Drug Development and Industrial Pharmacy, 24(1), 81–88 (1998)

COMMUNICATION

Evaluation of the Mixing Effectiveness of a New Powder Mixer

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ABSTRACT

The effectiveness of the new powder mixer Canguro J tumbler was evaluated using lactose, microcrystalline cellulose, and salicylic acid as chemical indicator with the ratio 88:10:2 (w/w). The mixing time, the speed of the tumbler (rpm), its inclination, and filling percentage were varied in order to assess the limits of the mixer and the best parameters to use for obtaining a mixture as uniform as possible. The same experiments were then repeated after addition of 1% (w/w) magnesium stearate to the mixture of powders. The efficiency in the distribution of this lubricant was estimated by the progressive hardness reduction of the tablets derived from the compression of the powders, at a constant applied force. Finally, a comparison between Canguro J and a very efficient V-shaped mixer of the same capacity was performed. The results show that all investigated parameters influenced the mixing capability of Canguro J. The best effectiveness of the mixer occurred at the filling rate of 50% and a rotation speed of 20 rpm; in this case, Canguro J is even a little more effective than the V-shaped mixer. However, even at the filling rate of 70%, the same distribution uniformity of the powders can be obtained after a mixing time protraction of a few minutes.

INTRODUCTION

Solid–solid mixing is a very common and important operation in pharmaceutical industries which must be performed with well-established parameters in order to obtain homogeneous and reproducible blends. This can be obtained on an industrial scale by means of suitable mixers of different shape and size.

Canguro is a new industrial scale mixer, the shape of which is different from all other existing mixers (Fig. 1). In fact, it is a combination of a cone and a short parallelepiped. The specific model (Canguro J) taken into account

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Figure 1. Canguro Junior.

has a capacity of 50 liters, a rotation speed variable between 10 and 20 rpm, and the ability to rotate in sloped positions between 0 and 15°.

Several works have been performed to study the mixing effectiveness of mixers such as cubic, drum, biconic, planetary, and V-shaped mixers (1–14). The V-shaped mixer is world-wide considered one of the most effective.

The aim of this work was to verify if this new mixer could be classified among the most effective ones, and how experimental parameters could influence its mixing performance.

A series of experiments were carried out at different rotation speeds, mixing times, and slopes, using a specific mixture of lactose and microcrystalline cellulose to which was added, in the first step, 2% or 0.5% (w/w) of salicylic acid and then 1% (w/w) of magnesium stearate. In the first case, the distribution uniformity of the chemical indicator in the mixture of powders was checked; in the second case, the effect of the lubricant distribution on the crushing strength of tablets, directly compressed from the same mixture, was determined according to the method suggested in previous works (15,16). The results were also compared with those obtained from the same mixture processed with the V-shaped mixer.

MATERIALS AND METHODS

Scanning Electron Microscopy (SEM)

SEM analysis was carried out with a Stereoscan 360 scanning electron microscope (Cambridge Instruments Limited, Cambridge, UK) on the powders of salicylic acid, lactose, microcrystalline cellulose, and magnesium stearate, in order to obtain a visual image and evaluate differences of particle size and shape which could influence the mixing process.

V-shaped Mixer

First Phase

An amount of lactose (Tablettose EP, Meggle, Wasserburg, Germany), corresponding to 88% (w/w) of the final mixture, was mixed with an amount of microcrystalline cellulose (Microcel, Blanver, Brazil) equivalent to 10% (w/w) of the mixture, in the V-shaped mixer (50 liters capacity) for 15 min, at 25 rpm.

This mixer has a fixed rotation speed of 25 rpm.

Then, a quantity of salicylic acid, previously sieved, corresponding to 2% of the whole mass, was added, so that a final volume of 25 liters was reached. Finally, the mixing process was started and after 0.5, 1, 2, 4, 8, 16, and 32 min, 12 samples were withdrawn with a grain thief and analyzed spectrophotometrically at 303 nm with a Cary 1E UV-Vis spectrophotometer (Varian) in order to verify the salicylic acid content and, consequently, its distribution uniformity. All withdrawals of the 12 samples with the grain thief at every mixer stop were carried out in the same way, to give the best repeatability to this step.

Second Phase

Magnesium stearate, 1% (w/w), was added to the previously formed mixture and the mixing process was restarted. After 0.25, 0.5, 1, 2, 4, 8, 16, and 32 min, samples were withdrawn with a grain thief. Powders of the unlubricated blend and of all blended samples were compressed into tablets with a 15-station Kilian (Koln-Niehl, Germany) rotary press to evaluate the rate of hardness reduction, caused by a more uniform distribution of the lubricant around solid particles of the mixture, with the increase of the mixing time. The compression load was kept constant for all the tablets prepared, in order to obtain, for the unlubricated blend, an initial hardness of 15 kp, measured with an Erweka (Heusenstramm, Germany) TBH 30 hardness tester connected to an AT computer. In all cases, hardness values were the mean of 10 measurements.

Canguro Mixer

First Phase

An amount of lactose, corresponding to 88% (w/w) of the final mixture, was mixed with an amount of microcrystalline cellulose equivalent to 10% (w/w) of the mixture, in the Canguro Junior mixer (50 liters capacity; Zanchetta, Lucca, Italy) for 15 min, at 20 rpm.

Successively, a quantity of salicylic acid, previously sieved, corresponding to 2% of the whole mass, was added until a final volume of 25 or 35 liters was reached, corresponding to 50% and 70% of the mixer filling capacity, respectively. The mixing process was then started with a tumbler inclination of 15° and using two of the possible rotation speeds: 10 and 20 rpm. After 0.5, 1, 2, 4, 8, 16, and 32 min, 12 samples were withdrawn with a grain thief and analyzed spectrophotometrically at 303 nm to verify the salicylic acid content and, consequently, its distribution uniformity.

Second Phase

Magnesium stearate, 1% (w/w), was added to the previously formed mixture and the mixing process was restarted. After 0.25, 0.5, 1, 2, 4, 8, 16, and 32 min, samples were withdrawn with a grain thief. Powders of all blended samples were next compressed into tablets (in exactly the same way described for the V-shaped mixer) to evaluate the rate of hardness reduction, caused by a more uniform distribution of the lubricant around solid particles of the mixture, with the increase of the mixing time. In all cases, hardness values were the mean of 10 measurements.

Additional Experiments

The already described experimental design was repeated three more times at the following conditions: tumbler rotating at 0° inclination, use of 0.5% (w/w) of salicylic acid instead of 2%, and the two situations altogether.

Statistics

One-way ANOVA was performed on the experimental values of all series to show any significant differences.

RESULTS AND DISCUSSION

Scanning Electron Microscopy

Figures 2–5 show the SEM images (magnification 383×) of the powders of lactose, microcrystalline cellulose, salicylic acid, and magnesium stearate, respectively. Particularly, the shape of the long, thin salicylic, acid crystals is very different from those of the other powders, making it difficult to obtain a homogeneous dispersion of this chemical indicator. So, eventual good mixing results should be even more appreciated. However, at the end of the mixing process (Fig. 6), long needle-shaped crystals of salicylic acid are broken in very short fragments.

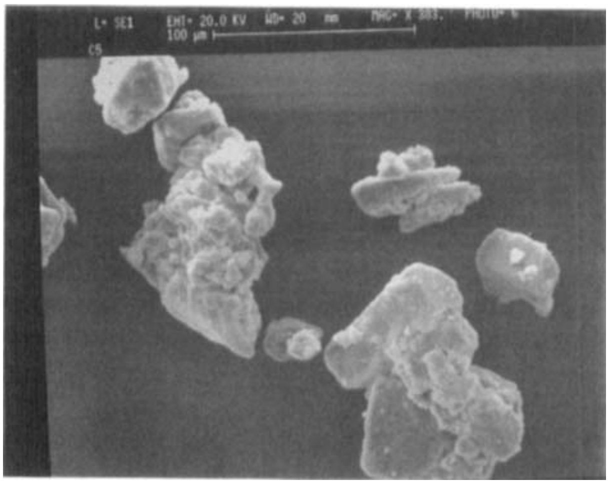


Figure 2. Powder of lactose (SEM).

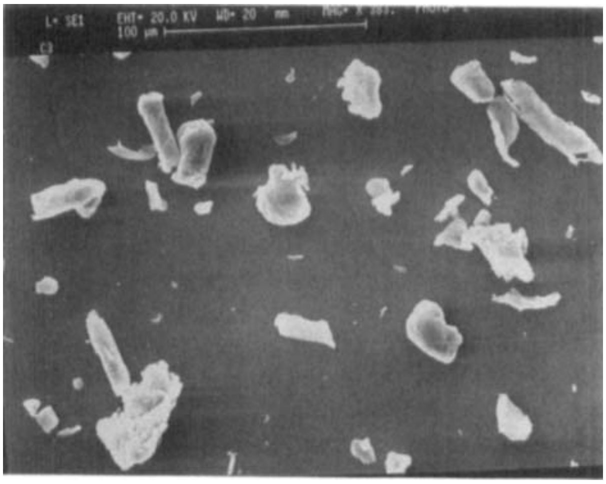
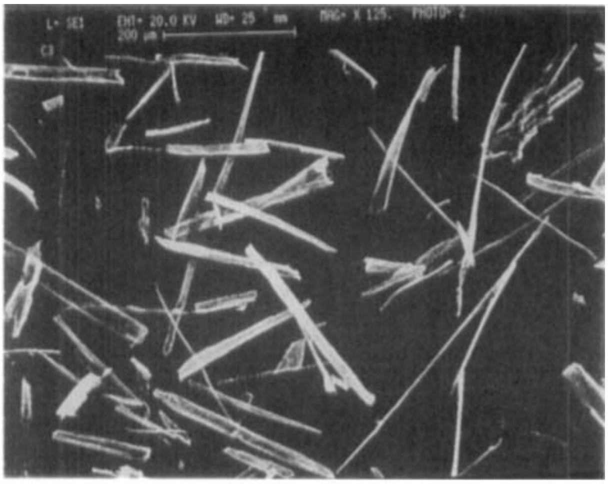


Figure 3. Powder of microcrystalline cellulose (SEM).

(a)



(b)

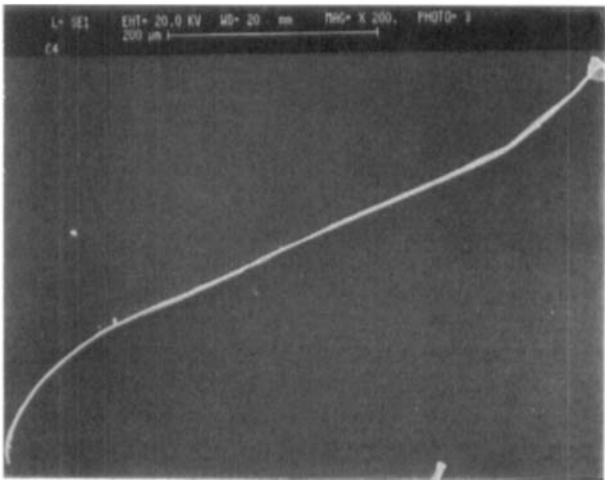


Figure 4. (a) Crystals of salicylic acid (SEM). (b) Single crystal of salicylic acid (SEM).

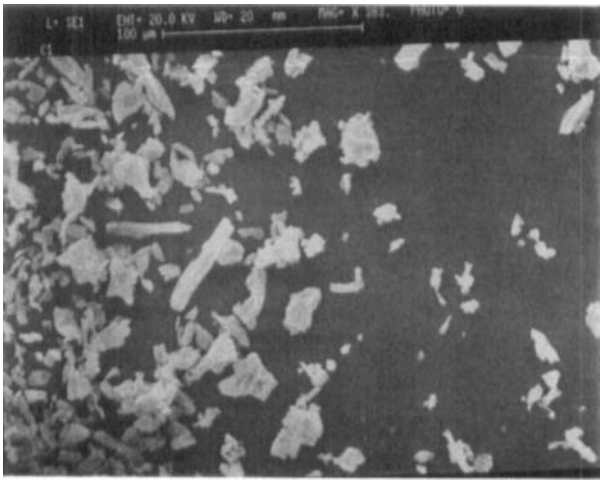


Figure 5. Powder of magnesium stearate (SEM).

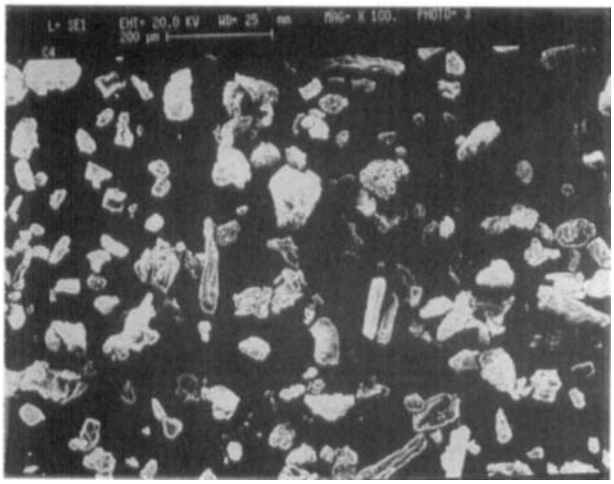


Figure 6. Powder at the end of the first phase (without magnesium stearate) of the mixing process.

Salicylic Acid Uniformity

Values reported for each considered minute are the mean of 12 samples. Standard deviation bars are omitted to avoid overlapping. Results shown by all figures are obviously valid for the mixing of the powders used.

Figure 7 shows the curves of the percentages of salicylic acid uniformity (2% of salicylic acid recovered in the sample is considered 100% of uniformity) against minutes for Canguro J rotating in sloped position (15°), loaded at 50% (19 rpm and 20 rpm) or 70% (10 rpm and 20 rpm) of its capacity, and using the 2% of chemical indicator, compared with the curve of the V-shaped mixer loaded at 50% of its volume.

The V-shaped mixer is confirmed to be very efficient since after 30 sec, a uniformity of 80% is reached.

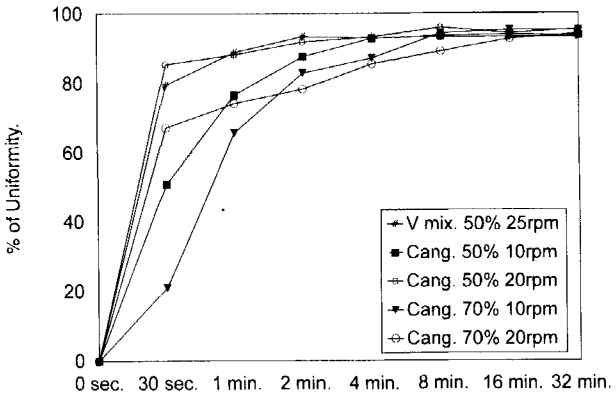
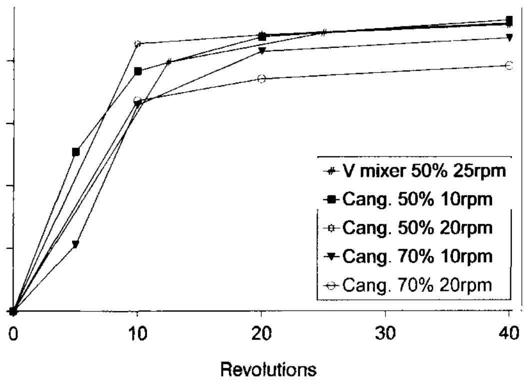


Figure 7. Effect of mixing time on the distribution uniformity of 2% salicylic acid.



Effect of revolutions on the distribution uniformity licylic acid.

ctedly, Canguro J, under certain conditions ad and 20 rpm rotation speed) is even a little ective, despite the lower rotation speed (and this good result). Besides, after 16 min, differences curves are no longer visible. This means that geneous mixture can be obtained also at the rotation speed or at higher load (70%). A load and a rotation speed of 20 rpm, are conditions ne best results, and a load of 70% with a rotaed of 10 rpm give the worst result. For this these basic conditions were used for further ents.

percentage of uniformity is reported against ns (Fig. 8) rather than minutes, a general ref the distance between curves is observed. This onstrates that the efficiency of a mixing process lepends on rotation speed.

e 9 shows the comparison between the best and t conditions either in sloped position (15°) or without inclination (0°). While there is practically no difference between the two trials with a load of 70%, under the best conditions (50% load and 20 rpm), the inclination of the tumbler seems to have some positive effect on the mixing performances.

Figure 10 shows the comparison between the best and the worst working conditions either with 2% or 0.5% of salicylic acid. The use of a 50% load and the maximal rotation speed provides practically identical results, independent from the percentage of salicylic acid used. However, with a powder load of 70%, the salicylic acid distribution is slowed down and even after 32 min, a lower percentage of uniformity is reached if a rotation speed of 10 rpm is used.

Figure 11 shows the comparison between the best and the worst conditions realized with 0.5% of salicylic acid either in sloped or not sloped position. In this case, if a small quantity of chemical indicator is used, the inclination of the tumbler does not remarkably influence

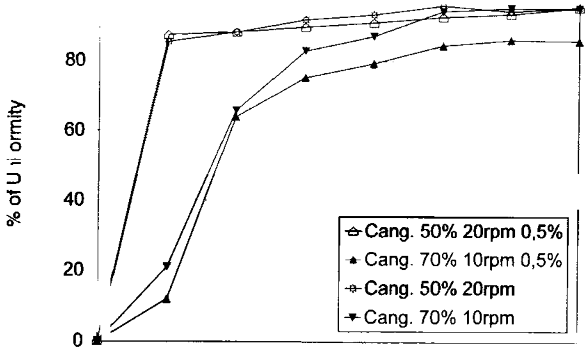
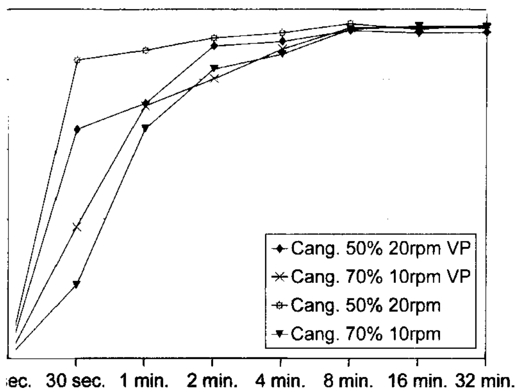


Figure 10. Comparison between the effects of mixing time on the distribution uniformity of 0.5% and 2% salicylic acid.



Effect of mixing time on the distribution unifor- % salicylic acid: comparison between sloped and not sition.

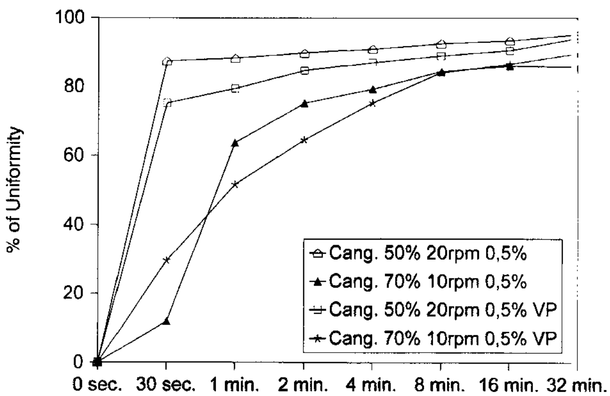


Figure 11. Effect of mixing time on the distribution uniformity of 0.5% salicylic acid: Comparison between sloped and not sloped position.

the effectiveness of the mixing process; the distance between the two sets of curves is only due to the different initial load of the mixer.

Hardness Reduction

Figure 12 shows the curves of tablets hardness reduction against minutes for Canguro J rotating in sloped position (15°), loaded at 50% (10 rpm and 20 rpm) or 70% (10 rpm and 20 rpm) of its capacity and using 1% of magnesium stearate, compared with the curve of the V-shaped mixer loaded at 50% of its volume.

A very fast decrease of hardness in all curves can be observed, but those obtained from a tumbler rotation speed of 10 rpm show a little lower lubricant distribution speed; it appears that for Canguro J, rotation speed is a more influential parameter than powder load.

Figure 12 substantially confirms the results of Fig. 6. In fact, after 2 min, hardness reduction of the tablets is practically complete in all curves; Canguro J, using a powder load of 50% and a rotation speed of 20 rpm, is even more effective than the V-shaped mixer. Also in this case, when results are expressed in revolutions (Fig. 13), overlapping tendency between curves can be noted.

Figure 14 shows the comparison between the best and the worst working conditions either in sloped position (15°) or without inclination (0°). The use of 1% magnesium stearate brings the same conclusions drawn from Fig. 3: there is practically no difference between the two trials with a load of 70%, but under the best conditions (50% load and 20 rpm), the inclination of the tumbler has a small positive effect on mixing capabilities.

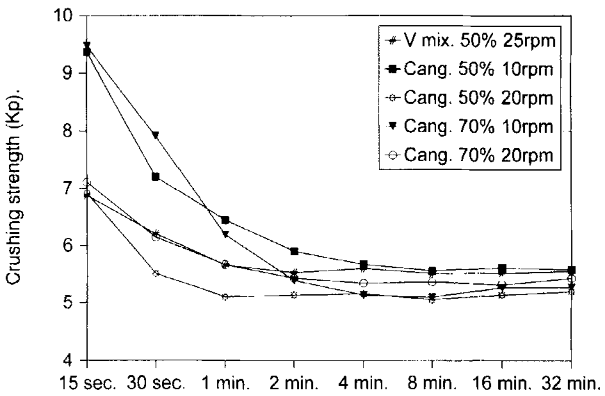


Figure 12. Effect of mixing time on 1% magnesium stearate influence on the crushing strength of tablets (sloped position).

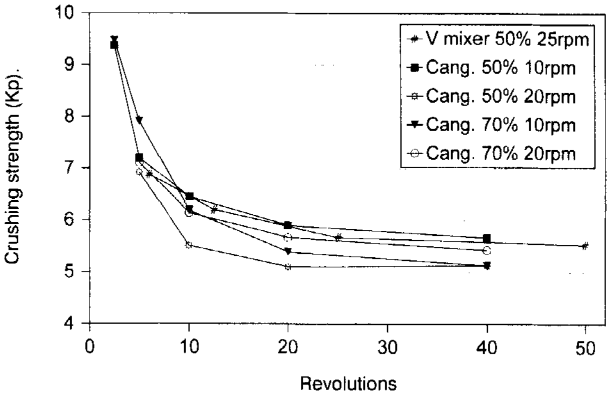


Figure 13. Effect of revolutions on 1% magnesium stearate influence on the crushing strength of tablets (sloped position).

Statistical Analysis

Tables 1 and 2 represent minutes after which one-way ANOVA (significance level 0.05), applied to values obtained from each mixing process (12 withdrawals for every stop of the mixer), reveals no significant difference between the series of 12 samples.

In practice, these "critical mixing minutes" indicate the time necessary to complete the mixing process under specific experimental parameters. A further prolongation of the mixing time is not expected to improve uniformity of the powder.

The first conclusion that can be drawn from Tables 1 and 2 is that magnesium stearate is distributed more quickly than salicylic acid, but, except for the 70% load

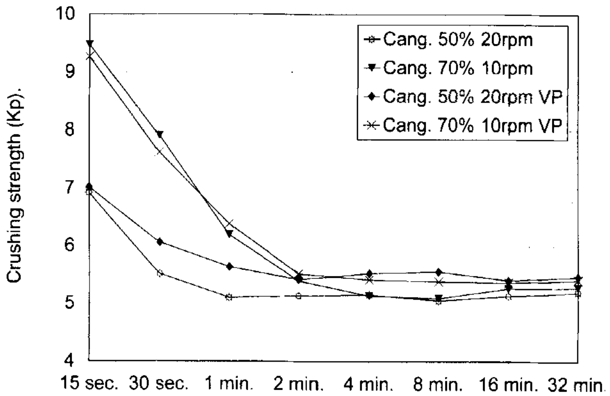


Figure 14. Effect of 1% magnesium stearate admixing on the crushing strength of tablets: comparison between sloped and not sloped positions.

Table 1

Critical Mixing Minutes for Chemical Indicator Distribution

Type	Load	rpm	% Salicylic Acid	Slope	Critical Mixing Minutes
V-mixer	50%	25	2	0°	1
Canguro	50%	10	2	15°	4
Canguro	50%	20	2	15°	2
Canguro	70%	10	2	15°	8
Canguro	70%	20	2	15°	8
Canguro	50%	20	2	0°	2
Canguro	70%	10	2	0°	8
Canguro	50%	20	0.5	15°	0.5
Canguro	70%	10	0.5	15°	2
Canguro	50%	20	0.5	0°	2
Canguro	70%	10	0.5	0°	8

Table 2

Critical Mixing Minutes for Magnesium Stearate Distribution

Type	Load	rpm	% Mg Stearate	Slope	Critical Mixing Minutes
V-mixer	50%	25	1	0°	0.5
Canguro	50%	10	1	15°	2
Canguro	50%	20	1	15°	0.5
Canguro	70%	10	1	15°	2
Canguro	70%	20	1	15°	0.5
Canguro	50%	20	1	0°	0.5
Canguro	70%	10	1	0°	1

and 20 rpm, the experimental parameters used have the same influence either on chemical indicator distribution or on lubricant distribution.

For salicylic acid, under the more effective mixing conditions (50% load and 20 rpm, 25 rpm for V-mixer), 2 min is enough to obtain homogeneous mixture; the other parameters do not have the same impact. After 8 min, even using the worst operating conditions, a good degree of uniformity is reached.

CONCLUSION

Canguro J is a very effective mixer, able to uniformly disperse in a mass of diluent even small quantities of drugs. Under certain conditions it is more efficient than the V-shaped mixer. Rotation speed and load are parameters which markedly influence uniformity of the mixture. Other parameters such as tumbler slope have only marginal influence in the mixing of the specific powders used.

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