International Journal of Pharmaceutics, 91 (1993) 217–226

IJP 03035

Physical interactions of magnesium stearate with starch-derived disintegrants and their effects on capsule and tablet dissolution

D.S. Desai, B.A. Rubitski, S.A. Varia and A.W. Newman

Bristol-Myers Squibb Co., New Brunswick, NJ (USA)

(Received 27 April 1992)
(Modified version received 15 July 1992)
(Accepted 10 September 1992)

Key words: Water repellant effect; Lubricant; Disintegrant; Overmixing; Dissolution; MG2 Futura capsule filler; Physical interaction; Tableting

Summary

Overmixing of magnesium stearate with granules in the hopper of a capsule filling machine can slow down their dissolution because of coating by magnesium stearate, which acts as a water repellant. This phenomenon was systematically investigated using three active ingredients representing a wide range of solubility in 0.1 N hydrochloric acid, the dissolution medium. The active ingredients were hydrochlorothiazide, an antiviral agent SQ32756 (BV-araU), and aztreonam, with solubilities in 0.1 N hydrochloric acid of 0.6, 5.0 and 12 mg/ml, respectively, at 37°C. When capsules of an aqueous wet granulated formulation containing one of the aforementioned active ingredients, hydrous lactose, pregelatinized starch, microcrystalline cellulose, and 1% w/w magnesium stearate were filled using the MG2 Futura capsule filler, capsules from the latter part of the filling run exhibited significantly slower dissolution compared to those from the beginning. The extent of slowdown in dissolution of the capsules varied depending upon the aqueous solubility of the active ingredient. The slowdown was maximum for hydrochlorothiazide capsules followed by SQ32756 and aztreonam capsules, respectively. Further studies using SQ32756 as the active ingredient indicated that replacement of magnesium stearate in the formulation with other hydrophobic lubricants such as calcium or zinc stearate gave similar results. However, replacement of magnesium stearate with hydrophilic lubricants such as Stear-O-Wet® or sodium stearyl fumarate did not result in a slowing of dissolution. Among the hydrophobic lubricants, magnesium stearate caused the maximum slowdown in dissolution, followed by zinc and calcium stearates, respectively. This observed rank order was correlated to the surface area of these lubricants. Furthermore, optimization of magnesium stearate concentration to 0.25% w/w provided enough lubrication for capsule filling while resulting in a capsule with satisfactory dissolution. Replacement of pregelatinized starch by starch-derived superdisintegrants such as Explotab® or Primojel® also resulted in no slowing of dissolution of capsules, even after overmixing with 1% w/w magnesium stearate. Although the granules overmixed with 1% w/w hydrophobic lubricants exhibited slow down in dissolution when filled into capsules, tablets compressed from these granules dissolved rapidly.

Introduction

Addition of a lubricant such as magnesium stearate into granules prior to their capsulation or compression into tablets is a crucial step. The quantity of magnesium stearate added and/or the duration of its mixing with granules can significantly affect inter-batch and intra-batch properties such as dissolution, hardness, and friability (Mitrevej and Augsburger, 1982; Jarosz and Parrott, 1984; Bolhuis et al., 1987). In many in-

Correspondence to: D.S. Desai, Bristol-Myers Squibb Co., P.O. Box 191, New Brunswick, NJ 08903-0191, U.S.A.

stances, formulators confront a problem in a batch, where capsules from the latter part of the filling run exhibit slower dissolution than those from the beginning. The cause of this problem is often attributed to overmixing of granules with a lubricant such as magnesium stearate in the hopper of a capsule filling machine. As a result of overmixing, granules are coated with a hydrophobic film of lubricant (Bolhuis et al., 1975) which slows their dissolution. Some formulators solved the problem by removing the propeller blade to prevent overmixing of magnesium stearate with the granules in the hopper and replacing the cylindrical powder hopper with a cone shaped hopper to facilitate the flow of granules from the hopper to the powder rotary container (Johansen et al., 1989). However, this approach is not always feasible since the hopper design varies significantly depending upon the type of capsule machine. Moreover, formulators are expected to develop a robust formulation not only from a stability view point, but also from a processing aspect. Therefore, in the present study, efforts were directed to address the problem by making changes in the formulation. In order to propose changes judiciously, the problem was studied using drugs representing a wide range of solubilities, hydrophobic and hydrophilic lubricants, and starch-derived disintegrants. Based on the result of the study, possible solutions to the problem were proposed. In addition, dissolution of granules overmixed with 1% w/w hydrophobic lubricants was also studied after their compression into tablets.

Materials and Methods

Materials

The following ingredients were used as received from the suppliers: hydrochlorothiazide (Profarmaco, New York, NY), aztreonam (Bristol-Myers Squibb Co., New Brunswick, NJ) SQ32756 (BV-araU) (Yamasa Shoyu Co., Choshi, Japan), hydrous lactose (Foremost Whey, Baraboo, WI), pregelatinized starch (Starch® 1500) (Colorcon Inc., Indianapolis, IN), sodium starch glycolate (Primojel®) (Generichem Corp., Little Falls, NJ), corn starch (A.E. Staley, Decatur, IL), microcrystalline cellulose (Avicel® PH 101) (FMC Corp., Newark, DE), magnesium stearate and Stear-O-Wet® (Mallinckrodt, St. Louis, MO), calcium and zinc stearates (Amend Drug & Chemical Co., Irvington, NJ), sodium stearyl fumarate and sodium starch glycolate (Explotab®) (Edward Mendell Co., Carmel, NY), and size no. 1 hard gelatin capsule shells (Capsugel, Greenwood, SC).

Equipment

Equipment used in the study included Hobart planetary mixer (Hobart Manufacturing Co, Troy, OH), tray oven (Shampaine Scientific Co., Roselle, NJ), MG2 Futura automatic capsule filler (MG2-Italy, distributed in the U.S.A. by MG America, Fairfield, NJ), instrumented beta press (Manesty Machine Ltd, Liverpool, U.K.), Vanderkamp 600-six spindle dissolution tester (Vankel Industries, Edison, NJ), 8451A Diode Array Spectrophotometer (Hewlett-Packard Co., Palo Alto, CA), and Quantachrome Autosorb-6 Sorption System (Quantachrome Co., Syosset, NY).

Preparation of granules

The formulation composition of the granules is given below:

Ingredient	% in formulation (w/w)
Active ingredient	12.5
Hydrous lactose and microcrystalline cellulose	76.5
Pregelatinized starch [a]	10.0
Lubricant [b]	1.0
Purified water [c]	q.s.
Total	100.0

[a] Whenever pregelatinized starch was replaced with other disintegrants, they were also used at 10% w/w level.
[b] Any reduction in lubricant level was accompanied by corresponding increase in hydrous lactose level.
[c] Not present in the final product, removed by drying.

An active ingredient and lactose were screened separately using a no. 20 mesh screen into a 12 quart Hobart bowl. The remaining ingredients of

a 3.0 kg batch, except the lubricant, were added into the bowl containing lactose and the active ingredient and were mixed for 5 min. Subsequent to mixing, the blend was granulated using purified water. The west mass was then screened through a no. 8 mesh screen and was dried in a tray oven at 50°C. The resulting dried granules were screened through a no. 24 mesh screen and mixed with no. 30 mesh screened lubricant for 3 min in a Hobart bowl. When corn starch replaced pregelatinized starch in the formulation, it was used as a 15% w/w paste.

Filling of granules into capsule shells

Hydrochlorothiazide, SQ32756, or aztreonam granules were filled into size no. 1 capsule shells using the MG2 Futura capsule filler. The machine was equipped with only four dosators, one-fourth of its normal capacity, because of the small batch size. In the beginning of the filling run, the fill weight was adjusted to 80 mg to obtain 10 mg potency capsules. After filling 10 mg potency capsules for 45 min, the fill weight was increased to 320 mg to obtain 40 mg potency capsules. The filling of 40 mg potency capsules was conducted for an additional 30 min. Capsule samples were taken at regular intervals during the filling of both 10 and 40 mg potency capsules and were tested for dissolution. The entire filling operation was finished in about 90 min.

In large-scale capsule production, a powder hopper is filled with a large quantity of granules which are continuously mixed by the rotating propeller blade of the hopper. To simulate this condition, the capsule machine was left on for up to 60 min without capsule filling. During that time, granules were constantly mixed by the rotating propeller blade in the powder hopper. Thereafter, capsules were filled and tested for dissolution. In order to rule out any mechanical effects such as the compression force of the dosators on capsule dissolution, capsules were hand-filled with granules from the capsule hopper before the beginning and at the end of a filling run. Overmixing of granules in the powder hopper was also simulated by mixing the granules with lubricant for 15 min in a Hobart mixer. The granules were hand-filled in capsule shells and tested for dissolution.

Compression of granules into tablets

Subsequent to encapsulation of granules into size no. 1 capsule shells, the remaining granules in the capsule hopper which were overmixed with 1% w/w lubricant, were compressed into 320 mg weight round tablets. For this purpose, an instrumented beta press equipped with four stations of 11/32 inch tooling was used. The compression forces used were between 750 and 2500 kg. Similarly, the granules overmixed with 1% w/w lubricant in a Hobart bowl were also compressed into 320 mg weight tablets. The tablet weight was the same as the capsule fill weight, resulting in 40 mg potency tablets.

Dissolution studies

Dissolution of six hydrochlorothiazide, SQ32756, and aztreonam capsules and tablets was monitored using a spectrophotometer at wavelengths of 272, 292 and 310 nm, respectively, in 1000 ml of 0.1 N hydrochloric acid at 37°C with a paddle speed of 75 rpm for capsules and 50 rpm for tablets. For capsules, sinkers were used to prevent them from floating in the dissolution

TABLE 1

Summary of HPLC methods of analysis for the active ingredients

Active ingredient	Column	Mobile phase composition	Detection at UV wavelength (nm)
Hydrochlorothiazide	C18 column	methanol : 0.2% phosphoric acid (15 : 85)	271
SQ32756	Lichrosorb	acetonitrile : water : TEAA (15 : 80 : 5)	254
Aztreonam	silica column	0.1% phosphoric acid	206

TABLE 2

Dissolution of 10 and 40 mg potency capsules containing 1.0% w / w magnesium stearate sampled at various time points during filling on the MG2 Futura

Drug and potency	Sampling time:	Mean % of drug dissolved (% RSD)					
		5 min	10 min	20 min	30 min	45 min	60 min
Hydrochlorothiazide							
10 mg potency	beginning of filling run	73.5 (29.2)	99.7 (1.3)	104.7 (1.5)	105.4 (1.4)	105.5 (1.5)	–
(80 mg fill weight)	end of 45 min run	39.3 (23.0)	84.8 (6.7)	97.4 (.5)	99.8 (9.5)	101.2 (9.0)	–
40 mg potency	beginning of filling run	6.5 (10.0)	12.5 (7.4)	21.5 (14.3)	28.9 (16.4)	50.5 (59.2)	54.0 (51.9)
(320 mg fill weight)	end of 30 min run	4.6 (26.4)	9.9 (13.7)	16.5 (10.3)	21.5 (10.5)	28.5 (13.0)	31.2 (15.5)
SQ32756							
10 mg potency	beginning of filling run	90.4 (3.8)	101.6 (1.7)	103.2 (2.1)	103.1 (2.3)	103.5 (2.3)	103.8 (2.2)
(80 mg fill weight)	end of 45 min run	71.9 (15.9)	96.3 (2.5)	100.2 (1.9)	100.5 (1.4)	100.5 (1.4)	100.5 (1.4)
40 mg potency	beginning of filling run	9.9 (15.0)	20.8 (6.5)	43.0 (22.4)	58.3 (25.4)	70.6 (20.1)	87.2 (14.0)
(320 mg fill weight)	end of 30 min run	9.7 (15.0)	20.8 (13.0)	36.7 (12.1)	49.8 (10.6)	69.1 (21.3)	79.8 (16.8)
Aztreonam							
10 mg potency	beginning of filling run	84.3 (44.5)	100.9 (1.1)	101.1 (1.3)	101.1 (1.3)	101.1 (1.3)	101.1 (1.3)
(80 mg fill weight)	end of 45 min run	70.1 (32.0)	99.8 (1.0)	101.1 (0.5)	101.1 (0.5)	101.1 (0.5)	101.1 (0.5)
40 mg potency	beginning of filling run	41.3 (44.5)	92.1 (23.4)	105.1 (2.8)	107.2 (0.1)	107.2 (0.1)	107.2 (0.1)
(320 mg fill weight)	end of 30 min run	25.0 (92.5)	78.1 (55.2)	92.9 (24.3)	95.2 (20.0)	96.8 (17.2)	106.3 (0.7)

medium. The HP 89026A Dissolution Testing System, in conjunction with the HP 8451A Diode Array Spectrophotometer, automated the sampling, analyzing, data processing and report generating tasks.

Solubility determination of active ingredients in the dissolution medium

The saturated solubilities of hydrochlorothiazide, SQ32756, and aztreonam were determined by equilibrating excess amount of the material in the dissolution medium in a water bath at 37°C for 48 h. The solutions were then filtered through a 0.45 μm Millipore filter and analyzed using HPLC. For the HPLC analysis, Perkin Elmer SEC-4 Pump (Perkin Elmer, Norwalk, CT), Waters 712 WISP injector (Waters, Morristown, NJ), and ABI 783A UV detector were used. The HPLC conditions for analysis are summarized in Table 1.

Surface area measurements for stearates

Surface area measurements were obtained on a Quantachrome Autosorb-6 Sorption System. Sample sizes of 1–2 g of material were used for analysis, and samples were outgassed at room temperature while under vacuum. Data were obtained using five pressures of nitrogen adsorbent, with P/P_0 values between 0.10 and 0.31. The results were analyzed using a multi-point BET equation, and correlation coefficients of 0.9995–0.9999 were obtained for all samples.

Results and Discussion

As outlined in Materials and Methods, in-process capsule samples were tested for dissolution. As shown in Table 2, dissolution of 10 and 40 mg potency capsules samples at 45 min into the filling run was slower compared to those sampled at the beginning of the filling run. During the capsulation process, granules were constantly mixed in the hopper. As a result of this continuous mixing process, granules were coated with hydrophobic magnesium stearate (Bolhuis et al., 1975), which slowed down their dissolution. It was also noted that because of the coating of granules with hydrophobic magnesium stearate, dissolution of the capsules containing coated granules varied at earlier time points as indicated by high values of the relative standard deviation. Interestingly, 40 mg potency capsules of all three drugs sampled at the beginning of the filling run showed slower slower dissolution than 10 mg potency capsules sampled toward the end of 45 min filling run (Table 2). The probable reason for relatively quick dissolution of 10 mg potency capsules was that their 80 mg fill weight was too low for size no. 1 capsule shells. With the low fill weight, the powder blend

TABLE 3

Dissolution of 40 mg potency capsules hand filled with granules containing 1.0% w/w magnesium stearate sampled at various time points during capsule filling on the MG2 Futura

Drug and sampling time of granules	Mean % of drug dissolved (% RSD)					
	5 min	10 min	20 min	30 min	45 min	60 min
Hydrochlorothiazide						
Before capsule filling run	11.8 (34.2)	35.9 (29.1)	79.0 (14.5)	93.4 (3.5)	95.6 (2.7)	96.4 (2.2)
End of 30 min filling run	3.6 (22.5)	7.9 (13.3)	13.8 (12.4)	20.8 (20.4)	30.3 (31.6)	35.9 (28.9)
SQ32756						
Before capsule filling run	15.8 (12.5)	45.7 (12.9)	86.1 (15.9)	96.8 (0.2)	97.7 (0.4)	97.7 (0.5)
End of 30 min filling run	4.9 (20.1)	13.8 (16.6)	26.5 (18.6)	40.4 (21.9)	55.2 (18.3)	65.5 (13.4)
Aztreonam						
Before capsule filling run	46.0 (31.0)	94.5 (10.6)	103.7 (1.0)	103.9 (1.0)	104.2 (1.3)	104.4 (0.8)
End of 30 min filling run	17.5 (6.7)	31.0 (3.7)	58.2 (14.2)	73.8 (15.2)	92.9 (12.0)	103.2 (3.5)

was more loosely filled into the capsules, resulting in more surface area of the blend available for dissolution (Dahl et al., 1991).

In order to rule out the effect of any mechanical factors such as compression force used by the dosators of the machine in slowing down the dissolution of the capsules, the capsules were hand filled and tested for dissolution. As shown in Table 3, dissolution of the hand-filled capsules with granules from the hopper at the end of the filling run was significantly slower than that of the capsules filled with the granules at the beginning of the filling run. The extent of slowdown in dissolution of capsules varied with the solubility of the active ingredients. The solubilities for hydrochlorothiazide, SQ32756, and aztreonam in 0.1 N hydrochloric acid at 37°C are 0.6, 5.0 and 12.0 mg/ml, respectively. The extent of dissolution slowing due to overmixing of granules with the magnesium stearate can be correlated with drug solubility. Maximum slowdown in dissolution occurred for the least soluble active ingredient.

Of the three active ingredients, SQ32756 was selected for further study. When SQ32756 granules were mixed with other hydrophobic stearates such as calcium stearate or zinc stearate for 15 min in a Hobart bowl, capsules containing these granules also exhibited slower dissolution as compared to granules containing no lubricant (Fig. 1).

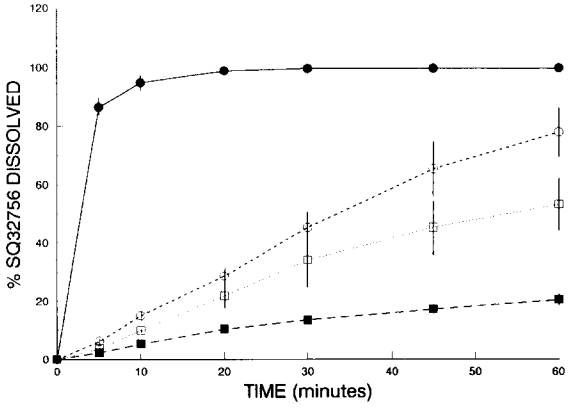

Fig. 1. Dissolution profiles of 40 mg potency SQ32756 capsules hand filled with granules overmixed with or without 1% w/w hydrophobic lubricant; (●) no lubricant, (○) calcium stearate, (□) zinc stearate, and (■) magnesium stearate. The bars represent the standard error of the mean ($n = 6$).

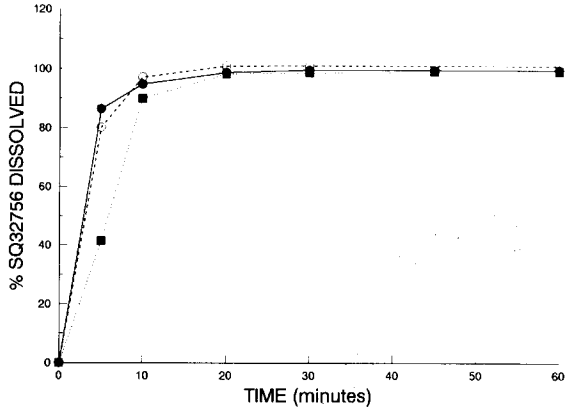

Fig. 2. Dissolution profiles of 40 mg potency SQ32756 capsules hand filled with granules overmixed with or without 1% w/w hydrophilic lubricant; (●) no lubricant, (○) Stear-O-Wet®, and (■) sodium stearyl fumarate.

Among the three hydrophobic lubricants studied, magnesium stearate caused the maximum slow down in dissolution, followed by zinc and calcium stearate, respectively. This was correlated with the surface area measurements of the three hydrophobic stearates which were 8.0, 7.0, and 3.4 m^2/g for magnesium, zinc, and calcium stearate, respectively.

Replacement of a hydrophobic lubricant such as magnesium stearate by any hydrophilic lubricant such as Stear-O-Wet® or sodium stearyl fumarate did not slow down the dissolution of capsules containing the overmixed granules (Fig. 2), irrespective of the lubricants' surface area differences. The surface area measurements of the two hydrophilic stearates, Stear-O-Wet® and sodium stearyl fumarate were 4.3 and 3.8 m^2/g, respectively.

The data discussed above were on formulations containing 1% w/w lubricant. An effort was made to optimize the concentration of magnesium stearate in such a way that the concentration is enough to provide necessary lubrication for the capsulation process without adversely affecting dissolution of the capsules. For this purpose, as outlined in Materials and Methods, capsules were filled for 10 min. Then the machine was left on for 30 min without capsule filling during which time granules were constantly mixed in the capsule hopper. Next, there was a second

TABLE 4

Dissolution of 40 mg potency SQ32756 capsules containing 0.5% w / w magnesium stearate sampled at various time points during filling on the MG2 Futura

Sampling time:	Mean % of SQ32756 dissolved (% RSD)					
	5 min	10 min	20 min	30 min	45 min	60 min
Beginning of capsule filling run						
Beginning of 1st 10 min, filling run	50.3 (9.4)	96.3 (1.6)	101.0 (1.0)	101.3 (0.6)	101.8 (0.6)	101.9 (0.5)
End of 1st 10 min filling run	46.3 (32.7)	98.7 (2.1)	102.0 (1.0)	102.3 (1.1)	103.0 (1.0)	103.3 (0.6)
Machine was left on for 30 min without capsule filling						
Middle of 2nd 10 min filling run	21.0 (33.3)	72.0 (8.3)	98.7 (2.6)	99.3 (2.1)	100.0 (1.7)	100.0 (1.7)
End of 2nd 10 min filling run	19.7 (38.1)	55.6 (21.7)	98.5 (4.2)	100.8 (1.5)	101.4 (1.1)	101.5 (1.1)
Machine was left on for 60 min without capsule filling						
Beginning of 3rd 10 min filling run	17.0 (33.3)	40.5 (61.1)	65.9 (14.1)	74.5 (10.4)	81.5 (7.8)	86.5 (7.4)
End of 3rd 10 min filling run	10.1 (15.8)	20.8 (12.4)	45.5 (33.0)	77.1 (39.1)	84.3 (27.3)	94.0 (8.4)

10 min filling run followed by another 60 min during which the machine was left on. Following that there was a third 10 min filling run. Capsules were tested for dissolution at the beginning and at the end of each filling run. As shown in Table 4, dissolution of capsules slowed down as the filling run progressed even when magnesium stearate was used at 0.5% w/w level. However, when magnesium stearate concentration was reduced to 0.25% w/w, there was no slowdown in capsule dissolution in as shown in Table 5. This low level of magnesium stearate provided sufficient lubrication for high speed capsule filling in the MG2 Futura without adversely affecting the dissolution due to overmixing of granules in the hopper. In another approach to overcome the problem, pregelatinized starch was replaced with either corn starch or super disintegrants such as Explotab® or Primojel®. Dissolution of capsules filled with granules containing either of these two super disintegrants did not slow down even when the granules were overmixed with 1% w/w magnesium stearate (Fig. 3). However, dissolution of capsules filled with granules containing corn starch or pregelatinized starch slowed down (Fig. 3). Based on the hypothesis of Proost et al. (1983),

TABLE 5

Dissolution of 40 mg potency SQ32756 capsules containing 0.25% w / w magnesium stearate sampled at various time points during filling on the MG2 Futura

Sampling time:	Mean % of SQ32756 dissolved (% RSD)					
	5 min	10 min	20 min	30 min	45 min	60 min
Beginning of capsule filling run						
Beginning of 1st 10 min filling run	91.3 (2.3)	98.3 (0.6)	100.3 (1.5)	100.7 (2.1)	100.6 (1.2)	–
End of 1st 10 min filling run	86.0 (3.1)	98.3 (1.6)	100.0 (1.7)	100.0 (1.7)	100.7 (2.3)	–
Machine was left on for 30 min without capsule filling						
Middle of 2nd 10 min filling run	72.7 (11.9)	98.3 (1.6)	100.0 (1.0)	100.3 (0.6)	100.3 (0.6)	–
End of 2nd 10 min filling run	80.7 (9.6)	99.0 (2.2)	101.3 (1.1)	101.7 (1.5)	102.0 (1.7)	–
Machine was left on for 60 min without capsule filling						
Beginning of 3rd 10 min filling run	54.0 (17.0)	95.7 (0.6)	98.7 (0.6)	99.3 (0.6)	99.3 (0.6)	–
End of 3rd 10 min filling run	49.0 (16.3)	96.3 (4.2)	99.3 (2.1)	100.0 (1.0)	100.2 (1.1)	–

the hydrophobic film of magnesium stearate does not envelop the granules completely, and therefore the swelling of super disintegrants is not inhibited once they come in contact with the dissolution medium. The highly swelling super disintegrants disrupt the surface structures of granules completely, allowing further penetration of the dissolution medium into the granules. Corn starch and pregelatinized starch lack the swelling capacity of super disintegrants to disrupt the hydrophobic film present around the granules. Further as shown in Fig. 3, granules containing pregelatinized starch showed greater decrease in the dissolution compared to corn starch. This can be explained by the fact that pregelatinized starch is a slightly better binder (Sheth et al., 1980) than corn starch.

As discussed above, the dissolution of granules filled into capsule shells is dependent on hydrophobic lubricant concentration, mixing time of granules with the hydrophobic lubricants, efficiency of the disintegrant, and solubility of the active ingredient in the dissolution medium. However, when the granules, which exhibited a decrease in dissolution rate, were compressed into tablets of various hardnesses, dissolution occurred rapidly in all instance. For example, dissolution of tablets compressed from granules of the three active ingredients, before their loading into the MG2 Futura capsule filler and after their overmixing with magnesium stearate in the hopper of the MG2 Futura capsule filler was indistinguishable (Table 6). Similarly, dissolution of tablets compressed from the granules overmixed with different hydrophobic lubricants was very rapid (Fig. 4) compared to the dissolution of the

TABLE 6

Dissolution of 40 mg potency tablets compressed from granules containing 1.0% w/w magnesium stearate sampled at various time points during capsule filling on the MG2 Futura

Drug and sampling time of granules used for compression	Tablet hardness (scu)	Mean % of drug dissolved (% RSD)					
		5 min	10 min	20 min	30 min	45 min	60 min
Hydrochlorothiazide							
Beginning of capsule filling run	8	82.9 (1.1)	91.5 (0.5)	93.4 (0.4)	93.4 (0.4)	93.5 (0.4)	93.5 (0.4)
	17	71.0 (1.9)	90.7 (0.2)	95.5 (0.3)	95.7 (0.3)	95.7 (0.3)	95.7 (0.3)
End of 30 min capsule filling run	6– 7	86.6 (1.1)	95.1 (1.2)	97.1 (0.8)	97.2 (0.8)	97.3 (0.8)	97.4 (0.8)
	11–12	74.6 (6.7)	95.2 (1.2)	98.0 (0.6)	98.1 (0.6)	98.2 (0.6)	98.2 (0.6)
SQ32756							
Beginning of capsule filling run	16	68.0 (1.3)	96.0 (0.3)	97.4 (0.4)	97.6 (0.4)	97.7 (0.5)	97.7 (0.4)
End of 30 min capsule filling run	10	90.4 (1.8)	95.5 (1.4)	96.1 (1.5)	96.1 (1.5)	96.2 (1.4)	96.3 (1.4)
Aztreonam							
Beginning of capsule filling run	5	94.8 (0.5)	96.4 (0.4)	96.5 (0.2)	96.5 (0.2)	96.5 (0.2)	96.5 (0.2)
	13	93.3 (1.0)	95.4 (0.5)	95.4 (0.5)	95.4 (0.4)	95.4 (0.5)	95.4 (0.5)
End of 30 min capsule filling run	6	96.2 (0.4)	96.2 (0.6)	96.8 (0.4)	96.8 (0.4)	96.8 (0.4)	96.8 (0.4)
	12	95.5 (0.2)	95.5 (0.2)	95.5 (0.2)	95.5 (0.2)	95.5 (0.2)	95.5 (0.2)

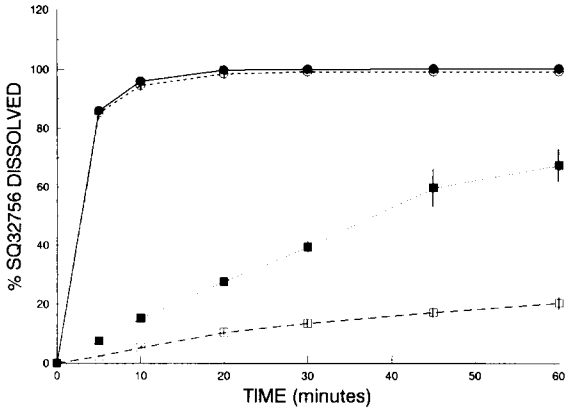

Fig. 3. Dissolution profiles of 40 mg potency SQ32756 capsules hand filled with granules containing either (●) Primojel®, (○) Explotab®, (■) corn starch, or (□) pregelatinized starch. The bars represent the standard error of the mean ($n = 6$). These granules were overmixed with 1% w/w magnesium stearate.

capsules containing the same granules (Fig. 1). This trend was further witnessed in the dissolution of SQ32756 tablets compressed from overmixed granules containing different disintegrants (Figs 5 and 3).

Based on these observations, it was clear that by compression of granules into tablets, the effects of overmixing of granules with hydrophobic lubricants could be overcome. As mentioned earlier in the discussion, a lubricant film is formed

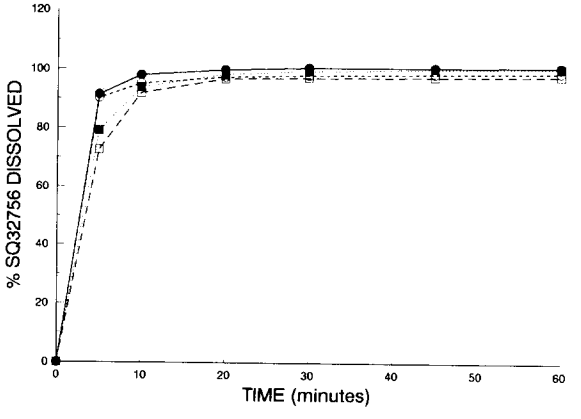

Fig. 4. Dissolution profiles of 40 mg potency SQ32756 tablets compressed from granules were overmixed with 1% w/w hydrophobic lubricant; (○) calcium stearate, (□) zinc stearate, or (■) magnesium stearate.

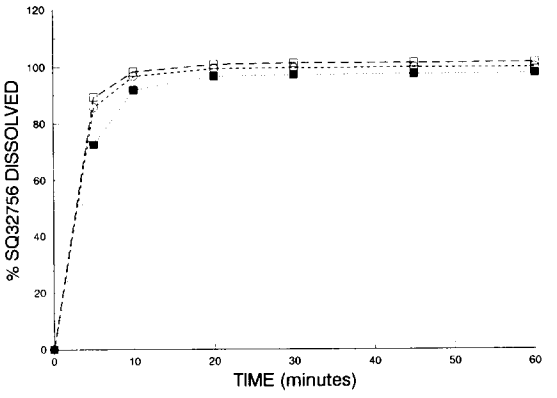

Fig. 5. Dissolution profiles of 40 mg potency SQ32756 tablets compressed from granules containing either (●) Primojel®, (○) Explotab®, (■) corn starch, or (□) pregelatinized starch. These granules were overmixed with 1% w/w magnesium stearate.

around the granules due to overmixing (Bolhuis et al., 1975). The hydrophobic nature of the film slows down the dissolution of granules. However, during compression, the film is disrupted and the granules are fragmented (De Boer et al., 1978). As a result of the fragmentation, new, fresh, uncoated surfaces are formed (Duberg and Nyström, 1982) whose dissolution remains unimpeded. Lactose, which was used as a diluent in the formulations, demonstrates a high degree of fragmentation following its compression (Duberg and Nyström, 1982). On the other hand, the other two ingredients of the formulation, microcrystalline cellulose and pregelatinized starch, do not fragment extensively (Bolhuis et al., 1975). Since lactose constituted significant percentages of the formulation, its extensive fragmentation provided new, uncoated surfaces. Moreover, the active ingredients are also expected to undergo some fragmentation.

Conclusions

Overmixing of granules with a hydrophobic lubricant in a hopper of a capsule machine can slow down their dissolution because of coating with a hydrophobic film of the lubricant. The extent of slowdown was maximum for the active ingredient with the lowest solubility in the disso-

lution medium. The extent of slowdown was dependent on concentration and surface area of the hydrophobic lubricants. The decrease in the dissolution rate can be overcome by using a high swelling capacity disintegrant in the formulation. Alternatively, the lubricant concentration can be optimized to levels sufficient enough to provide necessary lubrication for the capsulation process without adversely affecting dissolution. Furthermore, compression of granules exhibiting slow dissolution into tablets can result in rapid dissolution in all instances. This was probably due to fragmentation of lubricant coated granules following their compression, resulting in surfaces whose dissolution remained unimpeded.

References

Bolhuis, G., Lerk, C., Zijlstra, H. and De Boer, I., Film formation by magnesium stearate during mixing and its effect on tabletting. *Pharm. Weekbl.*, 100 (1975) 317–325.

Bolhuis, G., De Jong, S. and Lerk, C., The effect of magnesium stearate admixing in different types of laboratory and industrial mixers on tablet crushing strength. *Drug Dev. Ind. Pharm.*, 13 (1987) 1547–1567.

Dahl, T., Sue, I. and Yum, A., The influence of disintegrant level and capsule size on dissolution of hard gelatin capsules size on dissolution of hard gelatin capsules stored in high humidity conditions. *Drug. Dev. Ind. Pharm.*, 17 (1991) 1001–1016.

De Boer, A., Bolhuis, G. and Lerk, C., Bonding characteristics by scanning electron microscopy of powders mixed with magnesium stearate. *Powder Technol.*, 20 (1978) 75–82.

Duberg, M. and Nyström, C., Studies of direct compression tablets. VI: Evaluation of methods for the estimation of particle fragmentation during compaction. *Acta, Pharm. Suec.*, 19 (1982) 421–436.

Jarosz, P. and Parrott, E., Effect of lubricants on tensile strength of tablets. *Drug. Dev. Ind. Pharm.*, 10 (1984) 259–273.

Johansen, H., Andersen, I. and Leedgaard, H., Segregation and continued mixing in an automatic capsule filling machine. *Drug. Dev. Ind. Pharm.*, 15 (1989) 477–488.

Mitrevej, K.T. and Augsburger, L.L., Adhesion of tablets in a rotery press. II: Effects of blending time, and lubricant concentrations. *Drug. Dev. Ind. Pharm.*, 8 (1982) 237–282.

Proost, J., Bolhuis, G. and Lerk, C., The effect of the swelling capacity of disintegrants on the in vitro and in vivo availability of diazepam tablets, containing magnesium stearate as a lubricant. *Int. J. Pharm.*, 13 (1983) 287–296.

Sheth, B., Bandelin, F. and Shangraw, R., Compressed tablets. In Lieberman H. and Lachman, L. (Eds), *Pharmaceutical Dosage Forms: Tablets*, Vol. 1, Dekker, New York, 1980, pp. 124–125.