A NOVEL TECHNIQUE TO DETERMINE VERAPAMIL HCL DIFFUSION COEFFICIENTS THROUGH HYDROXYPROPYL METHYLCELLULOSE GELS

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Sustained release tablets which contain substantial amounts of gels such as hydroxypropyl methylcellulose (HPMC), exhibit surface swelling on contact with water, forming a gel layer matrix through which drug can slowly diffuse. It was considered of interest to establish the effect of gel molecular weight (MW) and degree of hydration (or water content) on the rate at which drug might diffuse through the tablet. The method described facilitates the use of relevant drugs rather than dyes, markers or isotopes, using standard laboratory equipment.

A method was developed to measure diffusion coefficient of verapamil hydrochloride through hydrated HPMC gels by non-invasive UV measurement of drug accumulation. Three HPMC grades of differing MW were prepared at concentrations representing various degrees of hydration. Water was heated to 80°C, and HPMC added slowly whilst stirring. When homogenous, the suspension was cooled with constant stirring just until it began to gel, then poured into a 1cm UV cell. This constituted the acceptor phase. This process was repeated using a 6% w/v verapamil hydrochloride HPMC solution as donor phase. The cells were sealed separately and stored for three days at 37°C to allow complete hydration. After cooling to room temperature, the open ends of the acceptor and donor cells were pressed together excluding air and the cell junction sealed with tape. The 'double cell' was stored vertically at 37°C with the denser donor phase in the lower position to prevent convective movement. The concentration of drug at specified distances from the interface was measured at intervals up to a week by placing the cells horizontally in a modified six cell compartment carriage of a spectrophotometer and measuring absorbance at 300nm at room temperature in each of the six cell positions. Light absorbance values of verapamil hydrochloride in the gel solutions over the range of concentrations used, have been shown to comply with Beer's law.

The diffusion coefficient D cm^2/s was calculated from equation 1 (Crank 1956) for each time point at x = 0.8cm from the interface, by measuring drug concentration $C_{(x,t)}$ in the acceptor phase. Since this simple equation is only valid for a system with infinite accepting phase, calculations were based on values of $C_{(0,8cm,t)}$ only if $C_{(4cm,t)} = 0$. Where C_o is the initial drug concentration in the donor phase, and t is the time in seconds.

Table 1 Verapamil HCl diffusion coefficients through HPMC gels

HPMC GRADE	MW APPROX	VERAPAMIL HCl DIFFUSION COEFFICIENT D X $10^{-6}cm^2/s$ THROUGH THE FOLLOWING HPMC CONCENTRATIONS (% W/V)			
		1.25	2.5	5	10
E4M	92500	#	3-3.5	2-3	1-1.5
E10M	120000	#	3	2-2.5	1.5-2
K100M	250000	4-5	3-5	2.5-3	##

Not viscous enough to remain in cells. ## Too viscous to pour.

Equation 1

$$C_{(x,t)} = 1/2\ C_o \mathrm{erfc} \frac{x}{2\sqrt{(Dt)}}$$

The results presented in Table 1 show that rate of diffusion is independent of HPMC MW. Rate of diffusion, is however, limited by degree of HPMC hydration, higher degrees of hydration result in faster diffusion. This is probably due to the structure of hydrated HPMC, which consists of a complex matrix of molecules which become more relaxed as hydration increases, causing less restriction to drug diffusion.

J. Crank (1956) The Mathematics of Diffusion. Oxford University Press