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The effect of V-mixer scale-up on the mixing of magnesium stearate with direct compression microcrystalline cellulose

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Abstract

The effect of V-mixer size on the mixing of magnesium stearate with directly compressible microcrystalline cellulose is reported. The mixers used were geometrically similar with a seven-fold difference in the volumes of the smallest (320 cm^3) and biggest mixer (2250 cm^3). To evaluate the mixing process and compare the performance of the mixers, the extent of the decrease in tablet crushing strength was measured. The kinetics of the decrease in crushing strength were best described by the sum of two separate processes, one first-order and the other second-order. Overall, the faster second-order process dominated mixing because the first-order rate decreased, while the second-order rate increased, with an increase in mixer volume. Results show that the limiting crushing strength increased with an increase in mixer size and that there was a linear relationship between the limiting crushing strength and the logarithm of the volume of the mixer. A decrease in mixer load from 33 to 18% also led to an decrease in tablet strength. The results can be used to scale-up the lubricant mixing process in V-mixers.

Keywords: Crushing strength; Magnesium stearate; Scale-up; Tablets; V-mixer

1. Introduction

Over the years an almost bewildering array of solids mixers have been developed to meet the demands of the pharmaceutical industry [1]. In the past, the design and selection of these mixers has been an empirical process, but recently, there has been a growing interest in designing mixers based on material properties, mixing mechanisms and mixing quality [2]. This resulted in clearer criteria for the selection of the right mixer for a specific application. Generally, the mixing of solids involves two main mechanisms: convection and interparticulate diffusion. Mechanical agitation in tumbling mixers, i.e. V-mixers, represents one way of achieving both these mixing mechanisms [3].

When using a V-mixer in the manufacturing process of a solid dosage form, the determination of the effect of an increase in mixer volume, from pilot to production batches, on the performance of the finished product is essential for ensuring successful scale-up [4]. Although we cannot totally rely on experience gained from experiments with a pilot-scale mixer for predicting the effect of scale-up, many problems can be avoided if three similarities, geometric, kinematic and dynamic, are considered in the scale-up of a V-mixer [5]. Geometric similarity involves a constant ratio of the linear dimensions of the prototype and scale-up system. Kinematic similarity requires an equal ratio of velocities and dynamic similarity refers to an equal ratio of forces between corresponding points in the different mixers.

This paper reports the effect of the size of a V-mixer on the mixing of a lubricant with a directly compressible tablet diluent. The mixers used were geometrically similar with a seven-fold difference in the volumes of the smallest and biggest mixer. To evaluate the mixing

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process and compare the performance of the mixers, the extent of the decrease in tablet crushing strength was measured. The effect of scale-up on the lubricant mixing process was chosen because it is known that changes in the duration and mechanism of the lubricant mixing process changes the physical properties of tablets [6,7]. The magnitude of these changes depends on the properties of the mixing equipment, concentration and type of lubricant, and particle properties of the lubricant and excipients [8].

2. Experimental

The tablet lubricant, magnesium stearate (Saarchem, South Africa), was mixed with directly compressible microcrystalline cellulose (Avicel PH102®, Chemserve, Ireland). Mixing experiments were carried out in three stainless steel V-mixers with volumes of 320, 760 and 2250 cm^3, respectively. The volumes of the mixers were measured by measuring the volume of water necessary to fill them to the brim. The mixers were scaled by keeping constant the ratio of diameter to length of the tubes that represents the two legs of the V that forms the mixer. Outlets were fitted at the end of one leg without changing the shape of the mixer.

The mixers were filled with accurately weighed amounts of magnesium stearate and Avicel PH102® to fill 25% of the mixer volume. To determine the effect of mixer load on tablet crushing strength, the small V-mixer was filled to 18, 21, 25, 29 and 33%, respectively. The lubricant concentration of all the mixtures were 1.2% w/w and the mixers were rotated at 60 rpm. Mixtures were prepared for each mixing time and a mixture was only sampled once. Mixing times were: 1, 2, 3, 4, 8, 16, 32, 64 and 128 min.

After mixing, a mixture was divided into five equal parts. Two samples, accurately weighed to 300 mg, were randomly taken from each part and tabletted in a Beckman die and press used for preparing tablets for IR spectroscopy. Samples were compressed at 1500 kPa and kept under pressure for 15 s. The crushing strengths of all the tablets were measured with a hardness tester (Pharma Test, type PTB 103, Switzerland).

Mean crushing strengths at each mixing time for the three mixers and mixtures with different mixer loads were compared according to the Student–Newmans–Keuls multiple range test (CSS: Statistica, Statsoft). A 95% confidence level ($P \leq 0.05$) was considered satisfactory for indicating significant differences.

3. Results and discussion

In Fig. 1, the mean crushing strengths of the ten tablets, from each mixture, is plotted as a function of mixing time and mixer size. Mixer load (25%) and the mixer speed (60 rpm) were kept constant. The mixing of magnesium stearate with microcrystalline cellulose, as presented in Fig. 1, is an example of a cohesive powder mixture [3], also known as ordered or interactive mixtures [7]. In such mixtures, the independent movement of particles is restrained by a variety of interparticulate forces. The relevant mixing mechanism is interparticulate bonding due to enhanced contact between the magnesium stearate and the microcrystalline cellulose particles with the formation of an ordered mixture. Such mixtures are mechanically stable and less prone to segregation.

Cohesive mixing between magnesium stearate and microcrystalline cellulose leads to the formation of a magnesium stearate film around the carrier particles [9]. An increase in film formation due to an increase in mixing intensity causes a decrease in tablet crushing strength [7]. As shown in Fig. 1, film formation is enhanced by an increase in mixing time because the mean crushing strengths of tablets decreased as a function of mixing time. For example the crushing strength of tablets prepared from mixtures mixed in the smallest mixer decreased from 96 N after 1 min to 20 N after 128 min.

In trying to determine the kinetic process describing the decrease in crushing strength with an increase in mixing time, it was found that an equation representing the sum of two separate processes, one first-order and the other second-order, best describe, the data in Fig. 1.

$$dx/dt = k_1^{n_1} t + [k_2/(1 + k_2 n_2 t)] + c \quad (1)$$

where c is the limiting crushing strength, k_1 the first-order rate constant, k_2 the second-order rate constant, t is time, and n_1 and n_2 the computed reaction orders. This

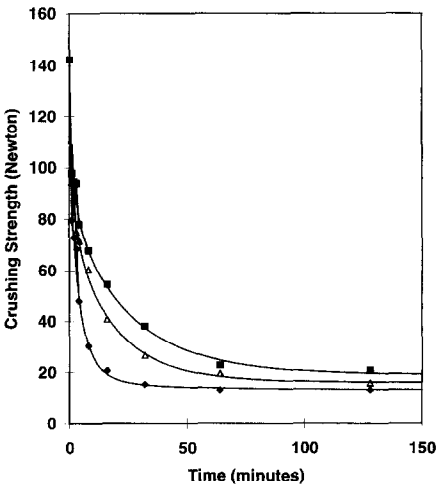

Fig. 1. The effect of mixing time on the crushing strength of tablets prepared from mixtures mixed in different sized V-mixers: (■) 320 cm^3; (△) 720 cm^3; and (◆) 2250 cm^3. Markers represents the mean measured values and lines the fit according to Eq. (1).

Table 1
Kinetic data, Eq. (1), describing the decrease in crushing strength with an increase in mixing time and mixer volume

Mixer volume (cm^3)	c (N)	k_1 (N/min)	k_2 (N/min)	r^2	Least square error of fit	F-statistic
320	19 ± 2.2	55 ± 8.9	68 ± 8.9	0.997	2.82	426
760	16 ± 2.6	52 ± 9.3	75 ± 10.3	0.007	2.94	414
2250	13 ± 1.3	47 ± 6.1	83 ± 17.1	0.999	1.67	1422

n_1 ranged from 0.04 to 0.20 and n_2 from 0.01 to 0.02.

equation described the data because the F-statistic, measuring the extent to which the equation represented the data (Table 1), was the highest for this equation when the data was fitted to 58 kinetic equations (Tablecurve 2D, Jandel Scientific, San Rafael, CA).

Rate constants, k_1 and k_2, listed in Table 1 indicated that the rate of decrease in crushing strength with time is predominantly a second order process, $k_1 = 55$ and $k_2 = 68$ N/min. As the mixer volume increased, the second-order component of the mixing process accelerated and the first-order component slowed down. Mixing in the largest volume mixer, 2250 cm^3, was well described by only the second-order equation, $r^2 =$ and the F-statistic = 1780. The second order rate constant was 132 N/min. This was significantly higher than the value listed in Table 1.

Results in Fig. 1 also showed that significant different crushing strengths between mixers with different sizes were obtained from 8 min mixing time and longer ($P \leq 0.05$). The curves in Fig. 1 levelled after mixing times longer than 60 min and the values for crushing strength after 128 min represent the limiting crushing strength that was reached under the experimental conditions studied. Measured and calculated limiting crushing strength values, Table 1, were not significantly different. These limiting values decreased significantly with an increase in mixer size. Mean crushing strengths after 128 min mixing were 20 N for tablets prepared from mixtures mixed in the smallest mixer and 13 N for tablets prepared from mixtures mixed in the largest mixer.

In Fig. 2 the limiting crushing strength is plotted against the logarithm of mixer volume. The correlation coefficient was 0.98 indicating a reasonable fit. This showed that although the three mixers were geometrically similar they did not produce similar mixtures. Differences could be the result of different kinematic and dynamic properties of the mixers. In larger mixers, an increase in the kinematic and dynamic forces is produced which may cause an increase in the speed at which the material is being exchanged, both horizontally and vertically, in the mixer. This leads to an increase in mixing intensity resulting in a decrease in tablet crushing strength due to improved magnesium stearate film formation over the surface of the microcrystalline cellulose particles.

In Fig. 3, the effect of mixer load on the limiting crushing strength of tablets prepared from mixtures mixed in the small mixer is shown. If the decrease in tablet crushing strength was the result of an increase in mixing intensity, due to an increase in the exchange of material both horizontally and vertically in the V-mixer, then mixer load would also have an effect on the crushing strength. An increase in mixing time again led to a decrease in crushing strength, irrespective of mixer load. However, after 128 min, a limiting crushing strength is achieved and a significant decrease in this crushing strength ($P \leq 0.05$) was observed with a decrease in mixer load. After 128 min the tablet crushing strength decreased from 30 N at a mixer load of 33% to 20 N at a mixer load of 18%, Fig. 3. The limiting crushing strength stayed constant at small loads (18–25%) but increased significantly when the mixer load increase from 25 to 29%. A further increase in load from 29 to 33% also caused a significant increase in the limiting crushing strength. These changes, shown in Fig. 3, could be because bigger mixer loads resulted in less movement and a decrease in the extend whereby material was being exchanged inside the mixer.

Results obtained during this investigation showed that an increase in mixer size caused an increase in mixing although the mixers were geometrically similar. This was probably due to differences in the kinematic and dynamic properties of the mixers. There was also a

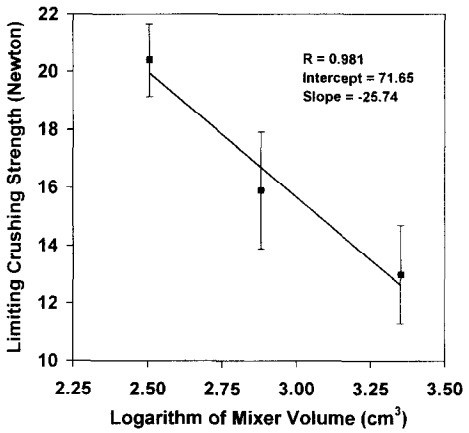

Fig. 2. The limiting crushing strength as a function of the logarithm of the volume of the V-mixer. Markers represents the mean and error bars, the S.D. measured values and the solid line, the best fit.

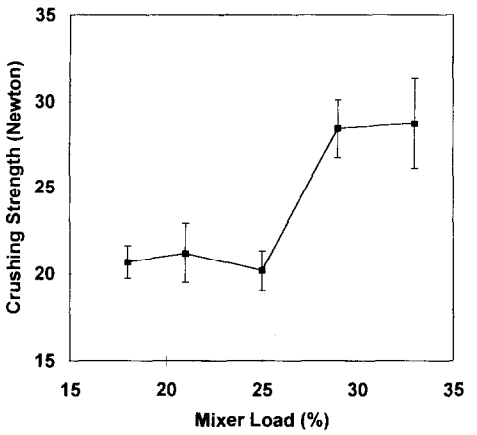

Fig. 3. The effect of V-mixer load on the limiting crushing strength of tablets prepared from mixtures mixed in the small mixer.

linear relationship between the limiting crushing strength and the logarithm of the mixer volume if the mixer load was the same. A decrease in mixer load led to a further increase in mixing resulting in an additional decrease in tablet crushing strength. During scale-up of the lubricant mixing process in V-mixers, mixing depended mainly on the extent of exchange of material inside the mixer. Both an increase in mixer size and decrease in mixer volume led to an increase in extend that material was being exchanged inside the mixer, resulting in better mixing and a decrease in tablet crushing strength. The kinetics of the decrease in crushing strength was best described by the sum of two separate processes, one first-order the other second-order. Overall the faster second-order process dominated mixing.

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