The method does not measure dissolution of a pharmacologically active ingredient or any other ingredient in the solid dosage form.

With minor detector modifications, this method should contribute significantly in the evaluation of viscosity gradients and sedimentation rates in heterogeneous dosage forms.

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Interaction of Tablet Disintegrants and Magnesium Stearate during Mixing I: Effect on Tablet Disintegration

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Abstract □ The effect of magnesium stearate on the disintegration of tablets was studied. Three different preblends, containing a slightly or a strongly swelling disintegrant, were mixed before compression with magnesium stearate for different time periods. The results show that a strongly swelling disintegrant, such as sodium starch glycolate in contrast to potato starch, can reduce the deteriorating effect of hydrophobic lubricants on tablet disintegration. However, the interaction between magnesium stearate and potato starch or sodium starch glycolate and the resulting differences in disintegration characteristics can be masked by the use of disks in the USP disintegration apparatus.

Keyphrases □ Tablets—disintegration, effect of magnesium stearate during mixing □ Magnesium stearate—effect on tablet disintegration during mixing □ Disintegration—tablets, effect of magnesium stearate during mixing

Previous work (1, 2) showed that magnesium stearate can have a strong negative effect on binding properties of tablet excipients. The phenomenon of decreasing crushing strength with increasing mixing time is caused by the formation of a lubricant film interfering with particle binding. The lubricant film is a result of adhesion to the substrate of magnesium stearate molecules, which are sheared off mechanically from the magnesium crystals during mixing (1–4). The formation of such a hydrophobic film can dramatically decrease the wettability of a powder mix, as was shown for sodium chloride–magnesium stearate blends (4). Thus, the deteriorating effect of hydrophobic lubricants on tablet disintegration is not only dependent on the nature and concentration of the lubricant used (5–11) but also on the mixing intensity of the tablet ingredients with the lubricants (12, 13).

The present study concerned the effect of magnesium stearate on tablet disintegration. Three different preblends, containing a slightly or a strongly swelling disintegrant, were mixed before compression with magnesium stearate for different time periods. Particular attention was focused on the effect of disks in the USP disintegration apparatus.

EXPERIMENTAL

Materials—The disintegrants used were dried potato starch[1] (moisture content ~8%) and sodium starch glycolate[2] NF XV. The other excipients were unmilled dibasic calcium phosphate dihydrate[3], extra-fine crystalline lactose[4], aspirin[5] (crystalline acetylsalicylic acid), and magnesium stearate[6].

Methods—*Mixing*—Preblends of filler and disintegrants were prepared by mixing[7] the excipients for 15 min, using glass vessels with a loading of ~20%. If not stated otherwise, the rotation speed was 90 rpm. After addition of 0.5% magnesium stearate, mixing was continued for a specified period.

Tablet Compression—Tablets were prepared by introducing manually 520.8 mg of the blend containing sodium starch glycolate or 625 mg of the blend containing potato starch into a prelubricated 13-mm die of a compression device mounted between the plattens of an instrumented hydraulic press[8]. The samples were compressed at a compression force of 20 kN with a loading rate of 2 kN/sec.

Crushing Strength—The crushing strength of the tablets was determined immediately after compression using a motorized instrument[9]. The data given are the means of at least five tablets.

Disintegration time—The disintegration time of the tablets was determined using the USP XIX apparatus. If not stated otherwise, the test was performed without disks. The data given are the means of the dis-

[1] Avebe G. A., Veendam, The Netherlands.
[2] Primojel, Avebe G. A., Veendam, The Netherlands.
[3] Emcompress, Edward Mendell Co., New York, N.Y.
[4] Lactose EFC, N. V. Hollandse Melksuikerfabriek, Uitgeest, The Netherlands.
[5] Feinkristallin (40-mesh USP), Bayer, Leverkusen, West Germany.
[6] Ph. Ned. grade, Lamers en Indemans's-Hertogenbosch, The Netherlands.
[7] Turbula mixer model 2P, W.A. Bachofen, Basel, Switzerland.
[8] Hydro Mooi, Appingedam, The Netherlands.
[9] Heberlein model WTP-3, Dr. K. Schleuniger, Zürich, Switzerland.

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Table I—Effect of Mixing [a] with Magnesium Stearate on Properties of Tablets from Aspirin with Potato Starch or Sodium Starch Glycolate

Mixing Time with Magnesium Stearate, min	20% Potato Starch		4% Sodium Starch Glycolate	
	Disintegration Time, sec	Crushing Strength, kg	Disintegration Time, sec	Crushing Strength, kg
0	6	4.7	20	5.7
2	24	<0.1	15	2.8
5	50	<0.1	16	2.3
30	55	<0.1	30	2.5

[a] A 0-min mixing time means no lubricant was added.

Table II—Effect of Mixing [a] with Magnesium Stearate on Properties of Tablets from Dibasic Calcium Phosphate Dihydrate with Potato Starch or Sodium Starch Glycolate

Mixing Time with Magnesium Stearate, min	20% Potato Starch		4% Sodium Starch Glycolate	
	Disintegration Time, sec	Crushing Strength, kg	Disintegration Time, sec	Crushing Strength, kg
0	10	9.1	5	5.9
2	15	5.6	8	5.5
5	825	4.5	13	5.0
30	>1800	4.2	56	5.2

[a] A 0-min mixing time means no lubricant was added.

Table III—Effect of Mixing[a] with Magnesium Stearate on Properties of Tablets from Lactose with Potato Starch or Sodium Starch Glycolate

Mixing Time with Magnesium Stearate, min	20% Potato Starch		4% Sodium Starch Glycolate	
	Disintegration Time, sec	Crushing Strength, kg	Disintegration Time, sec	Crushing Strength, kg
0	22	5.5	16	4.5
2	40	0.1	18	1.0
5	125	<0.1	21	0.9
30	375	<0.1	26	0.4

[a] A 0-min mixing time means no lubricant was added.

integration time of six individual tablets.

RESULTS AND DISCUSSION

Table I gives the effect of mixing time for mixing filler–disintegrant preblends with 0.5% magnesium stearate on both disintegration time and crushing strength of tablets compressed from aspirin with 20% potato starch or 4% sodium starch glycolate. The effect of mixing with magnesium stearate on the crushing strength of tablets without disintegrant is given in Fig. 1. Since the aspirin tablets showed only a slight decrease in crushing strength (from 4.5 to 3.2 kg) during 30 min of mixing with magnesium stearate (Fig. 1), the dramatic decrease (down to 0.1 kg with 2 min of mixing) in crushing strength of the tablets containing 20% potato starch must be attributed to a strong interaction between potato starch and magnesium stearate. This finding is consistent with previous results (3) showing that lubricants can exercise a strong negative effect on the binding properties of starch and starch derivatives.

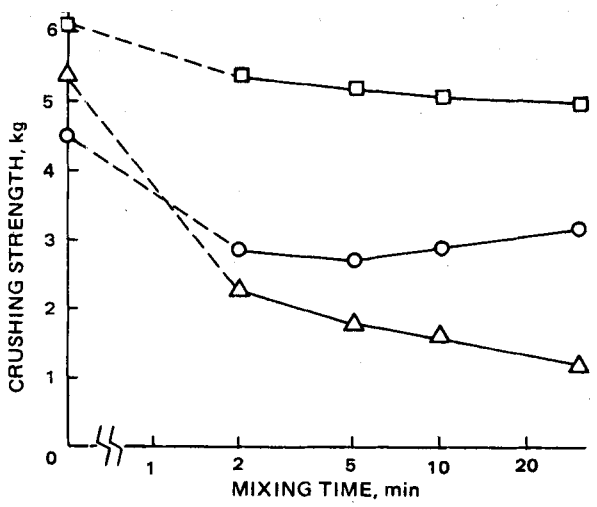

Figure 1—*Crushing strength* versus *mixing time (log scale) for tablets of fillers without disintegrants with 0.5% magnesium stearate. Key:* ○, *aspirin;* □, *dibasic calcium phosphate dihydrate; and* △, *lactose.*

In contrast to the decrease in crushing strength, the tablets showed a 10-fold increase in disintegration time after 5 min of mixing of the preblends with magnesium stearate. Since sodium starch glycolate is generally used in lower concentrations, the crushing strength of the aspirin tablets containing only 4% of this disintegrant exhibited a smaller decrease than the tablets containing 20% potato starch (Table I). The tablets initially showed a slight decrease in disintegration time with increasing mixing time with magnesium stearate, followed by a slight increase to values that are relatively low (especially when crushing strength is considered) compared with those of the tablets containing potato starch.

Table II shows the effect of mixing 0.5% magnesium stearate on tablets from dibasic calcium phosphate dihydrate with either 20% potato starch or 4% sodium starch glycolate. Since magnesium stearate hardly affected the binding properties of materials such as dibasic calcium phosphate dihydrate (Fig. 1), which undergo complete fragmentation under compression (3), the decrease in crushing strength of the tablets containing disintegrant must be caused by an interaction of the lubricant with the disintegrant.

Like the aspirin tablets, the dibasic calcium phosphate dihydrate tablets showed an increase in disintegration time with increasing mixing time with magnesium stearate. The most pronounced increase in disintegration time was exhibited by tablets containing 20% potato starch (Table II).

The lactose tablets showed an extremely strong decrease in crushing strength with an increase in mixing time of the blend with magnesium stearate (Table III). This result may be due to the effect of lubricant on the binding properties of both lactose (Fig. 1) and the disintegrants. A strong increase in disintegration time, which is consistent with the other results, was found for tablets with 20% potato starch; tablets with 4% sodium starch glycolate maintained fast disintegration, even when the

Table IV—Effect of Mixing Velocity during Mixing[a] with Magnesium Stearate on Disintegration Time of Tablets from Dibasic Calcium Phosphate Dihydrate with 20% Potato Starch or 4% Sodium Starch Glycolate

Mixing Time with Magnesium Stearate, min	Disintegration Time, sec			
	20% Potato Starch		4% Sodium Starch Glycolate	
	Mixing Velocity of 65 rpm	Mixing Velocity of 90 rpm	Mixing Velocity of 65 rpm	Mixing Velocity of 90 rpm
0	10	10	5	5
2	13	15	7	8
5	21	825	9	13
10	325	>1800	11	20
30	>1800	>1800	14	56

[a] A 0-min mixing time means no lubricant was added.

Table V—Effect of Mixing[a] with Magnesium Stearate on Disintegration Time, Measured without and with Disks, of Tablets from Dibasic Calcium Phosphate Dihydrate with 20% Potato Starch or 4% Sodium Starch Glycolate

Mixing Time with Magnesium Stearate, min	Disintegration Time, sec			
	20% Potato Starch		4% Sodium Starch Glycolate	
	Without disk	With disk	Without disk	With disk
0	10	8	5	4
2	15	15	8	8
5	825	37	13	11
10	>1800	65	20	11
30	>1800	90	56	13

[a] A 0-min mixing time means no lubricant was added.

tablet blend had been mixed for 30 min with magnesium stearate.

These results indicate that all increases in tablet disintegration time must be caused by the formation of a lubricant film on substrate particles of magnesium stearate molecules during mixing. As expected from previous work (2), the deleterious effect of magnesium stearate on disintegration time was dependent on mixing intensity. Table IV shows that the disintegration time of the dibasic calcium phosphate dihydrate tablets with 20% potato starch after 5 min of mixing with lubricant decreased from 825 to 21 sec when the velocity of the mixer decreased from 90 to 65 rpm. Tablets with 4% sodium starch glycolate acquired a still shorter disintegration time when mixing intensity decreased.

The remarkable difference in effect of mixing the preblends containing potato starch or sodium starch glycolate with magnesium stearate on tablet disintegration must be attributed to the difference in disintegration behavior of these materials. The hydrophobic magnesium stearate film formed during mixing will have a negative effect on the wettability of the tablet ingredient particles and, therefore, retard water penetration into the tablets. Since a complete coating of lubricant is not formed during mixing (12), the lubricant film will not be perfect and water will enter the disintegrant particles. Since sodium starch glycolate particles, in contrast to potato starch particles, swell extensively when brought in contact with water (14), it may be assumed that a small amount of water can already destroy the hydrophobic lubricant film. Microscopic examination of lubricated sodium starch glycolate particles confirmed that the particles bulge when brought into water. However, the swelling of potato starch may be insufficient to collapse the lubricant film on the disintegrant particles.

The disintegration times given in Tables I–IV refer to the method described in USP XIX but without disks. Table V gives the effect of the disks on the disintegration times obtained. The results show that the deleterious effect of magnesium stearate on the disintegration time of dibasic calcium phosphate dihydrate tablets can largely be masked by the disks.

The differences in disintegration time obtained with and without disks are likely due to the mechanical damage of the lubricant film during the disintegration test by the disks used, so that water can penetrate even the lubricant-coated, slightly swelling, potato starch particles.

These results prove that the use of disks in the USP disintegration apparatus can mask differences in tablet formulation (15, 16) as well as differences in preparation conditions such as mixing intensity.

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