THE DIFFUSION CHARACTERISTICS OF ANTIBIOTICS IN MUCUS GLYCOPROTEIN GELS

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The ability of mucus glycoprotein (GP) sols and gels to retard the diffusion of drug molecules has been demonstrated previously (Marriott et al 1984) using a capillary method and radioisotopically labelled diffusants such as tritiated water and ^{14}C benzylpenicillin. It was shown that the GP sol to gel transition markedly reduces diffusion of small molecules and may be responsible for poor treatment of pseudomonal (PA) lung infections, particularly where embedded microcolonies are present (Lam et al 1980). However, the technique could not be used to compare a range of antibiotic molecules which might be used to treat such infections because of the lack of availability of labelled compounds. A method has therefore been developed to enable measurement of diffusion coefficient (D) of unlabelled diffusants through mucus GP gels.
An ultrasonic differential method for non-invasively monitoring the change of concentration gradient of diffusants between two planes in the gel was used. This change in concentration gradient was monitored with respect to time, and allowed determination of diffusion coefficients without effects due to interfacial barriers. The method used is a development of that described by Dela and Rassing (1978) and the gel consisted of 10% w/w purified porcine gastric mucus (Marriott et al 1981) maintained at 25°C: all compounds were stable under these conditions. Diffusant solutions (5% w/v antibiotic in pH 7.4 phosphate buffer containing phenylmethylsulphonyl fluoride) were passed across a face of the gel and sound velocity which is related to diffusant concentration was measured by a "sing around" technique in two planes within the gel. The time t' taken for maximum concentration difference was used to calculate diffusion coefficients.

Diffusant	t' (hrs)	D x 10^{-6} $cm^2 s^{-1}$
Water (Control)	3.752	4.37
Cefotaxime	4.502	3.64
Cefsulodin	5.002	3.27
Ceftazidime	4.787	3.42
Gentamycin	6.503	2.52
Carbenicillin	2.953	5.54
Mezlocillin	3.386	4.84
Benzylpenicillin	4.846	3.38

The results confirm that, like water, antibiotic diffusion is severely impaired within a mucus gel since the self diffusion coefficient of water has been shown to be 24.4 x 10^{-5} cm s^{-1}. An important observation is the high diffusion coefficient of carbenicillin, which may well account for its known efficacy in PA infections, and the lower value for gentamycin. However, the cephalosporins, whilst clinically effective, show no advantages in terms of diffusion through the mucus to the site of action. In contrast, the penicillins diffuse at similar rates to water, implying that diffusion is not controlled by molecular size, shape or charge for this class of antibiotics although these factors may be of importance in the case of cephalosporins. It is obviously relevant to consider the diffusion characteristics of antibiotic molecules particularly if it is intended to deliver them directly into the airway.

Marriott, C. et al (1984) 2nd Euro. Cong. Biopharm. & Pharmacokinetics, 176
Lam, J. et al (1980) Infect. Immun. 28: 546-556
Dela, K., Rassing, J. (1978) Acta Chem. Scand. A. 32: 925-928
Marriott, C. et al (1981) Am. Rev. resp. Dis. 124: 285-291