SURVIVAL OF MICROORGANISMS DURING COMPACTION OF VARIOUS DIRECT COMPRESSION MIXES

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Whilst microbial contamination of pharmaceuticals has been studied extensively, relatively little attention has been given to those factors which might influence survival of microorganisms in solid dosage forms. Fassihi et al (1977) examined the survival of *Aspergillus niger* spores during tabletting and observed a first-order dependency upon compaction pressure. They attributed this to high local surface temperatures produced during granule compaction. Similar observations have since been made for *Escherichia coli* in an Avicell/skimmed milk mixture (Yanagita et al 1978).

We have investigated the survival of *Saccharomyces cerevisiae* and *A. niger* and *Bacillus megaterium* spores during their compaction at various punch pressures (0-272MNm^{-2}) in Sta-Rx (Colorcon Ltd., Orpington, Kent), KCl, Lactose and Emdex (K & K Greef Chemicals Ltd., Croydon, Surrey). These direct compression mixes (DCM's) possess distinct compaction characteristics, the former two compact by plastic deformation, whereas the latter two fracture. Microorganisms, prepared as dried samples, were included in a dry mix of the appropriate vehicle together with disintegrants (Sodium starch glycollate 1% ^{w}/v) and mould lubricant (Magnesium lauryl sulphate, 1%^{w}/v). 500mg quantities were compacted in a ½" die with flat-faced punches and an Apex hydraulic press. Pressure was maintained for 30 s before release. Individual tablets were shaken for 10 min in sterile water and viable counts made upon appropriate dilutions, by spreading onto suitable predried agar plates. These were incubated at 35°C for 16 h for *B. megaterium* and for 48 h for the fungi. Results were expressed as the mean count obtained for three replicate tablets.

Survival in a given mixture was inversely related to cell size. For example with KCl and a compaction pressure of 195MNm^{-2} there were 99.94, 90 and 50% reductions in viability for *S. cerevisiae* (dia 8μm), *A. niger* (dia μm), and *B. megaterium* spores (dia 1.5μm) respectively. At any given compaction pressure these levels of survival varied between DCM's ad did the shapes of the dose-survival curve. With DCM's which exhibited plastic flow deformation during compaction, survival of the microorganisms was relatively unaffected at punch pressures <60MNm^{-2}. Above this range an inverse relationship of survival to punch pressure could be demonstrated, until at pressures >230MNm^{-2} no further decreases occurred with the larger organisms. Onset of these plateaus in the dose-survival curves varied with organism size, but generally corresponded to maximum compaction of the tablet. For those microorganisms incorporated into fracturing DCM's survival was inversely related to punch pressure over the entire range of pressures (0-272MNm^{-2}).

These data suggest that shearing forces within the tablet during compaction exert a direct effect upon microbial survival rather than through the intermediate effects of high temperature.

Fassihi, A.R. et al (1977) Proc. 1st Int. Conf. Pharm. Technol. APGI, Paris 5: 60

Yanagita, T. et al (1978) Chem. Pharm. Bull. 26(1): 185

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