recently by theory (Egermann 1985d) and by experiment (Egermann & Pesendorfer 1986).

Yip & Hersey (1977), in their experiments, used 0·1% micronized salicylic acid, mean particle size 2·6 μm, and coarse sucrose of 655 μm particle size as constituents. With this extreme difference in particle size, the Stange–Poole equation yielded highly erroneous values C_{Rx} up to about 3%, dependent on sample size M. From equation 1, however, which actually applies to the systems under consideration, the random content variations C_R may be estimated to be as low as in the order of 0·01%. This is two magnitudes below the coefficients of variation (CV) of 1–2%, which have been found with the mixtures in fact.

With actual ordered mixes, CV must be smaller than C_R of equation 1. Experimental data of this type are not available.

Apart from the theoretical limitations, a practical difficulty of proving the existence of the hypothetical ordered mixes is the high quality of random mixes containing micronized ingredients. C_R may be smaller than the analytical error, thus making impossible the judgement of a lower than the random content variation (Egermann 1985e).

In conclusion, the previous claims of the existence of ordered mixes are erroneous as a consequence of the inadequate use of the Stange–Poole equation to calculate the random degree of mixing. From the above considered theoretical and experimental limitations, it appears questionable whether ordered mixes may ever be verified by experimental evidence. However, with the high quality of the corresponding random systems in mind, not only the evidence but also the practical relevance of ordered mixes with respect to the dose uniformity of drugs may be questioned (Egermann 1985e).

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Comments to 'Order out of chaos'

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Recently, Staniforth (1987) proposed the terms 'adhesive' and 'non-adhesive' rather than 'interactive' and 'non-interactive' (Egermann & Orr 1983) to differentiate mixes of cohesive, interacting powders and of free-flowing, non-interacting constituents. Clearly, 'adhesive' and 'non-adhesive' are superior to the arbitrary use of ordered and randomized of previous years. However in our view, 'interactive' and 'non-interactive' still appear to be more accurate and preferable as standard nomenclature, for the following reasons:

(a) Interactive is the more general term with a broader range of applications. Unlike adhesive, it is not restricted to one type of interaction (adhesion). With cohesive powder constituents, particulate interactions may be—and usually will be—produced both by adhesion and by cohesion, and the powder mix may show cohesive properties. Thus adhesive—in contrast to interactive—does not fully apply.

(b) Interactive and non-interactive are the scientifically accurate terms. Staniforth broadly argues that a truly non-interactive mix could not exist due to the overall presence of gravitational forces. This is a rather surprising view, since the mixing of powders is considered and not the mixing of planets. With powder particles, in contrast to the planets mentioned by Staniforth, the masses involved are so small that the individual gravity fields would not be expected to produce particulate interaction forces of a sufficient magnitude.

The adhesional forces, as a consequence of the free surface energy of solids, will be much stronger than the gravitational fields even for the coarsest, free-flowing particles. Accordingly, taking Staniforth's view, a truly non-adhesive mix also could not exist, and any argument against non-interactive mix would apply to a greater extent against non-adhesive mix. In practice, however, neither gravitational nor adhesional forces are of significance with free-flowing constituents. Free-flowing implies that the particles may move individually under the influence of the gravitational earth force, and that particulate interactions are negligibly small, independent of the source of the interactions.

Further, Staniforth mentions gravity to be a predominantly stabilizing force for non-interactive mixtures. In contrast, any textbook dealing with stability of powder mixes assumes gravity

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to be a destabilizing force, which may create segregation of free-flowing constituents, eg. due to differences in particle density.

(c) In the sensitive field of nomenclature of powder mixtures, new terms should be introduced only after careful evaluation of their actual relevance. In the past, the inconsistent use of "ordered" has caused confusion and resulted in much discussion in the literature, this has been summarized elsewhere (Egermann 1985). Hence, the authors confirm interactive and non-interactive as standard nomenclature. These terms have been increasingly accepted by the scientific community, including Thiel (1984), Soebagyo & Stewart et al (1985), Sallam et al (1986), and Schmidt & Ben (1987). In contrast, adhesive and non-adhesive mix could not be traced in the papers cited by Staniforth (Drahun & Bridgwater 1983; Thiel 1984; Soebagyo & Stewart 1985). Rather, two of them (Thiel 1984; Soebagyo & Stewart 1985) even used interactive mixture in their titles. It must be regarded as a retrograde step to change terminology which is becoming increasingly widely accepted as scientifically accurate.

Another term of questionable relevance is total mix (Staniforth 1981, 1987). Obviously, total mix may be applied synonymously to powder mix. The traditional term powder mix, however, appears to be more informative and clearer. In contrast to total mix it does not provoke uncertainties about its actual meaning.

In conclusion, we do not see that the nomenclature proposed by Staniforth is an advance in the unambiguous description of powder mixes. More accurate alternatives are already in common use. The recent past has demonstrated that imprecise terminology may present a serious source of errors. From the misleading use of 'ordered', many workers implied interactive mixes to feature a higher degree of homogeneity than that exhibited by the non-interactive random mix. In fact, plain evidence of ordered mixes still is not available and from the present state of knowledge it appears questionable if it ever will become established (Egermann 1989).

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Chronic but not acute antidepressant treatment increases pentetrazol-induced convulsions in mice

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The neurochemical basis of depression and the biochemical mechanisms of action of antidepressants are matters of intense research, especially the hypothesis linking GABA function with depression and with antidepressant effects has recently received attention (Lloyd & Pichat 1986). Thus, GABA synthesis in the frontal cortex and its levels in CSF or plasma are low in depressed patients. Moreover, several reports have shown that some GABAergic agents have antidepressant-like activity both in animal models of depression (Borsini et al 1986a; Fernández Teruel et al 1988) and in depressive patients (for a review see Lloyd & Pichat 1986).

Accordingly, an involvement of $GABA_B$ receptors in the mechanisms of action of antidepressant treatments has been suggested by the finding that both the chronic treatment with antidepressant drugs and the electroshock administration induced $GABA_B$ receptor up-regulation in rat cortex (Lloyd & Pichat 1986). On the other hand, the chronic administration of several antidepressant agents (desipramine, zimelidine, bupropion, adinazolam and maprotiline) markedly decreased the binding of [^{3}H]flunitrazepam to the benzodiazepine binding sites on the $GABA_A$ receptor complex (Suranyi-Cadotte et al 1985; Barbaccia et al 1986). Additionally, the long-term imipramine (or nomifensine) treatment reduced the binding of [^{3}H]GABA to $GABA_A$ receptors in the mouse cerebral cortex and hippocampus (Suzdak & Gianutsos 1985).

In line with these results we have recently observed that the repeated administration of the antidepressant agent imipramine was able to reduce the GABA-stimulated $^{36}Cl^-$ influx in cerebral cortex synaptoneurosomes of rats (Fernández Teruel et al, in press). Furthermore, and agreeing with these results, the effects of imipramine in the behavioural 'despair' test in rats were potentiated by the concomitant administration of sub-convulsant doses of the $GABA_A$ antagonist picrotoxin (which reduces chloride channel functionality; Fernández Teruel et al submitted).

To further test the hypothesis on the interactions of antidepressant treatment and the GABA receptor-chloride ionophore complex, we investigated the effects of imipramine and desipramine on pentetrazol-induced convulsions in mice.

Male ICO-OF1 (IFFA-CREDO) mice (Autonomous Univer-

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