TEMPERATURE EFFECTS ON THE DISSOLUTION OF PROMETHAZINE HYDROCHLORIDE FROM HYDROXYPROPYLMETHYLCELLULOSE MATRIX TABLETS

K. Mitchell, T. Sogo[×], J. Ford[*], D. Armstrong, P. Elliott, C. Rostron, J. Hogan[+]
Drug Targeting Research Group, Centre for Pharmaceutical Sciences, School of Health Sciences, The Liverpool Polytechnic, Byrom Street, Liverpool L3 3AF. U.K.
[+]Colorcon Ltd., St.Paul's Cray, Orpington, Kent. ([*]Correspondence).
[×]Facultad de Farmacia, Universidad de Santiago de Compestela, Spain.

The release of water-soluble drugs from hydroxypropylmethylcellulose (HPMC) matrices is usually presented as a function of the square root of time. Ford *et al* (1987) fitted data obtained from HPMC matrices to the equation $M_t/M_\infty = kt^n$ (M_t/M_∞ = fraction of drug released, k = a kinetic constant, t = release time, n = the diffusional exponent for drug release) and found for water soluble drugs that $n \simeq 0.7$. This value indicates that the release mechanism is intermediate to Fickian controlled release (where $n \simeq 0.45$ for spheres) and case II transport where $n \simeq 0.89$ (Peppas & Sahlin 1989). Using promethazine hydrochloride [P] as a model drug we have examined the influences of temperature on the release rates from HPMC matrices to further elucidate the mechanisms of drug release.
Tablets (6.35mm flat face or 7.93mm shallow concave) containing 25mg P; HPMC K15M (Dow Chemicals) and 0.75% magnesium stearate (BDH) were prepared by direct compression. Dissolution was studied using a Copley Series 8000 dissolution tester into 1 litre water using the BP 1988 method 1 monitoring P at 250nm. Temperatures were 25, 30, 37, 45 or 50°C. Data were treated (1) as a function of the square root of time, (2) as first-order (amount undissolved) kinetics or (3) on a log dissolved-log time basis (Ford *et al* 1987) which enabled the diffusional exponent n to be determined following correction for lag times. Data obtained at 25, 30 or 37°C and treated on a root time basis gave straight line plots over the range 5-60% drug released. At 45 and 50°C the curves showed increasingly greater negative deviations from linearity once ∿30% of the drug had dissolved. These ranges were used in calculating drug release rates.

EFFECT OF TEMPERATURE ON FIRST ORDER DISSOLUTION RATE CONSTANTS (min^{-1} X 10^4) AND THE DIFFUSIONAL EXPONENTS (n) FOR P RELEASE FROM HPMC K15M MATRICES.

HPMC (mg)	25°C	30°C	37°C	45°C	50°C
50	37.4 (0.72)	45.9 (0.74)	62.2 (0.76)	75.8 (0.84)	89.1 (0.93)
75	31.3 (0.72)	37.0 (0.71)	44.6 (0.77)	59.3 (0.79)	64.7 (0.81)
100	21.3 (0.66)	25.1 (0.68)	28.5 (0.68)	38.1 (0.72)	40.9 (0.79)
150	18.8 (0.65)	21.6 (0.65)	24.9 (0.68)	28.0 (0.74)	34.8 (0.73)

The release rates and values of n increased with an increase in temperature or a decrease in HPMC content. Although increases in temperature will decrease the tortuosity in the matrix and increase the diffusion coefficient of the drug, the increases in n imply that the contribution of case II transport (associated with stresses in the HPMC and its concomitant erosion) also increases. A value of n = 1 is indicative of zero order release. Since n approaches 1 at 50°C in tablets containing 50mg HPMC, the data suggests that the nearer the gel point (∿67°C for 2% HPMC K15M) is to the temperature of dissolution, the greater the contribution of erosion to dissolution will become. Consequently a zero-order drug release should be obtained when a matrix has its thermal gelation temperature near to the dissolution temperature and contains low levels of polymer.
The estimated activation energies from the first order dissolution constants decreased with an increase in HPMC being 27.5, 23.8, 21.3 and 18.2 $kJmol^{-1}$ for the matrices containing 50, 75, 100 and 150 mg HPMC respectively. This confirms the role of erosion in matrices of low HPMC content since if diffusion was the sole controller of release rates from the matrices the obtained energies would be independent of drug:HPMC ratio within the matrix.

Ford, J.L. *et al* (1987) Int.J.Pharm. 40:223-234
Peppas, N.A., Sahlin, J.J. (1989) *Ibid.* 57:169-172