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COMMUNICATIONS

Ultrasonic velocity and diffusion of drugs through a gelatin gel

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The study of drug transport through gel structures is of potential value in evaluating the usefulness of gels as implants or as other sustained release dosage forms. The possibilities of using implanted polyacrylamide gels for the slow release of insulin (Davis 1972, 1974), prostaglandin $F_{2\alpha}$ (Davis & Chang 1972) and ethinyl oestradiol (Davis et al 1972) have been investigated. Similarly, the so-called 'hydrogels' formed from glycol methacrylate esters have been widely used in ophthalmology and otolaryngology (Majkus et al 1969).

Gel implants must be designed to release the drug at the desired rate and this may be achieved, for example, by modification of the degree of cross-linkage within the gel network. The assessment of the effectiveness of such modifications demands a precise method for the evaluation of diffusion rate within the gel network.

Previously, diffusion of aqueous solutions into gelatin gels has been followed by radioactive tracer, optical and conductivity techniques (Aussel et al 1965; Staaf 1967; Cartwright 1949). Diffusion of dyes into gels has been extensively investigated and the dependence of the diffusion of methylene blue in gelatin gels on Bloom grade, temperature and concentration has been reported (Nixon et al 1967). The diffusion of a compound through a gel depends on several factors. A very important factor is the effect of the diffusing compound on the gel structure. This particular effect cannot be studied separately by means of the experimental techniques previously applied to diffusion investigations.

In the present note we describe a method based on the determination of sound velocity which may be suitable for investigation of this effect.

The behaviour of ultrasonic waves in gelatin solutions has been studied by means of several techniques (Mikailov 1964; Wada et al 1967; Rassing & Dela 1978). The sound velocity at 4 MHz, measured by means of the sing around technique, has been applied to gelatin/water mixtures and the experiments show that the sound velocity increases with increasing pH (Wada et al 1967). The sound velocity, U, is given by the following equation:

$$U = (\beta\ \rho)^{-\frac{1}{2}}$$

where β and ρ denote the adiabatic compressibility and the density of the system respectively. The adiabatic compressibility of the system depends on the nature of the molecular interactions and thus this parameter is sensitive to small changes in both the gel structure and the concentration of other species present in the gel. Consequently the sound velocity seems to be ideal not only for following the changes in concentration of drug during the diffusion process but also for detecting any effect which the drug might have on the gel structure.

In our laboratory the sound velocity was measured by means of the sing around technique as described previously (Rassing & Dela 1978). In principle, the sample is contained in a cylindrical cell, the ends of which are sealed with piezoelectrical quartz crystals. By means of an oscillator, the sending crystal is excited with a radio frequency signal of 4 MHz and a duration time of 3 μs. The resulting low amplitude sound wave produced in the system is detected by the other crystal and the created voltage triggers the oscillator to produce a second frequency signal across the sending crystal and so on. Thus the pulse repetition frequency in the circuit is related to the velocity of the sound wave that travels through the sample. We have used a modified NUS—Sonic Solution Monitor (NUSonics Inc.) with an attachment making it possible for the oscillator successively to operate two different cells and to print the pulse repetition frequency at convenient time intervals. By means of this equipment the sound velocity at 4 MHz has been monitored for a gelatin gel inserted in solutions of several pharmaceutically relevant compounds. All experiments were carried out at 288 K, with an initial drug concentration of 0·5 mol dm^{-3} and gelatin gel of 3·5%. The cell contains a gel rod with a volume of 47 cm^3. The surface of this rod is in contact with 70 cm^3 of surrounding drug solution. Inside the gel rod the travelling sound wave passes through a well defined volume of 15 cm^3 symmetrically located around the centreline of the rod. The sound velocity in this part of the gel rod is related to the amount of drug that has diffused into the sound path. The results are presented as graphs of sound velocity against time in Fig. 1. In order to convert the measured velocity into molar concentrations of drug inside the gel, calibration graphs are needed. These were obtained from measurements on a series of aqueous drug solutions of known concentration and on gels prepared from these solutions. By this means the time dependence of the drug concentration

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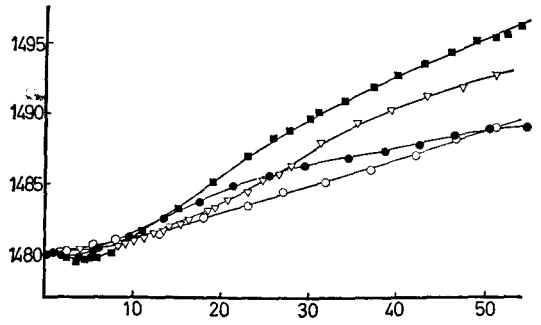

FIG. 1. Variation of sound velocity, U, with time during the diffusion of ●, sodium chloride; sodium salicylate; ■, mepyramine maleate and ○, carbachol into 3·5% gelatin gels. Ordinate: U (m s^{-1}). Abscissa: time (h).

inside the well-defined sound path in the gel rod can be obtained. Table 1 shows some preliminary results. For sodium chloride the results have been checked by means of chloride titrations carried out on samples taken from the appropriate gel volumes. Thus the technique here described may be a useful tool for fast and accurate monitoring of drug diffusion inside a gel rod.

To obtain diffusion coefficients from sound velocity measurements a new cell is being designed in which the sound velocity can be monitored at two positions of accurately known separation within the gel. The concentration and concentration gradient can thus be measured at both positions simultaneously, generating the necessary data from which diffusion coefficients may be calculated.

This preliminary report shows that measurements of the sound velocity as a function of time provides a new and non-destructive method of studying diffusion of drugs through polymer networks. It is proposed that the experimental technique here described will be used in the investigation of the effect of increased cross-linkage on drug release rate and in the determination of the drug release characteristics of polymer networks more suitable for use as implants.

Table 1. The drug concentration expressed as mol dm^{-3} in the gel volume through which the sound passes.

Time (h)	Sodium chloride	Sodium salicylate	Mepyramine maleate	Carbachol
6	0·023	0·016	0·019	0·009
12	0·054	0·033	0·020	0·029
18	0·082	0·049	0·029	0·076
24	0·111	0·073	0·039	0·090
30	0·121	0·097	0·049	0·113
36	0·132	0·120	0·059	0·129
42	0·144	0·135	0·068	0·132

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Inhibition of rabbit PMN lipoxygenase activity by benoxaprofen

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A variety of arachidonate lipoxygenase products exhibit both chemokinetic and chemotactic activity for polymorphonuclear cells (PMNs) (Samuelsson 1979). Recent studies using human PMN homogenates as a source of lipoxygenase enzyme(s) have shown that 5-hydroxyeicosatetraenoic acid (5-HETE) possesses the highest chemotactic activity of the monohydroxy acids detected (Goetzl & Sun 1979). The authors suggest that endogenous formation and release of these compounds from intact cells upon suitable stimulation may be involved in the control of cell movement into inflammatory exudates.

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Vane (1971) proposed that the common mechanism of action of non-steroidal acidic anti-inflammatory compounds (NSAI) was the inhibition of the enzyme complex prostaglandin synthetase (cyclooxygenase). Many supportive data have been adduced since that time (Flower 1974; Ferreira & Vane 1979) but a number of workers have felt that the story was incomplete (Smith 1978; Dawson 1979a). The recent work of Higgs et al (1979) suggesting a link between cell migration and the lipoxygenase products of arachidonate may well provide a further insight into the mechanism of action of NSAI.

Benoxaprofen, a new anti-rheumatic/anti-inflammatory agent, exhibits low arachidonic cyclooxygenase