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A Comparison of Interaction and Solvent Deposition Mixing

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ABSTRACT

The mixing of microingredients with diluents may be conducted by various methods. The purpose of this report is to compare the uniformity of mixing of finely powdered reserpine after mixing by an interactive and a solvent deposition method. Reserpine was used in concentrations of 0.25% with Avicel PH 102 and Sorbit Instant as carrier materials. The uniformity of the mixtures was compared by coefficients of variation (CV) of the content of powder or tablet samples. The dissolution of powder samples was measured in a rotating bottle apparatus. Interactive mixing with Avicel produced samples with larger variation in reserine content compared to solvent deposition. The variation in content was not significantly different when the drug was mixed interactively or by solvent deposition on Sorbit. Smaller coefficients of variation in content were observed for tablet samples compared to powder samples in most cases. The CVs obtained with powder samples for all the mixtures, except for solvent deposition on Avicel, were larger than 5% and would therefore not comply with pharmaceutical content uniformly standards. The CVs for all tablet samples, however, were less than 5%, and based on these results all the mixtures were sufficiently mixed so that the tablets complied with content uniformity standards. The dissolution profiles were not influenced by mixing method.

INTRODUCTION

The mixing of powders to ensure uniformity of dose is a critical step in the manufacture of pharmaceuticals. Train (1) discussed a general approach to the mixing of pharmaceutical solids and concluded that variation in potency may be attributed to a mixing problem rather than any other cause in the processing step. A potent medicinal compound that constitutes only a fraction of a percent of the total blend must be mixed to a uniformity within acceptable safety limits. Potent medicinal compounds are frequently micronized to improve bioavailability. Micronization often produces cohesive particles which aggregates and thus hinders the randomization and therefor the mixing of individual particles.

The mixing of microingredients with diluents may be conducted by various methods (2). In the solvent deposition method the drug is distributed by spraying a solution of the drug on a carrier material. The solvent is evaporated after mixing is completed, which leaves the drug deposited on the carrier. In ordered, or interactive, mixing the micronized medicinal compound is mixed because the drug particles are absorbed on particles of a carrier excipient (3). Interactive mixing increases the dissolution characteristics of fine powder drugs which have a low water solubility (4). The mixing process breaks agglomerates of drug particles, which causes an increase in the surface available for dissolution.

The purpose of this report is to compare the uniformity of mixing and the dissolution characteristics of reserpine when mixed by interactive mixing and by a solvent deposition method. Two commercial carrier materials were used with a reserpine concentration of 0.25% or 0.25 mg per 100-mg tablet.

MATERIALS AND METHODS

Materials

All materials were obtained from commercial sources. Sorbit Instant, lot number 850M263240, was obtained from Merck; and Avicel PH 102, low number 7734 was obtained from FMC. Both carriers are granular, free-flowing powders. Reserpine was obtained from CH Boeringer Sohn. The particle size distribution of reserpine was determined with a Coulter Counter using 0.9% NaCl as electrolyte solution which contained 0.06% Tween 80 as wetting agent. The density of the reserpine was determined with a Beckman air comparison pycnometer.

Preparation of the Solvent-Deposited Mixtures

A sufficient quantity of reserpine to obtain a drug to carrier weight ratio of 1:400 (0.25% reserpine) was dissolved in 300 ml chloroform. The reserpine solution was added to 500 g of the carrier material while it was mixed in a Kenwood planetary mixer. Small quantities of the solution were added in order to wet the carrier uniformly. After the solution was added, mixing was continued until the mixture appeared to be dry. The mixture was then removed and dried in a convection oven for 2 hr at 55°C.

Preparation of the Interactive Mixtures

One and a quarter grams of reserpine were added to 500 g of the carrier material and mixed for 2 hr in the Turbula model T2C mixer at a speed of 90 rpm.

Sampling

After drying or mixing the total mixture was spread out in a flat tray (40 cm long and 30 cm wide) and divided into six equal blocks. Ten samples, each weighing ± 100 mg, were taken randomly from each block. An additional six random samples were also taken to determine the dissolution rate of reserpine from the mixtures. The remainder of the mixtures were retained for tableting.

Tableting

Tablets weighing 100 mg were prepared on a Korsch single-punch tableting machine. Flat beveled punches with a diameter of 6 mm were used. The maximum amount of a mixture was tableted. The tablet machine was adjusted to obtain, within reasonable limits, tablets with constant weight and crushing strength. The mean weights of 20 randomly sampled tablets from each lot varied between 97.5 and 100.0 mg. The crushing strength of these tablets, measured with a Pharmatest PTB 301 hardness tester, varied between 67 and 74 N. Sixty tablets were randomly selected from every lot to determine the content uniformity.

Drug Content Analysis

The reserpine concentration in the samples was determined by an ultraviolet spectroscopic method. Accurately weighed 100 mg of powder samples or tablets

were dissolved in 100 ml solvent. The solvent contained 10 ml 1,2-propylene glycol, 0.2 ml concentrated phosphoric acid, and distilled water to make 100 ml. The sample and solvent were placed for 2 min in an ultrasonic bath to facilitate dissolution. The ultraviolet (UV) absorbency of a sample was measured at 219 nm, and the reserpine concentration calculated from a calibration curve that was obtained from the absorbency of six samples with reserpine concentrations ranging between 0.1 and 0.5 mg reserpine per 100 ml. The drug content was calculated and expressed as mass fraction reserpine. The 60 samples from a mixture were analyzed in triplicate, each run consisting of 20 mixture samples and 20 standard samples. The standard samples contained either 0.2 or 0.4 mg reserpine per 100 ml. Two standard samples were analyzed after every two mixture samples in order to determine the accuracy and the reproducibility of the analytical method. This procedure gave 20 values for standard samples with known concentrations for a run of 20 mixture samples.

Dissolution Properties

The dissolution profiles of powder samples were measured at 37°C in a rotating bottle apparatus with 60-ml flasks that contained 50 ml dissolution medium. The solvent, described under the drug content analysis, was used as dissolution medium. About 100 mg powder was transferred into a flask. Flasks were removed at appropriate times, a sample was withdrawn through a 0.22 mm filter, and the amount dissolved was determined by the UV method. After sampling, the flask with its contents was placed in an ultrasonic bath to ensure that all the reserpine present dissolved. A filtered sample was again removed, and the reserpine concentration determined. Three measurements per time were taken for every lot.

The percentage dissolved was calculated from the ratio of the amounts dissolved in the timed sample and the ultrasonic sample. The values were corrected for the amount of reserpine lost through sampling.

RESULTS AND DISCUSSION

Numerous mixing indices have been suggested in the literature (2). The relative standard deviation or coefficient of variation (CV) was selected to compare the extend of mixing as a result of mixing method. The CV of the reserpine content, C_V, was calculated from the fraction drug content according to Eq. (1).

$$C_V = \frac{100\sqrt{\Sigma(x_i - x)^2/(n-1)}}{x} \quad (1)$$

where x_i = fraction reserpine in sample i and x = mean content of n samples.

$(C_V)_{sam}$ was calculated from the content of the powder samples or tablets, and $(C_V)_{anal}$ was calculated from the standard samples. The latter estimates the variation due to the analytical method. The CV for the mixtures or tablets (C_V) mix, was calculated by subtracting the coefficient resulting from the analytical method, $(C_V)_{anal}$, from the coefficient of the sample, $(C_V)_{sam}$, according to Eq. (2).

$$(C_V)_{mix} = (C_V)_{sam} - (C_V)_{anal} \quad (2)$$

The mean values of each of the three coefficients were calculated for every run consisting of 20 samples. The coefficients of variation for the samples from the interactive and the solvent-deposited mixtures, and the coefficients of variation for the corresponding analytical errors are given in Table 1. The values for tablets are given in Table 2.

The coefficients were compared by calculating F, the ratio of the CVs according to Eq. 3. The tabulated F value for a statistical significant difference at $p = 1\%$, for 60 degrees of freedom in the numerator and denominator is $F \geq 1.84$. The degrees of freedom for F in all the comparisons were 60 - 1 = 59 in the numerator and denominator (5).

$$F = \frac{[(C_V)_a]^2}{[(C_V)_b]^2} \quad (3)$$

where $(C_V)_a > (C_V)_b$.

Coefficient of Variation as Function of Method

Solvent deposition gave better mixing with Avicel than interactive mixing when the results for the powder samples are compared. The F values are listed in Table 3 with $F = 2.67$ for $(C_V)_{sam}$ and 4.16 for $(C_V)_{mix}$. This difference due to method for Avicel could not be demonstrated for tablets.

Although there were no significant differences for Sorbit as a result of mixing method when the coefficients of variation, $(C_V)_{sam}$, are compared, opposing results are obtained with $(C_V)_{mix}$. When the CVs are corrected for analysis variation, the powder samples

Table 1

Coefficients of Variation for Powder Samples (3 × 20) from Interactive Mixing and Solvent Deposition for Avicel PH 102 and Sorbit Instant

Filler	Mixing Method	Mean Content (mass fraction)	$(C_V)_{sam}$ (%)	$(C_V)_{anal}$ (%)	$(C_V)_{mix}$ (%)
Avicel	Solvent dep.	0.002160	4.14	1.65	2.49
		0.002420	3.94	1.73	2.21
		0.002190	4.54	1.10	3.44
	Mean	0.002257	4.21	1.49	2.71
	Inter. mixture	0.002460	8.07	1.79	6.28
		0.002590	6.09	1.14	4.95
		0.002540	6.50	1.36	5.53
	Mean	0.002530	6.89	1.36	5.53
Sorbit	Solvent dep.	0.003119	4.21	1.22	2.99
		0.003218	7.83	1.19	6.64
		0.002846	6.97	1.37	5.60
	Mean	0.003061	6.34	1.26	5.08
	Inter. mixture	0.002348	4.75	1.78	2.97
		0.002678	7.96	4.30	3.66
		0.002427	4.28	1.91	2.37
	Mean	0.002484	5.66	2.66	3.00

have a higher variation for solvent deposition than for interactive mixing. For tablets the CV for interactive mixing is higher than for solvent deposition. The fact that the CV due to the analytical error is about one half the magnitude of the CV of the samples makes comparison of the CVs due to mixing difficult. This might be an explanation for the conflicting high F values for $(C_V)_{mix}$ for powder samples in Table 3.

Table 2

Coefficients of Variation for Tablets (3 × 20) from Interactive Mixing and Solvent Deposition for Avicel PH 102 and Sorbit Instant

Filler	Mixing Method	Mean Content (mass fraction)	$(C_V)_{sam}$ (%)	$(C_V)_{anal}$ (%)	$(C_V)_{mix}$ (%)
Avicel	Solvent dep.	0.002386	2.05	1.56	0.49
		0.002470	3.00	1.84	1.16
		0.002509	4.66	0.98	3.68
	Mean	0.002455	3.24	1.49	1.78
	Inter. mixture	0.002503	4.61	1.18	3.43
		0.002470	2.98	0.99	1.99
		0.002509	1.99	0.57	1.42
	Mean	0.002494	3.19	0.91	2.28
Sorbit	Solvent dep.	0.002378	2.62	1.25	1.37
		0.002734	1.32	0.73	0.59
		0.002684	4.02	1.90	2.12
	Mean	0.002599	2.65	1.29	1.36
	Inter. mixture	0.002218	2.26	0.64	1.62
		0.002370	2.78	1.17	1.61
		0.002188	4.95	0.96	3.99
	Mean	0.002259	3.33	0.92	2.41

Table 3

F for $(C_V)_{sam}$ and $(C_V)_{mix}$ for Different Mixing Methods

Mixing Method	Carrier	F for $(C_V)_{sam}$		F for $(C_V)_{mix}$	
		Powder	Tablets	Powder	Tablets
Solvent dep.	Avicel	—	1.03	—	—
Inter. mixture	Avicel	2.67	—	4.16	1.64
Solvent dep.	Sorbit	1.25	—	2.86	—
Inter. mixture	Sorbit	—	1.58	—	3.14

Note. $F \geq 1.84$ for a significant difference at $p = 1\%$.

Coefficient of Variation as Function of Carrier

Avicel was the best carrier for solvent deposition (Table 4). The $(C_V)_{sam}$ and $(C_V)_{mix}$ for solvent deposition on Sorbit were significantly higher than the CVs for Avicel for the powder samples. This difference was not obtained for tablets.

Sorbit gave more uniform interactive mixtures than Avicel according to $(C_V)_{mix}$ for powder samples. This was the only significant difference between the carriers for interactive mixing.

Coefficient of Variation of Tablets Compared to Powder Samples

The results in Tables 1 and 2 indicate that smaller coefficients of variation were obtained for tablets (<4%) than for powder samples (>4%), which means that either the sampling procedure or the tableting process had an influence on the homogeneity (Table 5). Garrett and Olson (6) found similar results; i.e., that a blend was less homogeneous than the tablets compressed from that blend.

The Extent of Mixing

The extent of mixing was estimated by comparing the coefficient of variation, $(C_V)_{mix}$, with the theoretical value for a completely random mixture. The latter value was calculated according to the equation of Johnson (7):

$$C_V = 100(\pi\rho/6G)^{1/2}(\Sigma f d^3)^{1/2} \quad (4)$$

in which C_V is the CV of a medicinal compound expressed as a percentage of the mean weight, G, of medicinal compound per sample, and $m = (\pi/6)d^3r$ the weight of drug particles with diameter d and f the weight fraction of these particles. The results from the particle size analysis and density determination gave a mean particle size $d = 8.51$ mm and density $r = 1.326$ g/cm^3.

Substituting in Eq. (4) gives $C_V = 0.13\%$. According to the results in Tables 1 and 2, this value was not reached for any of the mixtures. This means that in the interactive mixing process, either the particle size distribution does not corresponds to the size determined by the size analysis or the reserpine particles was not completely randomized. In the solvent deposition the drug

Table 4

F for $(C_V)_{sam}$ for Different Carriers

Carrier	Mixing Method	F for $(C_V)_{sam}$		F for $(C_V)_{mix}$	
		Powder	Tablets	Powder	Tablets
Avicel	Solvent dep.	—	1.49	—	1.71
Sorbit	Solvent dep.	2.26	—	3.51	—
Avicel	Inter. mixture	1.48	—	3.39	—
Sorbit	Inter. mixture	—	1.09	—	1.11

Note. $F \geq 1.84$ for a significant difference at $p = 1\%$.

Table 5

F for $(C_V)_{sam}$ and $(C_V)_{mix}$ for Powder and Tablet Samples

Carrier	Mixture Type	*F* for $(C_V)_{sam}$	*F* for $(C_V)_{mix}$
Avicel	Solvent dep.	1.68	2.31
Sorbit	Solvent dep.	5.72	13.95
Avicel	Inter. mixture	4.67	5.88
Sorbit	Inter. mixture	2.89	1.54

Note. $F \geq 1.84$ for a significant difference at $p = 1\%$.

is crystallized from solution, and the original particle size distribution is thus lost. A particle size comparison can therefore not be made for the solvent deposited mixtures. It can be argued that the CV due to the analytical error is too large to detect such a small CV value for the random mixture.

In order to comply with pharmaceutical content uniformity standards the CV should be less than 5%. That would correspond to a range of 15% with a 99.7% probability level on the condition that the content is normally distributed (8). The CVs for all the mixtures, except for of the solvent deposited Avicel, were larger than 5% and would therefore not comply with content uniformity standards. The largest CV for tablet samples was 3.33%, and based on this results all the mixtures was mixed to such an extent that the tablets would comply with content uniformity standards.

Dissolution Properties as Function of Method and Carrier

The mean dissolution curves of powder samples as a function of filler and method were similar, which indicates that the type of mixing or carrier had no effect on the dissolution properties.

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