DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 10(7), 1117-1130 (1984)

SHOULD MAGNESIUM STEARATE BE ASSESSED IN THE FORMULATION OF SOLID DOSAGE FORMS BY WEIGHT OR BY SURFACE AREA ?

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ABSTRACT

Three batches of magnesium stearate differing in morphology, particle size, bulk density and specific surface area were compared in the preparation of Pyrazinamide direct compression tablets. When the lubricants were used in the same amount they gave rise to tablets differing in hardness, disintegration and dissolution. When they were used in such amounts to develop equivalent lubricating areas, the final characteristics of the tablets were almost identical. A direct correlation was found between lubricating areas and ejection force.

INTRODUCTION

In spite of the variety of lubricants classified in the specialized books, magnesium stearate is the most commonly used in both capsule and tablet formulations. In fact, it is the most effective agent in reducing friction between particles and the die wall surface during compression (1). Unfortunately magnesium stearate has many draw-

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backs that can affect the physical, mechanical and biopharmaceutical characteristics of capsules and tablets (2-5). In fact it does not have a well defined chemical nature (6), it may present variable morphology and is highly hydrophobic (7-9).
The mechanism of action of magnesium stearate is explained in terms of the formation of a lubricant film around the substrate surfaces (10-13). This means that not only the initial physico-chemical characteristics of magnesium stearate are important but also its amount. In fact there should be a relationship between the amount used and the surface area developed or between the particle size and surface area. Holzer studied the effect of twelve batches of magnesium stearate having different surface area (14). He found that there was a direct relationship between the specific surface area and the disintegration time of tablets.
In spite of the evidence of the influence of both physico-chemical characteristics and specific surface area developed, the Official Compendia requirements for magnesium stearate are still based on chemical specifications only.
Since we deem it insufficient and incorrect to express the amount of magnesium stearate in a formula by weight, we compared the effect of three batches of magnesium stearate , having different specific surface areas, on the main characteristics of Pyrazinamide tablets. In one experiment the magnesium stearate from the three different batches was present in the three formulations in the same weight. In the other experiment the magnesium stearate was present in varying amounts in order to develop equivalent surface areas.

EXPERIMENTAL

Materials

The following materials were used :

- Pyrazinamide-J.P. grade (Sankyo Co.,Japan).
  particle size: V.M.D. = 54.6 μm ; σ g = 1.90317
  contact angle: 45° ± 1.3
- Corn starch - U.S.P. grade; moisture 8 % .
- Mg stearate type A - U.S.P. grade (Carlo Erba,Italy).
- Mg stearate type B - U.S.P. grade (Petrac,U.S.A.).
- Mg stearate type C - U.S.P. grade (Witco Co.,U.S.A.).

Methods

The morphology of magnesium stearate was assessed by scanning electron microscopy.
The particle size measurements were made by a H.I.A.C. mod. PC 320 equipped with a 1-60 um probe.
The surface area measurements were made by Quantasorb (Quantachrome) after conditioning the samples for twelve hours at room temperature.
Thermal analyses were made with a Du Pont 990 analyzer equipped with a differential scanning calorimetry cell (DSC) and a thermogravimetric analyzer (TGA).

Formulas studied in experiment one :

Product (%w/w)	I	II	III
Pyrazinamide	95.0	95.0	95.0
Corn starch	4.5	4.5	4.5
Mg stearate type A	0.5(a)	-	
Mg stearate type B	-	0.5(b)	-
Mg stearate type C	-	-	0.5(c)

(a) : equivalent to 17.5 cm^2
(b) : equivalent to 30.0 cm^2
(c) : equivalent to 91.5 cm^2

Formulas studied in experiment two :

Product (w/w)	IV	V	VI
Pyrazinamide	95.0	95.209	95.404
Corn starch	4.5	4.500	4.500
Mg stearate type A	0.5[(a)]	--	--
Mg stearate type B	-	0.291[(d)]	--
Mg stearate type C	-	--	0.096[(e)]

(a);(d);(e) : equivalent to 17.5 cm^2

Preparation of the mixtures for the direct compression : the powders were passed through a no. 80 A.S.T.M. sieve and mixed in a cube mixer for ten minutes. The mixing time was chosen after having checked the minimum time needed for the uniform distribution of magnesium stearate in the mixture assuming that at this point a uniform film of magnesium stearate was obtained. It is well known that the mixing time may be critical since an insufficient mixing may produce a surface area smaller than the potential one. On the other hand , an excessive mixing time may produce an increase of the potential surface area due to delamination (15-17).
The evaluation of the end point of the spreading of the magnesium stearate on Pyrazinamide during the mixing was evaluated by means of contact angle measurements. As shown in Fig. 1, the contact angle sharply increases up to a maximum in the first eight minutes, reaching a steady level that lasts not less than fifty minutes. Therefore, the mixing time chosen in the present study can be considered the minimum mixing time.

Preparation of tablets : the tablets were obtained on an instrumented single-punch machine (Korsh EK/0)

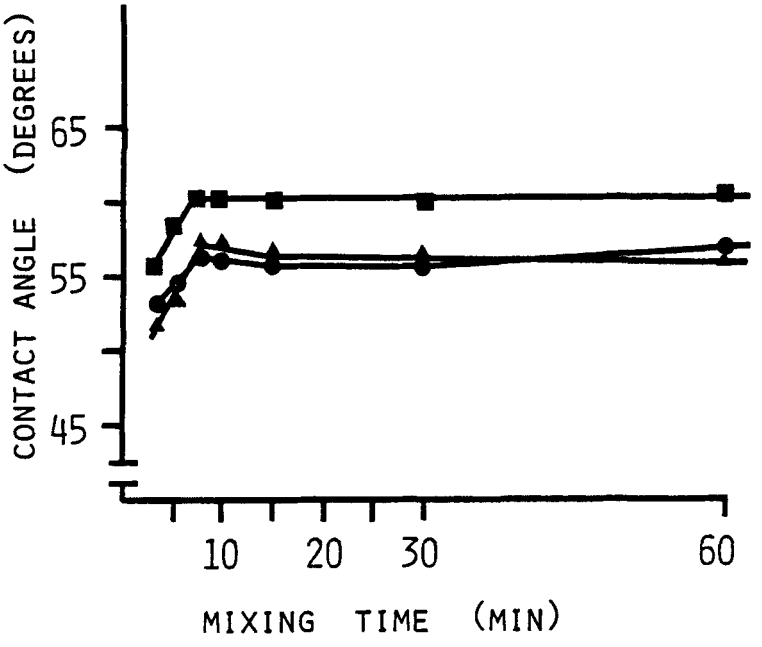

FIGURE 1

Effect of mixing time on the contact angle of Pyrazinamide-Mg stearate compacts.
Key : ● type A; ▲ type B; ■ type C.

equipped with a flat-faced 13 mm diameter punch, placed in a room at 38% R.H. . Each tablet was obtained by introducing 600 mg of mixture, accurately weighted, into the die. The applied force was kept constant at 1,450 kg cm^{-2}; the applied, transmitted and ejection forces were recorded on a U.V. recorder.

Hardness : the test was carried out on six tablets by a Schleuniger mod. 2E/205 hardness tester immediately after tabletting.

Disintegration : the test was carried out on six tablets following the U.S.P. directions.

Dissolution : the test described on page 236 of the U.S.P. XX, addendum 1982, was carried out on four tablets.

Contact angle measurements : the contact angle of the Pyrazinamide/magnesium stearate (99.5:0.5) mixtures was determined following the method of Mack (18).

RESULTS AND DISCUSSION

The physico-chemical characteristics of the three batches of magnesium stearate are summarized in table 1. Magnesium stearate type A differs from types B and C mainly for morphology, specific surface area and bulk density. Type B differs from C essentially in the specific surface area and the particle size. The lack of correlation between specific surface area and particle size may be due to the limits of the light blockage principle in particle size measurements (19) and to the particular morphology of the three batches of magnesium stearate. Infact type A may be characterized as agglomerates of rounded particles while type B and C as aggregates of thin flakes.

The lubricant efficiency was evaluated by means of the ejection force (20-22). As shown in figure 5, the same amount of magnesium stearate of different batches, produced statistically significant differences ($P=0.01$) in the ejection force. It is noteworthy that there is a inverse correlation between the ejection force and surface area.

Also the final characteristics of the tablets varied with the variation of the batch of magnesium stearate . In fact, as shown in figures 2, 3 and 4 , there is a good correlation between the surface area of magnesium stearate and hardness, disintegration and dissolution of the tablets. The relationship between the surface area and hardness is reverse. On the contrary, there is a direct relationship between the surface area and disintegration or dissolution. This is in agreement with the findings of some authors (9,15) who discovered that different sources of magnesium stearate produced tablets with varying characteristics. Our study confirms the findings of Holzer (14) who correlated the disintegration of the tablets with the surface area of the lubricant present in the formulation. Our work also shows the direct correla

TABLE 1

Physical properties of magnesium stearate.

Type	Particle shape* by SEM	Particle size (VMD) μm	Specific surface area $m^2\ g^{-1}$	Bulk density $g\ ml^{-1}$	Moisture %	Melting range °C
A	Modular	15.27	3.53	0.45	4.2	115-120
B	Flaky	16.19	6.02	0.25	3.4	115-120
C	Flaky	10.68	18.03	0.24	4.0	120-127

* for definitions see Glossary of Terms relating to powders from British Standard 2955.

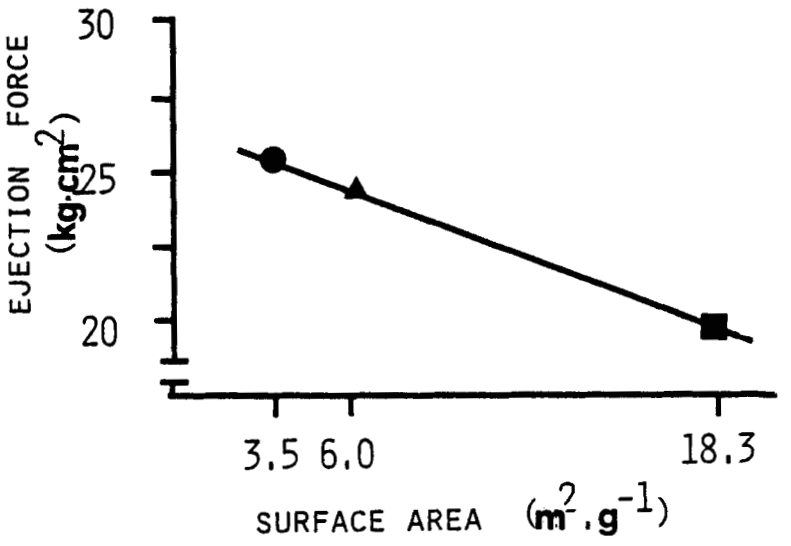

FIGURE 2

Influence of 0.5% (w/w) Mg stearate on the ejection force.
Key : ● type A; ▲ type B; ■ type C.

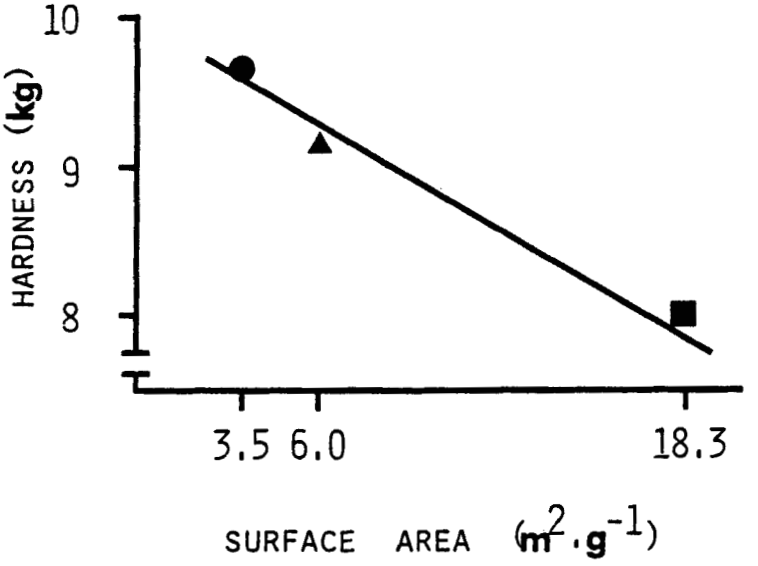

FIGURE 3

Influence of 0.5% (w/w) Mg stearate on the hardness.
Key : ● type A; ▲ type B; ■ type C.

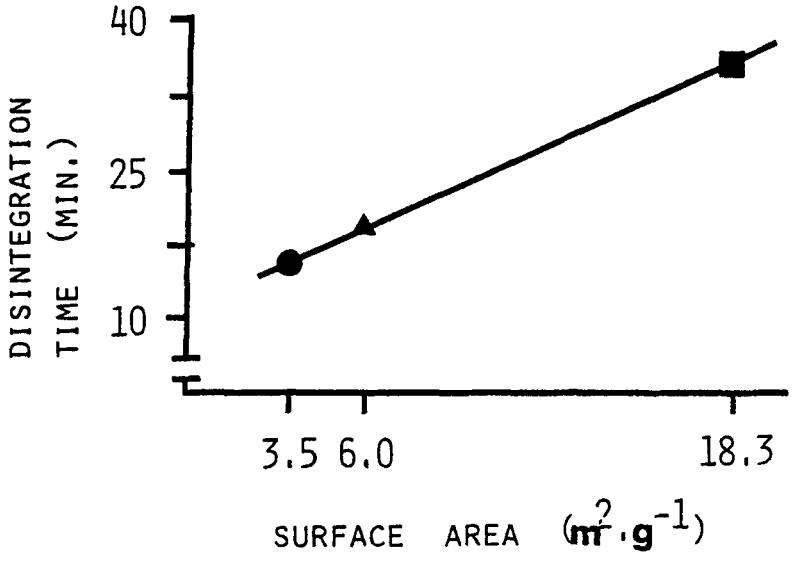

FIGURE 4

Influence of 0.5% (w/w) Mg stearate on the disintegration.
Key : ● type A; ▲ type B; ■ type C.

tion between the surface area and dissolution rate. In the second part of our study we investigated the effect of the above mentioned three batches of magnesium stearate present in the formula in such amounts to produce the same surface area. As shown in figures 6, 7, 8 and 9 the same surface area of lubricant produced tablets with the same final characteristics (the differences were not statistically significant; P = 0.05).

CONCLUSIONS

The present work shows that the different physical characteristics of magnesium stearate affect the ejection force, hardness, disintegration and dissolution of Pyrazinamide tablets. In fact, equal amounts of different batches produced relevant differences in the final characteristics of the tablets.

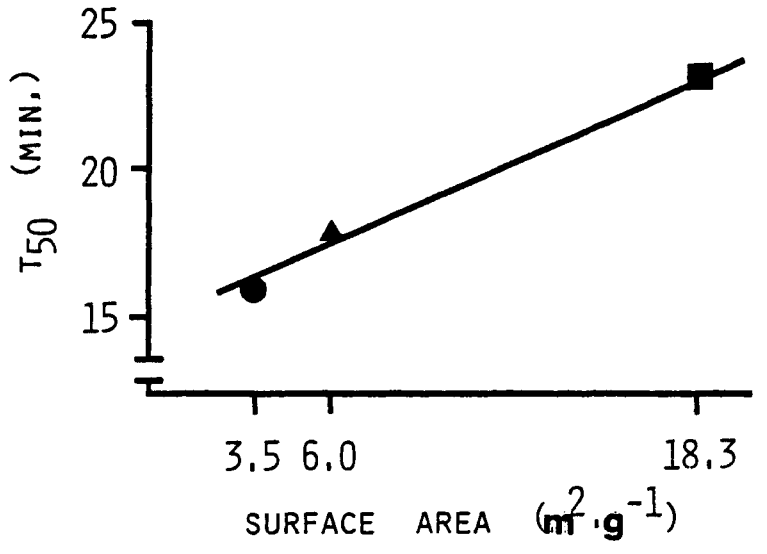

FIGURE 5

Influence of 0.5% (w/w) Mg stearate on the dissolution.
Key : ● type A; ▲ type B; ■ type C.

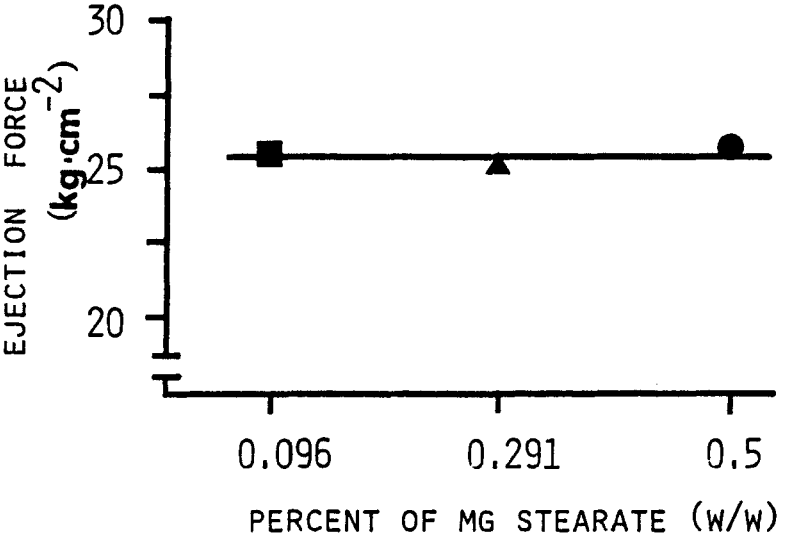

FIGURE 6

Influence of equivalent surface areas of Mg stearate on the ejection force.
Key : ● type A; ▲ type B; ■ type C.

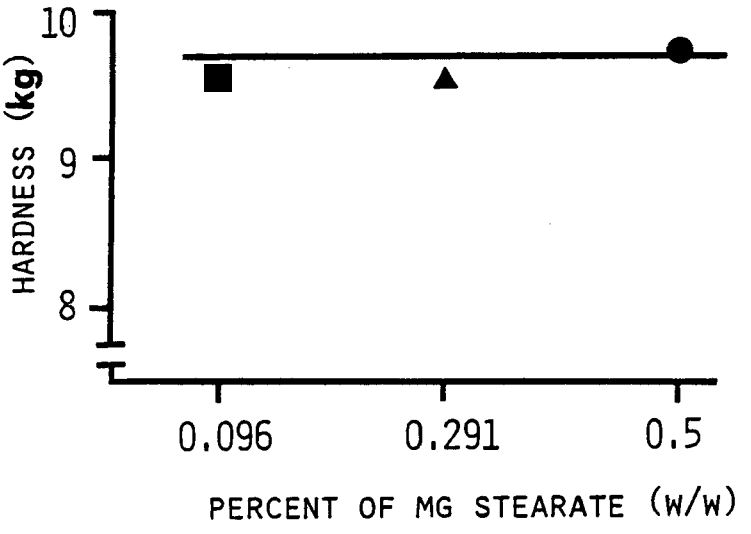

FIGURE 7

Influence of equivalent areas of Mg stearate on the hardness.
Key : ● type A; ▲ type B; ■ type C.

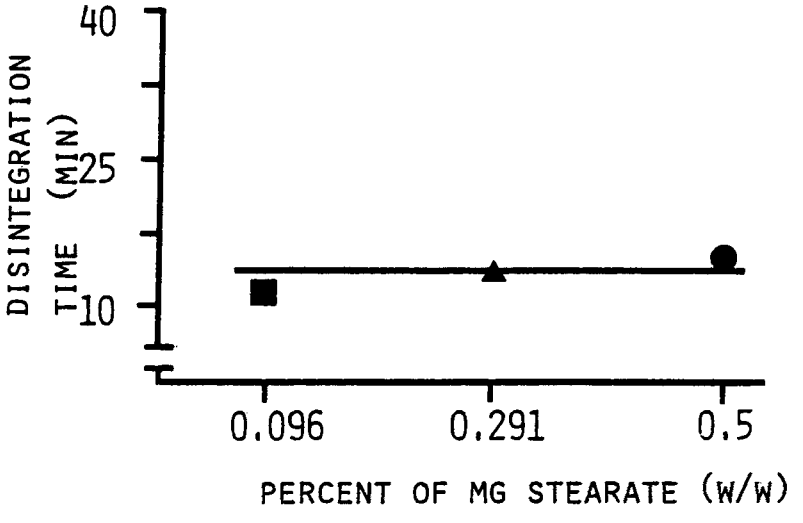

FIGURE 8

Influence of equivalent areas of Mg stearate on the disintegration time.
Key : ● type A; ▲ type B; ■ type C.

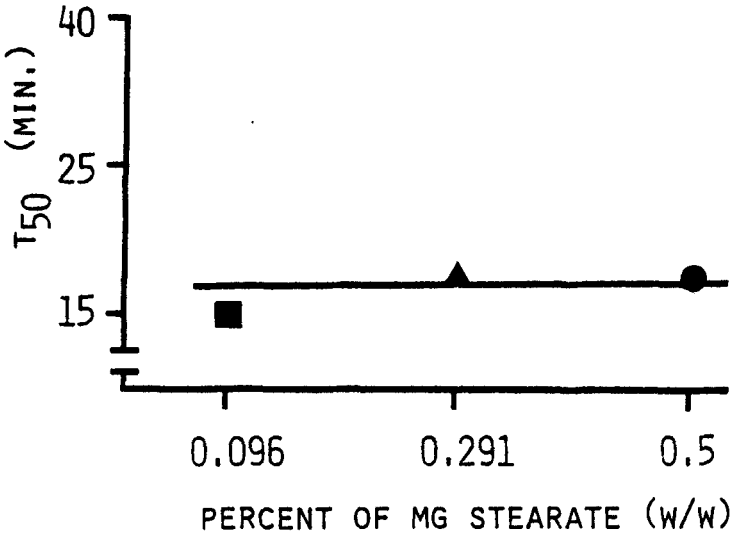

FIGURE 9

Influence of equivalent areas of Mg stearate on the dissolution rate.
Key : ● type A; ▲ type B; ■ type C.

Of the three batches of magnesium stearate used, one has totally different physical properties; the others differed essentially in the specific surface area. In spite of the different morphology and bulk density, when used in such an amount to develop the same lubricating area as the others, it produces tablets with almost identical characteristics. Therefore surface area seems to be the critical parameter.
If one considers that all the three batches studied in the present work complied with the Pharmacopoeias specifications, it can be concluded that the Official Compendia requirements are unsatisfactory.
Moreover, as in the present case, if 3 mg of type A magnesium stearate are equivalent to 0.57 mg of type C, what amount of magnesium stearate should be declared in the formula?
In our opinion magnesium stearate can be declared by weight only if well defined specifications of

the surface area are set. Otherwise constant weight of lubricant would not necessarily mean constant quality of the product.

ACKNOWLEDGEMENTS

The authors wish to express their thanks to M. Nebuloni for his analytical support.

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