The Use of Statistical Indices to Gauge the Mixing Efficiency of a Conical Screening Mill

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INTRODUCTION

A conical screen mill was incorporated into a direct compression process to help eliminate the presence of white agglomerates found in a direct compression lubricated mix, prior to compressing.

Conical screen mills have been demonstrated to be efficient size reduction mills (1–3) and have also been used to improve color dispersions (4). Because the impeller does not touch the screen, one major advantage of this type of mill over an oscillator is that the chances of screen breakage and introduction of unwanted metals are greatly reduced.

EXPERIMENTAL

Production lots of a dicalcium phosphate-based direct compression formula were sampled at various stages of manufacture. Conventional production methods used a V-blender for blending and an oscillator fitted with a No. 20 mesh screen for dispersing the lubricants. A Model 196 COMIL (COMIL, Quadro Inc., Park Ridge, New Jersey) was substituted using a 0.025-in.-thick screen having hole diameters of 0.032 in., yielding an open area of 28%. In both cases, a Stokes 513-35 tablet press was used to compress the powders into tablets.

Lots A and B were processed using an oscillator for production of tablets containing 2.5 mg of active ingredient. Lots C and D were processed using oscillator for production of tablets containing 5 mg of active ingredient and the mix contained white agglomerates. A COMIL was used in Lots E and F for production of tablets containing 2.5 mg of active ingredient and Lot G for production of tablets containing 5 mg of active ingredient.

Samples were taken from the lubricated powder in a V-blender using a sample thief. The thief was adjusted to collect approximately three times the weight of a tablet. The seven sampling regions are shown in Fig. 1. The assay was performed on a sample equal to the weight of a tablet and content is expressed as micrograms per milligram. A total of 30 samples (15 samples per side of the tablet press) was collected throughout the run and assayed. The results of each side were combined and are reported in micrograms per milligram to compensate for minor differences that can be encountered in tablet weights.

RESULTS

The content uniformity mean and RSD for these lots are summarized in Table I. The data were evaluated statistically to determine the influence of the COMIL process on uniformity of the active drug. Using the established quality control limits, the capability index, C_p, and the percentage of samples expected to fall outside of these limits were calculated and are given in Table II. These two measures fully describe a process with respect to the requirements: the potential price of nonconformance (C_p) and the actual price of nonconformance (percentages falling outside limits).

The capability index, C_p, is a measure of the potential of the process to meet requirements and is defined as

$$(\text{USL} - \text{LSL})/6s$$

where USL and LSL are the upper and lower quality control limits, respectively, and s is the standard deviation of the process. The C_p compares the width of the process requirements (i.e., USL-LSL) to the spread of the process output distribution (6s). Assuming that the data from the process has a Gaussian distribution, a C_p of 1 indicates that about 99% of the sampled points will fall between the limits *if the process is centered exactly in the middle of the limits*. The larger the C_p, the more samples potentially can meet the limit requirements (e.g., with a C_p of 2, more than 99.9999% of the samples can meet requirements); the smaller the C_p, the fewer the samples that meet requirements (e.g., with a C_p of 0.5, more than 13.0% of the samples will not meet requirements).

A process with a large value for C_p can still have 100% of its products fail to meet requirements. This would be the case if the mean of the process falls outside of the quality control limits. However, the larger the C_p, the closer the

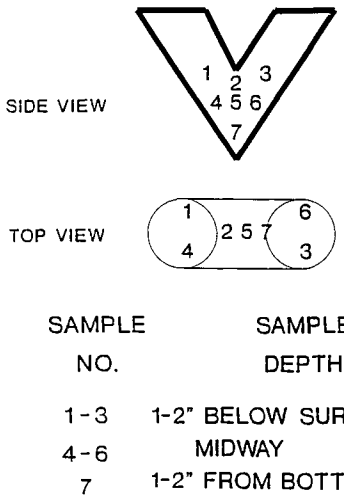

Fig. 1. Twin shell blender sampling points.

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Table I. Content Uniformity of Lubricated Mixtures and Compressed Tablets

Lot	Strength (mg)	Process	Sample collected	μg/mg			% RSD
				Theory	Mean	SD	
A	2.5	Oscillator	Mix	11.49	11.38	0.534	4.69
B	2.5	Oscillator	Mix	11.49	11.71	0.582	4.97
C	5.0	Oscillator	Mix	22.72	23.15	1.285	5.55
D	5.0	Oscillator	Mix	22.72	23.45	2.382	10.03
E	2.5	COMIL	Mix	11.49	11.66	0.092	0.79
			Tablets	11.49	11.51	0.115	1.00
F	2.5	COMIL	Mix	11.49	11.69	0.104	0.89
			Tablets	11.49	11.43	0.111	0.97
G	5.0	COMIL	Mix	22.72	23.14	0.278	1.20
			Tablets	22.72	22.62	0.274	1.21

process mean can be to a limit and still minimize the percentage of samples not meeting requirements.

The percentages above and below the limits are calculated using statistical theory. The distances the limits are from the mean are calculated and expressed in terms of the number of standard deviations. Then, assuming that the content uniformity is approximately normally distributed, the percentages corresponding to the distances are obtained from a z or t table.

The content uniformity distribution for some lots of lubricated sample is plotted in Figs. 2 and 3. From these plots it is obvious that use of the COMIL greatly improves content uniformity by decreasing the nonconformance and increasing the flexibility where the process must be centered. This same conclusion can be reached by comparing the C_p and predicted percentages falling outside the requirement limits for lots without COMIL to lots using COMIL. (Note: the assumption of the Gaussian distribution was not explicitly checked for these data, however, historically content uniformity data have been approximately Gaussian.)

For example, Lot A has a C_p of 1.07, compared to 5.51 for lot F, i.e., the process for Lot F has a much smaller potential nonconformance than that for Lot A. Further, in order for Lot A to achieve its potential, the lot mean must be centered very closely to the middle of the target limits, unlike Lot F, which, because of the large value for the C_p, has more flexibility. It comes as no surprise, therefore, that Lot A has a total of 1.88% of the samples with content uniformity values outside the target limits, compared to 0.0% for Lot F; i.e., it has the greater price of nonconformance.

The C_p and predicted nonconformance percentages for all the lots are listed in Table II. The statistics demonstrate that with the use of the COMIL process, the variability of the content uniformity has been greatly reduced and that, as a result, the process can be operated so that no samples fall outside of the established quality control limits.

From the above, it is clear that a process can be thoroughly described by the C_p and percentages above and below statistics. On the other hand, it is easier to use a single statistic, such as the RSD, to evaluate a process. In the above analysis the same conclusion regarding the use of the COMIL would have been reached by looking at the RSDs. The RSD, however, does not give an accurate picture of a process and its capability. For example, look at the hypothetical data in Table III. Based on the RSD, process C is the best, process D is the worst, and processes A and B are between these extremes and equivalent to each other. A different set of conclusions would be reached regarding the four processes from looking at Fig. 4. This example points out the shortcoming of the RSD. The RSD, calculated as (standard deviation/mean) × 100 includes information on the process location (i.e., mean) and process spread (i.e., standard deviation) but does not include in its calculations any information regarding the position of the process relative to the target specifications. Therefore, the RSD for a process can be decreased (indicating an improvement in the process) by

Table II. Quality Measures of the Lubricated Mixtures and Compressed Tablets

Process	Lot	Sample collected	Predicted or theoretical		C_p	C_{pk}
			% above	% below		
Oscillator	A	Mix	0.7	1.18	1.07	1.00
Oscillator	B	Mix	2.1	0.79	0.99	0.86
Oscillator	C	Mix	2.97	1.22	0.88	0.77
Oscillator	D	Mix	14.9	6.44	0.48	0.38
COMIL	E	Mix	0	0	6.22	5.62
		Tablets	0	0	4.98	4.93
COMIL	F	Mix	0	0	5.51	4.87
		Tablets	0	0	5.17	4.98
COMIL	G	Mix	0	0	4.09	3.59
		Tablets	0	0	4.15	4.03

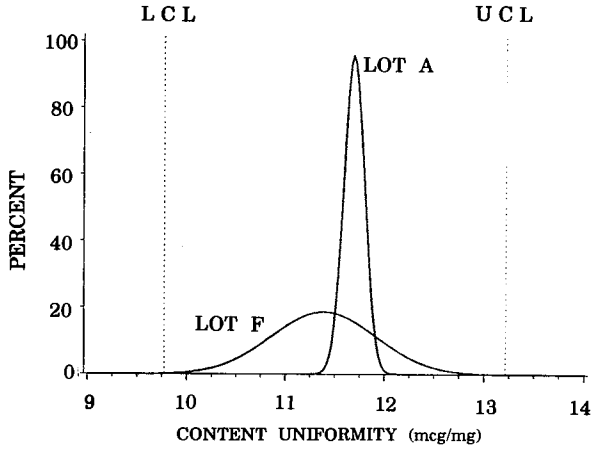

Fig. 2. Distribution of content uniformity of a lubricated mixture of a 2.5-mg dose. Lot A represents the standard oscillator process, whereas Lot F represents the distribution using a conical screening mill process.

Table III. Hypothetical Data

	Lot			
	A	B	C	D
	20.4	28.3	26.8	20.1
	18.6	26.5	25.0	17.8
	21.7	24.2	28.2	21.9
	21.6	27.4	28.0	21.7
	21.1	27.6	27.5	21.0
	20.6	31.5	27.0	20.4
	21.2	26.8	27.6	21.1
	24.2	28.1	30.6	25.0
	22.5	28.2	28.9	22.8
	21.8	29.3	28.1	21.8
RSD	6.8	6.8	5.2	8.7
Mean	21.4	27.8	27.8	21.4
SD	1.5	1.9	1.5	1.9
C_{pk}	0.8	−0.5	−0.6	0.6

simply increasing the mean (compare process A with process C, or process D with process B). To avoid such misinterpretations with the RSD, the value of the mean needs to be used along with the RSD in the interpretation. However, use of the mean alongside the RSD runs contrary to using the RSD as a single, tell-all statistic.

The C_{pk} index overcomes this problem with the RSD. The C_{pk} is equal to the smaller of C_{pl} and C_{po}, where C_{pl} = (mean − LSL)/3s and C_{po} = (USL − mean)/3s. The interpretation of C_{pk} is similar to that for C_p except that C_{pk} measures what is actually happening, not potentially. A C_{pk} values of less than 1 indicates a process with product falling outside the specifications, a value between 1 and 1.33 indicates a process that just meets target specifications, and a value greater than 1.3 indicates a process that easily meets targets specifications. Furthermore, if the process has an approximately normal distribution, the percentage of process output that falls outside of the target specifications can be determined from the value of the C_{pk} much like for the C_p index.

The values calculated for the C_{pk} index for the lots investigated are given in Table II. The same conclusion regarding the use of the COMIL would have been reached by examining the C_{pk} index.

CONCLUSION

The use of a COMIL, implemented primarily to minimize active drug agglomerates, improved the distribution of active ingredient of the lubricated mix and tablets. The shearing action of the mill impeller is thought to be the primary factor for this improvement in mixing. The dual action of conical screening mills (e.g., size reduction and mixing action) makes this equipment more desirable than the use of traditional oscillators.

Further, the C_p, C_{pk}, and percentage outside of target are easily calculated indices which have proven useful in quantifying effects of process changes on measurable attributes. Additional information regarding these statistics can be found in the paper by Kane (5).

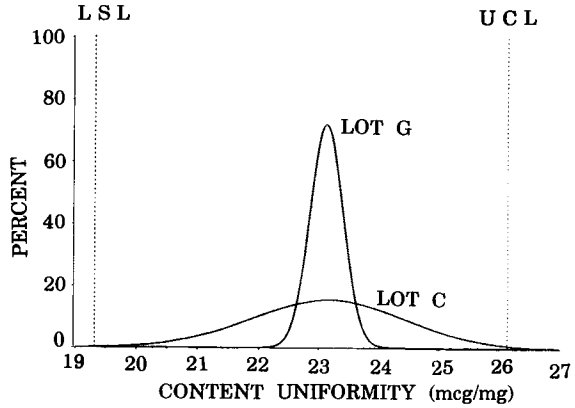

Fig. 3. Distribution of content uniformity of a lubricated mixture of a 5-mg dose. Lot C represents the standard oscillator process, whereas Lot G represents the distribution using a conical screening mill process.

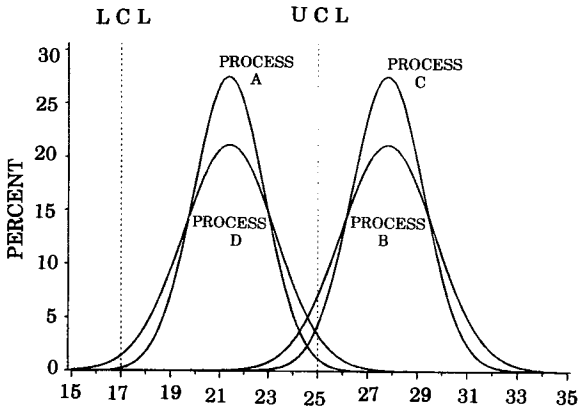

Fig. 4. Hypothetical content uniformity distributions that depict potential misinterpretations of process improvement when relative standard deviation (RSD) values are used.

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