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EFFECT OF MIXING ON THE LUBRICATION OF CRYSTALLINE LACTOSE BY MAGNESIUM STEARATE

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ABSTRACT

It is well known that magnesium stearate, used as tablet lubricant, can form a continuous hydrophobic film around solid particles when mixing times are too long, so that disintegration time increases and mechanical strength of tablets fails. It was also shown in previous works that the addition of colloïdal silicon dioxide is in some cases able to interrupt the lubricant film, and allows to recover the good tabletting properties of some mixtures.

This work studied the lubrication of crystalline lactose with magnesium stearate. A Turbula and a cubic mixer were used, and the properties of resulting tablets were studied on an excenter tablet press fitted out with strain gauges. It appeared that the hydrophobic film formation occurs after a very short time. This film formation depends not only of mixing time, but also of the speed of mixing and the kind of mixer used. In the studied case, the lubricant film could not completely be broken by addition of colloïdal silicon dioxide, and it seems not to be possible to produce good lactose tablets when the best mixing time has been exceeded.

Lactose is an interesting excipient at an economical point of view, but its tabletting is not without difficulties : it needs hight compression forces and it is always necessary to add a lubricant.

Recent publications [1-5] have reported what an important influence on tablettability the mixing of an excipient with a lubricant may have. A bad mixing procedure can induce weaker mechanical properties and longer disintegration time of tablets. This effect of the lubricant can be described by invoking at least three different mechanisms[4] :

- adsorption or surface contact adhesions ;
- diffusion or solids penetration, which includes mechanical interlocking ;
- delamination or deagglomeration of the lubricating agent to form a film coating on the substrate particles ; this film coating is usually discontinuous . Whichever mechanisms may be involved, the effect of mixing time should modify both glidant and lubricant roles of the agent.

This bad effects were reported for several products, but it seems that the degree of the effect depends of the kind of lubricant and the physical structure of the excipient : for example, the polytetrafluoethylene used as lubricant, seems not to induce bad properties to the mixture[3], and dicalcium phosphate dihydrate (ENCOMPRESS) seems to be an excipient which properties are not influenced badly by any lubricant [1,2]. The effect of the lubricant, especially of magnesium stearate, seems, according to De Boer, Bolhuis and Lerk[2] to be dependent on the compression behavior and the bonding mechanism of the excipient. These authors[2] make a difference beetween excipients which, under pressure, present a plastic deformation of particles followed by bonding of adjacent surfaces, and other excipients which consolidate by extensive fragmentation ; they reported several publications in which powders as potassium chloride or starch

were classified in the first category, and sucrose, lactose, or dicalcium phosphate dihydrate were included in the second.

For all these reasons the effect of a lubricant on the tabletting properties of an excipient are not undoubted, and often difficult to anticipate without further studies.

As a part of a study of tabletting of crystalline lactose[6,7], the effects of mixing of lactose with magnesium stearate were studied with more accuracy in this work.

MATERIALS AND METHODS

Materials used in the mixing study were crystalline lactose (H.M.S. - "extrafine crystals") which presents a mean particle size of 145 µm, magnesium stearate (Merck and colloidal silicon dioxyde (Degussa - "Aerosil 200").

Mixing operations were performed either in a TURBULA 2A mixer, which has a 2 liters capacity, or in an ERWEKA KB 15 VG cubic mixer, which has a capacity of 3.4 liters. Unless specified otherwise, 500 g of lactose and 2.5 g of magnesium stearate (0.5 %) were passed though a 1000 µm sieve, to break eventuel agglomerates, and introduced in the mixer. Under these conditions, there is a sufficient void space in the mixers to allow a good circulation of the particles and to perform homogenous mixtures. The influence of the mixing conditions was studied by variing the mixing time and the mixer's speed. The mixtures compression study was performed on a KORSCH EK/0 excenter tabletting machine, fitted out with 12 mm diameter flat punches and instrumented with strain gauges to allow a continuous measure of the pressures during compression. To allow a good study of the lubricating properties, the output of lower punch's gauges was amplified twice so that it was possible to appreciate exactly the maximal transmitted force and to measure accurately the force needed by the ejection of the tablet from the die even when this ejection forces were extremely low.

Each mixture was compressed at forces about 1000, 1500, 2000 and 3000 daN. During the compression various data were registred : the degree of lubrication was evaluated by the force transmission ratio ; the tablettability was definited by the measure of the ejection force, because a previous work[8] had shown that this kind of parameter is usefull for an evaluation of the compression. This ejection force was given in a relative manner (E.F. %), according to the formula :

$$E.F.\ \% = \frac{2 \times E.F. \times 100}{(F_{max}\ U.P. + F_{max}\ L.P.) \times A_{CD}}$$

where E.F. is the measured ejection force (daN)

F_{max} U.P. is the maximal force at the upper punch (daN)

F_{max} L.P. is the maximal force at the lower punch (daN)

A_{CM} is the contact aera (cm^2) between tablet and die during the ejection.

To obtain an accurate value of E.F. %, the ejection force was measured for various compression forces and related to a mean compression force of 2000 daN by the less squares method.

The tablet hardness was measured at least, on ten tablets per lot, with an ERWEKA TBT apparatus. To account for the thickness variations between lots, the values given by the ERWEKA apparatus were corrected according to the formula proposed by Timoshenko and Goodier[9], and then the relation between the compression force and the tablet hardness calculated by the less squares method in order to reach a precise evaluation of the force needed by the fabrication of a tablet of given strength.

Disintegration times of tablets were measured in water a 37° with an ERWEKA VZ4 apparatus.

RESULTS AND DISCUSSION

To be able to compare the results to a precise reference value, an experiment of compression of pure crystalline lactose, without lubricant was realized. This compression is difficult, because a quick seizure of the tabletting machine occures. On figure 1, for example, are reported the values of the force

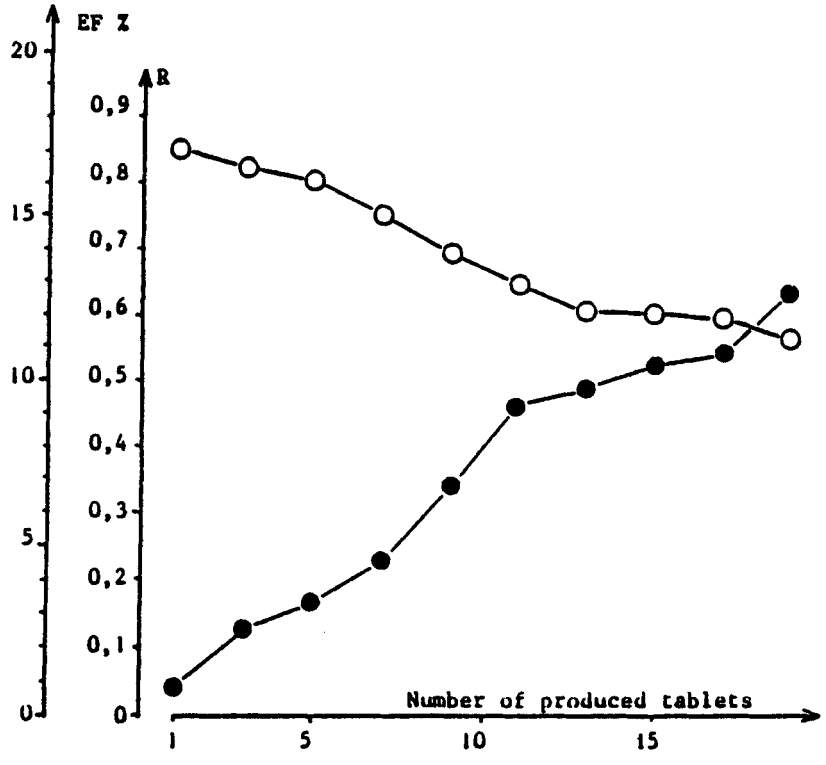

Figure 1

○ Force transmission ratio (R) and ● relative ejection force (EF %) in function of the number of produced lactose tablets.

transmission ratio (R) and the values of the relative ejection forces (E.F. %) as a function of the number of produced tablets : it was not possible to carry on the tabletting after twenty compressions, but this experiment allowed nevertheless to have a reference value for non lubricated crystalline lactose. This references values are reported in table I.

After this preliminary experience, mixtures of lactose and 0.5 % magnesium stearate were prepared with the TURBULA mixer rotating at 25 or 90 r.p.m. and their compression was studied. The compression forces needed to realize tablets with 4 kg hardness are represented in figure 2 as a function of mixing time : one can notice, as reported by the previous works, that necessary compression forces grow with mixing time, and this is the case when mixing is realized at 25 r.p.m. or 90 r.p.m.

At 90 r.p.m., it needs 2000 daN after 30 sec. mixing to produce a tablet with 4 kg hardness (non lubricated lactose needed only 1400 daN). This required forces increase in function of time : 2400 daN after 1 minute, 3100 after 12 minutes and, after 10 minutes, the maximum is practically reached : it is

Table I

Tabletting of non lubricated crystalline lactose : properties of the first realized tablets

Hardness of a tablet compressed at 2000 daN	7.2 kg
Compression force needed for the realisation of a 4 kg hardness tablet	1400 daN
Disintegration time of a tablet (hardness = 4 kg)	1 minute

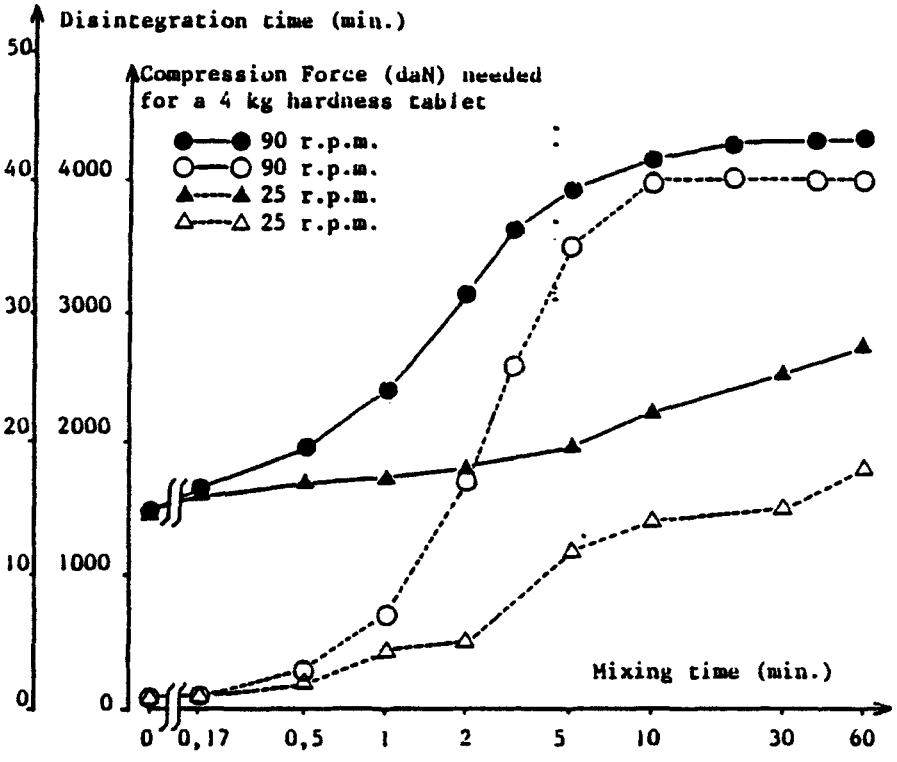

Figure 2

Hardness and disintegration time of lactose tablets lubricated with 0.5 % magnesium stearate in function of mixing time at ▲ △ 25 and ● ○ 90 r.p.m. (Turbula mixer).

necessary to apply more than 4000 daN to produce a tablet with 4 kg hardness.

At 25 r.p.m., this effect appears distinctly slower, as during the five first minutes, the required compression force remains lower to 2000 daN, and even after one hour mixing time, this force does not reach the 3000 daN level.

Tablets disintegration time follows a similar way : at the beginning, the disintegration time is one minute. If the mixer

rotates at a high speed (90 r.p.m.), it appears that after one minute mixing time, the disintegration is already lengthened : it reaches 8 minutes ; after five minutes mixing, the disintegration time is half an hour ; and after ten minutes mixing, the disintegration time reaches a maximum level which is around 40 minutes. It seems therefore, that a continuous layer of magnesium stearate is formed after ten minutes mixing at 90 r.p.m.

By comparison of equal mixing times if appears evidently that there are differences between the mixtures obtained at a low speed and those performed at high speed. However, to take into account the whole number of rotations operated by the mixer, the compression force needed for a 4 kg hardness tablet was represented in figure 3 as a function of the number of rotations instead of the mixing time. One can see that with an equal number of rotations, the too regular film of magnesium stearate, which influences the tablettability, appears slower at 25 r.p.m. than at 90 r.p.m. This signifies that a slow mixing gives better results, at a tabletting point of view, than a fast mixing.

To confirm that statement the ratio of the hardnesses of tablets obtained after mixing at 25 r.p.m. and 90 r.p.m. were calculated ; these ratios were established at the same total numbers of revolutions, and related to the same tabletting pressure (2000 daN). The disintegration times ratio were also calculated. These two datas were reported as a function of mixer's number of rotation on figure 4.

The hardness of tablets prepared after a slow mixing is higher, what ever the mixing time may be. One can assume that the random division of magnesium stearate is better at 90 r.p.m. than at 25 r.p.m. ; this signifies a better force distribution in the tablets, and a hardness decrease. But the better random division of lubricant does not signify that each particle is surrounded by hydrophobic magnesium stearate : the comparison of disintegration times of tablets prepared after mixing at 25

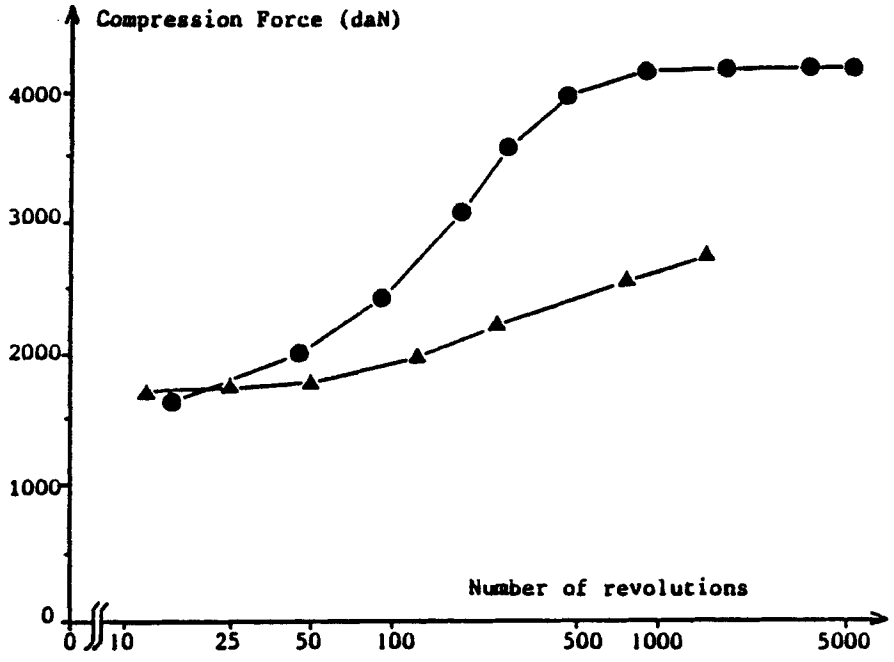

Figure 3

Force needed for a 4 kg hardness tablet in function of the number of rotations of the Turbula mixer (● 90 and ▲ 25 r.p.m.)

and 90 r.p.m. indicates that during the first 150 rotations, the mixtures prepared at 25 r.p.m. disintegrate slower.

It seems therefore that a slow rotation of the mixer improves, during the first minutes, the magnesium stearate film formation ; a quick rotation gives, in the first minutes, a good random division of the lubricant without continuous hydrophobic film formation.

With a TURBULA mixer, which is a very efficient mixer, the hydrophobic film formation is however achieved in a short time, and it can seem hazardous to mix an excipient and a lubricant during only a few seconds to avoid bad side effects of mixing. For this reason the results obtained with the TURBULA mixer were

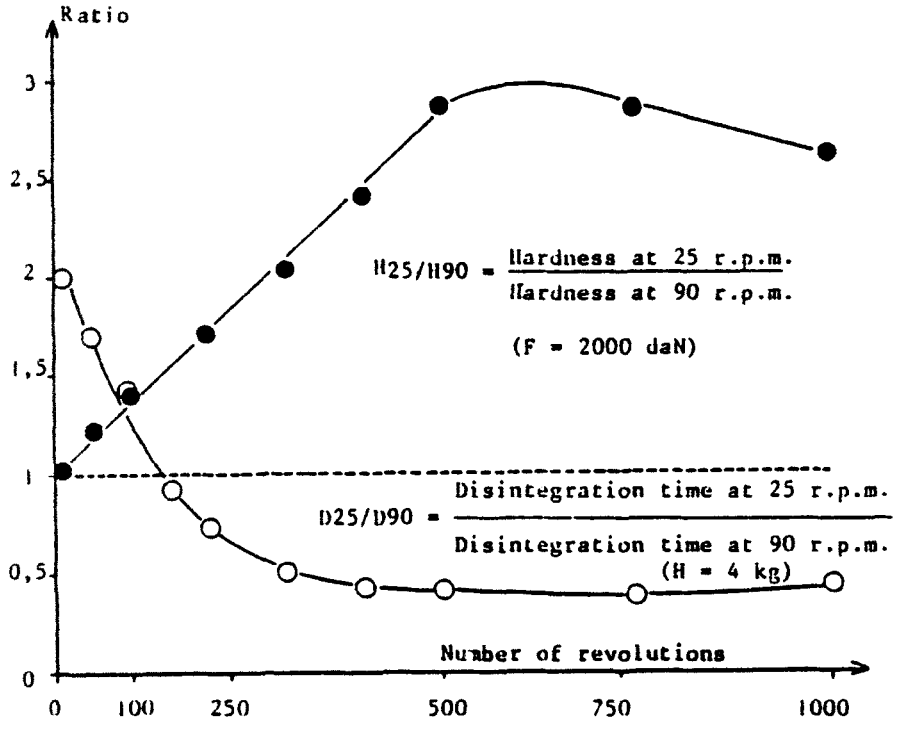

Figure 4

Hardness and disintegration time ratios in function of the number of rotations of the Turbula mixer

compared to those given by an other kind of mixer : the cubic mixer. This cubic mixer was used at the same speed than the slowest of the TURBULA mixer (25 r.p.m.) in purpose to facilitate the comparisons.

On the figure 5 are given the hardnesses of tablets prepared at 2000 daN as a function of mixing time : the hardness decrease is, in part, a linear function of the logarithm of mixing time. The cubic mixer, which is often considered as non effective, gives results which are intermediate between those observed at 25 r.p.m. and at 90 r.p.m. with the TURBULA mixer. It seems the-

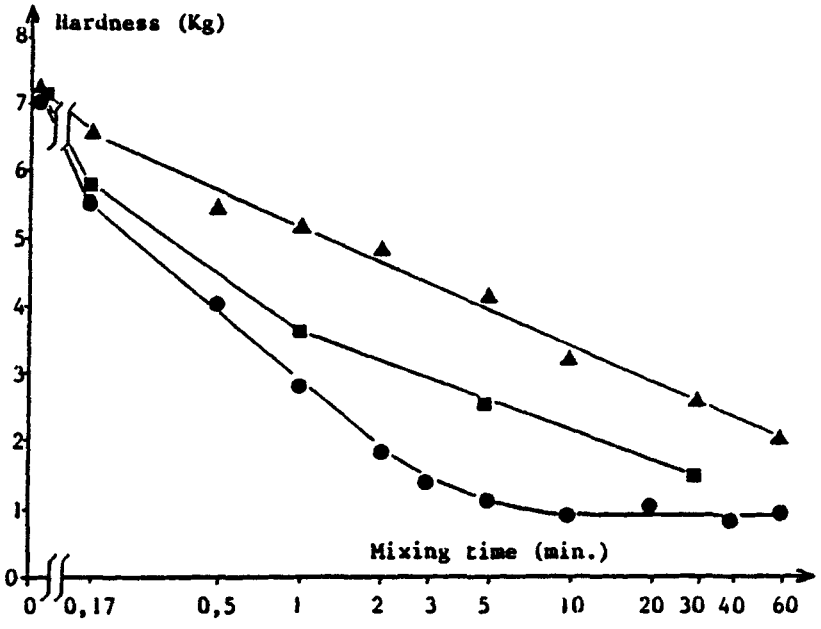

Figure 5

Hardness of tablets produced with a 2000 daN force in function of mixing time (■ cubic mixer, ● Turbula mixer at 90 r.p.m., ▲ Turbula mixer at 25 r.p.m.)

refore that the surface film formation occurs easily in a tumbling mixer although the mixture's homogeneity is not perfect.

These results are confirmed by the study of the ejection force (figure 6), which indicates that the anti-adherent effect of magnesium stearate reached in the cubic mixer is similar to that reached with the TURBULA mixer rotating at high speed.

Bolhuis and Lerk[10] have shown that the magnesium stearate film can be interrupted by the addition of silicon dioxide. Figure 7 shows, for example, the data obtained by these authors during the compression of a direct compression excipient (Amylose) : Bolhuis and Lerk[11] could recover the initial hardness of tablets, before mixing, by use of silicon dioxide (AEROSIL 200)

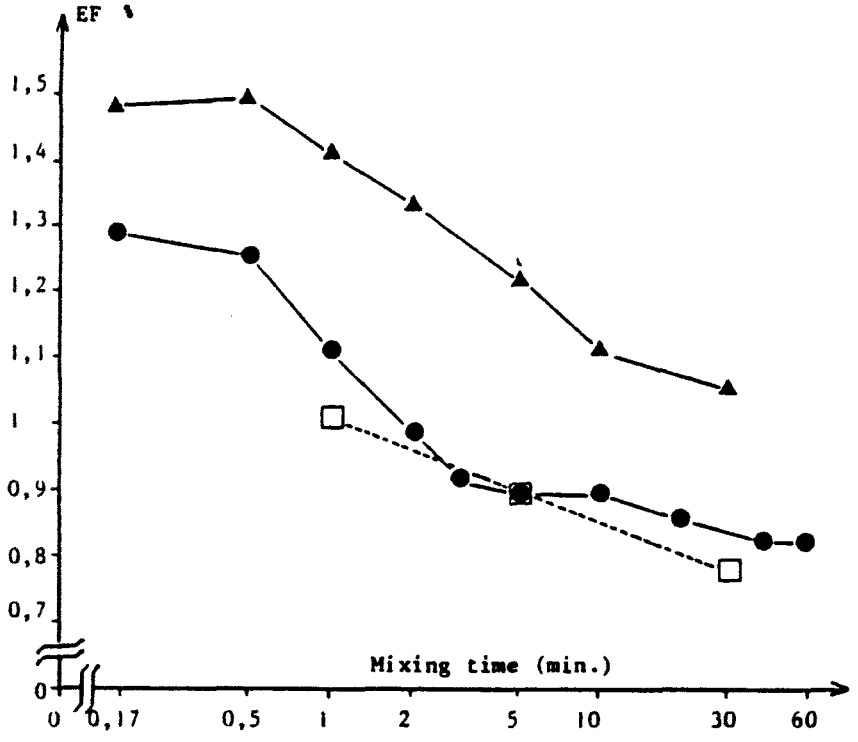

Figure 6

Ejection forces in function of mixing time (□ cubic mixer, ▲ Turbula mixer 25 r.p.m., ● Turbula mixer 90 r.p.m.)

at concentrations of 0.2 or 0.5 percents. (The numerical values reported in figure 7 are not strictly comparables to our's, because the hardness was not measured on the same kind of apparatus).

Considering these interessant results, we tried to brake, in a similar manner, the magnesium stearate film formed around lactose crystals : after five minutes mixing time on the TURBULA mixer rotating at 90 r.p.m., 0.5% AEROSIL were passed through a 500 µm sieve and added to the mixture ; the resulting mixture was mixed again on the TURBULA mixer at 90 r.p.m., and the rela-

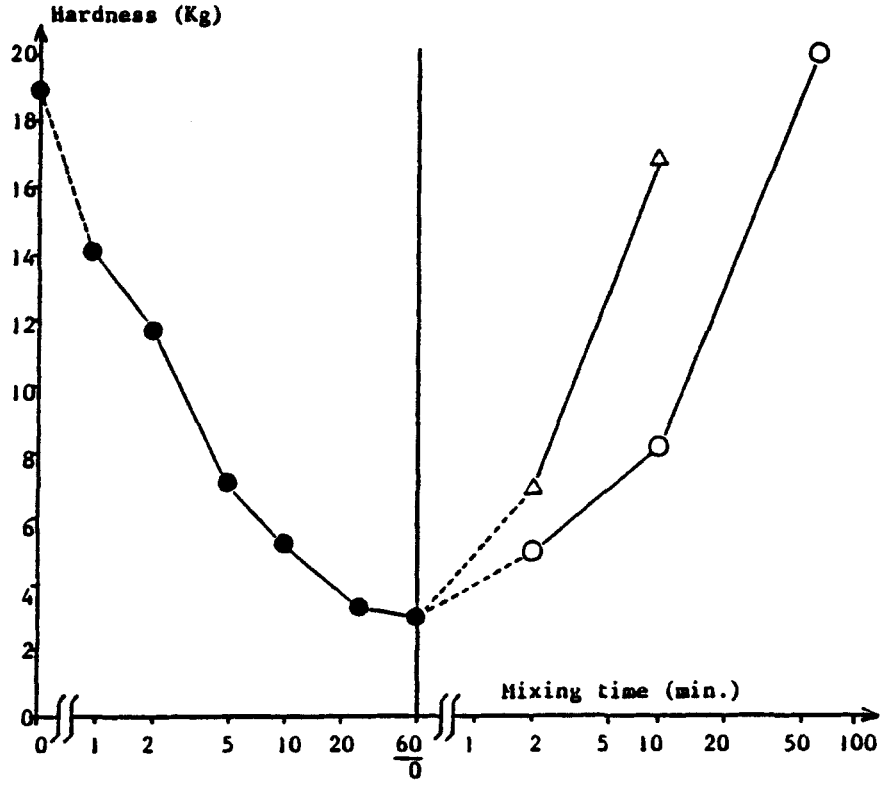

Figure 7

Influence of silicon dioxide on hardness of Amylose - magnesium stearate tablets (according to Bolhuis and Lerk[10]) - △ 0.5 % ○ 0.2 %).

tion between compression force and hardness was studied as a function of additionnal mixing time.

This study is represented in figure 8 : it shows that the hardness of tablets compressed at 2000 daN decreases from 7 kg to 1 kg during the mixing period of lactose with magnesium stearate. The addition of AEROSIL 200 and an additionnal mixing of 5 to 10 minutes allow a slight increase of the mechanical strength of tablets (2.5 kg) : this assumes that the magnesium

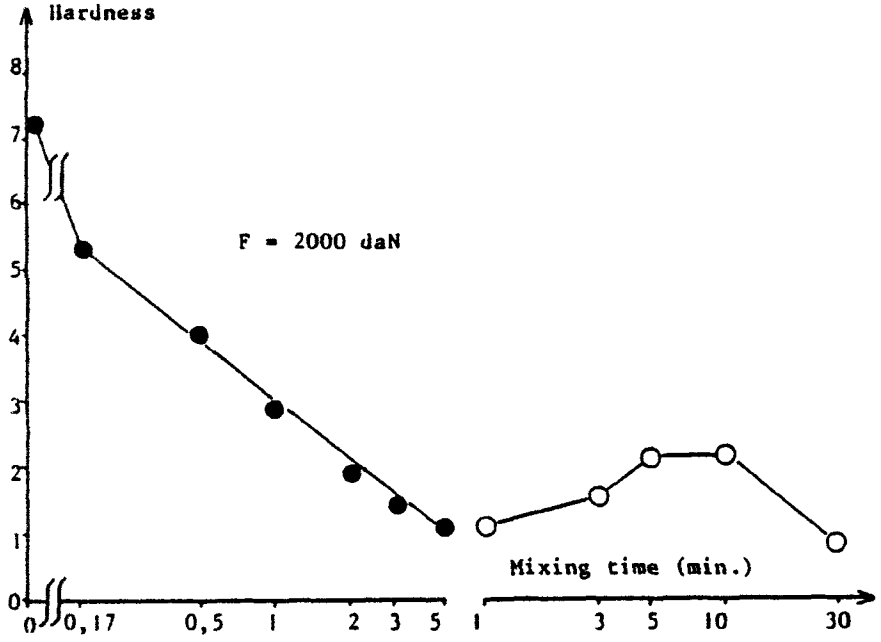

Figure 8

Influence of silicon dioxide on hardness of lactose - magnesium stearate tablets

stearate film can indeed be interrupted by colloïdal silicon dioxide, but the initial hardness value (7 kg) can not be reached, even after prolonged mixing time. On the contrary, beyond ten minutes additionnal mixing, a hardness decrease appears, which seems to show that the magnesium stearate film is formed again, in spite of the important quantities of silicon dioxide used.

These results are confirmed by the study of disintegration time (figure 9) : AEROSIL does not allow to shorten the disintegration time of tablets although colloïdal silicon dioxide is very hydrophilic ; this could signify that the magnesium stearate film is not realy interrupted, but that AEROSIL may create some small clean surfaces of lactose, which can give bonding between crystals. Disintegration time of tablets increases after 10 minutes addition-

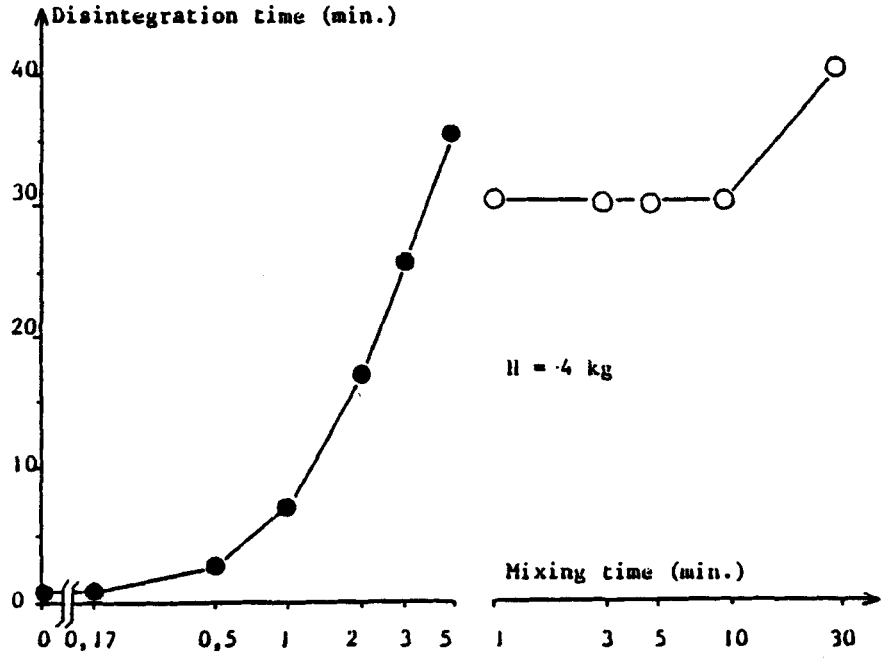

Figure 9

Influence of silicon dioxide on the disintegration time of lactose - magnesium stearate tablets.

al mixing time, and this indicates that the film is quickly formed again.

All the results concerning the use of silicon dioxide reported here do not completely agree with those published by Bolhuis, Lerk and al[1], who used the same kind of mixer, the same crystalline lactose (E.F.C.) and the same proportion of magnesium stearate (0.5 %). These authors reported that the maximal hardness reduction of tablets is 1/2,7 after 2 minutes mixing, and that the hardness remains constant after this time. On the contrary, we established a more important hardness decrease (ratio 1/8) ; and this decrease is gradual, reaching its maximum at the 10th minute of mixing. The difference between the litterature[1] and our data may be

explained by a difference in the compression material used : Bolhuis and al[1] prepared their tablets on an hydraulic press, and our tablets were compressed under normal conditions, using an instrumented excenter press.

The whole results show that once the magnesium stearate is uniformely spread at the lactose surface, it is very difficult to break this continuous layer. It is therefore important to avoid this uniform spreading. A possible way for this could be the use of "activated" lactose : for exemple Hüttenrauch[10] treated crystalline lactose in a mill to create transitory lattice deffects. After this treatment, the author separated the fraction between 100 and 250 µm and lubricated it with 0.1 % magnesium stearate. Using a TURBULA mixer during periods up to 3 hours, Hüttenrauch mixed the particles, prepared tablets and studied the relation between compression force and hardness : he noted no influence of the mixing.time on the tablet's hardness : parallel experiments with non treated lactose showed the classical hardness decrease in function of mixing time.

This interesting possibility, which could eventually avoid the bad magnesium stearate effect is only mentioned here ; it was not experimented in the present work, because of the practical difficulties which could arise, on an industrial scale, with a milling of lactose just before mixing. It seems more judicious to select well the mixer and the mixing time to avoid the formation of an uniform lubricant layer at the particles' surface.

CONCLUSION

The purpose of the present work was not to demonstrate the influence of mixing time between an excipient and a lubricant ; this influence is well known since several years. This work was realized to study with more accuracy an often used diluent - lubricant pair (lactose + magnesium stearate). The results showed that not only the mixing time has an influence but also

the speed and the kind of the mixer used. The choice of an appropriate mixer is important because, once a lubricant film is formed around lactose particles, it is difficult to interrupt it, and the addition of colloïdal silicon dioxide is poorely effective.

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