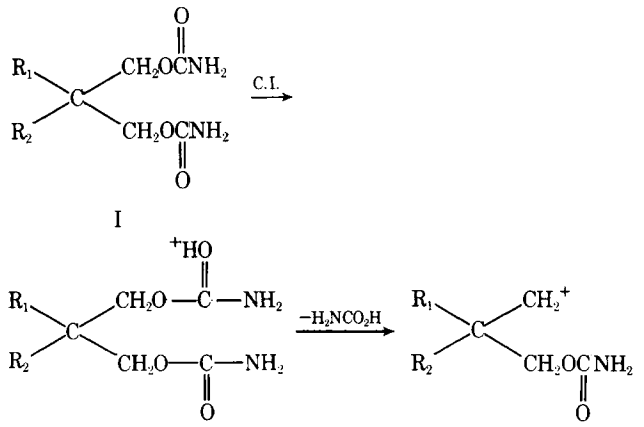
Table I—High-Resolution Chemical Ionization[a,b] Mass Spectral Data for MH^+ Ions

R_1	R_2	Elemental Composition	Theoretical	Found	Relative Intensity: Chemical Ionization	Relative Intensity: Electron Impact[c]
CH_3	$CH_3CH_2CH_2$	$C_9H_{19}N_2O_4$	219.1344	219.1361	100%	0%
CH_3	$ClCH_2CH_2CH_2$	$C_9H_{18}ClN_2O_4$	253.0954	253.0925	100%	0%
$CH_3CH_2CH_2$	$ClCH_2$	$C_9H_{18}ClN_2O_4$	253.0954	253.0970	100%	0%
CH_3CH_2	$ClCH_2$	$C_8H_{16}ClN_2O_4$	239.0815	239.0798	100%	0%
$CH_2=CHCH_2$	H	$C_8H_{15}N_2O_4$	203.0998	203.1031	100%	0%
$CH_3CH_2OCH_2$	$CH_2=CHCH_2$	$C_{11}H_{21}N_2O_5$	261.1445	261.1440	100%	0%
$CH_3OCH_2CH_2$	CH_3	$C_9H_{19}N_2O_5$	235.1293	235.1276	100%	0%
CH_3OCH_2	CH_3OCH_2	$C_9H_{19}N_2O_6$	251.1238	251.1229	100%	0%
$CH_3CH_2OCH_2$	CH_3	$C_9H_{19}N_2O_5$	235.1293	235.1301	100%	0%
$CH_3OCH(CH_3)$	CH_3	$C_9H_{19}N_2O_5$	235.1293	235.1287	100%	0%

[a] 500 ev. [b] Perfluorokerosene-H was used as an internal standard for exact mass measurements. [c] Molecular ion, M^+.



I

Scheme I

High-resolution data were obtained in both modes, so the combined use of the two modes provides a very potent method for structural elucidation of dicarbamates. The electron-impact spectra are rich in readily interpretable fragment ions from which much detailed structural information can be derived, while the high-resolution chemical ionization mode allows an unequivocal determination of the molecular formula. In Table I, the exact measured mass of all MH^+ ions is listed and compared with the theoretical mass.

Although the application of field desportion mass spectrometry to dicarbamates allows the determination of an unequivocal molecular weight (1), chemical ionization mass spectrometry offers a distinct advantage in the precise determination of molecular formula and ease of application[4].

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[4] High-resolution data were not obtained by Rouse and Brent (1). At present, considerable effort and time are required to obtain field desorption mass spectra.

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Powder Mixing by Frictional Pressure: Specific Example of Use of Ordered Mixing

Keyphrases □ Powder mixing—frictional pressure, example of use of ordered mixing □ Mixing, powder—frictional pressure, example of use of ordered mixing □ Dissolution rate—effect of ordered mixing

To the Editor:

A recent study (1) reported the effect of different methods of preparing triturations of either digoxin or hydrocortisone with lactose on the dissolution rates of these drugs. It was demonstrated that frictionally deposited drug, *i.e.*, where the drugs were spread over the surface of the diluent by frictional pressure in a mortar and pestle, gave the highest dissolution rate. The other trituration methods investigated were simple blending by bottle tumbling, simple blending with ground drug, and solvent deposition.

In view of the fact that the trituration prepared using spreading by frictional pressure gave the highest dissolution rate, it was concluded that this method of powder mixing was worthy of further study. Since frictional forces are used at various stages in the preparation of dosage forms in milling, blending, slugging, granulating, and tableting, an explanation of batch variations in the dissolution rates of tablets and capsules may be forthcoming from such a study.

Where a film of drug is spread over the surface of the diluent material, some degree of order is being introduced to the powder mixture. This is different from the random mixing of noncohesive powders, from which powder mixing theory has been developed. To distinguish between these two forms of powder mixing, the terms random mixing (for the mixing or shuffling of noncohesive particles) and ordered mixing (for the mixing, spreading, or coating by cohesive particles) have been used (2).

Random mixing has been more widely studied due to the ease of handling systems of noncohesive particles, whereas ordered mixing probably occurs widely in actual powder mixing practice, where cohesive particles usually have to be employed. This is particularly the case in pharmaceutical systems requiring a high degree of homogeneity and high dissolution rates, both of which can only be satisfied by the use of fine cohesive particles.

Just as the completely randomized system in random mixing is only approached in practice (3–5), in ordered mixing the completely ordered system would be difficult to attain. It would require homosized diluent particles with a layer of equal thickness (or an equal number of homosized particles) of drug. Ordered mixing requires the use of cohesive or spreadable material and, for most materials, is dependent upon particle size. For large noncohesive particles, mixing is predominantly random. As the particle size is reduced, the cohesiveness, as measured by angle of repose, flow through an orifice, shear cell, *etc.*, increases until the mixing is predominantly by the ordered mechanism. The transition occurs in the region of 100 μm, depending on the hardness and surface properties of the material.

The standard deviation of the theoretical, completely randomized binary mixture, σ_R, decreases with increasing sample size, M, according to:

$$\sigma_R = \left(\frac{xyw}{M}\right)^{0.5} \qquad \text{(Eq. 1)}$$

where x and y are the proportions of the two homosized ingredients of particle weight w. In contrast, the completely ordered mixture would have zero standard deviation until the sample weight, M, was reduced to such an extent as to contain less than one single particle of diluent and associated drug adhering or spread onto it.

Of the methods used for the formation of the digoxin–lactose and hydrocortisone–lactose triturations (1), the solvent deposition method may also be classified as an ordered process, since a thin film of drug should be deposited at the surface. The success or failure of this method to produce improved dissolution rates depends largely on the drying conditions and solution migration. Thus, a good dispersion may be obtained, such as aspirin deposited on a lactose–starch mixture, resulting in increased dissolution rates (6).

It is apparent that both decreased particle size and greater dispersion of the drug with the diluent are required for increased dissolution rates. Ordered mixing may give better results than random mixing, but only at the cost of the increased energy input required to bring about this degree of order. The use of frictional pressure to induce spreading of the drug over the diluent is one example of ordered mixing, where with extra energy input, more efficient dissolution rates have been obtained.

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Particle-Size Requirements Related to Content Uniformity of Solid Dosage Forms

Keyphrases □ Particle size—requirements related to content uniformity of solid dosage forms, particle-size limit compared to particle-size distribution □ Content uniformity, solid dosage forms—particle-size limit and particle-size distribution discussed

To the Editor:

In a recent publication (1), the particle-size requirements to achieve satisfactory content uniformity in a compound tablet were discussed. An example was given for a three-component system containing 50, 5, and 0.5% of the respective drugs with the requirement that these percentages be present in the final 100-mg tablet within ±10% of the nominal values at the 99.7% probability level. The resultant σ values related to the tolerance range of ±10% were