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The effect of the particle size of microcrystalline cellulose on tablet properties in mixtures with magnesium stearate

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Summary

Magnesium stearate was mixed with different sieved fractions (80–180, 180–250, 250–350 μm) of microcrystalline cellulose (Avicel PH 102). The influence of mixing time on crushing strength and disintegration of tablets compressed from these mixtures were studied. The disintegration time increased and the crushing strength decreased with increasing particle size of the Avicel fractions. When magnesium stearate is mixed with table excipients the size of these materials could have an effect on the deterioration of the tablet properties as a function of mixing time.

Introduction

The effects of mixing time on tablet properties when magnesium stearate is mixed with excipients and drug particles have been investigated extensively (Bolhuis et al., 1975; Shah and Mlodozeniec, 1977; Lerk et al., 1982; Johansson, 1985). It is now generally accepted that the magnesium stearate forms a hydrophobic film on the surface of the particles which delays the penetration of water or hydrophilic liquids into the tablets. This film and the extent to which the surface is covered by magnesium stearate cause the increase in disintegration and dissolution times when the mixing time or mixing intensity is increased.

Bolhuis and Lerk (1982) related this film formation to the creation of an ordered mixture between the magnesium stearate and other mixture components. An ordered mixture is formed when a very fine minor component adheres to the coarse major component (the carrier) during the mixing process.

Numerous factors which affect the formation of ordered as well as magnesium stearate mixtures have been reported. Malmqvist and Nyström (1984) indicated that the rate at which ordered mixtures are formed increases with increasing mixer size and increasing particle density of the carrier. The rate of the formation of the magnesium stearate film will therefore probably depend on the size of the particles of the carrier because larger particles would create larger shear forces in the mixer (Yeung and Hersey, 1979). Investigations on magnesium stearate mixtures include experiments with different excipients (Shah and Mlodozeniec, 1977), combinations of excipi-

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ents and other tablet ingredients (Bolhuis et al., 1981) and with magnesium stearate particles with different particle properties (Billany and Richards, 1982; Johansson, 1986).

In this investigation the influence of the particle size of microcrystalline cellulose (Avicel PH 102) on tablet properties was studied when it was mixed, for different mixing times, with magnesium stearate.

Materials and Methods

Materials

Magnesium stearate (chemical pure from Saarchem, Johannesburg) with a mean particle size of 32.8 μm and maximum size equal to 68.3 μm (determined with a Coulter Counter) and microcrystalline cellulose (Avicel PH 102, FMC) were used. The mean particle size of the Avicel, determined with a sieve analysis, was 96 μm. The magnesium stearate was worked through a 180-μm sieve to break any large agglomerates present. The Avicel was sieved into 3 fractions, namely 80–180, 180–250 and 250–350 μm, in order to obtain carrier particles with different sizes. Both sieving operations were performed at least two weeks before the mixing experiments. After sieving the materials were stored in tightly closed plastic containers.

Mixing

Mixtures of the different Avicel fractions, including the unsieved product, were mixed in 340 ml glass cylinders (60 mm diameter and 120 mm length), in a Turbula mixer (model 2 P) at 90 rpm. One mixture (30 g Avicel and 300 mg magnesium stearate) was prepared for every fraction for each of the mixing times which ranged from 2 to 128 min.

Compression

Ten samples of approximately 300 mg were taken randomly from each mixture and an accurately weighed amount of 300 mg was compressed with flat-faced punches in a 13-mm die. A Beckmann hydraulic press with a calibrated pressure gauge was used to compress the tablets at 1000 kN for 15 s. The die and punches were cleaned after each compression with a cloth dampened with ethanol. The tablets were manually pushed from the die with a punch. Unmixed samples from each sieve fraction as well as samples from the Avicel PH 102 were also compressed in the same manner.

Tablet properties determined for each mixture

The disintegration times of 6 tablets were measured with a Manesty tablet disintegration test unit according to the method of the British Pharmacopoeia (1980), without using discs. The crushing strength of 4 tablets was measured with a Pharma Test (type PTB 103) meter. Both properties were determined at least 10 h after tablet preparation.

Statistical interpretation

The mean values of the crushing strength and disintegration time at each mixing time were compared for significant differences, at a 95% confidence level, with the Student–Newman–Keuls multiple-range test. The calculations were done with a BMDP7d program (BMDP Statistical Software, University of California).

Results and Discussion

The mean values for the disintegration time and crushing strength for the tablets prepared from each carrier fraction as a function of the mixing time are shown in Figs. 1 and 2, respectively. Disintegration times longer than 120 min were obtained after 32 min for the 250–350 and after 64 min for the 180–250 μm fractions. These values were not plotted in Fig. 1 because they are far out of the range of the graph.

According to the statistical analysis, the disintegration times at the different mixing times differed significantly from 16 min mixing time onwards. The disintegration times of the tablets from the PH 102, the 80–180 and the 180–250 fractions were the same up to 32 min mixing and did not differ from the values for the 250–350 fraction at 2 and 4 min. All other results were significantly different at a 95% confidence level.

The crushing strength and the disintegration

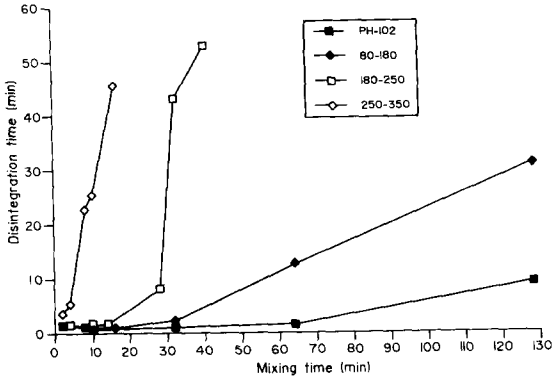

Fig. 1. Disintegration time vs mixing time for sieved fractions of Avicel PH 102. Unsieved Avicel is indicated with PH-102, and the sieve range is given for the fraction. Disintegration times after mixing times longer than 32 min for the 250–350, and 64 min for the 180–250 μm fractions, were not plotted because they were longer than 120 min. The mean disintegration time for all the unmixed fractions was 3.5 min.

time for tablets made from the unmixed fractions did not differ significantly between fractions and the mean values were 122 N and 3.5 min.

The disintegration time of the tablets increased with increasing mixing time for all the carrier fractions. The rate of increase in disintegration time increased very rapidly with increasing particle size of Avicel. The disintegration time of the tablets made from the mixtures of the unsieved Avicel appears to be rather insensitive to the mixing time compared to those made from the sieved fractions.

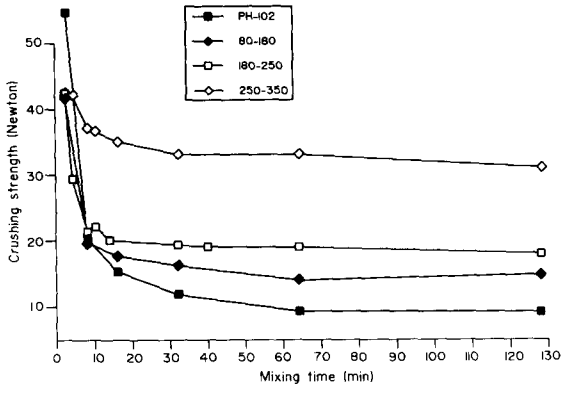

Fig. 2. Crushing strength vs mixing time for sieved fractions of Avicel PH 102. Unsieved Avicel is indicated with PH-102, and the sieve range is given for the fractions. The mean value for all the unmixed fractions was 122 N.

The crushing strength of the tablets decreased with increasing mixing time for all the fractions. It appears that a limiting value for crushing strength is reached after long mixing times. This limiting value increased with increasing particle size.

The large differences in the rate of increase of disintegration time could be explained by the rate at which the ordered mixtures are formed. The larger the carrier particles, the larger are the shear forces in the mixer, giving a much faster rate of film formation.

The increased disintegration time and decreased crushing strength as a function of mixing time are in agreement with what is reported in the literature. The large differences in the properties after the same mixing time for the different particle sizes of the carrier, however, were not reported previously. This may be of significant value in the following circumstances.

- When unsieved Avicel is mixed with magnesium stearate the water repellent properties of the mixtures would be influenced by the particle size distribution of the carrier.
- When combinations of carriers with different particle sizes are mixed an additional factor is included if there are differences in the particle size distributions of the carriers.
- When different carriers are compared with respect to the influence of mixing with magnesium stearate, the differences in particle size and size distribution may be a factor which cannot be ignored.

Comparing tablet properties from different mixtures should be done between mixtures with comparable homogeneity (with respect to magnesium stearate) properties rather than between mixtures prepared for the same mixing times.

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