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The role of fine particle lactose in agglomerated dry powder aerosol formulations

M. J. CLARKE, G. LAYZELL, M. J. TOBYN AND J. N. STANIFORTH

Research Group, Department of Pharmacy and Pharmacology, University of Bath, Bath BA2

As an alternative to carrier based dry powder aerosol formulations, certain drug particles may be aggregated to form free flowing spheres, reducing the surface free energy of the micronised drug powder. The aerosol performance of the agglomerated system is dictated predominately by the interparticulate forces acting between the drug particles. Optimal inhalation performance requires that the dispersive forces, generated within the device upon patient inspiration, exceed the strength of the interparticulate forces acting between the drug particles. The *in vitro* aerosol behaviour of nedocromil sodium (NS) and terbutaline sulphate (TS), either self-agglomerated or spheronised with fine particle lactose (FPL), was investigated.

NS was a gift of Rhône Poulenc Rorer (Cheshire, U.K.). The micronised drug particles had a volume median diameter (VMD) of 1.1μm as measured by laser light diffraction. TS (VMD = 1.8μm) was obtained by emptying the drug contents of the Turbohaler® (Astra Pharmaceuticals, U.K.). Formulations containing FPL (Sorbolac 400, Meggle, Germany; VMD = 7.3μm) were mixed in a high shear bladed blender. The blending protocol has been previously optimised to promote maximum intercalation of FPL within the self agglomerated drug system. Uniform aggregates of the pure drug or the FPL/drug formulations were produced by rolling the powders on a metal mesh (spheronisation) producing particle agglomerates with excellent flow characteristics. The *in vitro* aerosol characterisation of the dry powder formulations was performed using a twin stage impinger (TSI) (Apparatus A, BP 1993) The internal diameter of the stage one jet was modified to give an effective aerodynamic cut-off diameter of approximately 5.0μm when operated at a flow rate of 60 l min^{-1}, Hallworth & Westmoreland, (1987). Powder formulations were delivered using the Cyclohaler® device. Fine particle fraction (FPF) is the mass of drug deposited in stage two of the TSI expressed as a percentage of the emitted dose.

Table 1: *In vitro* aerosol performance of the dry powder aerosol formulations.

Formulation (Drug:FPL)	% Emitted	% FPF
NS (100:0) powder	75.48 (2.41)	15.80 (2.53)
NS (100:0) Spheres	72.62 (5.01)	14.09 (2.84)
NS:FPL (40:60) powder	87.20 (1.46)	48.3 (5.67)
NS:FPL (40:60) Spheres	86.20 (0.85)	50.1 (1.49)
TS (100:0) Spheres	54.15 (3.89)	59.74 (5.03)
TS:FPL (50:50) Spheres	66.59 (3.96)	55.49 (3.41)

Values are mean (SD; n=10)

The addition of FPL to the agglomerated nedocromil system significantly increases both the FPF and the percentage of drug emitted from the device ($p < 0.05$). Environmental and low temperature scanning electron microscopy suggest that the mechanism of action of FPL in nedocromil formulations occurs as a result of physical disruption of interactions between drug particles. Intercalation of the FPL within the self-agglomerated drug system, increases the generation of discrete drug particles upon application of a dispersive force. The addition of FPL to the terbutaline aggregates has no significant effect on the FPF but it does improve device emptying. The functional effects of the FPL in these systems appears to be material dependent.

Hallworth, G. W & Westmoreland, D. G (1987)
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