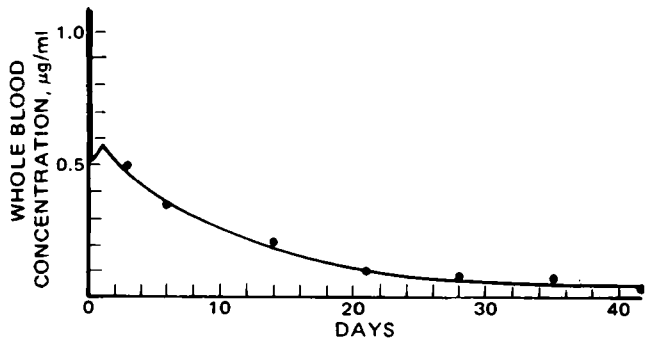

Figure 4—*Time course of the whole blood mefloquine concentration in a beagle dog given a single 250-mg tablet.*

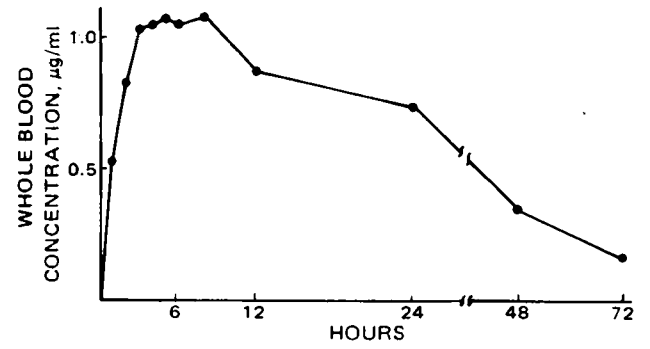

Figure 5—*Time course of the average whole blood II concentration in two beagle dogs given 250-mg tablets.*

5 hr, and then decreased slowly. From the semilogarithmic time course data plot, an elimination half-life and an elimination rate constant for II were estimated to be 24.8 hr and 0.028 hr^{-1}, respectively. The results for I and II suggested that I is about 10 times more persistent than II in its elimination from dogs.

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Powder Homogenization Using a Hammer Mill

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Abstract □ Hammer mill applicability in the comixing milling operation is discussed with reference to a 1:1000 microfine salicylic acid–sucrose binary system. The hammer mill would not serve as a mixing machine under most circumstances because of the low holdup capacity. Grinding of pure materials was preferable to mixture grinding since active ingredients could be lost during the milling operation. Remixing was always necessary following comminution of the mixture in the hammer mill. Grinding followed by remixing considerably enhanced mixture homogeneity. A large size range was produced by comminution, which resulted in the segregation of ordered units such that the final mixture could be described as a randomized ordered mixture.

Keyphrases □ Powders—homogenization using a hammer mill, sucrose–salicylic acid □ Pharmaceutical formulations—powders, homogenization using a hammer mill, sucrose–salicylic acid □ Hammer mill—powder homogenization, sucrose–salicylic acid

Many raw materials are supplied in a form requiring no further processing. However, grinding or cutting may be indicated with waxes and vegetable drugs or when agglomeration of starting materials occurs on storage. If grinding is a necessary stage in manufacturing or is required to attain a desired homogeneity, the hammer mill is frequently used for comminution.

Mixing is impossible when σ_R, the theoretical standard deviation of the fully randomized system, is equal to or greater than σ_A, the specification index (1). The σ_R value can be calculated from the sample size and the known proportions of the powders to be mixed using Lacey's equation (2):

$$\sigma_R^2 = \frac{XY}{N} \qquad \text{(Eq. 1)}$$

where X and Y are the proportions of the two ingredients and N is the number of particles in the samples. The σ_A value is calculated from the desired homogeneity of the powder mixture (3). The value of σ_R can be reduced by increasing the particle number per sample, which implies that size reduction is necessary.

Even though the hammer mill has been extensively used in the pharmaceutical industry for size reduction, limited evaluation has been carried out on the mixing performance of industrial comminution equipment. Most equipment used in comminution was ineffective for powder mixing operations because of the low holdup capacity (4). With nonflowing materials, passing a preblend through a ham-

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Table I—Actual Mixing Time (Minutes) for Each Preblend

Preblend	Initial Mixing in Cube Mixer	Remixing after Passing through Hammer Mill Once	Remixing after Passing through Hammer Mill Twice	Final Remixing after Passing through Hammer Mill Three Times
1	1	1 (2)	2 (4)	6 (10)
2	2	2 (4)	6 (10)	10 (20)
3	4	6 (10)	10 (20)	20 (40)
4	160	160 (320)	—	—

mer mill increased the mixture homogeneity (5). The main problems associated with grinding were cost, contamination, and segregation (6).

Random mixing theory has been established for 25 years, but, in practice, mixtures rarely attain full randomization due to particulate size, shape, and density differences. Ordered mixtures exist in which one constituent adheres onto the surface of the other in a fixed proportion (7). The purpose of the present work was to investigate the application of the hammer mill to powder mixing operations with particular reference to ordered mixing. The binary system used had previously been shown to give an ordered mixture under some circumstances.

EXPERIMENTAL

Sucrose was the oversized fraction remaining when granulated sugar[1] was sieved through a 630-μm mesh screen[2]. Salicylic acid was previously sized using an air permeability technique (at 3.4-μm average diameter).

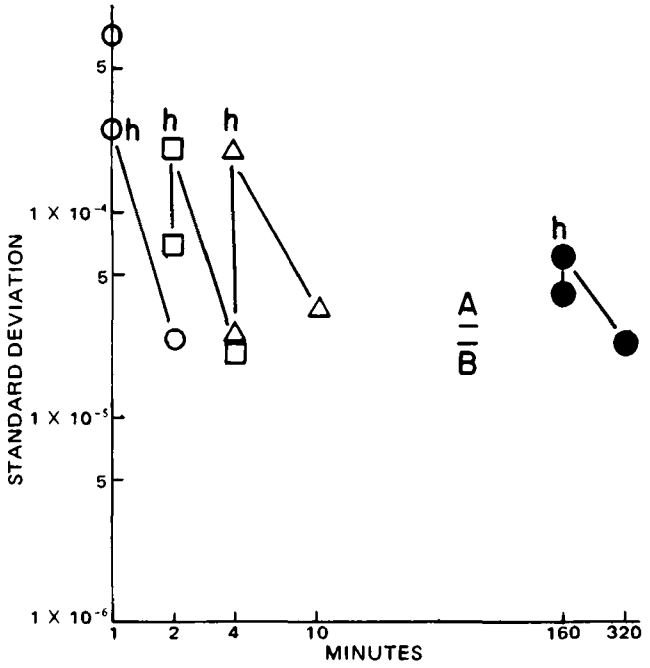

Figure 1—*Effect of passing the salicylic acid–sucrose mixture (1:1000) through the hammer mill once. Key: A and B, standard deviations of a fully randomized equivalent system before and after passing through the hammer mill, respectively;* h, *mixture that has been passed through the hammer mill;* ○, *Preblend 1;* □, *Preblend 2;* △, *Preblend 3; and* ●, *Preblend 4.*

[1] C. S. R. brand 1A.
[2] No. 29 mesh.

Table II—Sucrose Size Distribution [a] (Weight Fraction Undersize) before and after Passing through the Hammer Mill

Particle Size, μm	Number of Passes through Hammer Mill			
	Zero	One	Two	Three
1003	1	1	1	1
853	0.930			
710	0.492	0.902	0.985	0.999
600	0.065	0.710	0.923	0.988
500	0.016	0.565	0.834	0.956
425		0.516	0.788	0.932
355		0.468	0.731	0.895
250		0.380	0.605	0.794
180		0.291	0.459	0.645
150		0.264	0.415	0.593
75		0.163	0.248	0.364
<75		0	0	0
Σfw	335.63 μg	131.80 μg	47.64 μg	16.12 μg

[a] Determined by a nest of sieves and a sieve shaker.

The sucrose size distribution was determined using a nest of sieves and a test sieve-shaker[3]. The sucrose and salicylic acid densities were determined by air comparison pycnometry to be 1.44 and 1.59 g/cm, respectively (8).

Preblends were prepared by mixing 3.6 kg of powders (salicylic acid–sucrose, 1:1000) in a 7.5-kg stainless steel revolvo-cube mixer[4] for 1, 2, 4, or 160 min. Each preblend was subsequently passed through the hammer mill[5]. The revolvo-cube mixer was fitted with an internal agitator rotating at 37 rpm while the cube mixer rotated at 17 rpm.

After grinding, the mixture was reloaded into the revolvo-cube mixer and remixed according to the procedure given in Table I. The whole comminution and remixing process was repeated three times. Twenty random samples (250 mg) were taken immediately before grinding and before remixing in the revolvo-cube mixer at each cycle for each preblend. To investigate the sample size effect on the standard deviation, different sample weights were collected using a set of concentric cylindrical sampling thieves. The samples were individually assayed by dissolving the contents in 50% ethanol. The absorbance was measured at 300 nm using a spectrophotometer[6] connected to an autosampling unit. The blank consisted of 50% ethanol with an equivalent amount of sucrose. For

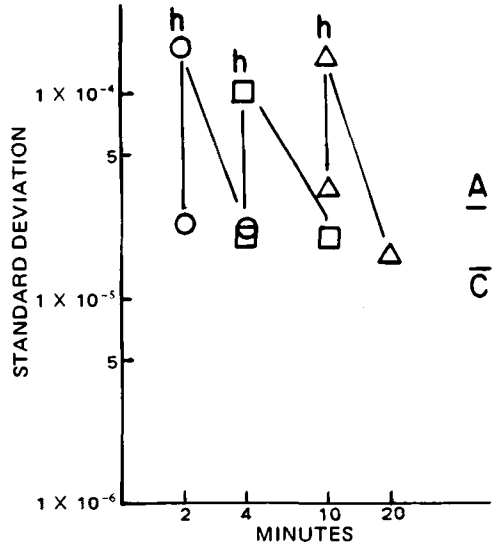

Figure 2—*Effect of passing the salicylic acid–sucrose mixture (1:1000) through the hammer mill twice. Key: A and C, standard deviations of a fully randomized equivalent system before and after passing through the hammer mill twice, respectively;* h, *mixture that has been passed through the hammer mill;* ○, *Preblend 1;* □, *Preblend 2; and* △, *Preblend 3.*

[3] A. C. Cheers Pty. Ltd.
[4] Garwood and Goodyear Pty. Ltd.
[5] Bauhnecht (Glen Creston Ltd.).
[6] Techtron model 634, Varian.

Table III—Salicylic Acid Content (Percent) for Each Group of 20 Samples Taken at Various Stages of the Experiment

Stage[a]	Preblend 1	2	3	4
m	112.7	89.9	98.7	96.8
m/h	100.8	109.1	97.4	100.0
m/h/m	99.5	101.2	98.5	103.9
m/h/m/h	98.0	95.6	89.4	
m/h/m/h/m	99.4	96.9	96.4	
m/h/m/h/m/h	94.8	95.4	90.1	
m/h/m/h/m/h/m	95.3	96.3	93.6	

[a] *m* = a single stage of mixing in the cube mixer, and *h* = a single passage through the hammer mill.

comparison, data previously obtained using salicylic acid and sucrose mixtures in a revolvo-cube mixer were used (8).

RESULTS

The sucrose size distribution is shown in Table II; the median diameter was 710 μm. The hammer mill comminution effect resulted in size reduction as the mix was passed through the hammer mill each time (Table II). Mixing was examined by the analysis of the samples removed at various stages, *i.e.*, after mixing and/or milling. The standard sample concentration deviation was calculated from:

$$S = \sqrt{\frac{\Sigma(x_i - \bar{x})^2}{n - 1}} \qquad \text{(Eq. 2)}$$

where x_i was the sample concentration and $\bar{x}$ was the mean sample concentration estimated from n number of samples.

Preblends were investigated after 1, 2, 4, and 160 min (Preblends 1–4, respectively). Figures 1–3 show the effect of passing the four preblends through the hammer mill once, twice, and three times. Preblend 4 was only passed through the hammer mill once. The graphs are plots of standard deviation against time. The *x*-axis is the cumulative time that the mixture was mixed in the revolvo-cube mixer.

Figure 4 shows the mixing of salicylic acid and sucrose or icing sugar in the revolvo-cube mixer. The effect of sample size on the standard deviation for Preblend 3 is shown in Fig. 5. Table III shows the mean salicylic acid content for the four preblends at different stages.

DISCUSSION

Figures 1–3 indicate that grinding should never be the last stage in any mixing operation. The comminution effect of the hammer mill induces segregation due to size differences; since the holdup capacity of the mill

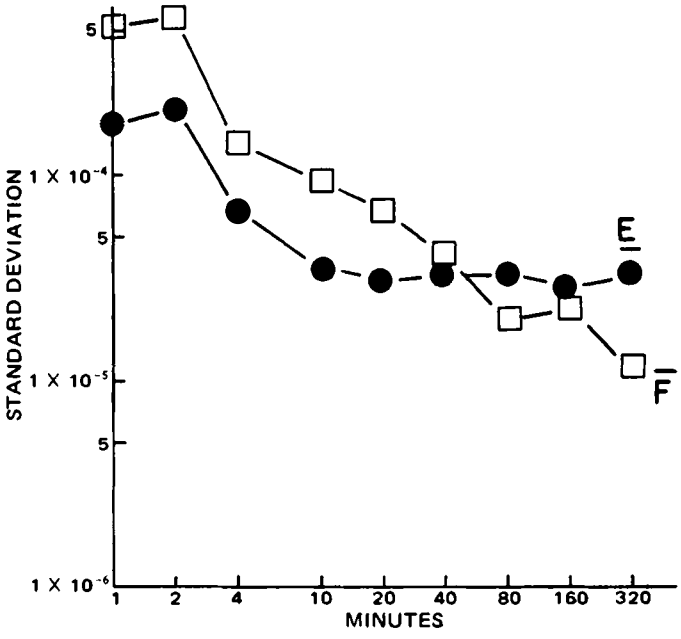

Figure 4—*Mixing of salicylic acid and sucrose/icing sugar (1:1000) in a cube mixer. Key:* E *and* F, *theoretical deviations of fully randomized mixtures of salicylic acid and sucrose and salicylic acid and icing sugar, respectively;* ●, *coarse sucrose system; and* □, *fine icing sugar system.*

is so low, no general mixing is possible. Therefore, before the materials are processed further, they must be mixed to improve homogeneity. Of the four different preblends, homogeneity increased during milling only when the preblend has been mixed in the cube mixer for the very limited period of 1 min.

The value of σ_R, the theoretical standard deviation of a fully randomized system, was calculated (9). There was a slight increase in mixture homogeneity through each cycle. This effect probably was due to the particle-size reduction and particles number increase.

If grinding is a necessary stage in the manufacturing process, it may be desirable to reduce the size of pure materials instead of the whole mixture. Table III shows the slight salicylic acid content decrease at each stage. Because of the highly cohesive microfine salicylic acid, the vigorous hammer grinding action possibly produces electrically charged fine particles and consequent particle attraction onto the mill and collecting bag walls. Thus, the salicylic acid content could vary from batch to batch.

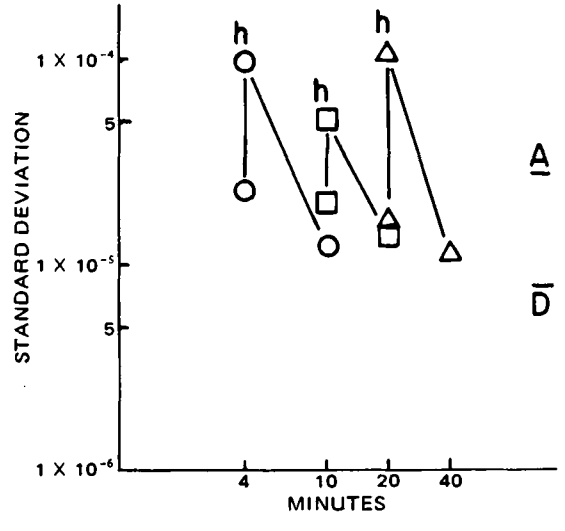

Figure 3—*Effect of passing the salicylic acid–sucrose mixture (1:1000) through the hammer mill three times. Key: A and D, standard deviations of a fully randomized equivalent system before and after passing through the hammer mill three times, respectively;* h, *mixture that has been passed through the hammer mill;* ○, *Preblend 1;* □, *Preblend 2; and* △, *Preblend 3.*

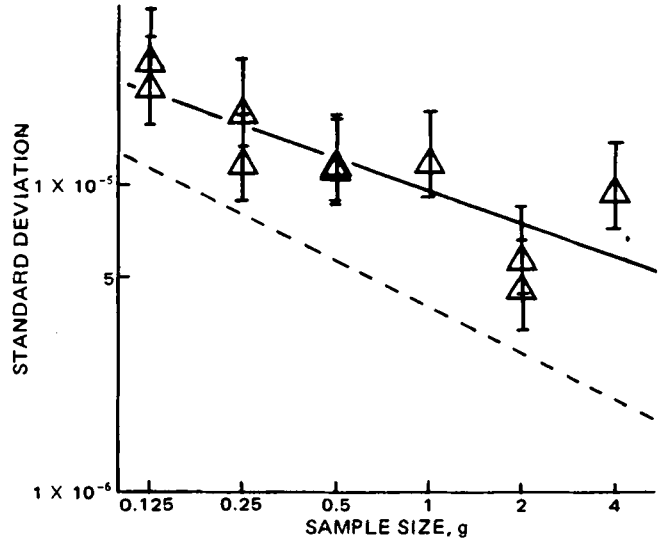

Figure 5—*Effect of sample size on standard deviation for Preblend 3 that was remixed after passing through the hammer mill three times. The dotted line represents the standard deviation for a fully equivalent randomized system. Error bars are 95% confidence limits for individual results.*

The active ingredient loss was only significant after three passes through the hammer mill.

Comparison of Fig. 1 with Fig. 4 shows that if the materials could be purchased in a fine form, it would probably be more economical to mix the preground fine material instead of grinding and mixing the coarser powders. The ordered mixture formation rate is slow when fine–fine components are mixed in a revolvo-cube mixer. With hammer mill mixture grinding, new surfaces are created by fracture of the coarse crystals. This procedure provides more area for drug particle adhesion. Furthermore, aggregates are broken down more rapidly in the hammer mill to facilitate mixing. Nevertheless, the cost of longer mixing time in the revolvo-cube mixer for fine–fine mixtures will be compensated by less handling of the mix than when the hammer mill is used.

Figure 4 also shows the mixing of a fine–coarse system in a revolvo-cube mixer where the desired degree of homogeneity is achieved after 10 min and the ordered mixture is stable and not prone to segregation (8). Even though homogeneity increases for fine particles, other problems such as fine powder flow (10) and storage effects (11) cannot be overlooked.

The sample size effect on the standard deviation for Preblend 3 is shown in Fig. 5. For a randomized mixture, the slope of the line will be −0.5. For an ordered mixture, it will approach zero. The 95% confidence limits for the slope were −0.554–−0.166. The mixture could not be classified as either completely randomized or completely ordered. In fact, it may have been a mixture of both systems, a description that may satisfy most powder mixtures used in pharmaceutical practice. A system with a large particle-size range is unlikely to be fully randomized due to size segregation. In practice, some degree of adhesional-type ordered mixture (12) may be formed. Due to the size differences of carrier particles, they will undergo ordered unit segregation (13, 14). Further mixing of this system will produce the randomized ordered unit powder mixture.

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Vehicle Effects on Ocular Drug Bioavailability III: Shear-Facilitated Pilocarpine Release from Ointments

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Abstract □ Pilocarpine release from water-in-oil emulsion ointments was studied *in vitro* and *in vivo*, using albino rabbits. Pilocarpine release from the vehicle to the ocular fluids was dependent on shear, *i.e.*, blinking, and the dosing system emulsifying efficiency. A mechanical shearing component was vital for correlating corneal drug penetration and the *in vitro* pilocarpine release pattern. Simple diffusion studies with the vehicles did not predict drug *in vivo* release, but the ointment systems were all superior to an aqueous pilocarpine solution. Incorporation of a mechanical shearing component to mimic blinking gave good correlation of *in vitro* and *in vivo* results. Also, increasing the vehicle emulsifying efficiency by surfactant addition decreased shear-facilitated drug release and *in vivo* performance. Finally, increasing the internal aqueous phase volume fraction decreased *in vivo* performance and was linked to the influence of effective drug concentration in the vehicle.

Keyphrases □ Dosage forms, ocular—pilocarpine, shear-facilitated release, ointments □ Pilocarpine—release, shear facilitated, ocular ointments □ Shear—facilitation of pilocarpine release from ocular ointments □ Ointments—pilocarpine, shear-facilitated release, ocular

Important considerations in vehicle design are the anatomical and physiological aspects of the drug delivery site. To improve drug bioavailability, ocular drug delivery system designs are based on comfort, contact time, and dose volume, each of which recognizes an important anatomical/physiological constraint. An additional ocular limitation is blinking, which can both increase and decrease drug bioavailability. On the positive side, blinking spreads instilled solution or ointment across the cornea, thus promoting corneal contact and drug absorption. On the negative side, it forces drug away from the precorneal area and into the drainage apparatus.

An important blinking feature is the shear that occurs when a vehicle is placed in the eye and blinking occurs. The proximity of the eyelids to the eyeball exposes an instilled vehicle to a considerable shearing stress during blinking. Non-Newtonian fluid vehicles should undergo rheological changes during blinking, and ointments should have an altered drug release profile. This report describes an ointment drug release that is dependent on blinking and on the shear created by blinking.

Drug solubility, prolonged contact time, and modest sustained release are some positive features of ointments. Unfortunately, ointments sometimes create blurred vision and are apparently less accepted by the patient than simple aqueous solutions. Nevertheless, one generally has greater control over drug release from an ointment than from a corresponding aqueous based product in terms of drug solubility, emulsion *versus* nonemulsion form, and contact time. Generally, drug release from an ointment is attributed to partitioning and/or diffusion, depending on the drug properties and the specific vehicle selected. A third possibility for drug release, specifically from water-

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