(phenethylbiguanide), and accords with physicochemical evidence that the partition coefficient of metformin in octanol/water is approximately one fortieth that of phenformin (Schafer 1980).

Metformin bears a single net positive charge at physiological pH, and it is likely that ionic interactions rather than hydrophobic effects contribute to its membrane binding properties. Ionic interactions may not be sufficiently strong to wholly withstand the present fractionation procedure, but the technique does provide clear evidence that metformin is associated predominantly with the cytosol of hepatocytes. We conclude that reports describing a membranal mode of action of long-chain substituted biguanides such as phenformin may not be directly extrapolated to metformin.

We thank Susan L. Turner for her excellent technical assistance.

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Communicated November 5, 1990

Characterization of the variation between batches of Fast-Flo lactose using low frequency dielectric spectroscopy

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Abstract—The dielectric response of four batches of lactose has been measured over a frequency range of 10^4 to 10^{-2} Hz. The spectra corresponding to three of the batches were identical, while the fourth showed a marked reduction in response. This particular batch has also been reported to exhibit longer disintegration times than the other three when formulated as a tablet. The potential use of dielectric spectroscopy as a means of screening batches of pharmaceutical materials is discussed.

In a recent study on inter-batch variation between Fast-Flo lactose samples (Boyd et al 1989), we demonstrated that tablets produced from a particular batch of lactose yielded considerably slower disintegration times than did other, supposedly identical samples. However, no significant physical differences could be found between the materials using optical microscopy or X-ray powder diffraction. Measurements of adsorbed water, water of crystallization, tap density and angle of repose yielded similar results for all four samples. The study therefore highlighted some of the problems associated with inter-batch variation, in particular the difficulty in finding a technique which can identify potential problems at an early stage.

In the present investigation, the same four batches of lactose were examined using low frequency dielectric spectroscopy (DISP) in order to ascertain whether any differences could be detected. DISP has been employed in the analysis of several pharmaceutical systems, some of which have been reviewed by Craig et al (1990). The method involves the application of a small alternating voltage to a sample and the subsequent measurement of the energy stored (as capacitance) and lost (as dielectric loss) over a range of frequencies. The resulting spectra may yield information on the structure and behaviour of a wide variety of systems. For a more detailed description of the theoretical aspects of the technique, the reader is referred to Dissado & Hill (1979) and Hill & Jonscher (1983).

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Materials and methods

Samples taken from four batches of Fast-Flo lactose (Foremost Whey Products, Wisconsin, USA), designated Batches A, B, C and D, were analysed as received. Three hundred milligrams of each material was compressed in an IR press to form discs of diameter 13 mm and thickness $1{\cdot}58 \pm 0{\cdot}03$ mm. Each sample was placed between two platinum electrodes (area 81 mm^2) in a Perspex dielectric cell, held at 298K in a cryostat (Oxford Instruments Ltd, Oxford). An AC signal of 0·5 V was generated by a frequency response analyser (FRA, Solartron, Hampshire) and passed through the sample via a Chelsea Interface (Chelsea Dielectrics Group, London). The returning signal was analysed by the FRA and the results presented graphically in terms of the capacitance and dielectric loss over a frequency range of 10^4 to 10^{-2} Hz. At least three measurements were made at each frequency and the average calculated automatically. Spectra

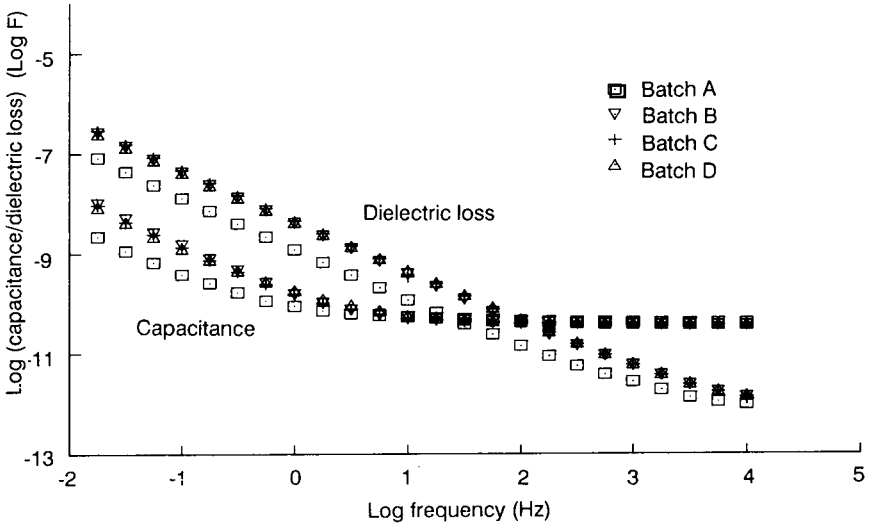

FIG. 1. Dielectric response of Fast-Flo lactose.

obtained from compacts prepared from the same batch were superimposable.

Results and discussion

The responses of the four samples are given in Fig. 1. Batches B, C and D produced very similar spectra, while Batch A yielded a lower response. This batch was the same as that reported by Boyd et al (1989) to produce tablets with slow disintegration times. The technique therefore identified the problem batch of lactose correctly.

It may be concluded that DISP has a potential application as a batch-screening technique. This is supported by previous studies, which have shown the technique to be sensitive to changes in crystal form (Shablakh et al 1982; Chatham 1985) and to the presence of impurities (Craig 1989; Lievens et al 1990). The spectra may also yield specific structural information on the sample, thus allowing identification of the cause of the inter-batch variation. While little precedent exists to date in order to facilitate this analysis, the results indicate that the difference is due to changes in crystal form, rather than due to the presence or absence of impurities such as residual solvents. This is suggested by the similarities in shape and order of magnitude of the spectra, despite the differences seen for Batch A. Previous studies (Lievens et al 1990) have indicated that the presence of residual solvent has a much greater effect on spectral shape than was seen in the present case, whereas differences in crystal form have been reported to result in spectral changes of this magnitude (Chatham 1985). However, this argument is contradicted by the observation that no differences were seen in the X-ray diffraction spectra for the four batches. More work therefore needs to be performed in order to interpret the observed results fully.

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