MIXING SEQUENCE OF A THREE COMPONENT POWDER FORMULATION AND IN-VITRO RELEASE FROM HARD GELATIN CAPSULES

E.M. Anno and J.E. Rees, School of Pharmacy and Pharmacology, University of Bath, Claverton Down, Bath, BA2 7AY, U.K.

Mixtures of powders may be ordered, random or partially ordered depending on individual particle properties and interactions. Adding a further component to an ordered mix may cause "stripping" of fines from carrier particles (Lai and Hersey 1979, Staniforth et al, 1982) and thus may influence dissolution behaviour (Lerk et al 1977).

Here we have studied the effect of mixing sequence of drug and excipients on in vitro release using phenytoin sodium (P) as a model drug. Powder blends were prepared using either lactose (LAC) or calcium sulphate dihydrate (CAS) as diluent (D), magnesium stearate as lubricant (L) at 4 concentration levels (0, 0.05, 0.5, 5% w/w) and 3 different mixing sequences (P-D-L, P-L-D and D-L-P). Mean specific charge on individual powders was measured and powder blends were characterised by SEM combined with X-ray microanalysis. Capsules were hand-filled and dissolution (USP paddle method) was followed spectrophotometrically in borate buffer pH 9.0.

The addition of diluent alone retarded drug release from capsules and the influence of magnesium stearate depended on the concentration level, type of diluent and sequence of mixing of the components.

With LAC as diluent (Fig.1a), magnesium stearate tended to retard drug release whilst, with CAS (Fig.1b), a significant improvement was noted on the addition of up to 0.5% magnesium stearate. At the 5% level, the lubricant had no significant effect on drug release from CAS formulations.

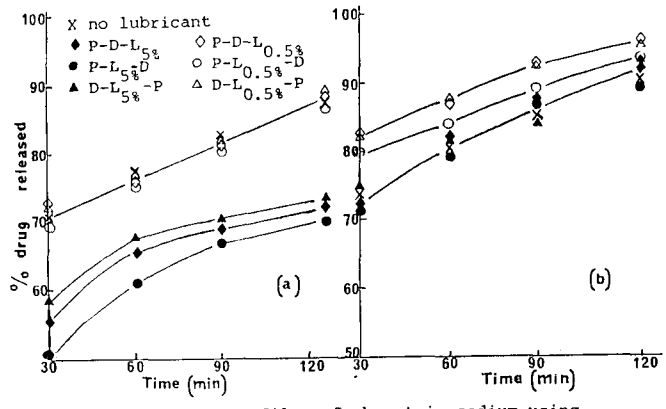

Fig.1 Dissolution profiles of phenytoin sodium using (a) lactose (b) Calcium sulphate dihydrate as diluent.

The effect of mixing sequence was statistically significant ($p<0.1$) for 0.5% lubricant in CAS and 5% lubricant in LAC capsules. In each case a higher release was observed when diluent particles were mixed first with magnesium stearate than when drug was mixed first with lubricant. When drug was mixed with CAS, random mixes were formed and, on the addition of magnesium stearate, preferential adhesion of the lubricant to CAS was observed. This would explain the similar release profile to the CAS-lubricant-drug system (Fig.1b)

Partially ordered mixes were formed between phenytoin and lactose but, on addition of magnesium stearate, the lubricant adhered to the diluent particles and caused stripping of drug from the lactose surface.

Preliminary results of studies in progress, using narrower size distributions of these same components, indicate even more marked effects of mixing sequence. Depending on the relative interparticle attraction of components of a powder mix, the sequence of mixing may significantly influence the dissolution of drug from capsules.

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