release from suppositories, the desirable release rate for the specific drug investigated has not been determined since its minimum effective concentration is not known. Considerably more research is needed in this area.

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Attainment of Highly Uniform Solid Drug Dispersions Employing Molecular Scale Drug Entrapment in Polymeric Latices

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Abstract □ The uniformity of distribution attainable for an amine drug in solid dispersions prepared using a molecular scale entrapment procedure was investigated. Excellent reproducibility of drug content throughout the entire entrapment product was demonstrated in both flocculated (high drug levels) and deflocculated (low drug levels) systems. Drug content and content uniformity were found to be predictable for deflocculated systems, even at high drug dilution ratios. Milling or particle-size fractionation appeared to have no effect on the distribution of drug throughout the solid dispersion entrapment products. Dry blending was inferior to molecular scale drug entrapment in distributing small quantities of drug uniformly.

Keyphrases □ Dispersions, solid—amine drugs, uniformity of distribution, molecular scale entrapment procedure, flocculated and deflocculated systems □ Molecular scale drug entrapment—utilized to prepare solid dispersions of amine drugs, uniformity of distribution studied □ Distribution uniformity—amine drugs in solid dispersions studied, molecular scale entrapment procedure, effect of milling or particle-size fractionation □ Amine drugs—uniformity of distribution in solid dispersions, molecular scale drug entrapment procedure

Safety, efficacy, and reliability are the three basic criteria that define the quality of any well-designed pharmaceutical dosage form. High standards of drug product quality are necessary for the protection of the public, and one important facet of quality assurance is the maintenance of content uniformity. Content uniformity directly bears on each of the three criteria defining drug product quality. The importance of content uniformity in solid unit dosage forms to the consumer's health, safety, and welfare becomes obvious when one considers the potency of many drugs in use today.

BACKGROUND

Failure to meet content uniformity specifications in a solid dosage form may be attributed to weight variation between dosage units or improper mixing (nonhomogeneity of drug distribution). Another factor resulting in inaccuracies of drug content in tablets, capsules, or powders is drug segregation. Improper mixing leading to nonuniformity can result from the inherent difficulty in setting the "ideal mixing time" for high dilution solid dosage forms. Homogeneity of a potent active ingredient throughout a powder mix is highly dependent on particle size and shape, particle-size distribution, density, moisture, and charge. Furthermore, the size, efficiency, and type of mixer can make a difference when choosing a mixing time specification.

A "perfect mix" for a powder formulation would be exemplified by a three-dimensional location of drug plus excipient in space, in which every drug particle is the same size and is the same distance in all planes from every other drug particle. Two miscible liquids most closely approach (in practice) a perfect mix, since mixing occurs at a molecular level and is completely random. This result is never attained in powder blending due to the finite number of particles involved and the factors previously listed that may contribute to unmixing or segregation. However, a reasonable mix is possible if there are enough particles per drug dose and if the optimum mixing time is selected after carrying out adequate testing and sampling of the powder blend.

A high degree of mixedness achieved in a powder mix, however, does not necessarily mean the final product will meet content uniformity specifications. Segregation can occur when the mix is removed from the mixer, transferred to another point in the plant, or subsequently treated by other processing procedures. Furthermore, for capsules and tablets, nonuniform flow and subsequent weight variation could hinder unit-to-unit drug content even more.

In addition to these manufacturing problems, other problems concerning the control of content uniformity include analytical methods and statistical procedures. To allow content uniformity determinations on individual unit dosage forms, the assay methods must be accurate, reliable, and specific as well as sufficiently sensi-

tive and precise. Statisticians are constantly seeking reliable and improved procedures by which a batch or lot may be judged acceptable or unacceptable by a minimum amount of sampling.

Recent investigations (1–7) of a novel physicochemical process, termed molecular scale drug entrapment, have been described. This process has broad application to the preparation of solid drug dispersions as sustained-release systems. Emphasis has been placed on reproducibility and reliability of such entrapment as a precise way of controlling the rate of drug delivery; however, little attention has been given to the process as a precise method of distributing drug uniformly throughout a powder mix. The basis for the molecular scale concept is the addition of a solution phase (Avogadro's number of particles per mole) to a colloidal polymer dispersion, commonly called a latex, which has been estimated to contain 10^{14} particles/ml of dispersion. Various physical or physicochemical means may then be employed to recover the solid dispersion.

X-ray diffraction studies demonstrated that distribution of an amine drug using this solid dispersion entrapment technique (3) occurred at the molecular level. However, no attempt was made to exploit the apparent distributing property of molecular scale drug entrapment as a potentially superior method of achieving a high order of content uniformity in solid unit dosage forms.

EXPERIMENTAL

Materials and Equipment—A linear, anionically charged, acrylic copolymer[1] composed of acrylic and methacrylic acids and esters, having a molecular weight exceeding 300,000, was supplied in latex form; it contained 40 ± 0.5% solids. The amine used in this study was methapyrilene hydrochloride NF[2], and all reagents used were analytical grade.

Liquid mixing was done by a mixer[3] equipped with a 5.1-cm (2-in.) diameter, marine-type propeller. An ultracentrifuge[4], using a No. 42 rotor and 96-ml polyallomar tubes, was employed to isolate mechanically the polymer phase of the colloidal latex drug formulations.

Micronization was accomplished using a fluid energy mill[5], while classification of granules and powders was carried out using a set of standard sieves. Densities of solid materials were determined utilizing an air compression pycnometer[6], and moisture contents were obtained using a moisture balance[7]. All solids blending was done in a metal blender[8], and analyses were performed with a spectrophotofluorometer[9].

Analytical Method—The basis for the assay technique used was given by Pearlman (8), who found that antihistamines with a nitrogen atom *ortho* to a pyridine nitrogen develop fluorescence when reacted with excess cyanogen bromide. Five milliliters of the methapyrilene solution to be assayed was pipetted into a 50-ml volumetric flask. To this solution, 2 ml of freshly prepared saturated cyanogen bromide solution was added. After stoppering and agitating, the mixture was allowed to stand at least 1 hr (fluorescence remained constant from 1 to 24 hr) before analysis. Because of the dangerous fumes caused by cyanogen bromide, any solution containing this substance was covered and kept under a hood.

Solutions for calibration curves were identical to unknowns except for drug content and ranged from 1.0×10^{-3} to 15×10^{-3} m*M*. Straight-line relationships resulted when the log relative intensity was plotted against the log of the drug concentration. All samples were read in a fluorometer (slit arrangement 3) with the excitation wavelength at 345 nm and emission at 407 nm. The precision of the fluorometric assay was determined by performing five replicate assays on aliquots of several methapyrilene standard solutions. Relative standard deviations of ±1.8 and 1.1% were found at 2×10^{-3} and 10×10^{-3} m*M* methapyrilene concentration levels, respectively.

[1] Rohm and Haas, Philadelphia, Pa.
[2] Abbott Laboratories, North Chicago, Ill.
[3] Model V7 Lightning, Type 70537, Mixing Equipment Co., Rochester, N.Y.
[4] Beckman L2-65B, Spinco Division, Beckman Instruments, Palo Alto, Calif.
[5] Gem T, George W. Helme Co., Rochester, N.Y.
[6] Beckman Instruments, Fullerton, Calif.
[7] Central Scientific Co., Chicago, Ill.
[8] Twin-Shell, Patterson-Kelly, East Stroudsburg, Pa.
[9] Aminco-Bowman, American Instrument Co., Silver Spring, Md.

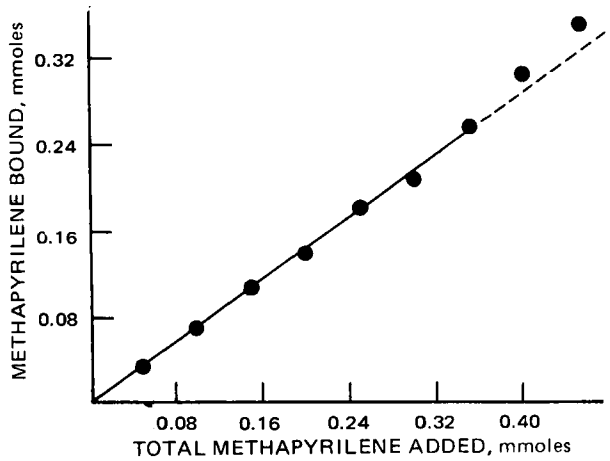


Figure 1—*Entrapment relationship between millimoles of methapyrilene bound and the millimoles of methapyrilene added to the latex.*

Preparation and Sampling of Polymeric Drug Dispersions—Formulations consisting of 50 ml of drug solution and 50 ml of polymer latex were mixed for 3 min at 300 rpm at room temperature. It was previously determined that temperature had no effect on the process and that equilibrium was established in 30 min (5). After a 30+ min equilibrium time, the systems, whether deflocculated or flocculated, were ultracentrifuged for 1 hr at 30,000 rpm. The supernates were retained for analysis as well as the precipitates.

The precipitates were pulverized and allowed to dry at 40°. It was determined that 12 hr was an adequate drying time. From each polymeric drug dispersion, 10 200-mg samples were chosen completely at random and with no regard to particle size or position in total population. These samples were dissolved in 0.2 *N* NaOH and analyzed with respect to drug content.

One formulation, consisting of 50 ml of 0.10 m*M* methapyrilene hydrochloride and 50 ml of latex, was prepared as already described for a micronization study. After drying, however, the isolated polymer product of this formulation was ground in a mortar and subsequently fed into a fluid energy mill using dry nitrogen at 54.5 kg (120 lb)/in.^{2} and a constant feed rate. The uniformity of distribution of drug throughout the micronized product was compared to the uniformity of distribution throughout a similar, but nonmicronized, product.

Uniformity of Distribution by Dry Blending as Compared to Molecular Scale Drug Entrapment—An entrapment formulation yielding a 1:10,000 dilution of methapyrilene to polymer was chosen for comparison to the following dry blended formulations: Formula I—methapyrilene hydrochloride, 100 mg, and lactose,

Table I—Typical Data for Distribution of Methapyrilene in the Isolated Dried Product of a Polymer Latex–Drug Formulation[a]

Sample[b]	Amount of Methapyrilene per 200 mg of Isolated Dried Product, μg
1	20.3
2	18.6
3	19.8
4	19.3
5	20.2
6	20.0
7	19.4
8	20.3
9	19.8
10	18.9
Average	19.7
SD	0.6

[a] This particular formulation consisted of 50 ml of a 0.5 m*M* methapyrilene hydrochloride solution and 50 ml of Acrysol ASE-75. [b] Samples were drawn at random from the isolated dried product.

Table II—Reproducibility of Methapyrilene Content in Samples of Solid Dispersions Obtained from a Flocculated Polymer Latex

Formulation[a]	Concentration of "Drug Solution"[a], m*M*	$\bar{X}$[b], mg	*RSD*
1	100	7.739 ± 0.132[c]	1.7
2	60	5.495 ± 0.181	3.3
3	15	1.778 ± 0.052	1.9
4	14	1.444 ± 0.045	3.1
5	10	0.959 ± 0.039	4.1
6	2	0.217 ± 0.009	3.9

[a] A formulation consisted of 50 ml of methapyrilene hydrochloride "drug solution" and 50 ml of Acrysol ASE-75. [b] Represents an average of 10 randomly selected samples drawn from the isolated dried product. [c] Standard deviation.

1000 g; and Formula II—methapyrilene hydrochloride, 100 mg, and flocculated polymer, 1000 g.

All ingredients were dried overnight at 40° and characterized as to particle size, density, and moisture content. The same basic procedure was used for mixing and sampling for Formulas I and II. First, a premix was made by adding about 300 g of diluent by geometric dilution to 100 mg of methapyrilene. To break up any lumps or agglomerates, the premix then was sized through a 60-mesh screen. The premix was then placed into a metal V-blender, and about 300 g more of diluent was added and allowed to mix for 5 min. Finally, the remaining diluent was added and blending was allowed to occur for 5 more min.

At this juncture, 4–5 g of mix was removed from the left top, bottom, and right top portions of the mixer and stored in tight containers for future analysis. Similarly, 4–5 g of mix was taken and stored after the following mixing times (in minutes): 10, 15, 20, 30, 45, and 60. From each of the three regional samples at each time interval, 20 200-mg samples were randomly selected and analyzed for drug content.

RESULTS AND DISCUSSION

The drug may be entrapped from solution by addition to a polymer latex, with the latex being isolated or separated by physicochemical means such as coagulation or by mechanical means such as ultracentrifugation.

At very low methapyrilene concentrations, a linear entrapment relationship appears to exist up to the point where flocculation begins (0.35–0.50 mmoles added) (Fig. 1). When the method of least squares is performed on the data in the range of 0.05–0.35 mmole added, the equation becomes:

$$\text{millimoles of bound methapyrilene} = (0.685) \times \text{millimoles of methapyrilene added} \quad \text{(Eq. 1)}$$

The fact that high levels of drug caused the latex to flocculate and low levels did not will be the subject of a future paper on mechanisms and factors affecting entrapment. Certainly, the direct relationship as seen in this region allows one to predict the amount of methapyrilene bound when other amounts of the same order of magnitude are added to the system. These findings also confirm that a drug–polymer dispersion may be formed independent of flocculation.

Table IV—Some Physical Characteristics of the Dry Mixing Components

Characteristic	Methapyrilene Hydrochloride	Lactose	Polymer[a]
Sieve fraction	80–100	80–100	80–100
Density	1.170	1.529[b]	1.342
Moisture content	0.2	0.0	0.0

[a] The isolated dried product was prepared from a flocculated latex system consisting of 4000 ml of 0.8 *M* KCl and 4000 ml of Acrysol ASE-75. [b] Literature value = 1.53 (17).

Table I illustrates the uniformity of distribution of a formulation consisting of 50 ml of 0.2 m*M* methapyrilene hydrochloride and 50 ml of latex. Since nearly 10% of the entire population was sampled, it is reasonable that inferences concerning the entire population are well justified.

Chiou and Riegelman (9) surveyed various types of solid dispersions but reported none of the techniques as improving solids mixing.

The data of Table I are typical of the uniformity of distribution data attained with entrapment formulations. This particular formulation did not appear to coagulate (flocculate) the latex; however, all formulations were treated similarly. The amount of drug present was normalized for what a 200-mg sample of polymeric drug dispersion should contain. With the normalized values, simple statistics (10–16) were used to treat the data. If it is assumed that the sampling data represent the entire population, a high degree of reproducibility of methapyrilene content throughout the isolated dried product is indicated. In fact, 19.7 ± 0.6 μg represents a mere 3.0% deviation from the mean amount found.

By employing this approach for all formulations, whether flocculated or deflocculated, data were accrued, treated, and summarized as shown in Tables II and III. The data indicate a high degree of uniformity of distribution in all of the solid dispersions, as shown by the low values of the relative deviation (percent deviation of a single determination from the mean amount found).

In the flocculated formulations (Table II), milligram amounts found distributed in 200 mg of dispersion are shown, with the percent deviations of drug content from the mean ranging from 1.7 to 4.1%. Table III shows the uniformity of distribution of drug in deflocculated systems. The relative deviations are lower for the deflocculated systems, ranging from only 1.6 to 3.0%. Among the several important differences that exist between Tables II and III are: (*a*) the presence or absence of flocculation, (*b*) higher percent deviations with flocculated systems, and (*c*) predictability of drug content in drug dispersions produced from deflocculated systems. When examining the data of Tables II and III, it should be remembered that a relative standard deviation of ±1.1–±1.8% was attributable to assay error (precision) over the concentration range employed.

The presence or absence of flocculation looms important in the isolation step. Due to the colloidal or near colloidal size of the particles in a polymer latex, isolation of the product in a deflocculated or peptized state cannot be accomplished by filtration or ordinary

Table III—Reproducibility of Methapyrilene Content in Samples of Solid Dispersions Obtained from a Deflocculated Polymer Latex

Formulation[a]	Concentration of "Drug Solution"[a], m*M*	$\bar{X}$[b], μg	*RSD*	Predicted $\bar{X}$[c], μg	Deviation from Predicted $\bar{X}$, %
1	1.00	88.1 ± 1.6[d]	1.8	94.2	6.5
2	0.50	44.9 ± 0.7	1.6	47.1	4.7
3	0.40	38.9 ± 0.7	1.8	37.7	3.2
4	0.20	19.7 ± 0.6	3.0	18.8	4.8
5	0.10	9.6 ± 0.2	2.1	9.4	2.1
6[e]	0.10	9.7 ± 0.2	2.1	9.4	3.1

[a] A formulation consisted of 50 ml of methapyrilene hydrochloride "drug solution" and 50 ml of Acrysol ASE-75. [b] Represents an average of 10 randomly selected samples drawn from the isolated dried product. [c] Predicted from Eq. 1. [d] Standard deviation. [e] Micronized granulation.

Table V—Drug Content Uniformity of 1:10,000 Blended Drug–Lactose and Drug–Polymer Physical Mixtures Obtained from Three Blender Sites at Various Mixing Times

Mixing Time, min	Lactose Formulation[a]				Polymer Formulation[a]			
	Top Left	Bottom	Top Right	$\bar{X}$[b]	Top Left	Bottom	Top Right	$\bar{X}$
	Micrograms per 200 mg of Mix							
5	23.3 ± 4.7[c]	22.1 ± 3.7	19.2 ± 1.8	21.5 ± 4.0	19.1 ± 4.1[d]	21.0 ± 5.1	21.7 ± 3.8	20.6 ± 4.4
10	22.0 ± 3.2	19.7 ± 2.8	21.1 ± 2.2	20.9 ± 2.9	17.3 ± 1.9[d]	19.0 ± 3.9	16.4 ± 2.0	17.6 ± 2.9
15	20.0 ± 3.1	22.8 ± 2.9	22.6 ± 3.2	21.8 ± 3.2	20.2 ± 5.1	19.4 ± 4.4	20.9 ± 4.8	20.2 ± 4.7
20	21.5 ± 2.9	21.8 ± 3.4	21.8 ± 2.9	21.7 ± 3.0	22.0 ± 4.2[d]	19.8 ± 5.0	20.6 ± 3.6	20.8 ± 4.3
30	19.0 ± 3.5	20.4 ± 2.5	20.0 ± 2.4	19.8 ± 2.9	20.8 ± 3.1	20.4 ± 3.1	23.1 ± 3.4	21.5 ± 3.4
45	18.4 ± 2.2	17.5 ± 2.3	18.1 ± 2.1	18.0 ± 2.2	19.6 ± 2.3	19.3 ± 2.3	17.4 ± 2.4	18.9 ± 2.5
60	16.5 ± 1.6	16.9 ± 1.9	16.5 ± 1.3	16.5 ± 1.4	18.6 ± 2.6	19.5 ± 3.1	19.7 ± 3.1	19.2 ± 2.9

[a] Formulations consisted of 100 mg of methapyrilene hydrochloride and 1000 g of diluent (lactose or polymer). [b] $\bar{X}$ represents average drug content based on all samples (top left, bottom, and top right) taken from the V-blender at a particular mixing time. [c] Standard deviation. [d] Drug content based on $n = 10$; all others are based on $n = 20$.

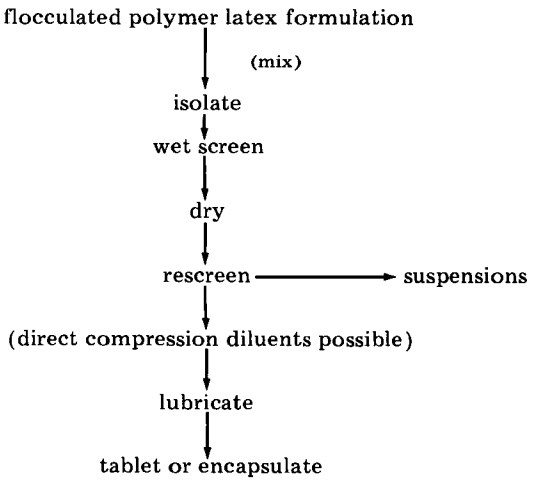
laboratory centrifugation but is possible by ultracentrifugation. Flocculated systems are readily isolated by filtration or centrifugation and their recovery, in general, is much simpler.

Probably the most important difference between the two types of systems is that uniformity of distribution can be reliably predicted for deflocculated systems (Scheme I and Table III). In only one case do percent deviations vary above the 5% level, illustrating that reliable predictability may be attained. Such prediction capability would allow a formulator to design, with mathematical certainty, a highly uniform product at any drug dilution ratio or dosage level desired.

No linear relationship existed for predicting the amount bound for flocculated systems, as can be seen from examination of Table II, although good batch-to-batch reproducibility for such systems was found previously (1, 2).

The ratios of mean amount found (column labeled $\bar{X}$) to sample weight (200 mg in each case) in Tables II and III vary on a weight-to-weight basis from 1:26 to 1:20,800 dilutions. Since even higher dilutions may be made, the dilution capability of polymer latex-produced solid dispersions has obvious implications when potent, low dose drugs are formulated. Formulations 5 and 6 of Table III correspond to dilutions of more than 1:20,000.

Another important property of entrapment products is apparent from a micronization experiment. The data in question are exemplified by Formulations 5 and 6 as listed in Table III. Formulations 5 and 6 are identical, except that 6 represents a micronized system. The results suggest that particle size does not make any difference when selecting samples from the isolated dried product for distribution studies. The fact that the strong forces of micronization do not reduce product uniformity by an effect of segregating drug and polymer is further evidence of a solid dispersion system. Since particle-size reduction and classification are important unit operations for solid dosage forms, the fact that milling the entrapment product does not affect drug distribution makes the molecular scale entrapment process that much more advantageous over conventional dry blending.



Scheme I—General scheme for scale-up of latex-generated solid dispersion systems

Uniformity of Distribution by Dry Blending as Compared to Molecular Scale Drug Entrapment—The dry mixing components were of the same sieve fraction and had little or no moisture content (Table IV). Good agreement was seen for the experimental density value (1.529) and the literature value (1.53) (Table IV). A greater density difference existed between the components of Formula I than between the components of Formula II (see *Experimental*).

Sampling results for the lactose and polymer physical mixtures are presented in Table V, which lists the average methapyrilene content in 200-mg samples taken from the three regions of the blender at various time intervals. To gain more information as to the homogeneity and deviation from the theoretical drug content of the dry blending process, the data of Table V are expressed as seen in Tables VI (lactose diluent) and VII (polymer diluent). Theoretically, each 200-mg sample should have contained 20 μg of methapyrilene if a perfect mix was attained.

The general picture that emerges from Tables V–VII is that the usual segregation and mixing problems of dry mixing are difficult to obviate, even when using only two components that are essentially the same size and have little or no moisture content. Definite similarities and differences existed between the lactose and polymer formulations. On the basis of homogeneity and predictability of drug content, both systems appeared to reach an optimum mixing time of 45 min, after which content uniformity in the analyzed samples dropped.

The drop in methapyrilene content after 45 min was quite rapid for the lactose formulation but gradual for the polymer formulation. Such an effect seems reasonable after considering the density differences (Table IV); however, other factors might include particle-size distribution, shape, and charge (18–24). Compared to the harder polymer particles, the softer lactose particles would be more likely to be susceptible to attrition or breakdown by bombarding against each other or the walls of the mixer. A wider particle-size distribution or a change to a more irregular shape may have contributed to the segregation and unmixing. Charge effects were not characterized, but a Plexiglas V-blender was purposely not used to minimize the creation of any charge.

Although the V-blender may be a very efficient mixer, a high degree of mixedness was not achieved for the two cases studied at many mixing times. The data in Tables VI and VII reveal that it was difficult to get within ±15% of the mean amount found, and below ±10% was only obtained when the theoretical content was too low or the methapyrilene content was not reproducible throughout all of the blend. Furthermore, as great as ±55% deviation occurred between sampling units, a situation mathematically predicted by Train (24).

These high dilution formulations thus suffer from the problems of segregation, unmixing, and the selection of a specific optimum mixing time. Treating these formulations as granulations could compound the difficulties in obtaining content uniformity due to poor or nonuniform flow and subsequent weight variation of tablets.

Under the conditions of this study, it appeared that the "best possible mix" for the dry blend formulations was attained after 45

Table VI—Homogeneity and Deviation from Theoretical Methapyrilene Content in 1:10,000 Drug–Lactose Physical Mixtures[a]

Mixing Time, min	RSD				Percent Deviation of Mean Amount Found from Theoretical Drug Content[b]			
	Top Left	Bottom	Top Right	$\bar{C}$[c]	Top Left	Bottom	Top Right	$\bar{T}$[d]
5	20.2	16.7	9.4	18.6	16.5	10.5	4.0	7.5
10	14.5	14.2	10.4	13.9	10.0	1.5	5.5	4.5
15	15.5	12.7	13.7	14.7	0.0	14.0	13.0	9.0
20	13.5	15.6	13.3	13.8	7.5	9.0	9.0	8.5
30	18.4	12.3	12.0	14.6	5.0	2.0	0.0	1.0
45	12.0	13.1	11.6	12.2	8.0	12.5	9.5	10.0
60	9.7	11.2	7.9	8.5	17.5	15.5	17.5	17.5

[a] The formulation consisted of 100 mg of methapyrilene and 1000 g of lactose. See Table V for corresponding mean values at the various time intervals. [b] Theoretical drug content equals 20 μg/200 mg of mix. [c] C represents the relative standard deviation based on the corresponding $\bar{X}$. [d] $\bar{T}$ represents the percent deviation of $\bar{X}$ from theoretical drug content.

min of mixing. Table VIII gives the results for a methapyrilene molecular scale drug entrapment formulation and also compares the results for the optimum mixes when methapyrilene was dry blended with lactose and polymer as diluents. All formulations were designed theoretically to yield 20 μg of methapyrilene/200 mg of sample, that is, a 1:10,000 ratio of drug to diluent. Even when particle size is controlled by mixing only 80–100-mesh material, the data clearly show that predictability and uniform distribution are much less for the dry-blended formulations than the solid dispersion entrapment product. The reproducibility of methapyrilene throughout the entrapment product was very satisfactory, deviating from the mean amount found by only 3.0% (compared to dry blending), and the deviation from the theoretical content was only 1.5%.

When considering the previous data and what has been established about molecular scale drug entrapment solid dispersions, several advantageous features of entrapment as a method of distributing drugs uniformly throughout a mix become evident. First, segregation due to density, particle size, and particle-size distribution are not serious problems as in dry blending. Entrapment occurs in solution to form a solid dispersion product following isolation and drying. The amount of drug entrapment is both predictable and uniformly distributed throughout the isolated dried product. Furthermore, milling or micronization does not adversely affect drug content or drug uniformity in an entrapment formulation.

In addition, temperature, rate of mixing, length of time between interaction, and separation do not substantially affect the results or the uniformity of results. The molecular scale entrapment method does not require the use of elevated temperatures to produce drug solution in a melt or drug fusion, as is required in other preparative methods for solid dispersions. The mixing time to at-

Table VII—Reproducibility and Predictability of Methapyrilene Content in Samples of a High Dilution Drug–Polymer Formulation[a]

Mixing Time, min	RSD				Percent Deviation of Mean Amount Found from Theoretical Drug Content[b]			
	Top Left	Bottom	Top Right	$\bar{C}$[c]	Top Left	Bottom	Top Right	$\bar{T}$[d]
5	21.5	24.3	17.5	21.4	4.5	5.0	8.5	7.0
10	11.0	20.5	12.2	16.5	13.5	5.0	13.0	12.5
15	25.2	22.7	23.0	23.3	1.0	3.0	4.5	1.0
20	19.1	25.3	17.5	20.7	10.0	1.0	3.0	4.0
30	14.9	15.2	14.7	15.8	4.0	2.0	15.5	2.5
45	11.7	11.9	13.8	13.2	2.0	3.5	13.0	5.5
60	14.0	15.9	15.7	15.1	7.0	2.5	1.5	4.0

[a] The formulation consisted of 100 mg of methapyrilene hydrochloride and 1000 g of polymer. See Table V for corresponding mean values at the various time intervals. [b] Theoretical drug content equals 20 μg/200 mg of mix. [c] C represents the relative standard deviation based on the corresponding $\bar{X}$. [d] $\bar{T}$ represents the percent deviation of $\bar{X}$ from theoretical drug content.

Table VIII—Comparison of Uniformity of Drug Distribution of 1:10,000 Physical Mixtures with a 1:10,000 Solid Dispersion

	Molecular Scale Drug Entrapment	Dry Blending I	Dry Blending II
Formulation constituents	0.20 m*M* I[a] 50 ml Latex[b] 50 ml	I 100 mg Lactose 1000 g	I 100 mg Polymer 1000 g
Mixing time, min	3	45	45
Sieve fractions	—	80–100	80–100
Mean amount per 200 mg sample, μg	19.7 ± 0.6	Top left 18.4 ± 2.2 Bottom 17.5 ± 2.3 Top right 18.1 ± 2.1 Overall[c] 18.0 ± 2.2	Top left 19.6 ± 2.3 Bottom 19.3 ± 2.3 Top right 17.4 ± 2.4 Overall 18.9 ± 2.5
RSD	3.0	Top left 12.0 Bottom 13.1 Top right 11.6 Overall 12.2	Top left 11.7 Bottom 11.9 Top right 13.8 Overall 13.2
Percent deviation of mean amount found from theoretical	1.5	Top left 8.0 Bottom 12.5 Top right 9.5 Overall 10.0	Top left 2.0 Bottom 3.5 Top right 13.0 Overall 5.5

[a] I = methapyrilene hydrochloride. [b] Latex = Acrysol ASE-75. [c] Overall values are based on all samples (top left, bottom, and top right) taken from the V-blender at the indicated mixing time.

tain, as well as the number of operations to produce, the uniform distribution of drug in granular solids is much less and more specific for latex-generated solid dispersions. Therefore, simpler, more specific manufacturing instructions are possible. Direct compression ingredients and lubricants can be added, or lubricants can be added to the entrapment product and tableted directly, with weight variation being the major factor impairing content uniformity. Entrapment may be compared to wet granulation as far as time to produce a finished tablet; availability and effectiveness do not appear to be problems for molecular scale drug entrapment (1–7).

For scale-up operations, a general scheme might include the steps indicated in Scheme I. The molecular scale drug entrapment method described herein appears to have great potential for distributing drugs uniformly, especially low dose, highly potent drugs where the usual blending techniques may be inadequate or unreliable.

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Contact Angles and Wetting of Pharmaceutical Powders

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Abstract □ Contact angles of pharmaceutical powders were determined by the h–ϵ method, which consists essentially of measuring the maximum height of a drop of liquid formed on a presaturated compact of the material. Determinations with aspirin as the test material indicate that the measured value is independent of the particle size of the powder and the porosity of the cake. The method was extended to include determinations on mixed powder systems. The results show that the hydrophobic material dominates with large particle-size powders; with small particle sizes, a linear relationship between the cosine of the contact angle of the mixed system and the proportion of the components is obtained. Results are presented for a wide variety of materials of pharmaceutical interest.

Keyphrases □ Powders, pharmaceutical—contact angles and wetting determined by h–ϵ method, effect of particle size and porosity of cake □ Contact angles—pharmaceutical powders, determined by h–ϵ method, effect of particle size and porosity of cake □ Wetting—pharmaceutical powders, effect of particle size and porosity of cake □ Aspirin powder—contact angles and wetting determined by h–ϵ method, effect of particle size and porosity of cake

The wetting of solid materials usually implies the replacement of air on the surface of a solid by a liquid. In addition to the components of the system, the type of wetting is also important. Osterhof and Bartell (1) distinguished between three types of wetting, namely those of adhesion, immersion, and spreading. The distinction between these three types may be made by considering the model, suggested by Parfitt (2), of a solid cube being immersed in a liquid (Fig. 1).

THEORY

The energy changes that take place when these processes occur may be written in terms of the measurable quantities of the liquid–vapor interfacial tension and the contact angle. If it is assumed that the solid surface before wetting is in equilibrium with the vapor of the liquid (1, 2), then:

$$W_a = -\gamma_{LV^\circ}(\cos\theta + 1) \qquad \text{(Eq. 1)}$$

$$W_i = -\gamma_{LV^\circ}\cos\theta \qquad \text{(Eq. 2)}$$

$$W_s = -\gamma_{LV^\circ}(\cos\theta - 1) \qquad \text{(Eq. 3)}$$