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Determination of localized transport coefficients of FITC-dextrans in gels using non-Fickian fluorescence recovery after photobleaching

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Diffusion of aqueous drug species in a polymer matrix pharmaceutical system is an important factor in drug release from hydrogel dosage forms. The ability to rapidly measure localised drug transport coefficients (D) inside the heterogeneous environment of a hydrogel matrix would be an effective tool to assess the performance of a dosage form. The techniques of continuous fluorescence multipoint microphotolysis (CFMM) (Cutts et al. (1995)) and fluorescence recovery after photobleaching (FRAP) (Axelrod et al. (1976)) can rapidly measure D. However, these techniques determine D by solving Fick's diffusion equation. A solution of Fick's equation employs definite assumptions, such as sample homogeneity; conditions which rarely exist in most pharmaceutical systems. Therefore we have developed a FRAP technique, using non-Fickian analysis to determine D values. This technique has been used in the present work to determine D values for a variety of molecular weight dextrans in agar gel. The results are compared with D values obtained using CFMM (Cutts et al. (1995)) and the classical double diffusion cell method (Bain et al. (1990)).

A BioRad MRC600 Confocal Laser Scanning Microscope was used to focus a 488 nm laser beam at a specific position in a FITC-dextran permeated agar gel. The sample was irradiated with a 5 mW laser beam for 5 sec., resulting in irreversible bleaching of the fluorophore. During the recovery period, diffusion of unbleached fluorophore into the bleached area was monitored using a 0.15 mW laser beam. Using image processing software, Semper 6.4 (Synoptics, UK), recovery images were locally averaged, the centre of the bleached spot was accurately found and radial profiles were calculated. A mathematical model was developed to integrate the recovery profiles and fit the profile area to an exponential curve, calculating D.

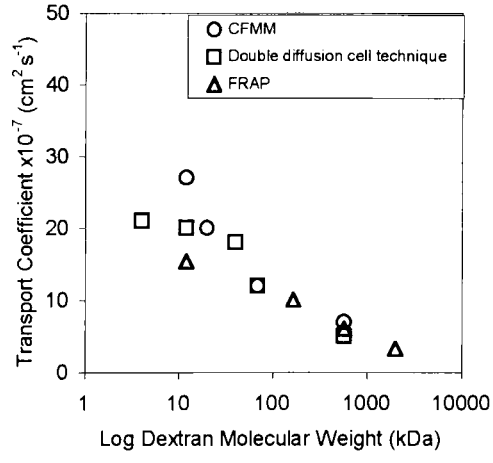

Figure 1. The effect of molecular weight on the D value of FITC-dextrans in agar gel, measured using CFMM (n=10), the double diffusion cell method (Cutts et al. (1995)) and non-Fickian FRAP (n=10).

An excellent correlation exists between CFMM, the double diffusion cell method and non-Fickian FRAP (Figure 1). The non-Fickian FRAP technique is experimentally simple and reproducible, determining D without the need to solve Fick's diffusion equation. Therefore, non-Fickian FRAP can rapidly measure D in localised microscopic areas of homogenous systems and can equally be used to measure D in heterogeneous pharmaceutical systems.

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