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# COMMUNICATIONS

## Investigation of the film formation of magnesium stearate by applying a flow-through dissolution technique

MATS E. JOHANSSON*, MARTIN NICKLASSON, *Astra Läkemedel AB, Research and Development Laboratories, Pharmaceutics, Solid Systems, S-151 85 Södertälje, Sweden*

The film formation of magnesium stearate on the surface of acetylsalicylic acid was investigated by applying a flow-through dissolution technique. The effect of mixing time, lubricant surface area, and the addition of colloidal silica was studied. The film formation increased by increasing mixing time. The final level reached was independent of the specific surface area of the lubricants, but granular magnesium stearate gave a lower surface coverage than the powdered lubricants. The lubricating effect was independent of the mixing time and specific surface area of the lubricants. Colloidal silica was found to interact primarily with the free fraction of magnesium stearate.

When a boundary type lubricant such as magnesium stearate is mixed with carrier material, it forms a hydrophobic film on the surface of the base material (Strickland et al 1956; Bolhuis et al 1975). The hydrophobic film negatively interferes with tablet properties such as crushing strength, disintegration time, and dissolution rate (Levy & Gumtow 1963; Bolhuis et al 1981; Jarosz & Parrott 1984). Magnesium stearate shows considerable batch to batch variation regarding both specific surface area and morphological properties (Müller et al 1982; Miller et al 1983; Frattini & Simioni 1984; Hölzer 1984). As reported by Bolhuis et al (1975) and Buehler (1978), the structure of the magnesium stearate film appears to be molecular rather than particulate. Colloidal silica has been shown to interact with magnesium stearate in terms of both tablet properties and the lubricating effect (Lerk & Bolhuis 1977; Lerk et al 1977; Ragnarsson et al 1979; Schrank-Junghäni et al 1983).

A few attempts have been made to quantify the degree of film formation of magnesium stearate. Pintye-Hodi et al (1981) and Lerk & Bolhuis (1977) used energy dispersion X-ray (EDAX) for the characterization of the lubricant film, but the method did not appear to be sensitive enough for application in the interesting concentration range of 0–1%. Nicklasson & Brodin (1982) and Rowe (1983) determined the extent of the surface coverage of the lubricant film on the tablet surface by applying a rotating disc technique and a film-coating/tablet adhesion technique. Both techniques were found to give comparable results.

Sekiguchi et al (1975) used a dissolution technique to measure the specific surface area of uncompressed powders by measuring the dissolution rate from the powders and correlating that to the dissolution rate obtained from compressed discs with known surface area. In the present work, the degree of surface coverage of magnesium stearate on acetylsalicylic acid before compaction to tablets is investigated by applying a flow-through dissolution technique. The degree of surface coverage is related to the lubrication at the compaction. The influence of magnesium stearate specific surface area, mixing time, and the addition of colloidal silica will also be discussed.

### *Materials and methods*

Acetylsalicylic acid (ASAGRAN 7026, Monsanto Chemicals, UK) was sieved and the fraction retained on a 0·4 mm sieve was used. Magnesium stearate from three different sources (specific surface area by permeametry, porosity = 0·5 (1) 1·2 $m^2 g^{-1}$, (2) 3·6 $m^2 g^{-1}$, (3) 6·1 $m^2 g^{-1}$; loss on drying (105 °C) (1) 5·7%, (2) 5·0%, (3) 4·7%) and colloidal silica (Aerosil, Degussa, West Germany) were of commercial grades. The fourth lubricant was a magnesium stearate granulation prepared from batch (2) by the compaction technique previously described (Johansson 1984). Its geometrical mass median diameter obtained by sieving was 240 μm, s.d. geom. 1·7.

*Lubricant mixing.* Portions of 250 g acetylsalicylic acid were mixed with 1% by weight of one of the four lubricants in a 1 litre glass vessel in a Turbula mixer (Turbula T2C, Willy Bachhofen, Switzerland) at 48 rev $min^{-1}$. The mixing times were 1, 2, 5, 10 and 30 min. From each mixture, samples of about 185 mg were withdrawn by spoon sampling from different positions in the mixer for measurement of the dissolution rate.

1% of colloidal silica was either admixed for 15 min after first mixing with magnesium stearate for 2 min or mixed for 2 min together with the magnesium stearate which was either the granulation or batch (2).

* Correspondence.

*Measurement of lubricating effect.* Tablets were compressed on an instrumented tablet machine (Korsch EKO) described elsewhere (Johansson 1984). Only tablets compressed at 200 ± 10 MPa and at a tablet weight of 200 ± 5 mg were further analysed. As a measure of the lubricating effect, the ejection force was recorded after the machine had been running for at least 5 min at 30 rev $min^{-1}$. The ejection force was compensated for variations in contact area between the compact and the die wall (Hölzer & Sjögren 1977). The crushing strength of the tablets was measured approximately 24 h after compaction on a motorized instrument (TBH 28 MD, ERWEKA, West-Germany) and recalculated to tensile strength in accordance with Fell & Newton (1968).

*Measurement of the dissolution rate.* A flow-through apparatus (DISSOTEST, Sotax AG, Switzerland) was used for the dissolution experiments (Langenbucher 1969; Langenbucher & Rettig 1977). At each run, water of 37 °C was recirculated via a piston pump (DISSO-PUMP, Sotax AG, Switzerland) through a flow-through cell with a diameter of 22 mm. The flow rate was 16 ml $min^{-1}$ and the total volume of the sink was 246 ml. During the dissolution process, samples were continuously taken from the sink, which was agitated with a magnetic stirrer, using a peristaltic pump. The samples were circulated through a flow cuvette in a spectrophotometer (Beckman DU-7). The absorbance following dissolution was registered at 274·5 nm.

The samples of acetylsalicylic acid or the mixtures with magnesium stearate were mixed with glass beads (diameter 1 mm) and placed on the bottom of the flow-through cell. The observed dissolution rate of acetylsalicylic acid (mg $min^{-1}$) was calculated from the initial part (0–4 min) of the amount dissolved vs time curves by linear regression. The mean values of 5 measurements are reported.

*Results and discussion*

The dissolution rates of the different mixtures of acetylsalicylic acid and magnesium stearate are shown in Fig. 1. For all lubricants, a nearly exponential decrease in dissolution rate with increasing mixing times can be seen. This pattern closely follows the theory of increased surface separation with increasing mixing time put forward by Shah & Mlodozeniec (1977). However, in contrast to them, we did not notice any corresponding decrease in ejection force with increasing mixing time, as seen in Fig. 2. On the contrary, the ejection force appears to be independent of the mixing time. If the decrease in dissolution rate of the mixtures with magnesium stearate compared to acetylsalicylic acid itself is considered to be proportional to the degree of surface coverage of magnesium stearate, the surface coverage can be calculated with the following expression:

$$\text{Surface coverage}\,(\%) = \left(1 - \frac{J_{MgSt}}{J_{ASA}}\right) \times 100 \quad (1)$$

where $J_{ASA}$ is the dissolution rate of the acetylsalicylic acid and $J_{MgSt}$ is the dissolution rate of the mixture with magnesium stearate.

In Fig. 3, the degree of surface coverage vs mixing time is shown. Lubricant (3) with the highest specific surface area covers about 70% of the surface of the base material, and between 10 and 30 min mixing, no further change is noticed. The other two powdered lubricants, with lower surface areas, show a slower increase in surface coverage, but after 30 min mixing time, the differences between the lubricants are negligible, and can by no means be correlated to the differences in specific surface area of the lubricants. This supports the theory of Bolhuis et al (1975) with a molecular or laminar coverage of magnesium stearate rather than particulate.

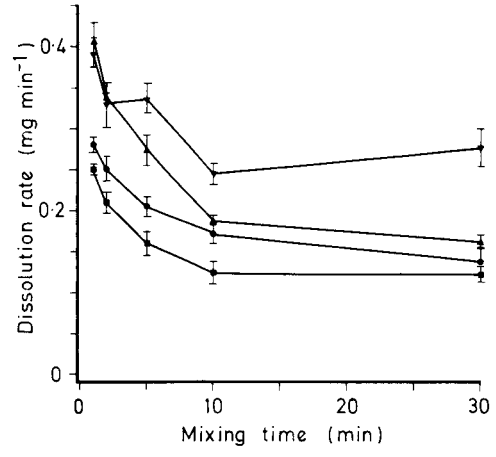


FIG. 1. Initial dissolution rate vs mixing time. Vertical bars indicate ± 1 standard deviation. △ Magnesium stearate 1. ○ Magnesium stearate 2. □ Magnesium stearate 3. ▽ Granular magnesium stearate 4.

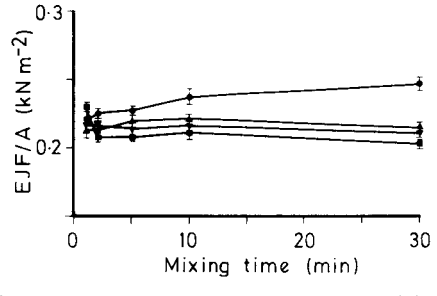


FIG. 2. Ejection force per unit surface area vs mixing time. Vertical bars indicate ± 1 standard deviation. Symbols as in Fig. 1.

The magnesium stearate in the granular form shows the same general trend of surface coverage as the corresponding powdered lubricant (batch 2). However, a lower constant level of surface coverage is obtained. This is also reflected in tablets of higher strength prepared by the granular lubricant than the tablets mixed with the powdered lubricants (Fig. 4). The lubricating effect of granular magnesium stearate is equal to the lubrication obtained with the powdered lubricants. From this, it can be concluded that a high degree of surface coverage is not a prerequisite for good lubrication.

When the acetylsalicylic acid is mixed with 1% magnesium stearate (batch 2) for 2 min, a surface coverage of 45% is obtained as seen in Table 1. The addition of 1% colloidal silica and 15 min additional mixing neither results in any further surface coverage, which could be expected from Fig. 3, nor in any stripping of the magnesium stearate film. It appears as if colloidal silica interferes primarily with the fraction of magnesium stearate that is not forming a hydrophobic film on the base material, and it also prevents this fraction from further coverage of the surface. The results of Lerk et al (1977), with the retained lubricating effect of magnesium stearate after addition of colloidal silica, could not be confirmed. On the contrary, a twofold increase in ejection force after the addition of colloidal silica can be seen. This is in agreement with the reports by Ragnarsson et al (1979), Schrank-Junghäni et al (1983), and Bossert & Stamm (1980) and indicates that a considerable amount of the lubricating effect is attributed to the free fraction of magnesium stearate. If the colloidal silica is mixed with the magnesium stearate initially, the film formation of magnesium stearate is prevented and the lubrication is partly destroyed as is also shown in Table 1. The mixing of colloidal silica, when granular magnesium stearate is used as a lubricant, shows the same general feature as with the powdered lubricant. However, the absolute magnitudes of the surface coverage are lower with the granular lubricant, even though the ejection forces are close to those obtained with powdered magnesium stearate. This also supports the assumption that the lubricating effect of magnesium stearate is not directly related to the coverage on the surface of the base material.

Table 1. *Dissolution rate, surface coverage, ejection force and tensile strength for the mixtures with acetylsalicylic acid (ASA), magnesium stearate (MgSt), and colloidal silica.*

| Mixture | Dissol. rate ($mg\ min^{-1}$) | Surface coverage (%) | EJF/A ($kN\ cm^{-2}$) | Tensile strength (MPa) |
|---|---|---|---|---|
| ASA + powdered MgSt 2 min | 0·22 | 45 | 0·22 | 1·75 |
| (s.d.) | (0·007) | | (0·003) | (0·26) |
| ASA + powdered MGSt 2 min + colloidal silica 15 min | 0·22 | 45 | 0·44 | 2·05 |
| (s.d.) | (0·012) | | (0·012) | (0·28) |
| ASA + powdered MgSt + colloidal silica 2 min | 0·32 | 20 | 0·41 | 2·22 |
| (s.d.) | (0·028) | | (0·011) | (0·12) |
| ASA + granular MgSt 2 min | 0·29 | 27 | 0·21 | 2·41 |
| (s.d.) | (0·023) | | (0·004) | (0·18) |
| ASA + granular MgSt 2 min + colloidal silica 15 min | 0·26 | 35 | 0·45 | 2·57 |
| (s.d.) | (0·010) | | (0·022) | (0·18) |
| ASA + granular MGSt + colloidal silica 2 min | 0·38 | 5 | 0·49 | 2·56 |
| (s.d.) | (0·041) | | (0·014) | (0·10) |
| ASA | 0·40 | 0 | 0·55 | 2·60 |
| (s.d.) | (0·019) | | (0·017) | (0·073) |
| ASA + colloidal silica 15 min | — | — | 0·54 | 2·66 |
| (s.d.) | | | (0·011) | (0·18) |

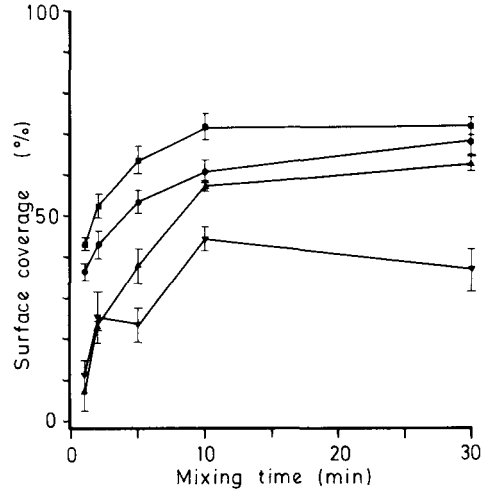


FIG. 3. Calculated surface coverage vs mixing time. Vertical bars indicate ±1 standard deviation. Symbols as in Fig. 1.

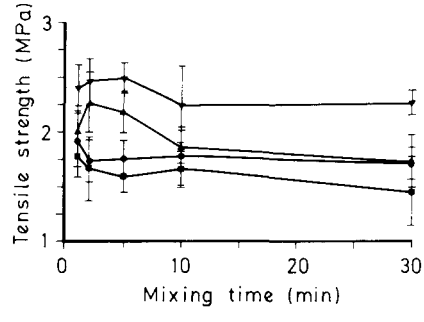


FIG. 4. Tensile strength vs mixing time. Vertical bars indicate ±1 standard deviation. Symbols as in Fig. 1.

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# Dose versus survival time curves in the evaluation of 'prompt' and 'delayed' acute toxicities

L. MOLINENGO*, M. ORSETTI, *Institute of Pharmacology and Pharmacognosy, Pharmacy School, University of Turin, C.so Raffaello, 31 Torino, Italy*

The acute toxicity of arecoline, diisopropylfluorophosphate, nicotine and pilocarpine alone or in association with atropine has been evaluated from percentage lethality and from the linear correlation of (doses/(survival time)) vs doses. The experimental points obtained with arecoline and diisopropylfluorophosphate, alone or in association with atropine 50 mg $kg^{-1}$, are apparently ordered according to two straight lines. That at lower doses gave the LD50 values of the compounds studied. The values found are comparable to those found with percentage lethality. The straight line found at high doses may indicate that over certain doses the drugs kill by a different mechanism. It is concluded that the evaluation of the survival time may be a reliable method in identifying and in evaluating quantitatively the two forms of toxicity.

The results obtained in the evaluation of acute toxicity from the hyperbola dose vs survival time (Molinengo 1979) are, in our experience, always in agreement with those obtained with the method which uses the percentage lethality at increasing doses. A particular situation was found with arecoline: the experimental points are apparently ordered according to two hyperbolae, causing some uncertainty in the evaluation of the LD50.

To confirm and extend this observation, we used both methods to measure the acute toxicity of arecoline hydrochloride alone and in association with atropine.

The acute toxicity of nicotine sulphate, pilocarpine hydrochloride and diisopropylfluorophosphate (DFP) was also evaluated alone and in association with atropine, to see if the particular doses vs survival time curve, found with arecoline, is a characteristic of drugs of cholinergic systems.

## *Methods*

Drugs were administered intraperitoneally to female, albino mice (25 g). Atropine sulphate (50 mg $kg^{-1}$) was given 30 min before the administration of the selected drug.

To evaluate the LD50 values by the method of percentage lethality, six doses of each drug alone, or in association with 50 mg $kg^{-1}$ of atropine, were used (n = 10/dose) and percentage lethality assessed after 48 h. To evaluate the LD50 values by the method based on survival time curves, the time after which each animal died at increasing doses was evaluated with an approximation of 10 s. All experiments were performed in the afternoon at a room temperature of 20 ± 2 °C.

* Correspondence.