DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 20(3), 343-355 (1994)

EFFECT OF MIXING TIME ON THE LUBRICATING PROPERTIES OF MAGNESIUM STEARATE AND THE FINAL CHARACTERISTICS OF THE COMPRESSED TABLETS

Jun-ichi Kikuta* and Nobuyuki Kitamori

Pharmaceutical Development Laboratories,
Takeda Chemical Industries, Ltd.
17-85, Juso-honmachi 2-chome, Yodogawa-ku,
Osaka 532 Japan

SUMMARY

The effect of mixing time on hardness, disintegration time and ejection force in tabletting of magnesium stearate and lactose granules was studied. The hardness of the tablets decreased with an increase in mixing time of the blends, as previously reported. A semilogarithmic plot of the hardness versus mixing time gave a straight line having a turning point. At the early phase of mixing the hardness was decreasing with a large first-order rate and then continued to decrease with another small first-order rate. The change in disintegration time or ejection force versus mixing time was basically the same as that in the hardness. This type of plot was applicable to the mixing magnesium stearate with not only granular but also powdered materials.

* To whom correspondence should be addressed.

In laboratory and industrial blending operations, second phase of mixing time should be selected, where the rates of change in characteristics of tablets will be small between batches.

INTRODUCTION

Magnesium stearate is widely used in tablet formulations as a lubricant. The primary function of tablet lubricants is to reduce friction between granules or powders and the die wall during compression and ejection cycles. Lubricants in tablet formulations are, however, known to decrease in the strength and to increase in disintegration time of tablets, due to their hydrophobic properties. The amount of lubricants to be used and the process of lubricant mixing could be a problem associated with magnesium stearate in tablet formulation.

In laboratory and industrial blending operations, the effective use of the proper quantities of lubricants and the homogeneous distribution of lubricants by mixing must be necessary to achieve the stable production of compressed tablets. On the other hand, an excess amount of lubricants or overmixing leads to the nonpredicted increase in disintegration time and the decrease in hardness of compressed tablets.

The effect of the amount of lubricants on the properties of compressed tablets have been reported by many authors. Little information is, however, presented on the effect of the lubricant mixing on the properties of tablets. Particularly, it appears that little attention has been paid to the mixing of magnesium stearate with granular materials.

In the present work, the effect of the amount of the lubricant and of the degree of mixing on the physical properties of the resultant compressed tablets and on ejection of tablets was investigated.

MATERIALS AND METHODS

Materials

Magnesium stearate (Sakai Kagaku Ltd., Japan) and lactose granules were used. The granules were prepared by massing lactose

Table 1 Particle size distribution of lactose granules measured by sieving

Sieve size (μ m)	Cumulative percentage oversize
590	8.3
350	26.3
177	42.1
105	76.7
77	91.8

powder (D.M.V., Holland) with 16.7% starch paste (3% by weight of a dry base), drying and sieving. The size distribution of the lactose granules used is shown in Table 1.

Procedure

Mixing operations were performed in a 5-litre stainless steel twinshell V-shape mixer (Patterson-Kelly Co., USA) at 35rpm. One kilogram of the lactose granules was transferred into the mixer and then a weighed amount of lubricant was added to the bed of the granules. About 7 grams each of blended mixtures were collected from five points in the bed of the blend in the mixer at known time intervals during mixing.

The mixtures were then compressed into tablets on a physical testing instrument (Autograph IS-5000, Shimadzu Seisakusho Ltd., Japan) using a 10 mm diameter flat-faced punch and die assembly at a compression pressure of 1500 kg/cm^2. The die wall was cleaned with a metal polisher and paper tissues between each tablet. Each tablet weighing 400mg was compressed at a constant strain rate of 50 mm/min and ejected from the die at the same strain rate. Ten tablets were compressed from each mixture collected from five points at each time.

The diametral crushing strength (hardness) of the tablets was measured using a motorized Heberlein hardness tester. Measurements for five out of ten tablets for each sample, from five points of the bed, were carried out for each sampling time and to obtain a mean value ($\bar{X}$). Therefore, 25 measurements were carried out at a time and the total mean value ($\bar{X}$) and the variance F-value in a completely randomized design with repetition as a factor of the sampling point was calculated.

The disintegration time for the tablets in distilled water was measured according to the JP method without discs. Five tablets were measured from the ten tablets and the mean value calculated. The data obtained were treated in the same way as the hardness.

The ejection forces were measured by recording the maximum force required to eject the tablet from the die. Five successive measurements with each sample from five points of the bed were carried out in the die without cleaning each time according to the previous report (Kikuta and Kitamori, 1983). The mean value ($\bar{X}$) and F-value were calculated.

RESULTS AND DISCUSSION

The results of hardness, disintegration time and ejection force for the blending of lactose granules containing 0.1, 0.3 and 0.5% magnesium stearate are summarized in Table 2.

Fig.1 shows the effect of mixing time on the hardness of tablets compressed from the blends of lactose granules with 0.3% magnesium stearate. The hardness of resultant tablets decreases gradually.

Fig.2 shows a semilogarithmic plot of hardness data shown in Fig.1, together with the results at other lubricant levels (0.1 and 0.5%). Two straight lines were obtained in each case. This result means that two apparent first-order processes for the change of hardness of resultant tablets may exist during the mixing of lactose granules with lubricant. Although both processes are first-order, the mechanism involved would be different. It can also be seen that each turning point, the time at which the slope of the line changes, is similar to, regardless of the lubricant level in the blended mixtures.

Bolhuis et al. (1975) reported firstly that the degree of mixing of particulate solids with magnesium stearate can greatly reduce the strength of the resulting tablets. This phenomenon is caused by

Table 2 Effect of mixing of lactose granules with magnesium stearate on hardness, disintegration time and ejection force of tablets

Mixing time (min)	Hardness (kg)		Disintegration time (min)		Ejection force (kg)	
0.1 % Magnesium stearate						
	mean($\bar{X}$)	F-value	mean($\bar{X}$)	F-value	mean($\bar{X}$)	F-value
0.17	12.8	0.20	6.5	1.08	26.8	2.65
0.5	12.5	0.87	6.5	8.56**	26.3	1.91
1	12.2	0.86	6.9	0.37	24.3	0.99
2	11.3	15.35**	7.4	2.25	21.0	1.45
3	11.1	0.38	7.6	1.08	21.0	0.82
5	10.4	3.77	8.6	3.83	19.6	0.79
10	9.8	12.10**	10.5	15.43**	17.8	2.08
20	9.1	2.07	20.3	1.41	16.8	1.91
30	9.0	5.15*	23.1	1.87	17.0	2.16
0.3 % Magnesium stearate						
Mixing time (min)	Hardness (kg)		Disintegration time (min)		Ejection force (kg)	
	mean($\bar{X}$)	F-value	mean($\bar{X}$)	F-value	mean($\bar{X}$)	F-value
0.17	12.2	7.46	14.8	68.75	13.2	3.13
0.5	11.9	5.29	14.6	8.21	13.1	2.88
1	11.7	18.79	14.0	1.54	12.4	0.35
2	10.7	6.79	19.9	0.62	11.6	1.11
3	10.6	3.73	19.5	5.69	11.4	0.95
5	10.5	0.67	25.0	5.80	10.2	0.75
10	9.7	9.95	45.3	2.74	10.4	1.72
20	9.1	6.97	52.8	4.41	9.6	0.64
30	8.9	4.20	64.1	4.90	10.1	0.86
0.5 % Magnesium stearate						
Mixing time (min)	Hardness (kg)		Disintegration time (min)		Ejection force (kg)	
	mean($\bar{X}$)	F-value	mean($\bar{X}$)	F-value	mean($\bar{X}$)	F-value
0.17	12.3	3.36	22.4	0.47	9.0	0.79
0.5	11.8	2.62	26.9	12.8**	8.8	0.24
1	11.0	2.85	28.2	1.1	8.3	0.17
2	10.0	1.36	31.8	7.3**	8.2	0.06
3	9.3	1.43	38.8	2.5	7.9	0.26
5	9.2	1.58	51.6	5.5*	7.8	0.24
10	8.7	4.80*	59.8	1.2	7.7	0.35
20	7.8	1.72	76.5	0.04	7.3	0.14
30	7.7	0.80	88.9	3.2	7.2	0.50

* : P<0.05, ** : P<0.01

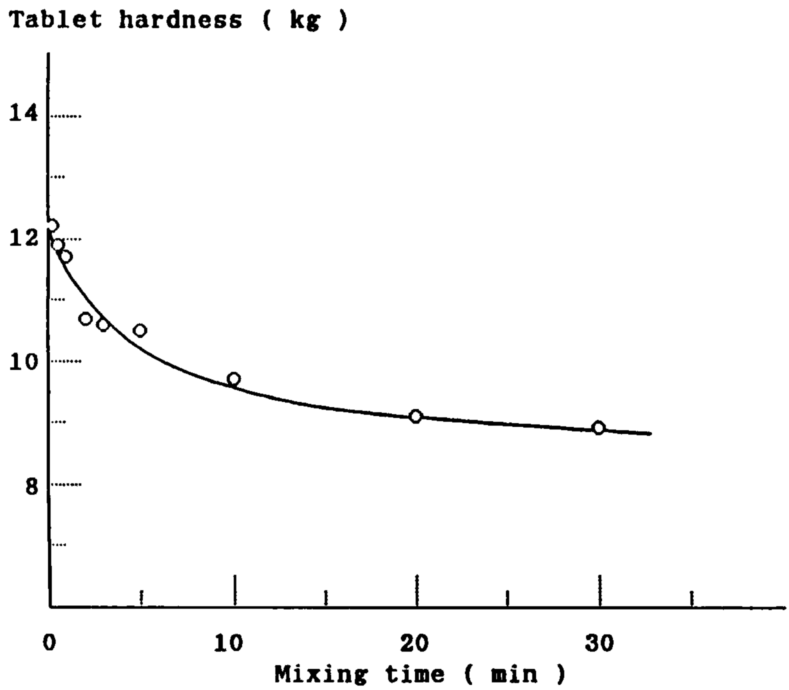

Fig.1 Effect of mixing time on the hardness of tablets compressed with 0.3% magnesium stearate

the formation of a lubricant film upon the substrate as a result of the adhesion of magnesium stearate layers to the substrate surface. The same phenomenon was also reported thereafter by other investigators (Shah and Mlodozeniec, 1977; Lerk et al., 1977; Ragnarson et al., 1979; Kahn et al., 1983).

Shah and Mlodozeniec (1977) assumed that the lubricant mixing is essentially a single three-dimensional shuffling operation. They described a two-step mechanism: during the mixing process lubricant particles are first adsorbed on the surface and then distributed uniformly upon the granules surface, the breaking of these lubricant particles by delamination or deaggregation may take place. Fig.2 clearly shows that there should be two mechanism in the lubricant mixing process. The first process of a rapid decrease in hardness would correspond to the adsorption process described by

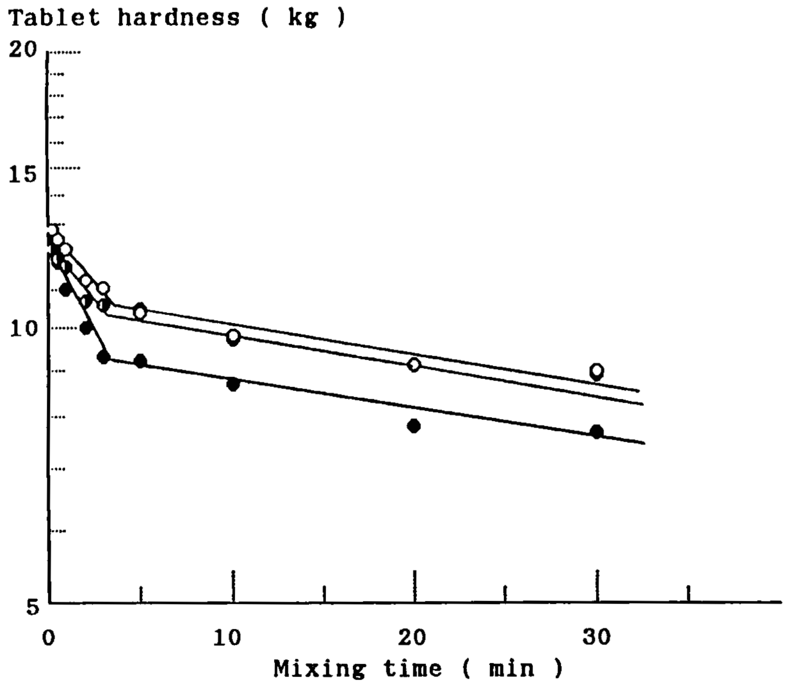

Fig.2 Semilogarithmic relationship of the tablet hardness
Key ; magnesium stearate 0.1%(○),0.3%(◑) and 0.5%(●)

Shah and Mlodozeniec (1977). In the relatively short mixing time, the uniform distribution of the aggregate particles of magnesium stearate would be realized. From the microscopic point of view, lubricants have not distributed uniformly by this stage, whereas macroscopically uniform distribution has already been achieved as a result of the adhesion of magnesium stearate to substrate particles or distribution of lubricants. Shah and Mlodozeniec (1977) also reported that the magnesium stearate content in the tablets by elemental analysis was reasonably uniform even after a short mixing time. This fact corresponds fairly well to the hypothesis in which aggregated magnesium stearate particles may be distributed uniformly even after short mixing time.

Fig.3 shows the relationship between the ejection force and mixing time. This relationship was basically the same as that

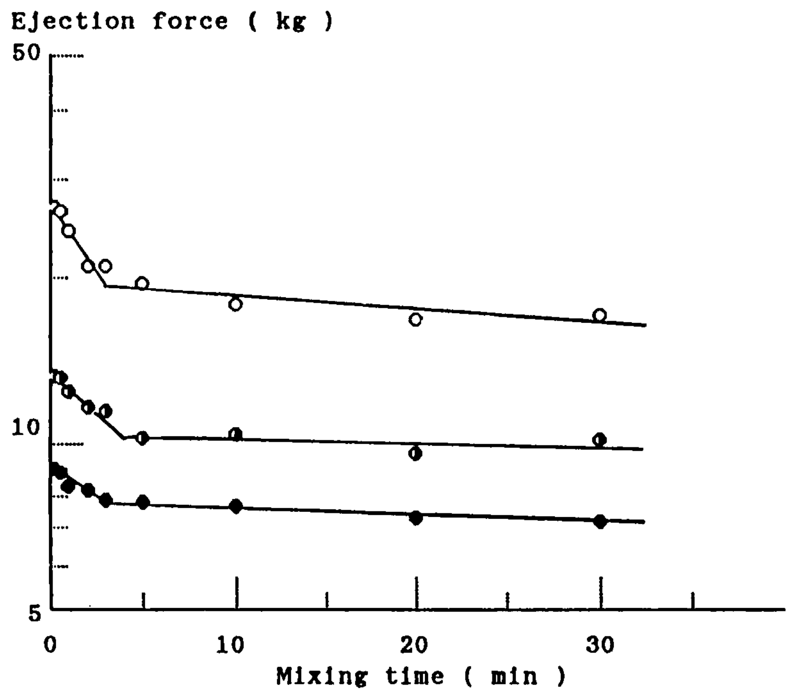

Fig.3 Semilogarithmic relationship of the ejection force
Key ; magnesium stearate 0.1%(○),0.3%(◑) and 0.5%(●)

between hardness and mixing time. It can be seen that the ejection force has already decreased even after short mixing time. The fact corresponds well to the description by Ragnarson et al. (1979) that magnesium stearate gives sufficient lubrication even when poorly distributed.

Fig.4 shows the relationship between disintegration time and mixing time. The rapid prolongation of disintegration time was observed in early stage of mixing and then continued to increase gradually thereafter. The change in disintegration time with mixing time was basically the same as that for the hardness, but the pattern was somewhat different. A semilogarithmic plot of disintegration time also gave two intersecting straight line. The time at which the slope of the line changes was slightly longer than

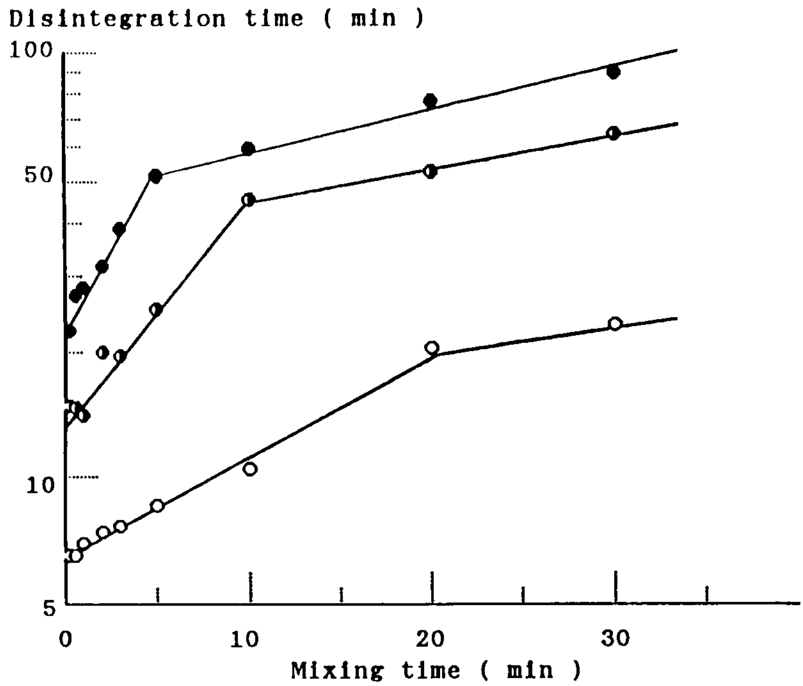

Fig.4 Semilogarithmic relationship of the disintegration time
Key ; magnesium stearate 0.1%(○),0.3%(◑) and 0.5%(●)

that in the hardness, and also was longer as the amount of lubricant added decreased. Disintegration time would depend on the average wettability of tablet matrix, that is microscopic distribution of hydrophobic lubricant. From this point the pattern of disintegration time change may differ from that of the hardness which depends on the macroscopic distribution of lubricants. In the early stage of mixing disintegration time clearly increases, but it is rather important to note that the values are scattered. It should be noted that since the hardness decreases with prolonged mixing time, the larger compression force could be needed with prolonged mixing time to obtain a constant hardness. Therefore, a change in disintegration time will be more severe for tablets having a constant hardness than for tablets compressed at a constant pressure.

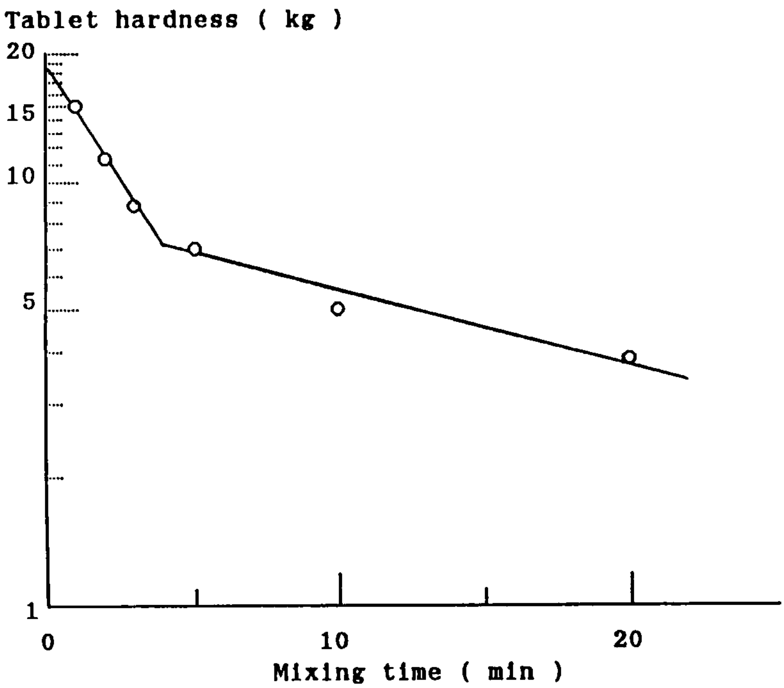

Fig.5 Semilogarithmic relationship of the tablet hardness from the data by Bolhuis et al.(1975)

As mentioned above, the steep decrease in the hardness at early stage of mixing should mean that aggregated magnesium stearate distributes by the shear force during mixing and interrupts the bonding between particles due to the formation of a lubricant barrier. In the second phase primary magnesium stearate particles should gradually be sheared off from the distributed aggregates during the mixing process. The two-step mechanism described here, is not limited in the case of blending of granular materials with magnesium stearate. In the mixing of powdered materials with magnesium stearate the similar mechanism can also be postulated. For example, semilogarithmic plots of data in the papers by Bolhuis et al. (1975), Shah and Mlodozeniec (1977) and Khan et al. (1983) are shown in Figs.5, 6 and 7, respectively. These figures clearly shows that the same type of plot results for the relationship between hardness and mixing time. It is interesting to note that the rate of

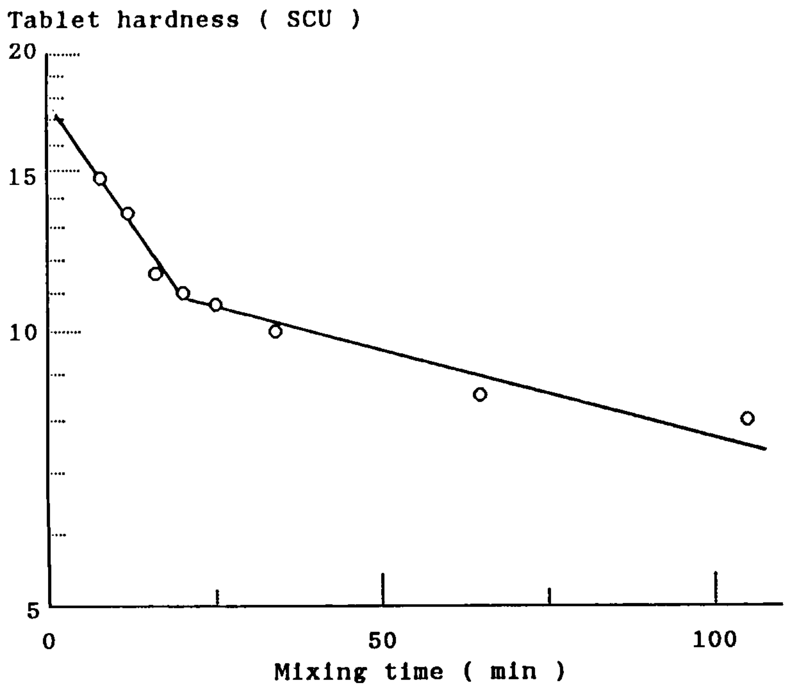

Fig.6 Semilogarithmic relationship of the tablet hardness from the data by Shah and Mlodozeniec (1977)

decrease in the hardness in the mixing of powdered materials with magnesium stearate is larger than in the mixing of granular materials with magnesium stearate. This would be caused that some new lubricant-free surfaces are created when the granular materials are compressed, whereas in powder compression clean and effective surfaces to adhere to are not formed, so that the surface coverage of particles with magnesium stearate will severely affect the tablet hardness.

The degree or rate of lubricant distribution during the mixing operation may depend on not only the specific surface area (or size distribution) of the substrates, but also the batches of magnesium stearate (Frattini and Simioni, 1984; Hussain et al, 1988). Blending efficiency may also be affected by mixing time, the scale and the type of mixer used (Bossert and Stamm, 1980). In view of the similar

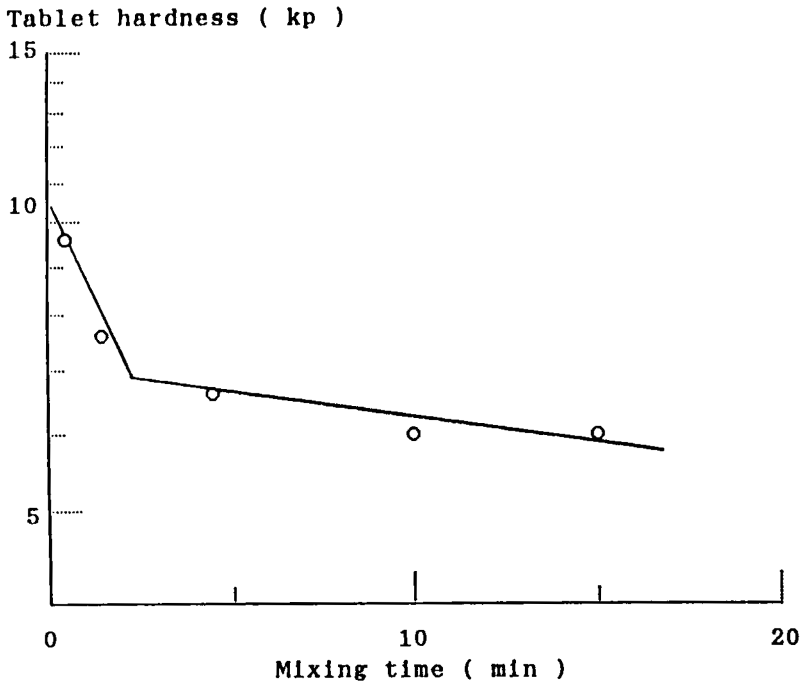

Fig.7 Semilogarithmic relationship of the tablet hardness from the data by Kahn et al.(1983)

conditions in both laboratory and industrial blending operations, too short mixing time, at which unexpected change in characteristics of resultant tablets may occur between batches should be avoided. Further study on the problem described in this paper will be needed.

REFERENCES

Bolhuis,G.K., Lerk,C.F., Zijlstra,H.T. and De Boer,A.H., "Film formation by magnesium stearate during mixing and its effect on tabletting. " Pharm.Weekbl., 110, 317-325 (1975).

Bossert,J. and Stamm,A., " Effect of mixing on the lubricant of crystalline lactose by magnesium stearate. " Drug Dev.Ind.Pharm., 6, 573-589 (1980).

Frattini,C. and Simioni,L., " Should magnesium stearate be assessed in the formulation of solid dosage forms by weight or by surface area ? " Drug Dev.Ind.Pharm., 10, 1117-1130 (1984).

Kahn,K.A., Musikabhumma,P. and Rubinstein,M.H., " The effect of mixing time of magnesium stearate on the tabletting properties of dried microcrystalline cellulose. " Pharm.Acta Helv., 58, 109-111 (1983).

Lerk,C.F., Bolhuis,G.K. and Smedema,S.S., " Interaction of lubricants and colloidal silica during mixing with excipients I. Its effect on tabletting. " Pharm.Acta Helv., 52, 33-39 (1977).

Ragnarson,G., Holzer,A.W. and Sjogren,J., " The influence of mixing time and colloidal silica on the lubricating properties of magnesium stearate. " Int.J.Pharm., 3, 127-131 (1979).

Shah,A.C. and Mlodozeniec,A.R., " Mechanism of surface lubrication : Influence of lubricant - excipient mixing on processing characteristics of powders and properties of compressed tablets. " J.Pharm.Sci., 66, 1377-1382 (1977).

Hussain,M.S.H., York,P. and Timmins,P., " A study of the formation of magnesium stearate film on sodium chloride using energy-dispersive X-ray analysis. " Int.J.Pharm., 42, 89-95 (1988)

Kikuta,J. and Kitamori,N., " Evaluation of the die wall friction during tablet ejection. " Powder Technol., 35, 195-200 (1983).