DETERMINATION OF THE GELLING POINT OF MUCUS GLYCOPROTEINS USING AN ULTRASONIC TECHNIQUE

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Successful drug therapy in respiratory tract infections requires the attainment and maintenance of antibiotic levels higher than the minimum inhibitory concentration in the immediate vicinity of the infecting organism. The highly vascularised nature of the lungs would appear to allow easily attainable effective drug levels in both the lung parenchyma and secretions via the systemic route. Although alveolar tissue antibiotic levels closely approximate to serum levels (Pennington 1981) a sigificant barrier to drug diffusion through mucus gels has been demonstrated (Marriott et al 1984). The concentration at which the mucus glycoprotein (GP) forms a gel has been considered crucial to such diffusion and previous measurements have been limited to rheological techniques. This work has used an ultrasonic resonance interferometric technique (Eggers 1968) which enables local configurational changes and internal rotation of domains to be studied.

Pig gastric mucus was purified by gel filtration (Marriott et al 1984) and the first order rate constant of time dependent conformational change was determined as a function of glycoprotein concentration. The results are shown in the table. The GP was found to exhibit a time dependent first order change in the mobility of the short oligosaccharide side chains either due to a slow averaging of the contributions of the different volume elements within the molecule or to a transition towards homogeneity amongst such domains. This type of behaviour has not been observed with any other polymers studied. The rate constant, k, varied with glycoprotein concentration and below 0.5% w/w a highly extended configuration of the GP molecule is indicated. Above this concentration a reversion to a more coiled arrangement occurs and the range between 0.5-1.0% w/w GP may be considered to be the sol/gel transition: this is much lower than the value reported by Allen (1978) using dilute solution viscometry. However, the value reported in this work correlates well with the concentration at which impairment of drug diffusion has been shown to occur (Marriott et al 1984). Above approximately 1% w/w the microconformation is essentially fixed once the gel has been formed and k becomes concentration independent. From this work it is clear that GP is therefore considerably more hydrated than has been previously reported: the hydrodynamic volume can be calculated to be 143 ml g^{-1} compared with the value of 40 ml g^{-1} calculated by Allen (1978).

% w/w GP	Rate constant k min^{-1}
0	0
0.005	0.48
0.01	0.72
0.05	3.45
0.1	3.78
0.44	4.77
0.75	5.55
1.00	1.1
1.25	0.98
1.50	0.92
2.25	1.05

Since the diffusion of water and drug molecules through mucus has been shown to be similar (Marriott et al 1984) this work indicates that both will be affected at a concentration of glycoprotein which is much lower than that at which a discrete gel is produced. This will have implications not only for the diffusion of drug molecules through mucus gels in the lung but also for the transfer of drug molecules from the lumen to the epithelium of the gastrointestinal tract.

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