Characterization of phenobarbitone samples

Phenobarbitone has been shown to exist in a number of polymorphic forms (Huang, 1951a & b; Cleverley & Williams, 1959; Mesley, Clements & others, 1968). One of these has been shown to be a monohydrate (Mesley & others, 1968; Riley, 1973a), and may therefore be more correctly described as a pseudopolymorph according to the definition of Pfeiffer, Yang & Tucker, (1970). It is this hydrate which exists in aqueous systems and which is produced by acid precipitation from an alkaline solution, a process frequently used in final purification. On drying the material by heating, polymorphic changes occur, the final form depending upon the temperature and duration of drying (Riley, 1973a).

In an investigation of the polymorphic changes, samples of phenobarbitone as marketed by various manufacturers were examined, and significant differences in physical characteristics, though not in polymorphic form, were observed in the different products. It is now suggested that, by examination of the product, the nature of its preparation process and its origin may be postulated.

On microscopical examination, the four commercial samples examined showed immediate differences, From the rounded appearance of the particles, Samples A and D appeared to have been further processed after preparation, possibly by ball milling, Sample C had acicular particles and did not resemble either of the other commercial samples or samples prepared and dried in the laboratory. It is suggested that this sample has been recrystallized from ethanol. Sample B microscopically resembled laboratory material dried at 110°.

Samples of phenobarbitone were prepared in the laboratory by acid precipitation from a solution of the sodium salt, followed by drying at room temperature (20°) in a current of air, or in a hot air oven at 110°. Particle size distributions of these, and of the commercial samples have been obtained using a Sartorius Sedimentation

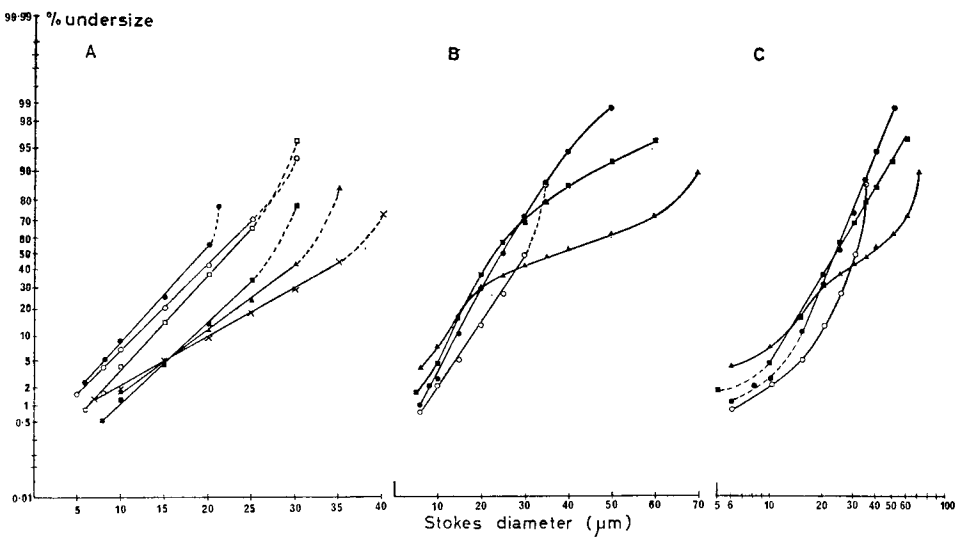

FIG. 1. Arithmetical—Probability plots for precipitated phenobarbitone prepared in the laboratory at ● 20°, ■ 30°, ▲ 40°, × 50° and all dried at room temperature (20°). ○ pilot scale batch prepared at 25° and dried at 20°. □ same batch dried at 110°.
B. Arithmetical-probability plots of the commercial samples of phenobarbitone.
C. Logarithmic-probability plots of the commercial samples of phenobarbitone. ■ Sample A. ▲ Sample B. ○ Sample C. ● Sample D.

Balance with a mixture of light petroleum (boiling range 100-120°) and light liquid paraffin B.P.C. 1963 as the sedimentation medium. The effects of different process conditions on median Stokes diameter have been previously reported (Riley, 1973b).

Examination of the size distribution curves, however, yields more information. It has been suggested that a distinction can be drawn between particles produced by a chemical process, which tend to a uniform size and show arithmetic-normal distributions, and those produced by crushing and grinding, which show logarithmic-normal distributions (Austin, 1939; Herdan, 1960).

Fig. 1A shows that precipitated material (monohydrate) follows the normal distribution law except at the extreme coarse end of the distribution. The reason for this deviation is not clear, but it may be because of growth of the larger particles at the expense of the very small ones, with the production of larger than expected weights for the larger size particles. The sedimentation system is not considered to be responsible, because calculation shows the Stokes range to extend to 96 μm. A pilot scale batch prepared in the laboratory shows the same type of distribution. After drying, the deviation of the coarsest particle size fraction becomes more marked and the median size decreases, possibly due to particle fracture during the necessary breaking up of caked material.

Fig. 1B and C show arithmetic and logarithmic probability plots for commercial samples with Sample C showing a normal distribution and Samples A and D showing log-normal distributions.

The size distribution of a powdered material, together with microscopical examination, is therefore capable of yielding valuable information about the history and origins of the sample. In the cases examined here, it is possible to postulate that Samples A and D are dried precipitated products which have been subsequently milled, that Sample B is a dried precipitated product with no further treatment other than breakage of caked material, that Sample C has been crystallized from a non-aqueous solvent, with no further treatment after solvent removal.

These observations underline the fact that the same chemical substance, prepared by different manufacturers, may show widely differing physical characteristics, with consequent differing behaviour in processing and when formulated and administered as a medicinal preparation.

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