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THE RELATIONSHIP BETWEEN THE DISSOLUTION RATE AND THE PARTICLE SIZE OF PREDNIMUSTINE: A DISAGREEMENT WITH THE NOYES-WHITNEY EQUATION

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It is widely known from textbooks that the particle size -- or the surface area, inversely related to the particle size -- of a drug influences its dissolution rate; this is the relationship expressed in the so-called Noyes-Whitney equation (1).

Studies of prednimustine -- a drug practically insoluble in water, and characterized by wide multimodal size distributions, composed of single crystallites as well as aggregates and agglomerates -- did not indicate any general correlation between particle size and dissolution rate, neither by means of regression analysis (2) nor by way of multivariate data analysis (3). Fair correlations were obtained with a set of small-scale batches, with wide intervals regarding both particle-size and dissolution-rate parameters. In respect of the full-scale batches, however, no general relationships were observed. Consequently, including particle-size control in the control specifications of this drug would be meaningless if undertaken with a view to predicting its dissolution rate.

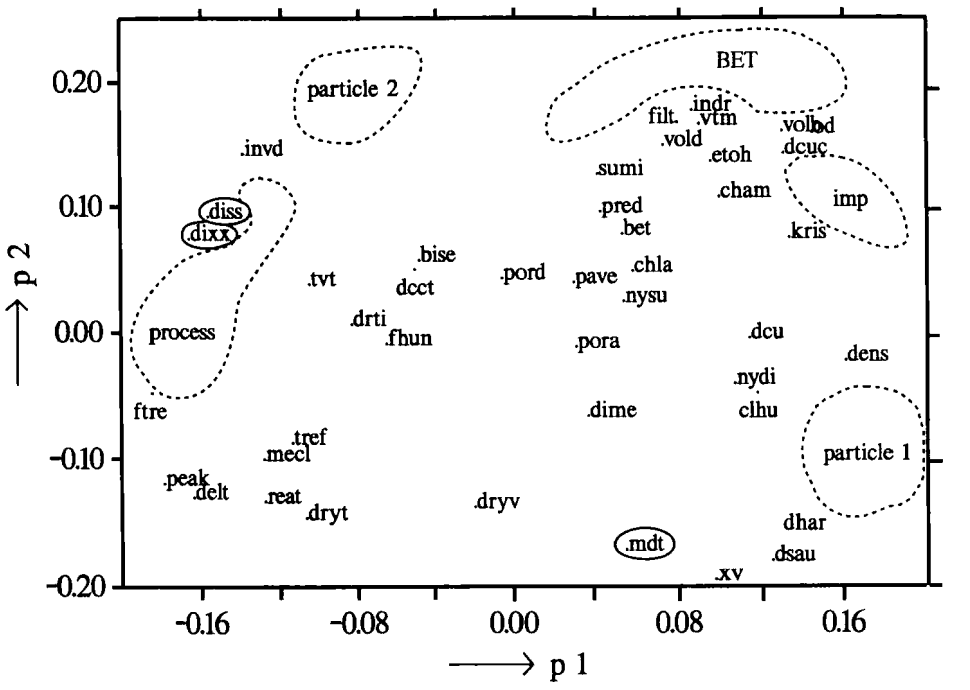

FIGURE 1. Loading plot

X-axis: principal component 1
Y-axis: principal component 2
Variables are denoted by a combination of three or four letters or grouped into clusters.

Principal component analysis (4) was applied to the data, 42 batches of prednimustine and 66 variables (3). The loading plots reveal which variables are correlated to each other and thus associated with the same properties on the part of the objects. Correlated variables will be described by reference to the same principal component. Such loadings are either projected as being close to each other (positive correlation) or as being each other's opposites with respect to the origin (negative correlation). Variables with a strong influence on the model are projected as being far from the origin.

It can be observed from Fig. 1 that the first principal component (PC 1) is mainly influenced by the dissolution-rate variables diss and dixx, some process variables (process), particle-size variables (particle 1) and impurities (imp). However, there is also an influence on the second principal component (PC 2) from diss, dixx, and

"particle 1", although it is of less importance than in the case of PC 1. PC 2 is mainly influenced by particle size variables (particle 2), gas adsorption variables (BET) and the dissolution-rate variable mdt. Consequently, there is not only a relationship between dissolution rate and particle size; impurities, process parameters and gas adsorption variables exert important influences, too.

Partial least squares projections to latent structure (PLS) modelling (5) were also applied to the data. The dissolution-rate block, the Y-block, was related to the other variables, the X-block, comprising particle-size data, impurities, process data etc. A reasonable relationship between the dissolution-rate block and the block containing the predictor variables -- the X-variables -- was indicated. Dissolution-rate prediction was acceptable, the correlation coefficient being 0.90 with regard to diss. This means that it was possible to predict the percentage of dissolved prednimustine after 60 min (diss) when all the predictor variables -- i.e., not only the particle-size parameters -- were known. However, such a prediction is not practically accomplished on a routine basis.

In the derivation of the Noyes-Whitney equation, it was assumed that h (the thickness of the diffusion layer) and S (the surface area of the exposed solid) were constant; but this is not the case (1). Consequently, a divergence from the equation would not be unexpected with a drug composed of aggregated/agglomerated crystallites which deaggregate/deagglomerate during the dissolution process.

Impurities can influence the crystallite size as well as the aggregate/agglomerate size of the drug. Besides, impurities may influence the surface roughness and wettability of the particles when adsorbed on the surface of the crystals. Impurities can originate from the raw materials used in the synthesis of the drug, i.e. due to process conditions.

Bearing these aspects in mind, it was no great surprise to find that some impurities, process and other variables, together with some particle-size variables, contributed to the formation of correlations with dissolution rate.

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