The *Penicillium* isolate was grown in the presence of acetamide 1% (w/v) and paracetamol 0·1% (w/v) + acetamide 1% (w/v) for 7 days at 25°. After harvesting and washing the cells, oxygen uptakes in the presence of paracetamol were determined by conventional manometric techniques.

Table 1.

Substrate	Total oxygen uptake (μ mol/μ mol substrate) Acetamide grown cells	Paracetamol-acetamide grown cells
Paracetamol	1·2	0·8
Acetate	1·1	1·2

Table 1 shows that oxygen uptakes for paracetamol were similar to those obtained for acetate metabolism. The slightly lower figure obtained for paracetamol adapted cells is possibly due to a decreased respiration of the cells exerted by toxic metabolites which accumulated during growth. Ultraviolet spectroscopy of the supernatent after oxygen uptake had ceased showed a decrease in paracetamol concentration and a characteristic shift in the paracetamol spectrum to one which was indicative of 4-aminophenol.

Grant & Wilson (1973) reported the degradation of paracetamol by *Corynebacterium pseudodiphtheriticum* to acetate, which was subsequently metabolized, and the corresponding amine. It is proposed that a similar degradation of paracetamol occurs with the *Penicillium* species isolated.

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Kinetics of microagglomeration in liquid suspension

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A novel method of agglomeration from liquid suspension in which a small amount of a second immiscible bridging liquid preferentially wets the solids has been developed (Sirianni Capes & Puddington, 1969). When microagglomerated powders produced by this so-called "Spherical Agglomeration Process" are separated from suspension and dried, a dustless free-flowing powder of high bulk density is produced. This technique has application in the pharmaceutical field as an alternative to spray drying and other size enlargement operations.

In a recent investigation, the authors (Kawashima & Capes, 1974) found that the kinetics of the microagglomeration of 1 to 4 vol. % suspensions of >70 μM sand in turbine-agitated vessels were first order. This "restricted-in-space" behaviour apparently resulted from agglomerate interaction and the relatively high solids concentrations which were used. The present work was undertaken to study the kinetics of the agglomeration of particle systems of much finer sizes and lower suspension concentrations.

Experiments were done with $CaCO_3$ particles (3·8 μM), ground glass (17·4, 23·7, 44·2 μM) or Ottawa sand (75·8 μM) suspended in 4 litres of carbon tetrachloride in a turbine-agitated polyethylene vessel. A 20% calcium chloride solution was used as the bridging liquid. The solid concentration in suspension, C_S, was 0·046 to 3·7 v/v% and the amount of bridging liquid, R_F, corresponded to 6 to 122% saturation of voids when the particles were in a close-packed, dry condition. The agitator speed was 700 to 1000 rev min^{-1}. Size and size distribution of the agglomerates were determined by a photographic counting method using a Zeiss TGZ3 particle size analyser.

In all the experiments the agglomeration kinetics could be represented as a first order process given by eqn (1), in spite of the fact that "free-in-space", second order agglomeration might have been expected to prevail with the most dilute solids concentrations:

$\ln(\nu-\nu_e) = -kt + \ln(\nu_i-\nu_e)$ (1) where ν is the agglomerate population density (cm^{-3}) at time t (min), ν_e is the population density at equilibrium, ν_i is the initial flocculated population density and k is the first order constant (min^{-1}).

Differences in behaviour were observed between the finer particles (<24 μM) and the coarse. The bridging liquid level, R_F, required for good microagglomeration ranged from 6 to 50% for the former and from 65 to 122% for the latter. The rate constant for primary agglomeration was at least an order of magnitude less for the fine particles. Both of these differences may be explained by the much larger capillary cohesive forces acting in the agglomerates of very fine powders. In addition, a secondary agglomeration phenomenon was observed with the fine materials at long agglomeration times for R_F in the range 25 to 50%. This secondary process was 15 to 25 times faster than the primary agglomeration and, as was the case with all the experiments with coarser particles, ν_e approached zero. In contrast, ν_e had a large finite value for the fines at R_F <25%.

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Self-association of some antihistamines in aqueous solution

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The self-association of the antihistaminic drugs, tripelennamine HCl, thenyldiamine HCl, mepyramine maleate, pheniramine maleate, chlorpheniramine maleate and brompheniramine maleate in aqueous solution has been investigated by light-scattering methods. The scattering intensity, S90, of these compounds was in excess of that calculated for unassociated monomers. No significant discontinuity in the concentration-dependence of S90, attributable to a critical micelle concentration (cmc) could, however, be detected. This is in contrast to antihistaminic drugs based on the diphenylmethane nucleus (e.g. chlorcyclizine HCl, diphenhydramine HCl, diphenylpyraline HCl and bromodiphenhydramine HCl) which exhibited appreciable discontinuities in their physico-chemical properties at well defined critical micelle concentrations (Attwood, 1972).

Two possible models for the association of these drugs were investigated. In the 'closed association' model normally encountered in micellar systems, the cationic micelle M^{P+} is assumed to be formed by an all-or-none process from N monomers (D^+) and (N-p) firmly bound anions (X^-).

$$ND^+ + (N\text{-}p)X^- \rightleftharpoons M^{P+}$$

The abruptness of the change in physical properties at the cmc decreases with decrease in N and in the equilibrium constant, k, of the micellization process. It was possible to simulate the light scattering plots of tripelennamine, thenyldiamine and pheniramine assuming aggregation numbers of N = 3 and 4 and k values of 10^{10} and 10^{14} respectively. It was not, however, possible to reproduce the scattering plots of the remaining compounds using this model.

The 'open association' model assumes micellar growth by monomeric addition and predicts a continuous distribution of multimers of varying degrees of association. An analytical method proposed by Steiner (1952) was used to calculate equilibrium constants, K_N, for the formation of N-mer from (N−1)-mer. Data were fitted using the polynomial

$$M_w/xm = 1 + 4k_2(xc/m) + 9k_2k_3(xc/m)^2 + \ldots\ldots\ldots N^2\left(\prod_{N=2}^{N} k\right)\left(\frac{xc}{m}\right)^{N-1}$$