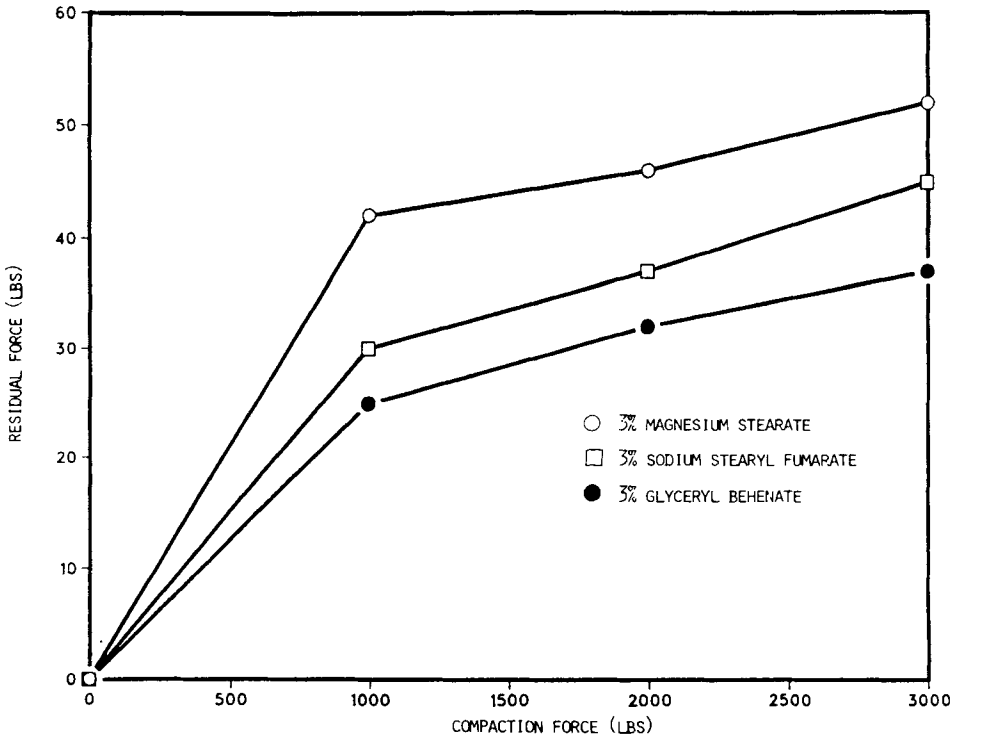

FIGURE 9. Effect of Lubricant Type on Adhesive Properties of Lactose Tablets

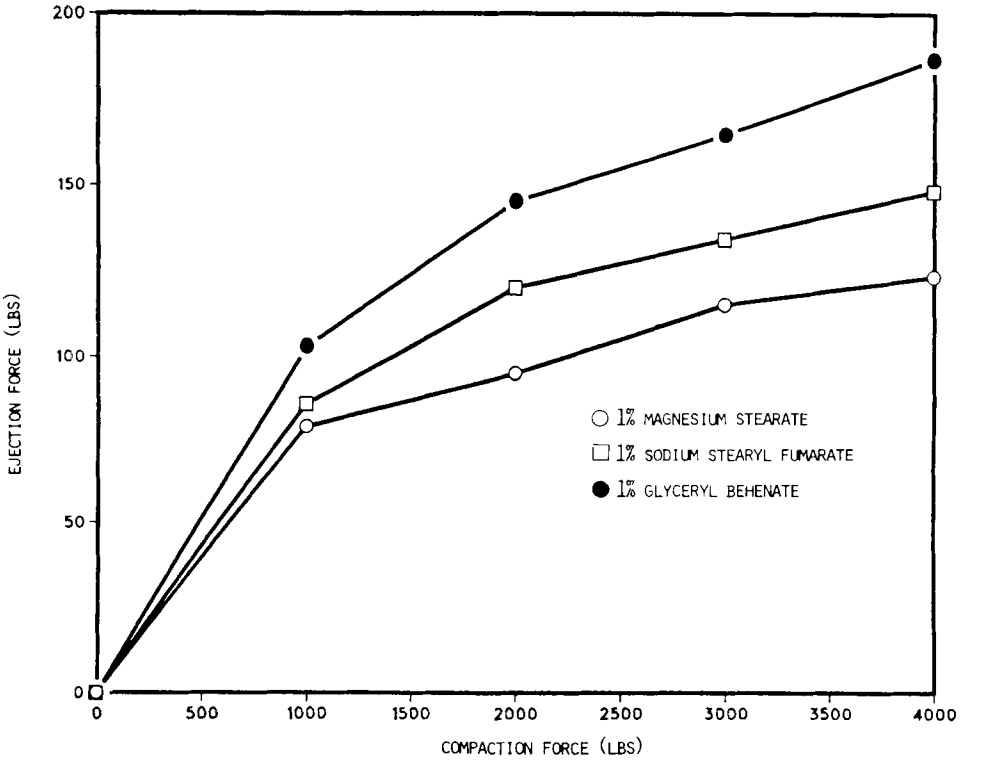

FIGURE 10. Effect of Lubricant Type on Ejection Profile of Salicylic Acid Tablets

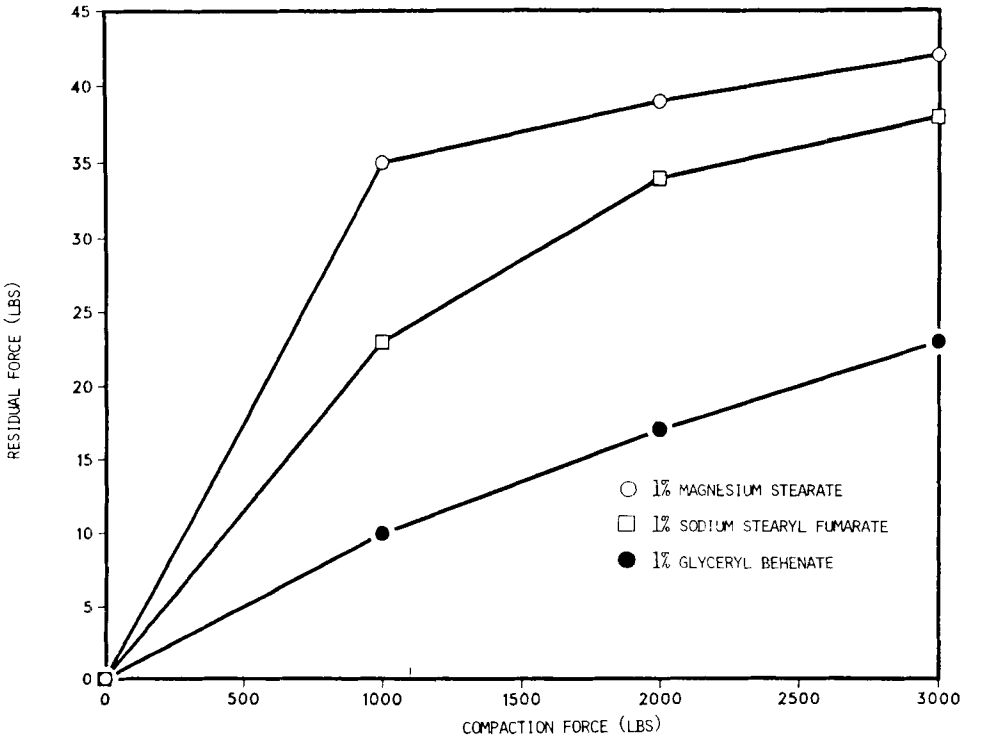

FIGURE 11. Effect of Lubricant Type on Adhesive Properties of Salicylic Acid Tablets

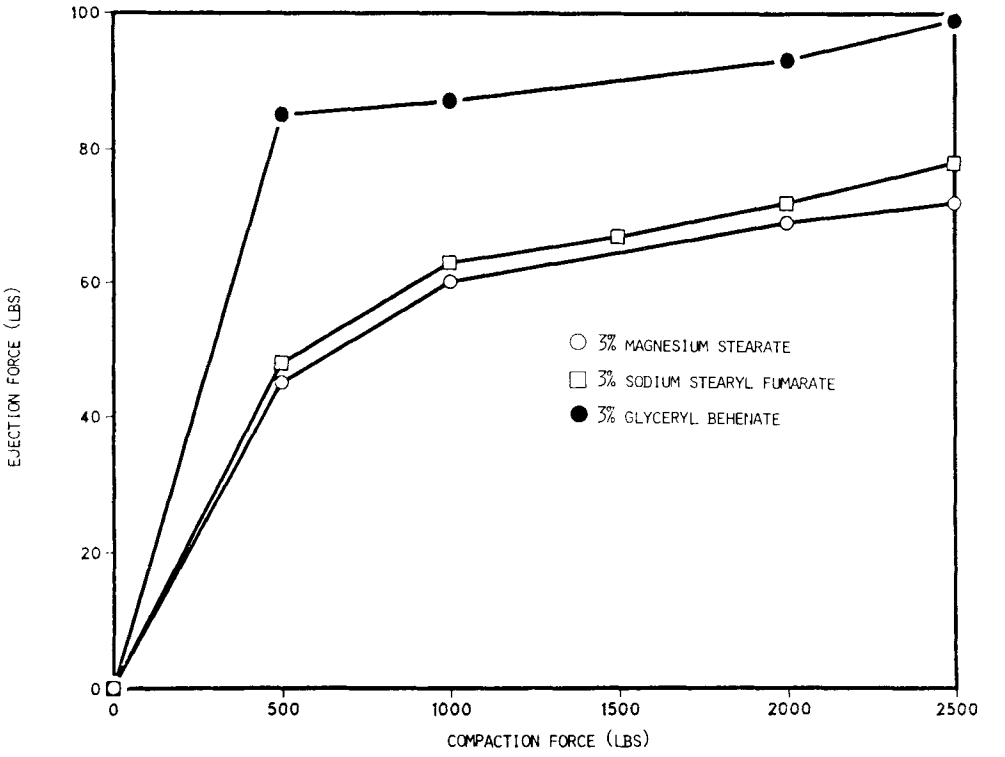

Figure 12. Effect of Lubricant Type on Ejection Profile of Salicylic Acid Tablets.

This same trend was also seen in the salicylic acid tablets (Figures 4 and 5) at these same lubricant concentrations. Salicylic acid tablets prepared with sodium stearyl fumarate and glyceryl behenate had superior compressibility to those prepared with magnesium stearate. The compressibility of sodium stearyl fumarate is slightly better than that of glyceryl behenate. The improved compressibility of sodium stearyl fumarate and glyceryl behenate could be due to lesser interference in the bonding mechanism and also due to some possible self-adhesive properties.

Lubricity, Friction and Anti-Adhesive Properties: Die wall lubricity can be evaluated by comparing profiles of compression vs. ejection forces for different granulations. A lower ejection force at a given compression force

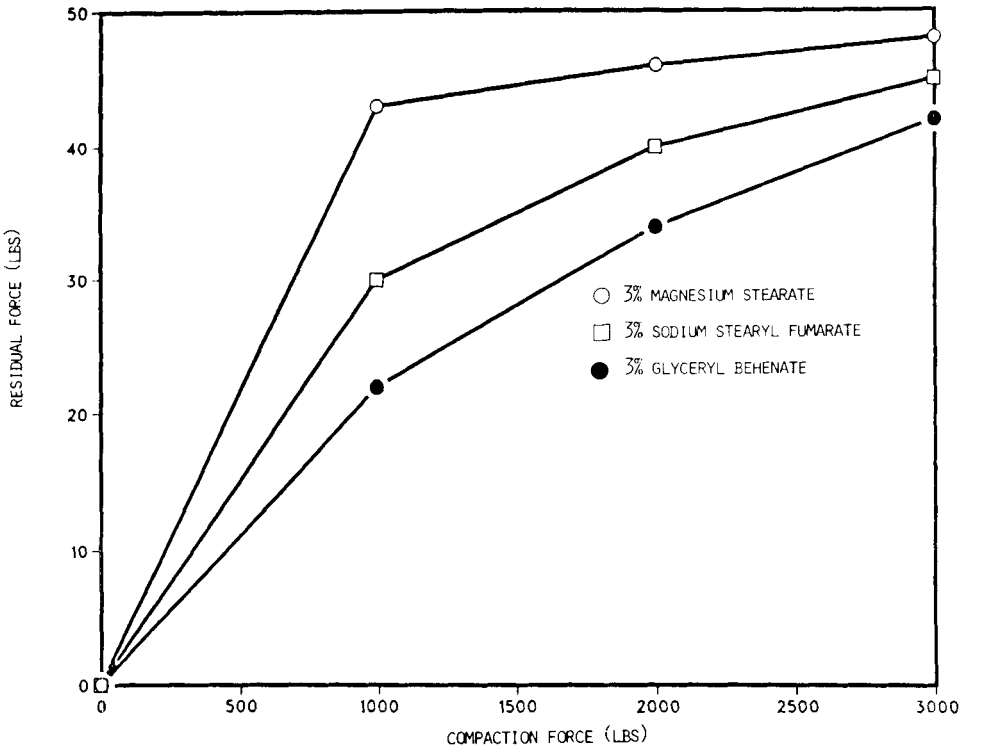

Figure 13. Effect of Lubricant Type on Adhesive Properties of Salicylic Acid Tablets.

indicates better lubrication. The tendency for picking or sticking to occur can be obtained by residual force measurements. Non-sticking formulations tend to yield higher residual forces because of the reduced tendency for the tablet to be raised away from the lower punch when the upper punch lifts away from the compact. Formulations that tend to stick or pick tend to be slightly withdrawn from the lower punch when the upper punch lifts following compression; this reduces the residual force on the lower punch.

At the 1% lubricant level in lactose tablets (Figures 6 and 7), the lubrication behavior of the three lubricants under investigation ranked in the following order: magnesium stearate $\geq$ sodium stearyl fumarate $>$ glyceryl behenate. With magnesium stearate, there was no picking or sticking at the surface of the

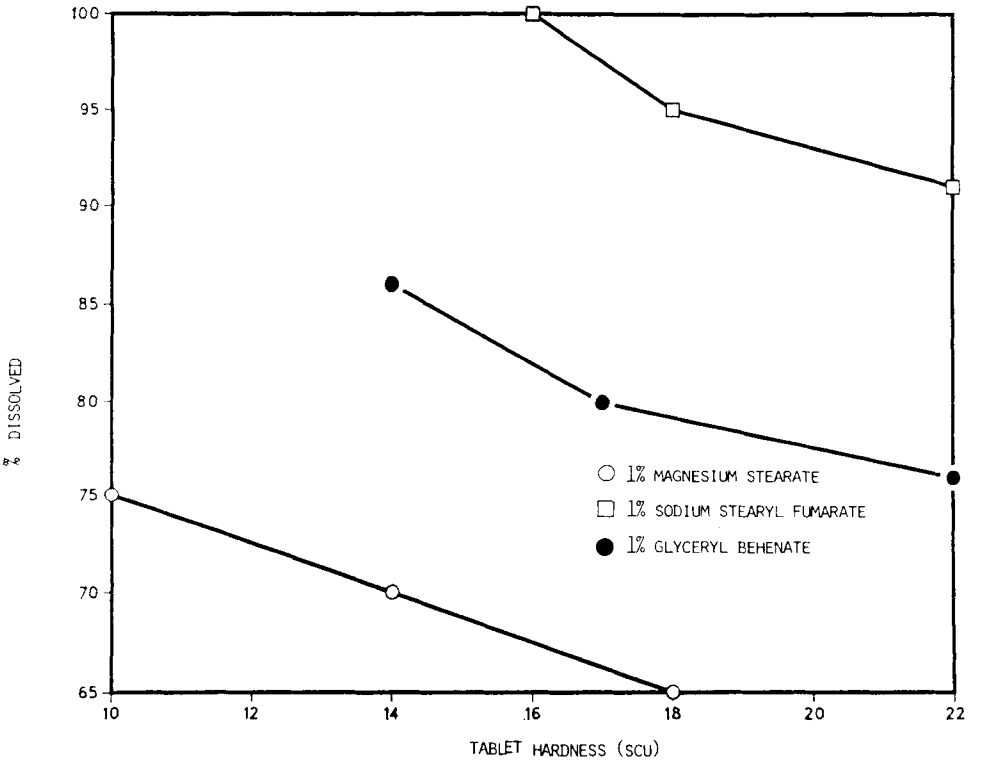

Figure 14. Effect of Lubricant Type and Tablet Hardness on Dissolution Rate of Lactose Tablets.

punches and die wall lubricity was excellent. Sodium stearyl fumarate gave very slight picking at lower compaction forces ($<$ 1000 lbs); however, with compaction forces above 1000 lbs., no picking or sticking was observed. Glyceryl behenate gave slightly higher ejection forces as well as lower residual forces at all compaction forces (1000-3000 lbs) indicating somewhat inferior lubrication properties. At the 3% level, the lubrication properties of all three lubricants were improved. Figures 8 and 9 clearly show that at the highest compaction force ($\approx$ 4000 lbs), the ejection forces were less than 120 lbs in all cases. Glyceryl behenate showed a trend in increased residual force with increase in compaction force indicating that at the 3% level, it showed imprvoed antiadhesive behavior.

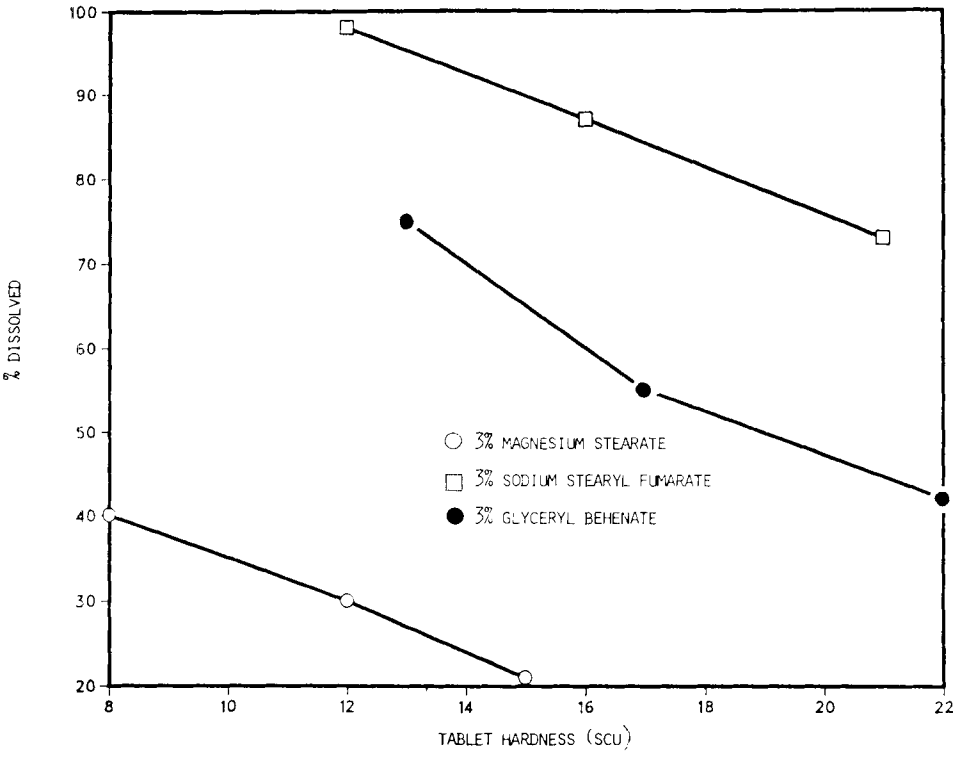

Figure 15. Effect of Lubricant Type and Tablet Hardness on Dissolution Rate of Lactose Tablets.

The three lubricants showed similar behavior in the salicylic acid tablets (Figures 10 to 13) as they did in the lactose tablets. The lubrication properties of magnesium stearate and sodium stearyl fumarate were acceptable at both the 1% and 3% levels. In the case of glyceryl behenate, the 3% level was the lowest level required for acceptable lubrication.

The residual forces for magnesium stearate at the 3% level were higher at all compaction forces indicating an absence of sticking or picking. Sodium stearyl fumarate at the 3% level showed a gradual increase in residual force with increasing compaction force indicating that a minimum of 1000 lbs compaction force was required for acceptable lubrication. In

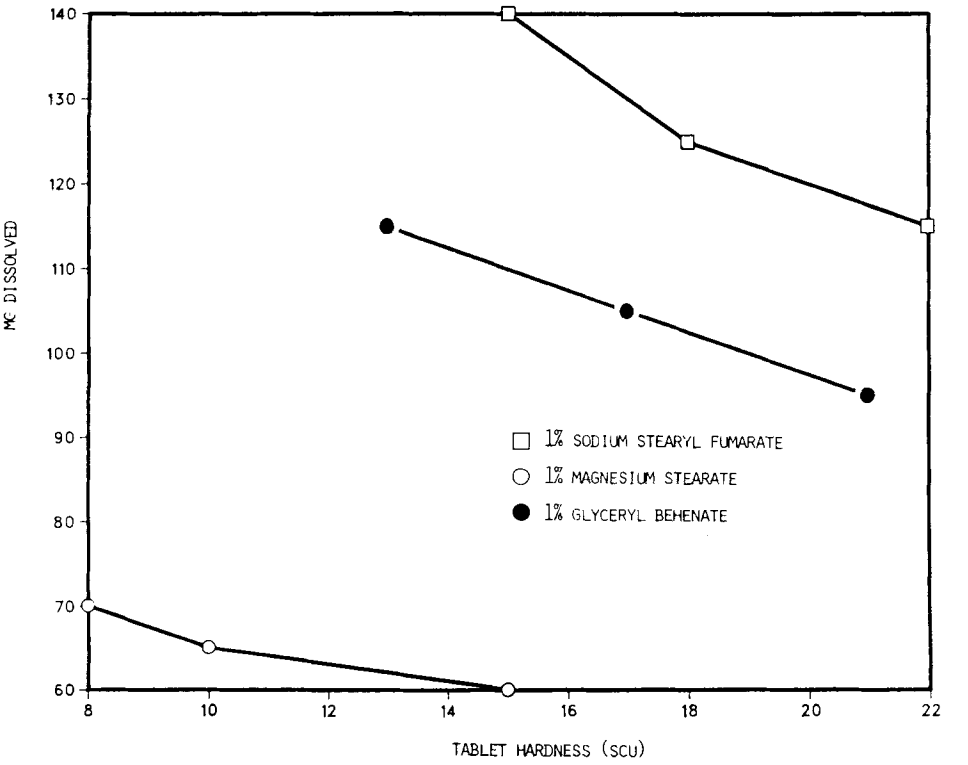

Figure 16. Effect of Lubricant Type and Tablet Hardness on Dissolution Rate of Salicylic Acid Tablets.

the case of glyceryl behenate, the residual force was minimal below 1000 lbs compaction force but increased to an acceptable level (> 30 lbs) at a compaction force of 2500 lbs, which was the minimum force required to avoid any sticking or picking.

Dissolution Rate Studies

The dissolution rates of the lactose and salicylic acid tablets with respect to each lubricant and tablet hardness are shown in Figures 14 to 17. The results clearly indicate that sodium stearyl fumarate has the least retardant effect on the dissolution rates of both tablets, whereas glyceryl

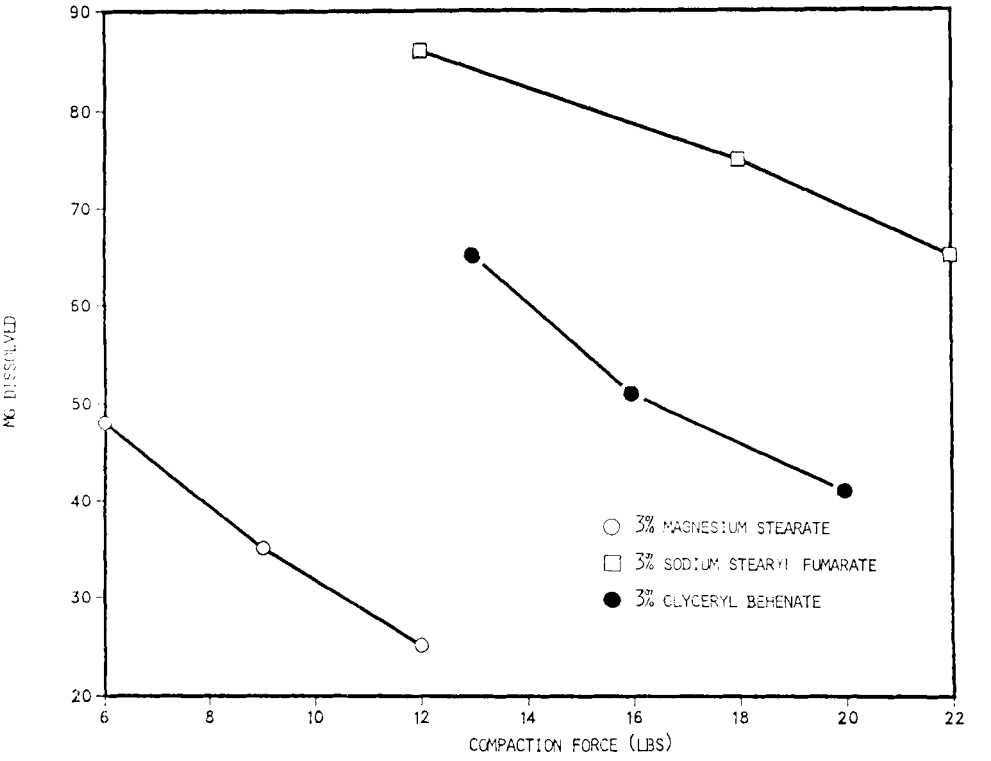

Figure 17. Effect of Lubricant Type and Tablet Hardness on Dissolution Rate of Salicylic Acid Tablets.

behenate has only a moderate retardant effect and magnesium stearate has the most retardant effect. In all three cases, lubricant at the 1% level was less inhibiting to the dissolution rate than at the 3% level. As expected, harder tablets showed a more retarding effect on dissolution rate than did softer tablets.

CONCLUSIONS

Sodium stearyl fumarate and glyceryl behenate can be satisfactorily used as lubricants in tableting. They show less interference in tablet strength (compaction) and have a lesser negative effect on the dissolution rate of

active ingredient than does magnesium stearate. Sodium stearyl fumarate was comparable to magnesium stearate in reducing die wall friction. The rank-order for antiadherent (sticking and picking) effect of the three lubricants studied was magnesium stearate $\geq$ sodium stearyl fumarate > glyceryl behenate. Magnesium stearate and sodium stearyl fumarate were effective at the 1% and 3% levels, whereas glyceryl behenate was required at least at the 3% level for effective lubrication.

In formulation research, where magnesium stearate causes problems in compaction or lubrication, or if magnesium stearate is contraindicated for chemical or physical stability reasons, sodium stearyl fumarate should be considered as the tablet lubricant of choice followed by glyceryl behenate as the next alternative.

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