J. Pharm. Pharmacol. 1998, 50 (Supplement): 52

Characterization and formulation of propranolol oleate

K. J. CROWLEY, R. T. FORBES, H. NYQVIST* AND P. YORK

*Drug Delivery Group, Postgraduate Studies in Pharmaceutical Technology, The School of Pharmacy, University of Bradford, Bradford BD7 1DP, and *Astra Arcus AB, Södertälje, S-151 85, Sweden*

Oleic acid has numerous gastro-intestinal effects that impact on oral dosage form performance. These can be utilised to alter dosage form transit time, drug release rate, and drug absorption. Reduction of first pass metabolism due to drug uptake into the lymphatic circulation is another interesting oleic acid effect (Charman & Stella 1992). This demonstrates the potential of this natural material as an 'active' excipient in oral dosage form design.

We have previously reported salt formation in propranolol base and high purity oleic acid binary mixtures (Crowley et al 1997). Propranolol oleate (POA) displayed interesting mesomorphic behaviour, a common property of long chain fatty acid salts. However, the unctuous nature of POA at room temperature created analytical and processing challenges. Particle size control was particularly problematic as a result of its adhesive and cohesive properties. This work describes methodology for characterizing oleate mesophases and a formulation approach for such material.

Preparation by solvent evaporation or by fusion led to different melting behaviour of POA suggesting subtle differences in mesophase structures. X-ray powder diffraction (XRPD) showed that these phases possessed significant long range order with little short range order. The absence of sharp diffraction peaks meant that these mesophases could not be differentiated using XRPD. Solid-state ^{13}C NMR was a more useful tool for mesophase characterisation enabling discrimination of different levels of disorder. Comparison with the chemical shift changes of oleic acid polymorphic forms allowed improved understanding of the oleate mesophases.

A melt granulation approach utilising the waxy properties of POA as a granule binder was investigated. Binder and diluent (lactose monohydrate 90-125 μm) were preheated to 65 °C, and liquid POA (melting point approximately 50 °C) was poured onto the diluent in a jacketed high shear mixer. 10 % $^{w}/_{w}$ POA, similar to oil binder concentrations used by Wakiyama (1994), resulted in free flowing granules. The in vitro dissolution properties of a 355-500 μm granule sieve fraction were tested using the USP XXIII paddle method with 900 ml of pH 7.4 buffer. Inclusion of 0.2 % $^{w}/_{v}$ sodium lauryl sulphate prevented formation of an immiscible oil phase. Quantities of granules equivalent to 37 mg POA were sprinkled onto dissolution media, and propranolol concentrations were measured at selected time intervals using HPLC. 90 % POA dissolution from granules occurred in under five minutes, compared to fourty minutes for unprocessed POA of a similar particle size. We hypothesise that this substantial reduction in dissolution time was due to rapid lactose dissolution from granulated POA producing a fine oleate dispersion.

Fast dissolution and absorption of oleic acid are required in the small intestine to stimulate lymphatic drug transport. Thus melt granulation is a viable approach for lymph targeting of an oleate salt.

The financial support of Astra Arcus AB is gratefully acknowledged by K.J.C., along with support from the EPSRC SSNMR facility, University of Durham.

Charman, W.N. & Stella, V.J. (eds. 1992) The Lymphatic Transport of Drugs. CRC Press, Boca Raton, Fl. USA
Crowley, K.J. et al. Pharm. Res. (1997) 14 (11) S188
Wakiyama, N. et al. (1994) S.T.P. Pharma Sciences 4 (3) 181-189