Dielectric analysis of hydrated mannitol by time-domain dielectric spectroscopy

H. M. DERBYSHIRE, G. SMITH, I. ERMOLINA*, Y. FELDMAN* AND C. R. BLAND†

Department of Pharmaceutical Sciences, De Montfort University, Leicester LE1 9BH, *Graduate School of Applied Sciences, Hebrew University of Jerusalem, Jerusalem, Israel, and †Astra Charnwood, Loughborough LE11 5RH

Mannitol is used as a crystallising excipient in the stabilisation of freeze-dried drugs. The properties of the residual water present in freeze-dried compounds are important because water can impact on the physical state of the compound. The dielectric properties of hydration water in biological systems have been investigated using dielectric spectroscopy for some time (Takashima 1989) but there have been few studies on the dielectric properties of hydration water in pharmaceutical excipients (Daoukaki-Diamanti & Pissis 1986; Millane & Arnott 1991; Smith 1995), and yet dielectric analysis provides information on both the quantity and state of water.

Dielectric measurements using time-domain dielectric spectroscopy (TDS), with non-uniform sampling overlapping the frequency range 10^5-10^{10} Hz, were performed on mannitol (presented as a powder). Samples of mannitol were hydrated between 2 - 45% w/w water and the dielectric response measured at 25°C. In addition, a single hydration level (25%) was selected and the effect of temperature on the dielectric response was investigated over the temperature range −16 to +30 °C.

The dielectric properties of each sample were approximated by fitting two exponential processes to the time domain response. Each process is characterised by $\Delta\varepsilon$ (the relaxation strength, which is proportional to the number of dipoles relaxing) and τ (the mean relaxation time of the dipoles). The high frequency dielectric permittivity is characterised by ε_∞. The fast process ($\tau = 0.1$ - 0.24 ns, $f_o = $ ~0.6 - 1 GHz) is attributed to the water of hydration (Takashima 1989). The slow process ($\tau = 25$ -75 ns, $f_o = 2.1$ - 6.4 MHz) seems to be independent of water content. This response could be related to internal relaxation in mannitol, possibly as a result of changes in the position/conformation of the mannitol chain.

The value of $\Delta\varepsilon$-fast increases slowly with low water content, until it reaches a critical point at which $\Delta\varepsilon$-fast changes sharply. This point marks a change in the nature of the adsorbed water as the second layer of hydration begins to form (Takashima 1989). The polarisability of the hydration water defines $\Delta\varepsilon$-fast. Thus, the first layer of hydration is tightly associated with the saccharide, having restricted mobility. The second layer is less tightly associated, having more rotational freedom. ε_∞ includes the fast vibrational and librational motions of the water molecule, and also increases with increasing water content due to the water molecules attaining an increased mobility.

The temperature study shows a sharp increase in $\Delta\varepsilon$-fast of about one unit between 0 and −5 °C. Above and below this temperature $\Delta\varepsilon$-fast changes very little. This transition is attributed to the change of state of water (i.e. melting/freezing). The relaxation time of the fast process increases with decreasing temperature, since at lower temperatures there are fewer molecules with sufficient energy to overcome the energy barrier for reorientation.

The parameters $\Delta\varepsilon$-fast and τ-fast give information about the polarisability of the hydration water, which is a function of the nature of the interaction with the hydration surface. These type of studies therefore have implications for improving our understanding of the mechanisms by which certain excipients enhance the stability of nearly dry pharmaceutical solids, e.g. by acting as buffers that immobilise residual water in freeze-dried products.

References

Daoukaki-Diamanti, D., Pissis, P. (1986) Zeitschrift für Physikalische Chemie 149: 27-40

Millane, R. P., Arnott, S. (1991) Ordered water in hydrated solid-state polysaccharide systems. In: Levine, H., Slade, L. (eds) Water relationships in food. Plenum Press, New York, pp 785-803

Smith, G. (1995) Pharm. Sci. 1: 419-422

Takashima, S. (1989) Electrical Properties of Biopolymers and Membranes. Adam Hilger, Bristol and Philadelphia

Acknowledgements