In Vitro Dissolution from Several Experimental Capsule Formulations

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Abstract □ The *in vitro* dissolution behavior of several experimental capsule formulations is presented. The first series of powder blends clearly demonstrated that the capsule lubricant, magnesium stearate, and the filler, lactose or dibasic calcium phosphate dihydrate, had the greatest influence on the disintegrations of the capsules. Additional blends of these ingredients with an added drug were studied. In those instances where a slow dissolution was observed, the capsule contents characteristically remained as a wet powder pack long after the gelatin wall had dissolved. The drug dissolution was thus limited by the rate of erosion, diffusion, and/or solution of the drug and/or filler from this wet powder mass. Auxiliary measurements of liquid penetration rates of the packed powders and water content and viscosities of the wet powder packs were performed. These data suggested that the high viscosities of several of these powder packs were due to their restricted water content arising from the added hydrophobic lubricant.

Keyphrases □ Capsules—*in vitro* dissolution □ Formulation components, effect—capsule dissolution □ Powder beds—liquid penetration rate □ Disintegration, capsules—lubricant, filler effects

Different dosage forms containing various drugs have been compared by several investigators (1–3). Reviews of the physical factors affecting drug availability have been published by Wagner (4) and Nelson (5). Wood (6) has considered the *in vitro* evaluation of the tablet in some detail. The influence of granulation, granule size, compressional load, particle size, and the presence of surfactants, lubricants, and other tablet additions on *in vitro* drug availability have been studied (7–13).

Capsule formulations have received considerably less attention than tablets, presumably because of their apparent simplicity and consideration as loose powders. Wood (14) pointed out that although the hard gelatin capsule is widely used in preliminary studies of a new drug, very little literature on drug availability, even *in vitro*, exists for this type of dosage form. He quoted the National Formulary XII (15) as follows: "Disintegration time limits are not specified for capsules, since the shell dissolves rapidly in the gastrointestinal tract."

He further reported the release of aspirin from hard gelatin capsules to be irregular and showed a mean delay time of about 15 min. The importance of particle dispersion from tablets and capsules has been reported (16, 17). The failure of the capsule contents to disperse during *in vitro* testing has also been reported. Calesnick *et al.* (2) stated that during their study, "the contents of the hard gelatin capsule remained as a pasty mass for some time after the gelatin capsule had dissolved." Aguiar *et al.* (18) reported a similar observation in the *in vitro* testing of several generic chloramphenicol preparations.

The method of assessing drug availability has also been the subject of much concern. The disintegration requirements of various official compendia have recently been reviewed and compared (19). Levy (20) and Steinberg (21) reviewed the medical literature and suggested that low agitation conditions should prevail in the *in vitro* dissolution studies. In addition, higher pH values than that of the USP simulated gastric fluid, pH 1.2, have also been reported in the stomach. Kuna (22) stated that the pH of the gastric juice of the human resting stomach is near neutral, pH 7.3.

The present study is concerned with the influence of commonly used pharmaceutical adjuvants on disintegration and drug dissolution from experimental capsule formulations. Capsule fillers employed were lactose and dibasic calcium phosphate dihydrate. The latter is water insoluble and acid soluble. Preliminary mixtures were made with different concentrations of talc, starch, and magnesium stearate. These preparations clearly indicated that the filler, lactose or dibasic calcium phosphate dihydrate, and the capsule lubricant, magnesium stearate, had the greatest influence on the disintegration and dissolution characteristics. A low concentration of a water-soluble dye was incorporated in these preparations to permit dissolution measurements.

More typically, capsules are formulated to contain a relatively high proportion of the drug moiety. Therefore, a second series of preparations were prepared in which a drug of moderate solubility and no dominant hydrophobic or hydrophilic characteristics was used as a test drug. It was incorporated at approximately two-thirds of the total capsule weight. The two capsule fillers, lactose and $CaHPO_4 \cdot 2H_2O$, and the lubricant, magnesium stearate, which were the dominant factors in the first study were also added.

As with the first series of powder blends, dissolution rates of capsules were measured. They were found to vary over a wide range. In those cases where the dissolution rates were slow, the capsule contents characteristically remained as a "slug" of wet powder; *i.e.*, after dissolution of the gelatin capsule walls, the powder, although wet, remained intact as one or a few large masses. Additional measurements of liquid penetration rates, water contents of the wet powder beds, and the viscosities of the wet powder beds were performed to aid in explaining this behavior. The data suggested that the wet powder beds remained essentially intact because of their high viscosities. It will be shown that these high viscosities resulted from a reduced amount of water in the wet bed due to the presence of hydrophobic magnesium stearate.

MATERIALS AND PROCEDURES

The capsule fillers used in this study were lactose USP No. 80-mesh powder and dibasic calcium phosphate dihydrate. The magnesium stearate, corn starch, and talc were each USP grade powders.

The dye tracer used at 0.1% level in the first portion of the study was F. D. & C. Red No. 1. The drug employed in the second

Table I—Powder Blends Studied Showing Disintegration Times for No. 2 Capsules Packed with These Powders

	Disintegration Time in H_2O, min. (6 Capsules) —% Magnesium Stearate—			
	0	1	2	5
Lactose	5–6	8–12[a]	10–19[a]	21–35[a]
Lactose–3% talc	6–11			
Lactose–10% talc	7–10		13–18[a]	29–31[a]
Lactose–10% starch	10–13		10–15[a]	
$CaHPO_4 \cdot 2H_2O$	8–12	>60[c]	>60[c]	>60[b]
$CaHPO_4 \cdot 2H_2O$–10% talc	10–15			
$CaHPO_4 \cdot 2H_2O$–5% starch	10–12		>60[c]	

[a] Capsule contents break up into small pieces which dissolve. [b] Capsule contents remain in capsule shape—powder does not wet. [c] Capsule contents remain in one or a few pieces which slowly dissolve or erode.

portion of the study was approximately 100-mesh chemical (90% through a No. 100-mesh screen and 50% through a 200-mesh). Dissolution test media easily wetted the drug. A powder blend of the drug with lactose yielded a 90% dissolution value in less than 5 min. under the test conditions employed. All of the powder mixtures were prepared by blending and screening the various ingredients. The low levels of magnesium stearate were added by serial dilutions. The No. 2 capsules were hand-filled to the desired weights.

Drug dissolution was measured in the USP disintegration apparatus without the use of disks. This is in keeping with the reduced agitation conditions suggested above and is essentially a return to the USP XV method (23). Test fluids employed were simulated gastric fluid (low pH) and water (neutral pH). All tests were run at 37 ± 1°. One capsule was added to 800 ml. of the selected media at zero time. Five-milliliter samples were withdrawn as a function of time and rapidly filtered through a type HA 0.45-μ Millipore[1] membrane held in a Swinney adapter.

All dilutions were made with distilled water and the amount of drug in solution was determined by visible or UV measurement on a Beckman DU spectrophotometer. The data were converted to percent drug dissolved.

The liquid penetration rate measurements and water contents of the various powder blends were determined by the method of Studebaker and Snow (24). A straight Plexiglas tube (1.25 cm. i.d., 12 cm. length) open at both ends was filled with 4.0 g. of the individual powder blends packed to a bulk density of 0.94 g./cm.[3] with the aid of the Fisher Sub-Sieve Sizer[2] compaction apparatus. This represented the same bulk density as in a No. 2 capsule. The packed tube, free of the packing plugs, was mounted in a vertical position. Eight milliliters of distilled water was added to the upper surface of the bed at zero time. The rate of movement of the water interface through the packed bed was measured with the aid of a Gaerdner cathotometer[3] except for the dibasic calcium phosphate powder blends at high magnesium stearate levels. These readings were made with a scale held up to the powder bed because insufficient visual contrast existed between the wet and unwet portions of the powder when viewed through the cathotometer. The additions of the 0.1% of a water-soluble dye to the first series of powder blends provided a clearer measure of the liquid interface since the dissolved dye migrated with the interface. Dye was not added to the second series of drug-filler-lubricant mixtures. These measurements were carried out at room temperature (no temperature controls). The data have been plotted as the square of the distance of penetration *versus* the elapsed time in agreement with the Washburn equation (25).

The water contents of the wet powder beds were determined on the samples after the completion of the liquid penetration rate measurements. The wet powder beds were removed from the Plexiglas tubes and segmented. Portions were immediately weighed and reweighed after overnight drying to constant weight. The water content was calculated based on the difference.

The comparative viscosities of the powder blends with varying amounts of water were measured with a Universal penetrometer.[4] Samples were prepared as follows: 40 g. of powder blend was mixed with 20 ml. of distilled water in a 250-ml. beaker. The wet mass was transferred to a glass conical container and packed to give a smooth surface. The penetrometer consisted of an inverted cone (30° and 90° double cone) and a rod with a combined weight of 150 g. The apex of the cone was adjusted so as to just touch the surface of the wet powder bed prior to release. The combined cone and rod assembly was allowed to free fall for a 5-sec. period into the wet mass. The depth of penetration of the cone was read in 0.1-mm. units on the attached scale. Several readings were made on each bed, remixing the wet mass and reforming the smooth surface each time. A portion of the wet powder bed was weighed, dried to constant weight, and reweighed to determine the water content; the remainder of the wet mass was mixed with additional water and the measurements repeated. By this procedure, a series of penetration measurements were obtained at various water contents.

[1] Marketed by Millipore Filter Corp., Bedford, Mass.
[2] Fisher Scientific Co., Pittsburgh, Pa.
[3] Gaerdner Scientific Co., Chicago, Ill.
[4] Precision Scientific Co., Chicago, Ill.

RESULTS AND DISCUSSION

The first series of powder blends using lactose or $CaHPO_4 \cdot 2H_2O$ as the filler with varying quantities of talc, starch, and magnesium stearate are listed in Table I. The lactose blends were filled to 350 mg.; the $CaHPO_4 \cdot 2H_2O$ to 400 mg. In addition, disintegration times—range values for six capsules—are shown. The values varied from the rapid, 5–6 min., to the very slow or nondisintegrating capsule, greater than 60 min. Magnesium stearate has the greatest influence on the disintegration times. The filler, lactose or $CaHPO_4 \cdot 2H_2O$, also appears to have a measurable effect on disintegration. The starch and the talc at the levels investigated in the blends with and without magnesium stearate did not markedly affect the disintegration times.

Dissolution data shown in Figs. 1 and 2 for several of these same blends confirm this interpretation. The physical nature of the wet capsule contents for several of these powder blends has been noted in Table I. The extended disintegration coincides with the observations that the capsule contents either remain intact or break up into a limited number of wet powder masses. In one instance the compacted powder mass did not wet. This occurred with the $CaHPO_4 \cdot 2H_2O$ plus 5% magnesium stearate blend.

Additional liquid penetration rate measurements were performed on these same powder blends. Figure 3 shows the decreased penetration rates measured for the lactose-magnesium stearate systems. Figure 4 shows the relatively slight decrease in liquid penetration caused by the addition of starch up to the 10% level. Similar data were obtained with the lactose–talc blends. In blends containing magnesium stearate, the influence of starch or talc on the liquid penetration rate was not detectable. This was true for both the lactose and the $CaHPO_4 \cdot 2H_2O$ systems. The data in Fig. 5 are for the $CaHPO_4 \cdot 2H_2O$–2% magnesium stearate blends with starch.

This first series of experiments has shown that magnesium stearate has the greatest influence on the disintegration/dissolution behavior of the various capsule blends. The nature of the filler has also been shown to be of importance.

The second portion of this study consisted of capsules prepared with a drug at a relatively high concentration (approximately

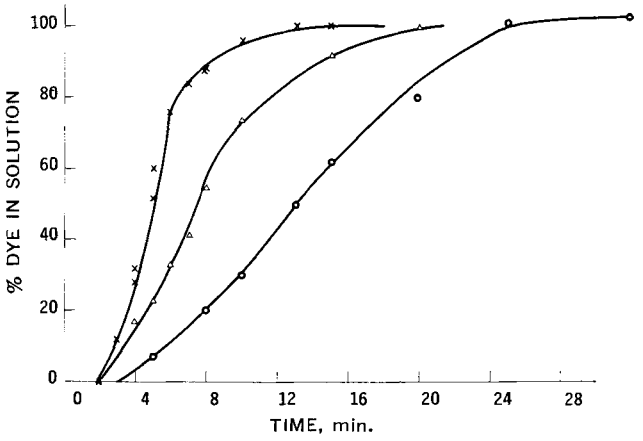

Figure 1—*Dissolution of dye from capsules of lactose–magnesium stearate. Key: ×, 0% magnesium stearate; △, 2% magnesium stearate; ○, 5% magnesium stearate.*

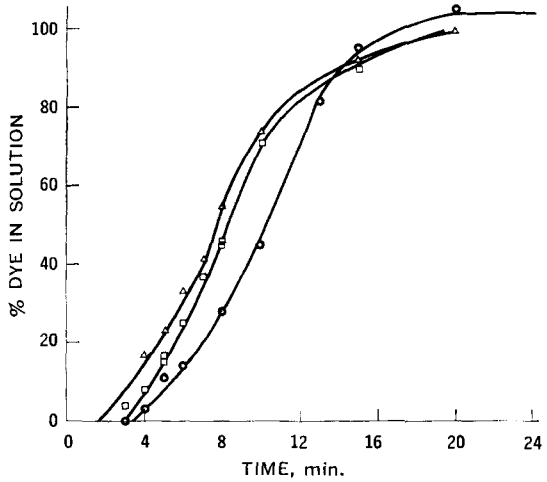

Figure 2—*Dissolution of dye from capsules (lactose + 2% magnesium stearate). Key: △, 0% corn starch; ○, 3% corn starch; □, 10% corn starch.*

two-thirds of total weight). The two fillers and the various levels of magnesium stearate found to be of importance in the first portion of the study were studied. The talc and starch were not included in these studies because of their apparently limited role. Dissolution behavior studies in both water and simulated gastric fluid were carried out. Disintegration times were noted in some of the figures.

The dissolution behavior of No. 2 capsules filled with the drug-lactose and drug-dibasic calcium phosphate dihydrate blends in water and in simulated gastric fluids are shown in Fig. 6. The dissolutions were rapid in all cases and essentially the same for the two different dissolution media and the two capsule fillers. The influence of 2% magnesium stearate on these two blends is shown in Fig. 7.

The slowest dissolution was observed for the drug-dibasic calcium phosphate–2% magnesium stearate system tested in water. This was due to the hydrophobic nature of the magnesium stearate and the insolubility of the calcium phosphate in the water. In simulated gastric fluid, this combination dissolved as fast as the comparable lactose system. In acid the dibasic calcium phosphate is soluble and the magnesium stearate is decomposed (26). The drug–lactose–2%

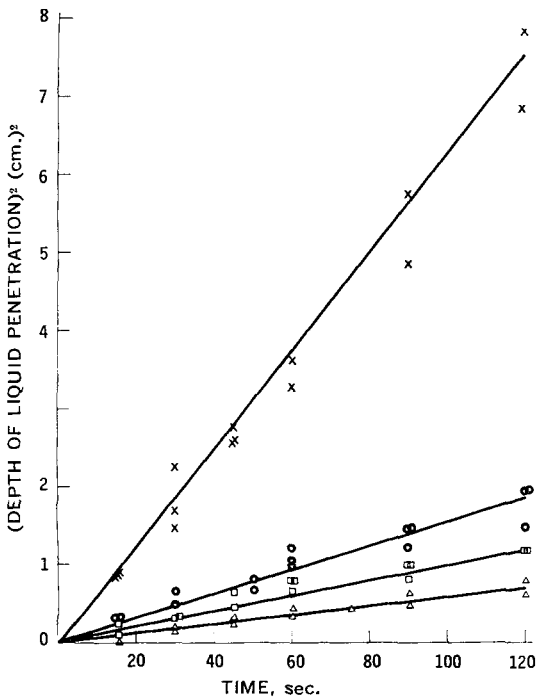

Figure 3—*Liquid penetration of packed powder beds. Key: ×, lactose; ○, lactose + 1% magnesium stearate; □, lactose + 2% magnesium stearate; △, lactose + 5% magnesium stearate.*

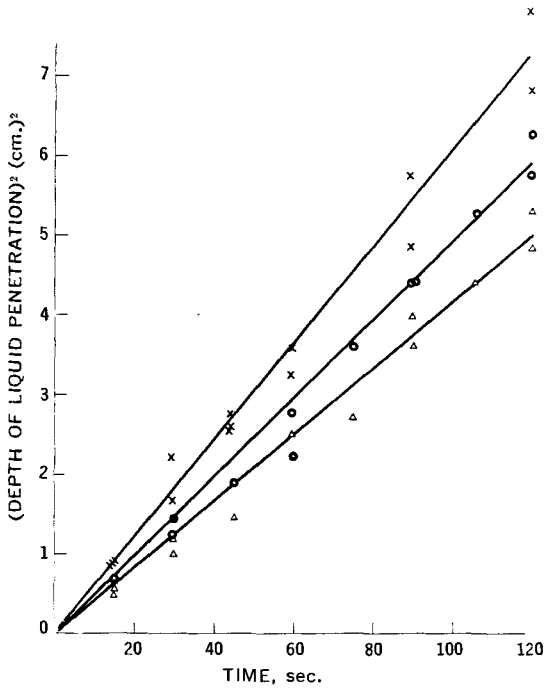

Figure 4—*Liquid penetration of packed powder beds. Key: ×, lactose; ○, lactose + 3% corn starch; △, lactose + 10% corn starch.*

magnesium stearate system also showed a difference in dissolution rate when tested in gastric fluid and water. The release in water, although slowed, was faster than the comparable dibasic calcium phosphate system. This probably was due to the water solubility of the lactose which permitted a faster erosion of the wet powder mass.

The magnesium stearate was further increased to 5% in both the lactose and dibasic calcium phosphate blends. In water these systems failed to wet after dissolution of the capsule walls. The powder remained as an essentially dry powder pack. Therefore, under these conditions, 5% magnesium stearate prevented dissolution when tested in water. In simulated gastric fluid, the powder beds did wet but remained as a wet mass during the dissolution process with erosion and dissolution slowly occurring. Figures 8 and 9 show the pronounced effect of this higher level of magnesium stearate with both fillers, even in simulated gastric fluid.

Figure 10 gives the dissolution data obtained in simulated gastric fluid by increasing the packing density in the No. 2 capsule with 0 and 5% magnesium stearate formulations (356 mg. *versus* 400 mg.). The data indicate that the packing density did not influence the dissolution rate in the absence of magnesium stearate. For the 5%

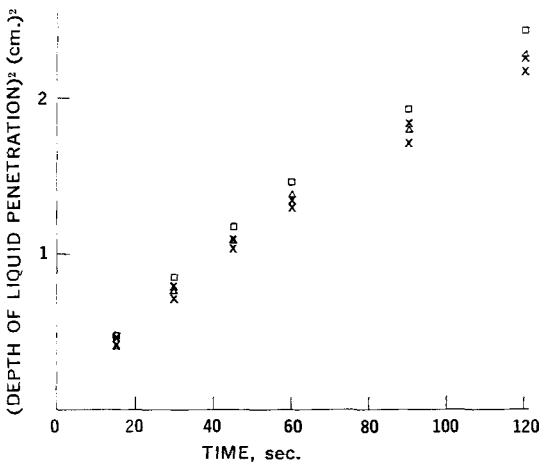

Figure 5—*Liquid penetration of packed powder beds. Key: ×, $CaHPO_4 \cdot 2H_2O$ + 2% magnesium stearate; △, $CaHPO_4 \cdot 2H_2O$ + 5% corn starch; □, $CaHPO_4 \cdot 2H_2O$ + 10% corn starch.*

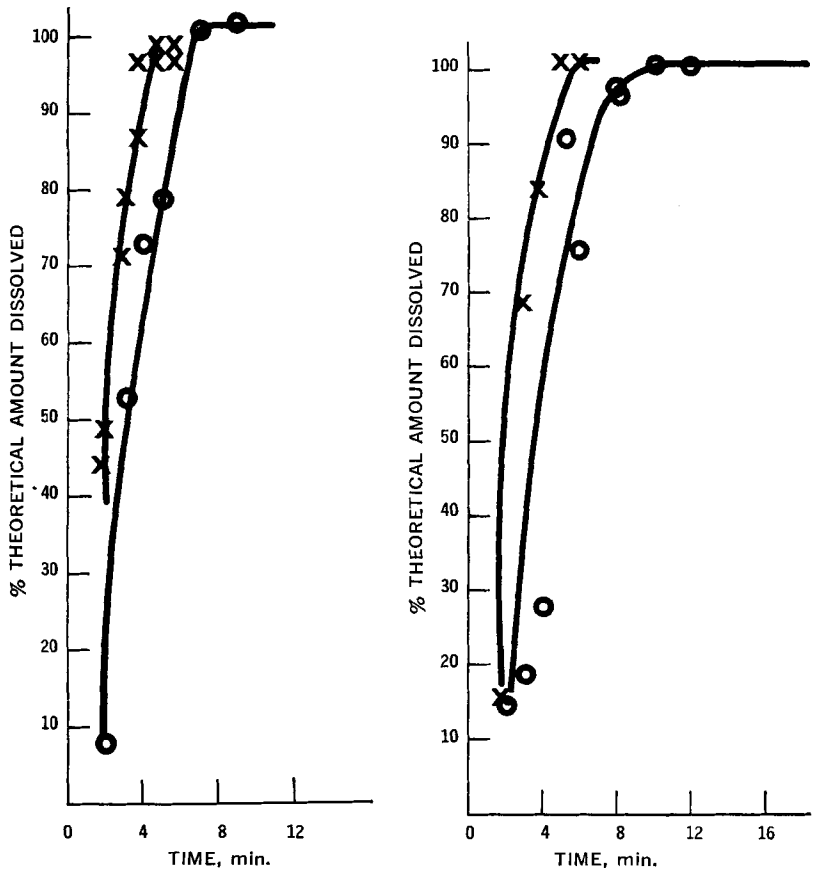

Figure 6—*Dissolution of drug from capsules; left, drug–lactose, no magnesium stearate; right, drug–$CaHPO_4 \cdot 2H_2O$, no magnesium stearate. Key: ×, simulated gastric fluid; ○, water.*

magnesium stearate samples, the 50% dissolution value did increase for both systems with increasing packing density; the dibasic calcium phosphate system showed the greatest increase of the 50% dissolution time, changing from about 7 min. to 23 min.

The behavior of the capsule blends shown in Fig. 6 indicates that the wettability and solubility of the drug used were adequate for rapid dissolution under these test conditions. In the majority of the systems in which the dissolution rate was slowed, the capsule contents—even after solution of the gelatin capsule walls—remained as an intact wet powder mass. Occasionally, this wet powder mass would break into more than one fragment. However, the dissolution was still essentially occurring from a very limited surface area. Because of these observations on the wet powder mass, further examination of the liquid penetration rates of the powder blends and water contents and viscosities of the wet powder beds were undertaken.

Due to the very limited size of the packed powder beds in an actual capsule, the measurements of liquid penetration, water content, and viscosities could more readily be carried out on larger samples of these powder blends. Using the method of Studebaker and Snow (24), the powder blends were therefore packed into open-ended cylindrical tubes for measurements. This method provided

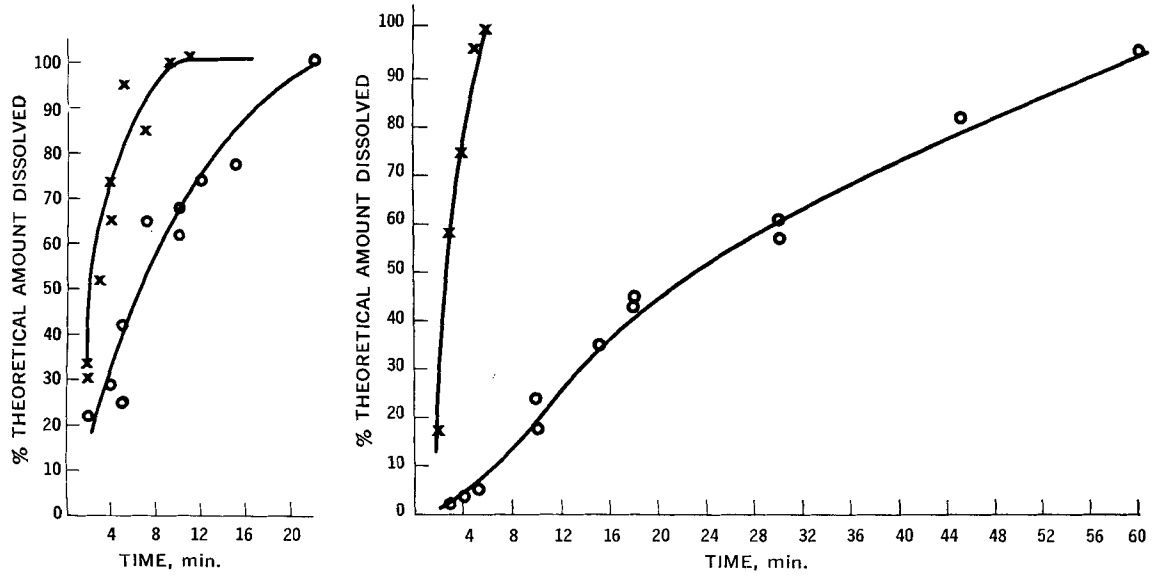

Figure 7—*Dissolution of drug from capsules: left, drug–lactose–2% magnesium stearate; right, drug–$CaHPO_4 \cdot 2H_2O$–2% magnesium stearate. Key: ×, simulated gastric fluid; ○, water.*

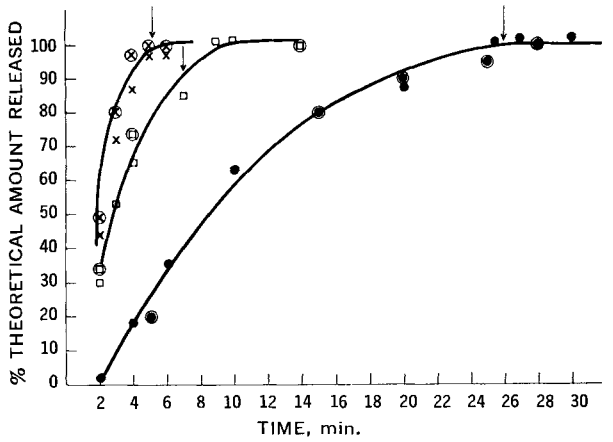

Figure 8—*Dissolution of drug from capsules in simulated gastric fluid (drug–lactose–magnesium stearate). Key: ×,⊗, 0% magnesium stearate; □,▣, 2% magnesium stearate; ●,◉, 5% magnesium stearate.*

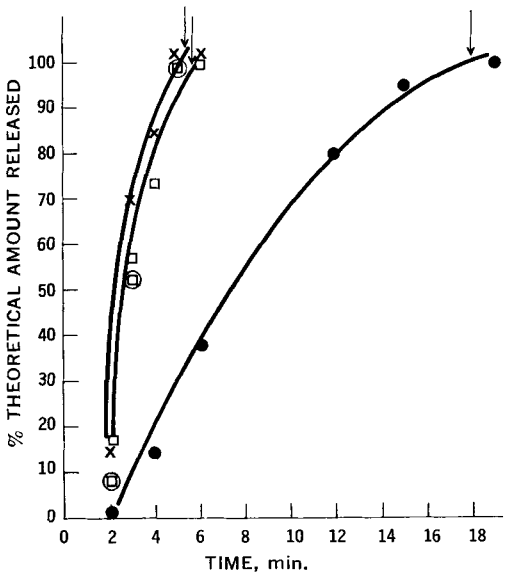

Figure 9—*Dissolution of drug from capsules in simulated gastric fluid (drug–$CaHPO_4 \cdot 2H_2O$–magnesium stearate). Key: ×, 0% magnesium stearate; □, ▣, 2% magnesium stearate; ●, 5% magnesium stearate.*

large samples, controlled packing density, and permitted measurements of penetration rates and water content of the wet powder beds.

The liquid penetration rates of the various drug–lactose and drug–dibasic calcium phosphate with magnesium stearate blends are shown in Figs. 11 and 12, respectively. The data were plotted as the square of the depth of liquid penetration *versus* time (25). From these figures, decreased liquid penetration rates are seen with increasing magnesium stearate levels. The dissolution data on some of these systems were shown in Figs. 6–9. It is clear that extended dissolution rates are obtained with powder blends that show reduced liquid penetration rates.

During these liquid penetration measurements, it was observed that the wet powder beds varied quite widely in viscosity when extruded from the Plexiglas tubes. Some of the wet compacted powders were thick pastes while others were quite fluid, almost to the point of flowing. Since many of the capsule blends remained intact long after the gelatin shells had dissolved, it would appear that these observations might also contribute to the prolonged dissolution rate measured.

Therefore, after completion of the liquid penetration experiments, the wet powder plugs were extruded from the tubes and segmented into two portions. The quantities of water present were

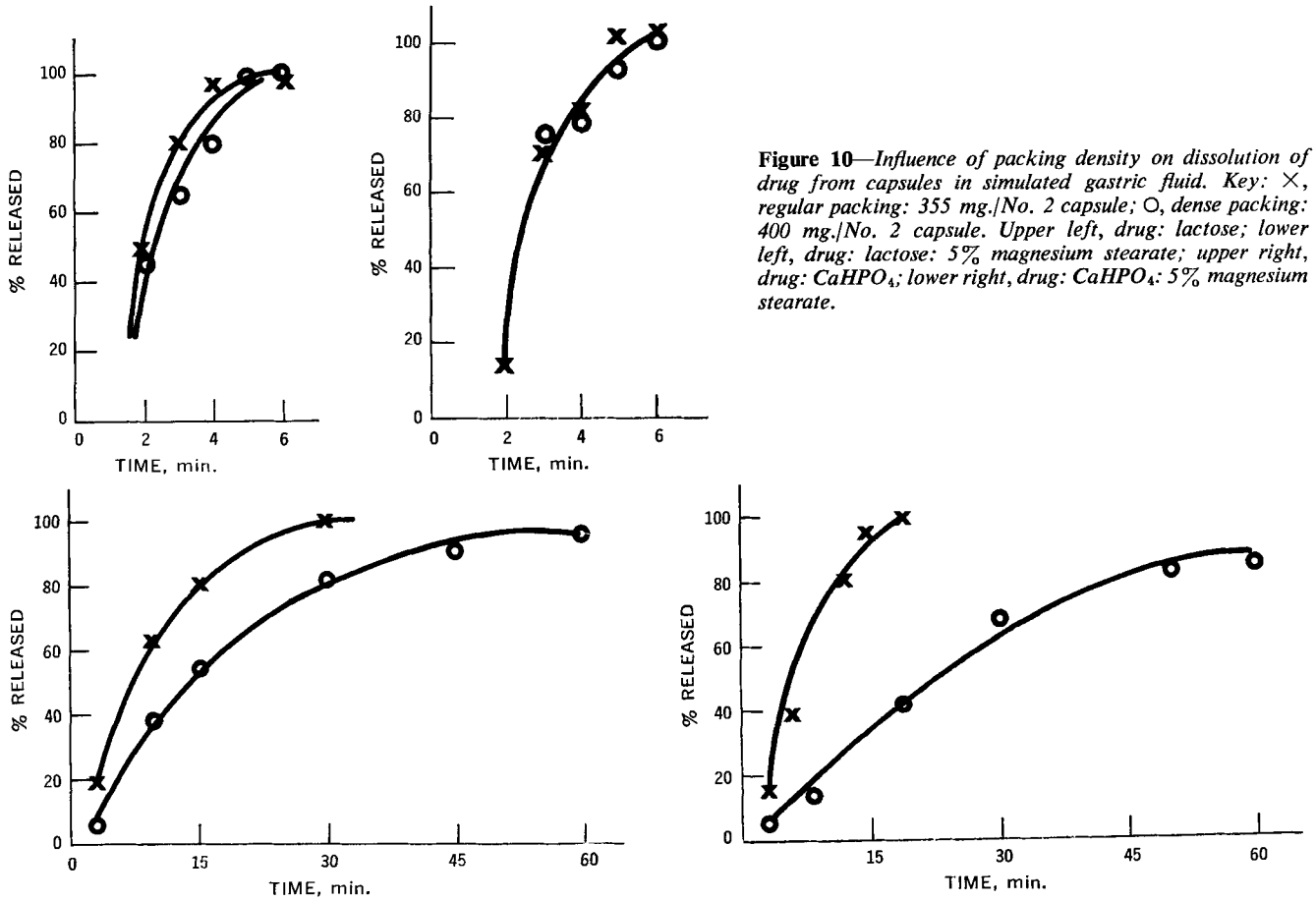

Figure 10—*Influence of packing density on dissolution of drug from capsules in simulated gastric fluid. Key: ×, regular packing: 355 mg./No. 2 capsule; ○, dense packing: 400 mg./No. 2 capsule. Upper left, drug: lactose; lower left, drug: lactose: 5% magnesium stearate; upper right, drug: $CaHPO_4$; lower right, drug: $CaHPO_4$: 5% magnesium stearate.*

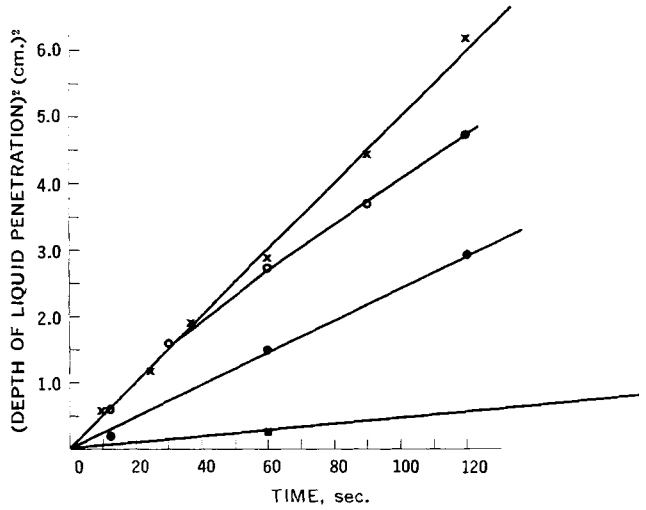

Figure 11—*Liquid penetration of packed powder beds (drug–lactose–magnesium stearate blends). Key: ×, 0% magnesium stearate; ○, 1% magnesium stearate; ●, 2% magnesium stearate; ■, 5% magnesium stearate.*

cetermined and are shown in Fig. 13. It can be seen that the water dontent did decrease with the added magnesium stearate level. Qualitatively, the physical appearance of the wet powder beds varied from a semifluid mass (no magnesium stearate) to a stiff paste (5% magnesium stearate) for both the lactose and dibasic calcium phosphate systems.

Comparative measurement of these viscosity changes with variable water content in the powder blends was carried out with a penetrometer. Three systems were checked: (*a*) drug–lactose–2% magnesium stearate; (*b*) drug–$CaHPO_4 \cdot 2H_2O$; and (*c*) drug–$CaHPO_4 \cdot 2H_2O$–2% magnesium stearate. Figure 14 shows the depth of cone penetration *versus* the amount of water in the powder. The samples low in water were more rigid and the depth of penetration was less than in the more fluid samples. The two $CaHPO_4 \cdot 2H_2O$ samples tested (with and without 2% magnesium stearate) described the same curve. This would suggest that the magnesium stearate affected the viscosity of the wet powder bed solely by limiting the water content in the bed.

At any given water content, the lactose-based capsule blend would appear to be more fluid than the $CaHPO_4 \cdot 2H_2O$ blend.

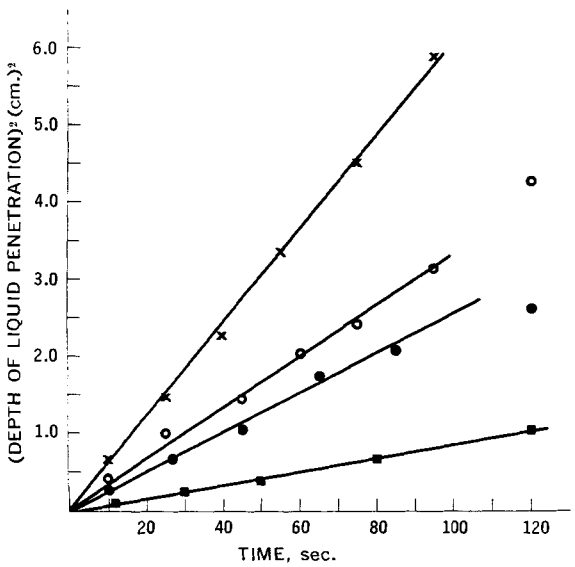

Figure 12—*Liquid penetration of packed powder beds (drug–$CaHPO_4 \cdot 2H_2O$–magnesium stearate blends). Key: ×, 0% magnesium stearate; ○, 1% magnesium stearate; ●, 2% magnesium stearate; ■, 5% magnesium stearate.*

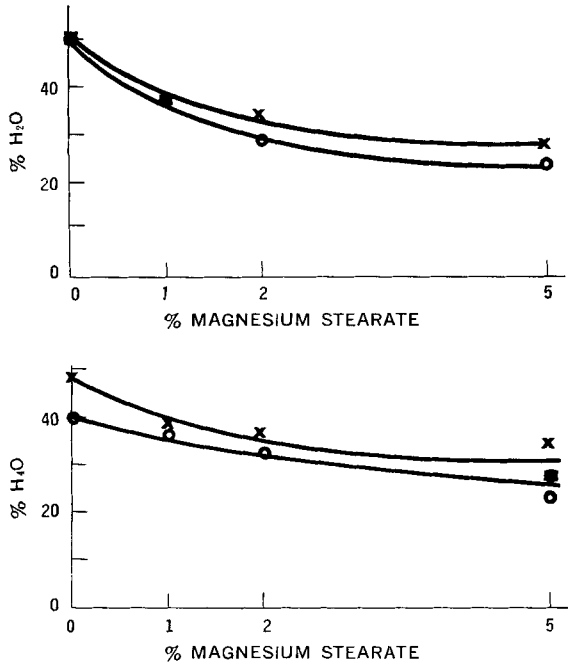

Figure 13—*Water contents of the wet powder beds; top, drug–$CaHPO_4 \cdot 2H_2O$–magnesium stearate blends; bottom, drug–lactose–magnesium stearate blends. Key: ×, first segment of bed; ○, second segment of bed.*

This may be due to partial solution of the lactose or other factors such as particle size and shape.

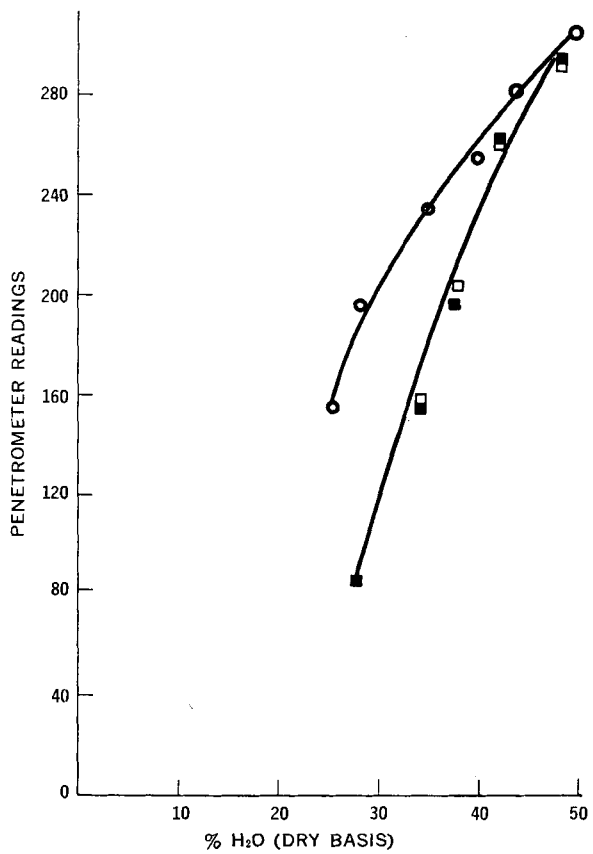

Figure 14—*Penetrometer measurements of powder beds containing varying quantities of water. Key: ○, drug–lactose–2% magnesium stearate; □, drug-$CaHPO_4 \cdot 2H_2O$-0% magnesium stearate; ■, drug–$CaHPO_4 \cdot 2H_2O$–2% magnesium stearate.*

Although these data clearly showed that the comparative viscosity decreased with added water as would be expected, the actual differences in viscosity between the various systems were felt to be greater than the numerical differences in the penetrometer readings. This is because the probe used for the measurements was an inverted cone and at greater penetrations, a greater cross section of the cone would contact the sample. Therefore, for greater penetration, a larger portion of the sample would support the load and prevent further penetration. A better estimate of the difference in relative viscosity of these samples would take into account this change in effective contact area of the probe with the sample. Considering this aspect, it would then be estimated that the sample with 27.5% water would be over 200 times as viscous as the sample with 48.5% water. From Fig. 14, the 5% magnesium stearate sample would therefore approximately correspond to the 27% water sample while the drug–$CaHPO_4 \cdot 2H_2O$ behaved like the 48% water sample.

The combined interpretation of Figs. 13 and 14 would suggest that magnesium stearate did reduce the water content in the powder bed and that this, in turn, yielded a wet powder blend of high viscosity. Dissolution of the drug would then be slowed due to the limited area of contact between the wet powder mass and the fluid. Dissolution would proceed by mechanical erosion, diffusion, and/or solution of drug and filler. *In vivo* it would seem these powder masses might remain intact for a considerable time if the agitation conditions are indeed low. In addition, an *in vivo* pH near neutral would favor stability of the wet powder mass.

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Hydrolysis of Lincomycin-2-phosphate and Clindamycin-2-phosphate

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Abstract □ The aqueous stabilities of lincomycin-2-phosphate and its 7-deoxy-7(S)-chloro analog, clindamycin-2-phosphate, were studied at a variety of temperatures and pH values. The predominant degradative routes of lincomycin-2-phosphate in the pH range 1–10 are thioglycoside and phosphate ester hydrolysis, and pH-rate studies show that it is most stable at pH 6–10. Clindamycin-2-phosphate degrades by three major routes from pH 1 to 10 with phosphate ester and thioglycoside hydrolysis predominating at pH less than 6 and scission of 7(S)-Cl to form the 7(R)-OH analog predominating at pH greater than 6. The rate of 7(S)-Cl to 7(R)-OH conversion was obtained using gas chromatography to measure the disappearance of clindamycin in reaction mixtures prepared under identical conditions as clindamycin-2-phosphate reaction mixtures. Rates of phosphate ester hydrolysis of the two compounds were measured by spectrophotometric determination of the amount of inorganic phosphate formed in reaction mixtures as a function of time. Apparent first-order rate constants of phosphate ester hydrolysis as well as activation energies (32.1 kcal./mole for lincomycin-2-phosphate and 32.9 kcal./mole for clindamycin-2-phosphate) agree favorably. The rate of lincomycin-2-phosphate hydrolysis in a formulated pediatric syrup at room temperature agrees favorably with extrapolated rates from high temperature hydrolysis in simple solutions.

Keyphrases □ Lincomycin-2-PO_4—hydrolysis kinetics □ Clindamycin-2-PO_4—hydrolysis kinetics □ Stability—lincomycin-, clindamycin-2-PO_4 aqueous solutions □ pH effect—lincomycin-, clindamycin-2-PO_4 hydrolysis rates □ Colorimetric analysis—spectrophotometer

The antibiotics lincomycin and clindamycin are highly effective in the treatment of infections caused by Gram-positive organisms (1, 2) and clindamycin possesses marked antiplasmodial activity as well (3). At times it is desirable to make derivatives from compounds such as lincomycin and clindamycin in order to circumvent disadvantages such as bitter taste or poor absorption inherent in the parent molecule. The derivatives must possess the same activity as the parent compound or be rapidly reverted to parent *in vivo*. Lincomycin has a bitter taste which is difficult to mask in pediatric liquid formulations. The C_2 phosphate ester of lincomycin