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RESEARCH ARTICLES

Effect of Shear Mixing on *In Vitro* Drug Release of Capsule Formulations Containing Lubricants

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Abstract □ The influence of shear mixing on the *in vitro* dissolution properties of several experimental capsule formulations containing lubricants was investigated. The studies were carried out in a 2.8-liter laboratory V-blender equipped with a high-speed intensifier bar, using nitrofurantoin and procainamide hydrochloride as active drugs, powdered lactose and starch as excipients, and magnesium stearate and magnesium lauryl sulfate as lubricants. These studies revealed a pronounced inhibitory effect on drug dissolution due to shear in powder mixtures containing magnesium stearate; even at the maximum lubricant level of only 2%, high shear mixing markedly altered the *in vitro* dissolution rate. In systems with magnesium lauryl sulfate, the shear effect was less pronounced (nitrofurantoin blends) or absent (procainamide hydrochloride blends). The poor dissolution characteristics noted with magnesium stearate–shear combinations seem to result from the formation of a hydrophobic film around the powder mass, preventing wetting and deaggregation.

Keyphrases □ Capsules—containing lubricants, effect of shear mixing on *in vitro* dissolution □ Dissolution, *in vitro*—capsules containing lubricants, effect of shear mixing □ Shear mixing—effect on *in vitro* dissolution of capsules containing lubricants □ Dosage forms—capsules containing lubricants, effect of shear mixing on *in vitro* dissolution

Magnesium stearate is a widely used lubricant in tablet and capsule formulations. In tableting, it is believed to reduce interparticle friction during compression and friction between the tablet and die wall during ejection (1, 2). In encapsulation with automatic capsule-filling equipment, magnesium stearate altered the force–time curves of the material being filled by reducing or eliminating the ejection forces (3).

BACKGROUND

One problem associated with magnesium stearate in solid dose formulations (4, 5) is its tendency to waterproof the dosage form and to retard *in vitro* drug release. Levy and Gumtow (5), based on their studies with nondisintegrating disks of salicylic acid, concluded that hydrophobic lubricants such as magnesium stearate decrease the effective drug–solvent interfacial area and thereby reduce the dissolution rate. Conversely, the dissolution rate enhancing effect of a hydrophilic lubricant, *e.g.*, sodium lauryl sulfate, was viewed as due to better penetration of the solvent into the tablets and component granules, resulting in greater availability of drug surface.

Samyn and Jung (6) studied the *in vitro* disintegration and dissolution rates of several experimental capsule formulations consisting of drug, lactose, or dibasic calcium phosphate, with magnesium stearate as the lubricant. The poor disintegration and dissolution properties noted were attributed to the limited area of contact between the powder mass and the solvent because of poor or incomplete wetting of the solid. They reasoned that this reduced erosion and drug dissolution.

Recently, a new water-soluble compound, magnesium lauryl sulfate, was investigated as a tablet lubricant (7). The evidence indicated that this material may possess lubricating properties comparable to magnesium stearate in the systems studied without its water-repellent effect (8).

In laboratory and industrial blending operations, the mixer is usually equipped with a mechanical device such as an agitator bar, deflector, or baffle to facilitate breakup of aggregates and to ensure good mixing. High speed attrition or shearing devices are often necessary for homogeneous distribution of the active component in high potency, low dose drug mixtures (9). Only a few studies are available concerning the effect of high speed shear mixing on *in vitro* drug release characteristics of powder mixtures containing lubricants. Ganderton (10) investigated the effect of the distribution of magnesium stearate on the penetration of tablets by water. His data suggested that the inhibition of liquid penetration in the presence of magnesium stearate is approximately proportional to the concentration of the lubricant in the system and is susceptible to the mixing method: the more intimate the dispersion of the lubricant, the greater the inhibition of liquid penetration.

The effects of magnesium stearate and the degree of mixing on the physical properties of amylose and sodium chloride tablets also were reported (11). Blending was carried out in a Turbula mixer at a loading level of 20% capacity. When the concentration of magnesium stearate or the mixing time was increased, the intrinsic dissolution rate of sodium chloride was reduced. Furthermore, the effects due to the degree of mixing were pronounced at low lubricant levels. Based on photomicro-

Table I—Composition of Powder Mixtures

Component, mg/capsule	Series I (Nitrofurantoin Blends) Formulations							Series II (Procainamide Hydrochloride Blends) Formulations						
	A	B	C	D	E	F	G	H	I	J	K	L	M	N
Drug	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Lactose powder	250	250	250	—	—	—	250	250	250	250	—	—	—	250
Starch powder	—	—	—	250	250	250	—	—	—	—	250	250	250	—
Magnesium stearate	—	1.75	7.0	—	1.75	7.0	—	—	1.75	7	—	1.75	7.0	—
Magnesium lauryl sulfate	—	—	—	—	—	—	7	—	—	—	—	—	—	7

graphic evidence, a mechanism was suggested involving the formation of a lubricant film around the solid particle during the mixing stage.

The aim of the current investigations was to evaluate the influence of shear mixing on the *in vitro* drug release of powder mixtures containing magnesium stearate as a lubricant in capsule blends of a relatively water-insoluble drug and a water-soluble drug. Nitrofurantoin was selected as the prototype of a low water-soluble drug, and procainamide hydrochloride served as the high water-soluble drug substance. Powdered lactose and starch were the diluents since they are common fillers, both soluble and insoluble, in capsule formulations. Although most investigations employed magnesium stearate as the lubricant, magnesium lauryl sulfate also was included.

EXPERIMENTAL

Magnesium stearate[1], nitrofurantoin[2], procainamide hydrochloride[3], lactose powder[4], and starch powder[5] were USP grade. These chemicals and magnesium lauryl sulfate[6] were purchased commercially and used as received.

The compositions of the various blends prepared and tested are shown in Table I. Series I (Formulations A–G) contains mixtures of nitrofurantoin, while Series II (Formulations H–N) is procainamide hydrochloride blends. Two levels of lubricant were studied, 0.5 and 2%. Both concentrations are relatively low and represent levels used or exceeded in marketed products.

The drug substances were prescreened through a No. 30 sieve to minimize any aggregates that might be present. The materials were introduced into a stainless steel 2.8-liter capacity V-blender[7] with the diluent at the bottom and the drug and the lubricant over it. The blender was loaded to about half its capacity when the total charge of 1.4 kg was present. Shear was applied through the action of the intensifier bar. The blending sequence adopted in these experiments was 15 min of tumble blending without the intensifier bar action followed by tumble blending with shear for 30 min. The powder was sampled immediately before the intensifier bar was turned on ("0"-min sample) and after applying 5, 15, and 30 min of shear.

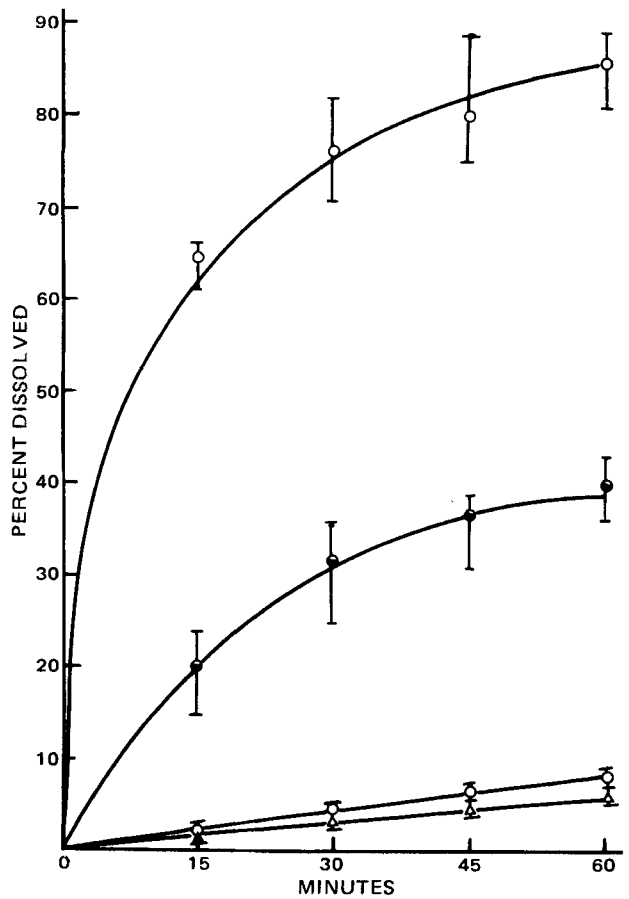

Figure 1—*Effect of shear on the drug dissolution in the nitrofurantoin–lactose mixture (Formulation C). Key: ○, 0 min; ◒, 5 min; ●, 15 min; △, 30 min of mixing with intensifier bar; and ⊖, intercapsule variation.*

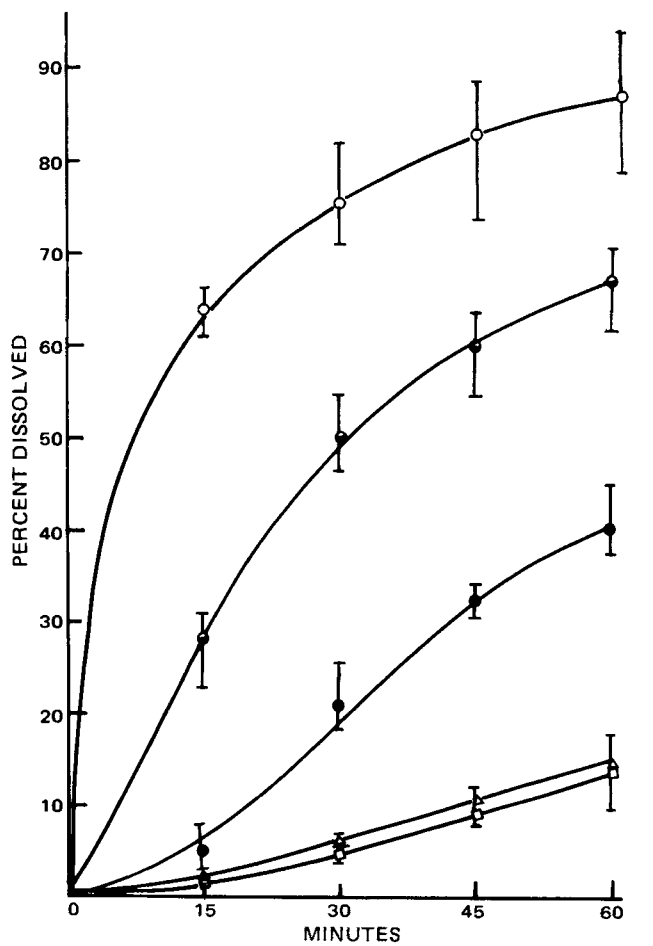

Figure 2—*Effect of shear on the drug dissolution in the nitrofurantoin–starch mixture (Formulation F). Key: ○, 0 min; ◒, 5 min; ●, 15 min; △, 30 min; and □, 45 min of mixing with the intensifier bar.*

[1] Mallinckrodt, St. Louis, Mo.
[2] H. Reisman Corp., Orange, N.J.
[3] Parke, Davis & Co., Holland, Mich.
[4] Humko Sheffield Chemical, Lyndhurst, N.J.
[5] A. E. Staley Manufacturing Co., Decatur, Ill.
[6] Alcolac Corp., Baltimore, Md.
[7] Porta-Shell lab blender equipped with disperser bar assembly, Patterson Industries, East Liverpool, Ohio.

Table II—Dissolution Values (Minutes) for Procainamide Hydrochloride–Lactose Mixtures in 0.1 *N* HCl at 100 rpm and 37°

Amount of Shear, min of Blending with Intensifier Bar	Formulation H			Formulation I			Formulation J			Formulation N		
	T_{20}	T_{50}	T_{80}	T_{20}	T_{50}	T_{80}	T_{20}	T_{50}	T_{80}	T_{20}	T_{50}	T_{80}
0	1.3	2.8	4.7	1.7	4.3	8.1	3.7	6.9	9.5	1.0	2.6	4.2
5	—	—	—	2.8	6.9	13.3	8.0	17.4	45.3	—	—	—
15	1.3	3.0	4.8	7.1	15.6	24.5	13.4	73.0	>180	1.1	2.8	4.5
30	1.2	2.9	4.6	8.1	19.8	27.2	14.0	75.0	>180	1.1	2.9	4.6

In testing nitrofurantoin powder mixtures for *in vitro* drug release, the dissolution apparatus[8] and the general conditions described in USP XIX were followed (12). The temperature was maintained at 37 ± 0.5°, the basket was rotated at 100 rpm, and 900 ml of pH 7.2 phosphate buffer served as the solvent medium. The powder mixture, 353 ± 7 mg, was hand filled into a No. 0 size natural capsule[9], which served as the dosage unit for the test. This fill weight corresponds to a low powder density and was chosen to avoid the effect on the drug release of the tightness of the powder bed packing within the capsule.

At periodic intervals, 5 ml of filtered samples was withdrawn and diluted 10-fold with distilled water. The absorbance of each sample was measured at 367 nm in a UV spectrophotometer[10]. The nitrofurantoin concentration in solution was determined from the standard Beer's law plot prepared with the pure drug material. Preliminary experiments showed that the error involved in not replacing the withdrawn volume of fluid was insignificant.

For procainamide hydrochloride mixtures, the test procedure used was identical to that described, except that the solvent medium and the diluting fluid were 0.1 *N* HCl and the sample absorption was read at 224 nm.

Except where the drug dissolution was very rapid, the release rates were followed through 60 min. Each dissolution profile is the average of three to five individual determinations. The ranges are indicated in the various graphs.

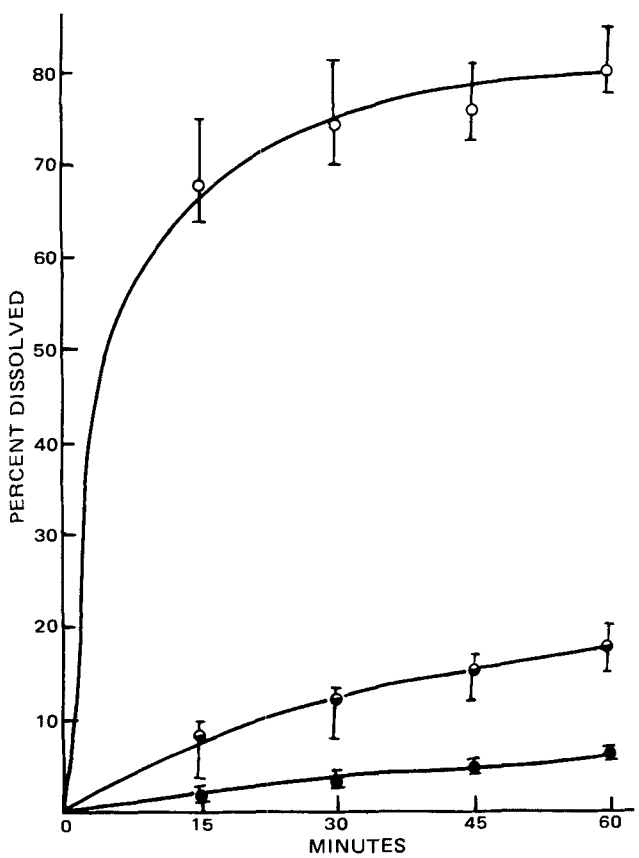

Figure 3—*Dissolution profiles of nitrofurantoin–lactose mixtures subjected to 30 min of shear as a function of lubricant concentration. Key:* ○, *Formulation A (0%);* ◒, *Formulation B (0.5%); and* ●, *Formulation C (2% magnesium stearate).*

[8] Multiple spindle dissolution drive, model 72B, Hanson Research Corp., Northridge, Calif.

[9] Parke, Davis & Co., Detroit, Mich.

[10] Model 25, Beckman Instruments, Fullerton, Calif.

RESULTS AND DISCUSSION

In each test series, two formulations (A and D in Series I and H and K in Series II) did not contain a lubricant and served as controls. Also, two different base materials, powdered lactose and powdered starch, were used. In addition to the controls, the blends studied contained lubricant concentrations of 0.5 or 2% of the drug–diluent mixtures. Formulations G and N contained 2% magnesium lauryl sulfate as the lubricant.

The effect of shear on the dissolution profiles of nitrofurantoin powder mixtures containing 2% magnesium stearate is shown in Fig. 1 (lactose as filler) and Fig. 2 (starch as filler). At this level of lubricant, shear mixing had a pronounced inhibitory effect on drug dissolution. In Fig. 1 (Formulation C), the amount of drug in solution at 1 hr declined from about 86% in the absence of shear to 8% after 15 min of blending with the intensifier bar. The shear effect appears to be greater with lactose as the base material compared to starch. This finding is somewhat unexpected in that water-soluble lactose should have aided in bringing about more rapid drug dissolution.

With both filler materials, after the capsule shells dissolved, the powders that displayed poor dissolution characteristics typically yielded an intact plug of solid with a central dry core at the end of the dissolution test run. This result occurred in spite of the intentionally low packing of the powder. Furthermore, the amount of drug released approached an equilibrium state with the application of shear. With the lactose blends, this state was attained after 15 min of blending time; with ni-

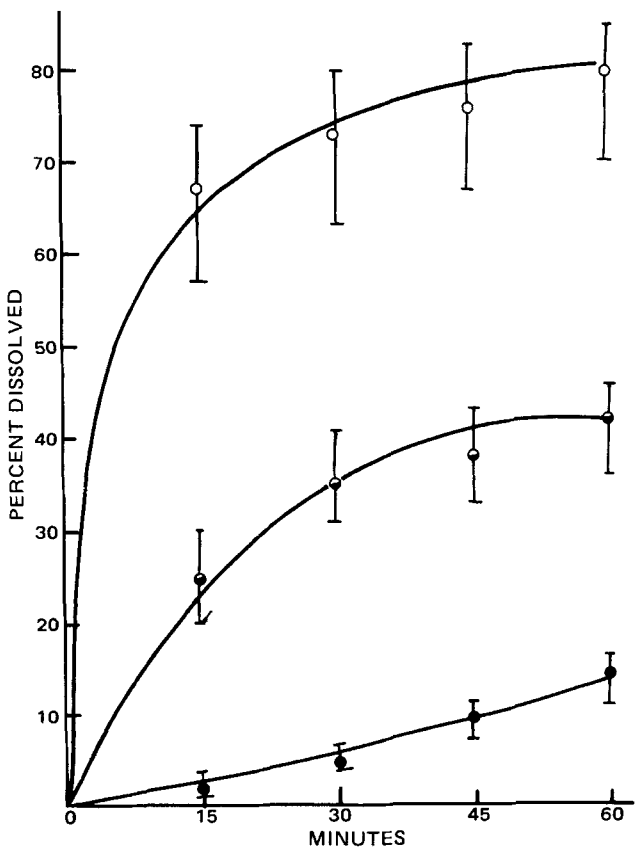

Figure 4—*Dissolution profiles of nitrofurantoin–starch mixtures subjected to 30 min of shear as a function of lubricant concentration. Key:* ○, *Formulation D (0%);* ◒, *Formulation E (0.5%); and* ●, *Formulation F (2% magnesium stearate).*

Table III—Dissolution Values (Minutes) for Procainamide Hydrochloride–Starch Mixtures in 0.1 *N* HCl at 100 rpm and 37°

Amount of Shear, min of Blending with Intensifier Bar	Formulation K			Formulation L			Formulation M		
	T_{20}	T_{50}	T_{80}	T_{20}	T_{50}	T_{80}	T_{20}	T_{50}	T_{80}
0	1.3	3.2	5.3	1.4	3.6	6.8	5.6	10.3	13.6
5	—	—	—	4.0	7.5	10.9	9.4	18.9	30.6
15	1.2	3.1	5.0	5.3	11.6	16.1	10.9	25.8	40.1
30	1.2	3.0	4.7	8.5	15.9	25.3	22.2	52.0	91.0

trofurantoin–starch–magnesium stearate mixtures (Formulations E and F), equilibrium was not reached until 30 min or longer of blending. Shorter high shear mixing times (5 min) resulted in a significant drop in the *in vitro* drug availability (Figs. 1 and 2). In the current investigations, rapid dissolution occurred at a level of 2% magnesium stearate when high shear was not applied.

Figures 3 and 4 summarize data on the *in vitro* release of nitrofurantoin in phosphate buffer at 100 rpm from formulations containing different concentrations of magnesium stearate. In these instances, 30 min of shear was applied to all powder mixtures. The retarding effect of shear on the dissolution rate was dependent on the level of magnesium stearate in the formulation; the larger the concentration of the lubricant, the slower was the drug release after the application of shear.

As shown previously, with any given concentration of magnesium stearate in the mixture, the inhibitory effect on drug dissolution is related to the degree of shear applied to the system. Thus, the greatest impairment of dissolution is likely to result in systems containing high levels of magnesium stearate subjected to long periods of shear. Among the blends investigated, formulations containing 2% magnesium stearate (C and F) experienced the largest reduction in dissolution rate after 30 min of mixing with the intensifier bar. There was no effect of shear in formulations devoid of lubricant (A and D).

Figure 5 illustrates the findings of shear studies carried out on Formulation G, which contained a water-soluble lubricant, 2% magnesium lauryl sulfate. The effect here was minimal. After 5 min of shear, the amount of drug in solution in 1 hr was reduced from 78 to 54%. Additional blending with the intensifier bar for up to 30 min resulted in no further reduction in the drug dissolution.

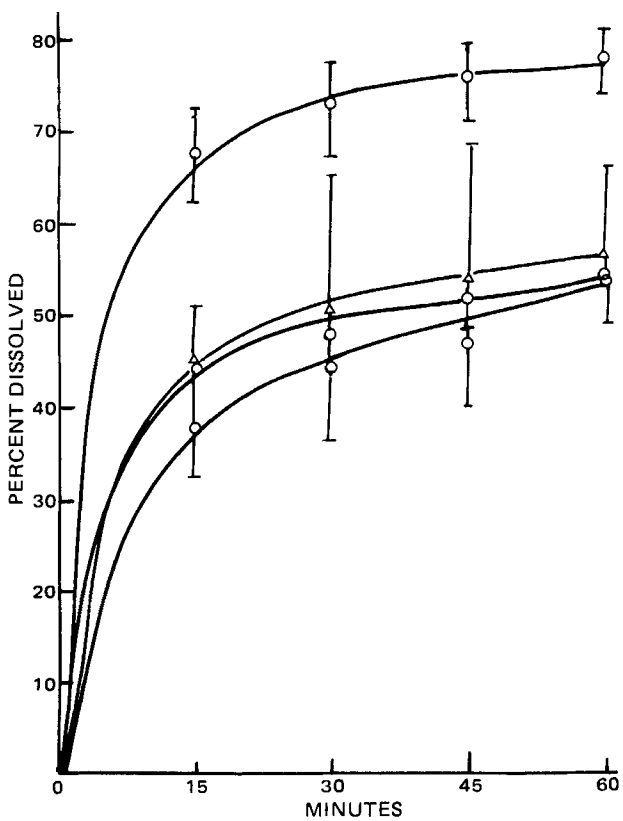

Figure 5—*Effect of shear on the drug dissolution in the nitrofurantoin–lactose–magnesium lauryl sulfate mixture (Formulation G). Key: ○, 0 min; ◒, 5 min; ●, 15 min; and △, 30 min of mixing with the intensifier bar.*

In Figs. 6 and 7, the dissolution rates of procainamide hydrochloride mixtures are shown at various mixing times with the intensifier bar. Figure 6 deals with Formulation J where lactose was used as the excipient, while Fig. 7 displays data for Formulation M where starch served as the base material. The lubricant was at the 2% level in both formulations. There was a marked reduction in dissolution due to shear in both blends, despite the high solubility of the drug substance. In Formulation J, the release rate reached an equilibrium state within 15 min of blending, in contrast to Formulation M where the system still showed a decreased dissolution rate even after 30 min of shear. Formulation J appeared to be particularly susceptible to the shear effect, since mixing for 5 min with the bar resulted in T_{80} (time for 80% of the drug to be in solution) values increasing from 9.5 to 45.3 min.

Tables II and III list the various T_{20} (time for 20% of the drug to be in solution), T_{50}, and T_{80} values of the procainamide hydrochloride formulations (H–M). The findings recorded with this water-soluble drug are similar to those for the nitrofurantoin powder mixtures in that the inhibitory effect on drug dissolution is related to the level of magnesium stearate in the formula and the duration of shear mixing. However, in contrast to the slight reduction in the dissolution rate noted for the nitrofurantoin mixture containing 2% magnesium lauryl sulfate (Fig. 5), no shear effect was apparent with Formulation N (Table II).

In addition to altering the dissolution properties, shear influenced both

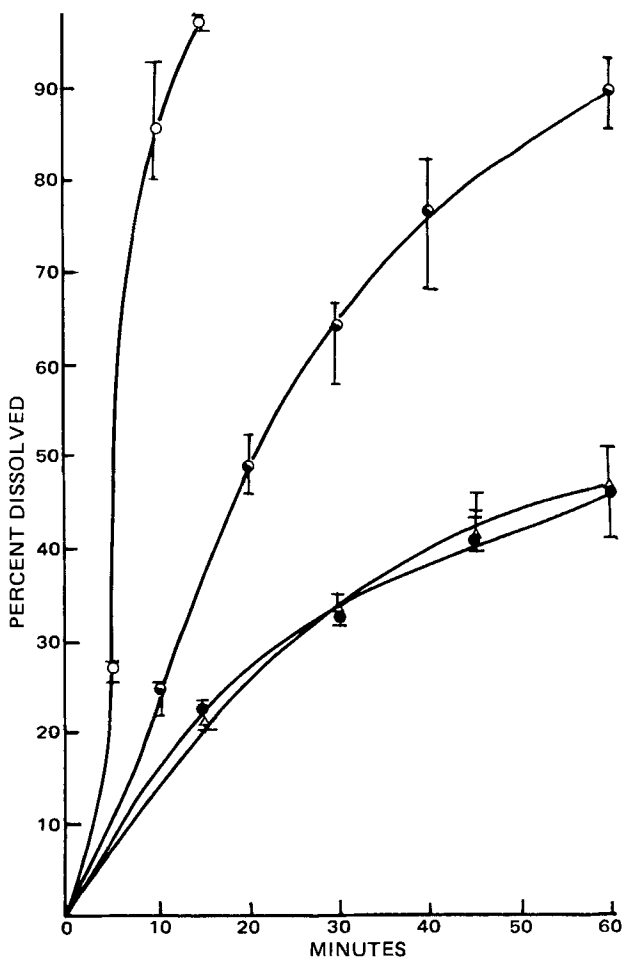

Figure 6—*Effect of shear on the drug dissolution in the procainamide hydrochloride–lactose mixture (Formulation J). Key: ○, 0 min; ◒, 5 min; ●, 15 min; and △, 30 min of mixing with the intensifier bar.*

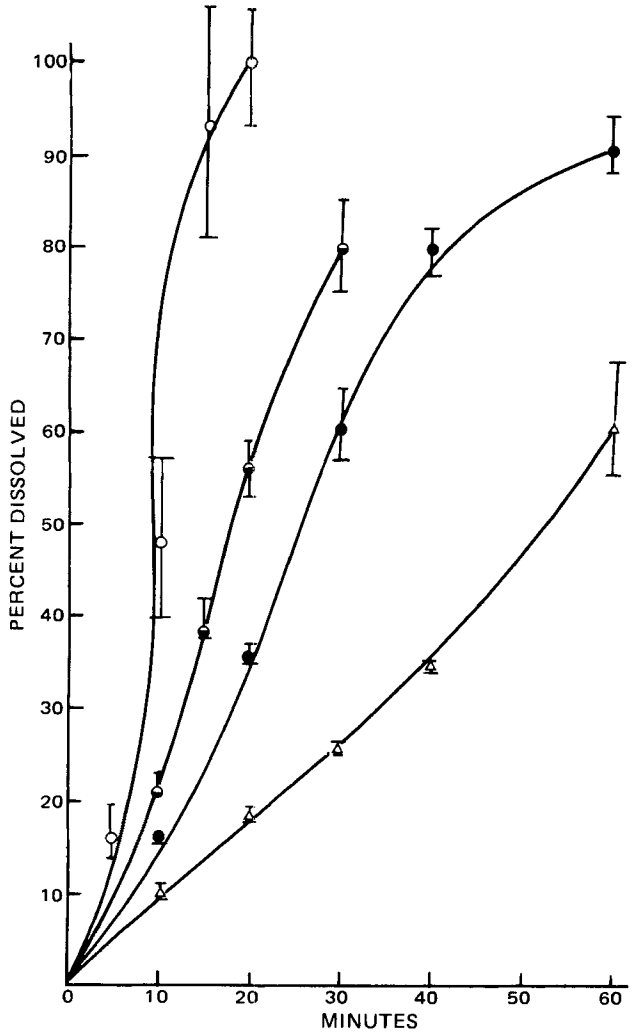

Figure 7—*Effect of shear on the drug dissolution in the procainamide hydrochloride–starch mixture (Formulation M). Key: ○, 0 min; ◒, 5 min; ●, 15 min; and △, 30 min of mixing with the intensifier bar.*

loose and packing densities of powder blends containing magnesium stearate. The powder densities increased with blending time up to maximum limiting values. These changes in the density characteristics of powders with shear are presumably related to improved flow properties and are frequently reflected in their subsequent processing, *e.g.*, in the fill weight and weight control during encapsulation.

The evidence presented in this paper illustrates the potential liabilities stemming from the indiscriminate use of shearing or mixing devices to break up aggregates in the blending operations where magnesium stearate and other hydrophobic lubricants are in the formula. The intensity of mixing is an important processing variable, capable of altering the *in vitro* availability characteristics of pharmaceutical formulations. This result, in turn, potentially may influence the bioavailability of the dosage form. A knowledge of the shear effect on drug dissolution should be an integral part of formula development and scale-up studies of drug preparations.

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High-Pressure Liquid Chromatographic Analysis of Methotrexate in Presence of Its Degradation Products

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Abstract □ Two high-pressure liquid chromatographic methods are described for the quantitative determination of methotrexate in the presence of its contaminants and degradation products. Method 1 takes less than 15 min and is recommended for routine assays of methotrexate in commercial products. Method 2 takes about 35 min and is the method of choice to detect and quantitate large amounts of degradation products. Quantitation to a level of 1 μg of methotrexate/ml is feasible by these methods and thus provides potential applicability for the analysis of methotrexate in biological fluids.

Keyphrases □ Methotrexate—high-pressure liquid chromatographic analysis, commercial preparations □ High-pressure liquid chromatography—analysis, methotrexate in commercial preparations □ Antineoplastic agents—methotrexate, high-pressure liquid chromatographic analysis in commercial preparations

Methotrexate is a folic acid antagonist widely used in cancer chemotherapy. However, methotrexate is contaminated with its degradation products and other closely related folic acid analogs. Quantitation of the contami-