Since the glass transition temperature of a particular polymer/plasticizer combination is a function of the polymer chain mobility, then the effect of plasticizers on this temperature will be a direct measure of plasticizer efficiency. In this respect, the curves in Fig. 1 are similar in shape to those reported for the same system showing the effect of plasticizer concentration on the glass transition temperature (Entwistle & Rowe 1979). There are, however, two anomalies: firstly, the rank order of plasticizer efficiency predicted by Entwistle & Rowe (1979) on the basis of decrease in glass transition temperature was propylene glycol > polyethylene glycol 200 > glycerol, and secondly, the difference in efficiency between glycerol and the other two plasticizers used in this study is greater than would be anticipated on the basis of this glass transition curve for the glycerol. The first of these discrepancies is probably due to the fact that the glass transition curves were calculated from a knowledge of the physical properties of the materials and the data used for polyethylene glycol 200 were averaged figures from manufacturer's literature. The second could well be due to plasticizer loss during the coating process. Since loss is dependent on the volatility of the plasticizer, its interaction with the polymer and its diffusivity through the polymer matrix, it would be expected that glycerol, with its low molecular weight and poor interaction with hydroxypropyl methylcellulose (as determined from intrinsic viscosity measurements—Entwistle & Rowe 1979), would be lost more readily than the other two plasticizers. This would have a detrimental effect on the incidence of bridging as shown for glycerol in Fig. 1. These results lend further support both to the concept of residual stresses in the film being the cause of bridging of the intagliations and to the adoption of a fundamental thermodynamic approach to the choice of plasticizers as advocated by Entwistle & Rowe (1979).

The authors would like to thank Mr L. Jessop for assistance in this work.

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J. Pharm. Pharmacol. 1981, 33: 175–176
Communicated November 13, 1980

0022–3573/81030175–02 $02.50/0

Relation between mixing time and segregation of ordered mixes

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A fundamental principle of ordered mixing is that fine particles of one powder adhere to other, usually coarse particles of another powder to form a near-uniform coating (Hersey 1975). The period which elapses before uniform adhesion occurs, along with any rearrangement of ordered units to produce the required homogeneity, can be defined as the ordered mixing time.

Ordered mixing times vary according to the powder system studied. Stephenson & Thiel (1980) and Travers & White (1971) found that ordered mixing was virtually complete between 4 and 10 min. Yip & Hersey (1977), studying the mixing of fine salicylic acid with coarser sucrose powder, found that after 10 min in a revolvocube blender the powders were within the required homogeneity. Bryan et al (1979) found that the ordered mixing time for microfine salicylic acid and starch/lactose granules was approximately 15 min. Similarly, Johnson (1975) reported periods of approximately 20 min for fine cyclopenthiazide mixed with various tableting excipients. In each of the cases described above, the maximum quantity of fine particles adhering to coarse particles was 1% but an increase in the percentage of fine component can significantly prolong the ordered mixing time. In the system studied by Bryan et al (1979) an increase in the fine powder component to 5 and 10% increased the ordered mixing time and even after 100 min mixing the coefficient of variation of the systems had not fallen below 10% despite an initial rapid decrease.

We have studied a system consisting of fine potassium chloride powder which formed ordered mixes with three coarse direct compression tableting excipients: a direct tableting sugar, Dipac (Amstar Corp., New York, U.S.A.); a spray crystallized maltose-dextrose, Emdex (Edward Mendell, U.S.A.) and a recrystallized lactose excipient made according to Staniforth (1980). When the potassium chloride was blended with each of the three excipients, by rotation in a Y-cone blender, the resulting ordered mixes showed different degrees of segregation tendency, or stability. Furthermore, the three excipients required different times to form ordered mixes and this also varied according to the percentage of potassium chloride in the system. In general, the more prolonged the ordered mixing time, the less stable the ordered mix that was produced. Table 1 shows the ordered

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Table 1. Ordered mixing times (OMT) and corresponding coefficients of variation (cv%) of different concentrations of potassium chloride blended with three direct compression tableting excipients.

Excipient	Concentration of potassium chloride									
	0·5%		1%		2%		5%		10%	
	OMT (min)	cv%	OMT (min)	cv%	OMT (min)	cv%	OMT (min)	cv%	OMT (min)	cv%
Dipac	60	1·1	330	0·55	—	—	480	1·22	540	1·19
Emdex	30	0·12	110	0·23	295	1·38	410	0·25	510	0·40
Recrystallized lactose	30	0·75	120	0·09	—	—	165	0·55	180	0·21

mixing times at which the coefficient of variation for 20 samples withdrawn from the mix fell to below 2%; also listed are the actual measurements of coefficient of variation corresponding to each ordered mixing time. It can be seen that the Dipac/potassium chloride systems require the longest ordered mixing times at any given concentration of potassium chloride. The Dipac ordered mixes were also far more susceptible to vibrational segregation than either Emdex or recrystallized lactose. For example, Table 2 shows the coefficient of variation for each ordered mix vibrated for 15 min in a specially constructed Perspex cylinder with a volume of approximately 250 ml at a frequency of 50 Hz and an acceleration force of 2 *g*. Clearly the Dipac powder forms an ordered mix with a very marked segregation tendency, even at 0·5% potassium chloride concentration, whereas both Emdex and recrystallized lactose form mixes with much lower segregation tendencies. Comparing these results with the data in Table 1, Dipac required 60 min to form an ordered mix whereas Emdex and recrystallized lactose only needed blending for 30 min.

It is not certain why systems which require long blending times to form ordered mixes should be more prone to segregation. We suspect that the two effects are linked by the mechanism governing the formation of an ordered mix. According to this concept two different powders with a strong affinity for each other will rapidly form stable, non-segregating ordered units. Conversely, weaker interparticle attractions will prolong the time required to form ordered units during the blending operations and will facilitate separation of adhering particles from carrier particles once ordered units have been formed. The increased mixing times noted with higher percentages of fine component in an ordered mix are attributed to the time taken for the larger number of fine particles to become uniformly dispersed on the coarser particles. The resulting ordered mixes containing higher concentrations of potassium chloride were found to be less stable, probably for the following reason. Even at the 10% concentration there are still many adherence sites vacant on the carrier excipient particles. However, during blending, adhesion will occur first at the strongest adherence sites, albeit under conditions of dynamic equilibrium. As the fine particle concentration increases, the most active sites will become fully occupied and the bonds formed between the carrier particles and the remaining fine particles will become progressively less strong; the latter bonds will be more susceptible to disruption in conditions such as occur during vibration in pharmaceutical processing. In addition, if fine powder becomes dislodged from some carrier particles during the mixing process, the homogeneity of the system will be influenced by random or partially ordered random mixing of the separate constituents as described by Hersey et al (1979). A powder mix which owes its homogeneity to a combination of random, partially ordered random and ordered mixing mechanisms will be more susceptible to segregation when processed than a powder mix which is produced solely by ordered mixing.

From our results it appears that the most stable ordered mixes are those which are formed after a short mixing time, usually less than 30 min duration.

Table 2. Effect of vibration for 15 min, at a frequency of 50 Hz and an acceleration of 2g on the segregation of ordered mixes listed in Table 1. (Coefficient of variation = cv%).

Excipient	cv% of different concentrations of potassium chloride following vibration				
	0·5%	1%	2%	5%	10%
Dipac	21·4	47·5	59·5	256·6	500·1
Emdex	1·3	14·3	25·7	76·2	123·4
Recrystallized lactose	2·2	18·7	31·1	93·0	15·7

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