AN IN-VITRO STUDY OF THE INFLUENCE OF PARTICLE SIZE ON DRUG RELEASE FROM A POLYETHYLENE-MINERAL OIL GEL, PLASTIBASE 50W

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The in-vitro drug release from two suspensions (A and B) of different particle size fractions of salicylic acid (0.6% w/w) in Plastibase 50W, into an aqueous sink (distilled water) at 32°C, was studied using a Perspex release cell which had no membrane between the sample of suspension and aqueous sink. After introduction of a sample into the release cell, precautions were taken to ensure that rheological equilibrium was attained prior to studying drug release. The choice of Plastibase 50W as the matrix permitted particle size (shear size) of the dispersed salicylic acid to be measured in situ by optical microscopy. The size distributions (on a number basis) were log normal giving geometric mean sizes and geometric standard deviations of 3.1 $\pm$ 2.1 μm and 124.1 $\pm$ 2.0 μm for suspensions A and B, respectively.

Plots of cumulative amount of drug release per unit area of exposed sample surface (Q) versus time showed that the amount of drug released from system A was always greater than that from B after the same time interval. A linear relationship between Q and $\sqrt{\text{time}}$ existed for system A thus indicating that release could be described by the diffusional model proposed by Higuchi (1961) i.e. the rate controlling stage in the release process is diffusion of dissolved drug through the matrix continuum. In contrast a similar plot for system B only became linear after approximately 840 minutes, the earlier part of this plot being a curve, which was convex to the $\sqrt{\text{time}}$ axis. Since the two systems differ only in the size of the suspended particles, variation in their drug release behaviours must be related to this difference. The effects of possible differences in the rates of sedimentation of the particles in systems A and B on drug release have been shown to be undetectable. Thus variation in the results can only be ascribed to either a deviation from the assumptions made in deriving the Higuchi equation or to the effects of particle size on the dissolution rate of the suspended drug in the matrix. Although one of Higuchi's assumptions was that the size of the suspended particles should be small relative to the thickness of the matrix layer, the larger particles in system B are still relatively small compared to the thickness (0.6 cm) of the sample in the release cell and conform to the official description of a 'fine powder'. Thus it is difficult to ascribe the release behaviour of system B to deviation from that original assumption. It seems that the rate of dissolution of drug in the matrix continuum is the rate limiting factor in the earlier stages of release. When the thickness of the 'zone of depletion' is sufficient to establish diffusion of drug in solution through this zone as the rate limiting process, then a plot of Q versus $\sqrt{\text{time}}$ for system B becomes linear and parallel to the slope of a similar plot for system A, where the effect of dissolution rate appears to be negligible. Since the total amount of drug released from system B over the period studied (i.e. 30 hours) only represents approximately 10% of the total initial drug content, the linearity of the Q versus $\sqrt{\text{time}}$ plot cannot be ascribed to complete exhaustion of the suspended drug phase in the system.

System B has thus provided evidence that under certain conditions drug release from a matrix containing suspended drug can be dissolution rate limited and remain so for a considerable time before eventually becoming diffusion rate controlled. Mathematical models for drug release from such systems need modifying in order to account for this change in release mechanism with time.

Higuchi, T. (1961) J. Pharm. Sci. 50 : 874 - 875

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