THE RELEASE KINETICS OF SOME PARA-SUBSTITUTED BENZOIC ACIDS FROM POLY(2-HYDROXYETHYL METHACRYLATE) HYDROGELS

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One of the aims of a controlled release device is the achievement of a constant rate of release of drug. Release from monolithic devices usually follows root time kinetics but zero order kinetics can be achieved if the drug has a high affinity for the matrix, and release is partition controlled (Roseman & Higuchi 1970). *In vitro* release kinetics from silicone devices change from a matrix to a partition controlled mechanism with changes in solubility and partitioning properties of the elution medium (Chien & Lambert 1974). However, the changes in the aqueous environment of a drug delivery system *in vivo* will not have the same effects on solubility as the reported changes in elution medium *in vitro*. Nonetheless, for a given elution medium, designed changes in the structure of a drug molecule suspended in a gel may influence solubility and partitioning properties sufficiently to bring about partition controlled release. In this work we have investigated release rates and partition coefficients of a series of para-substituted benzoic acids from polyHEMA gels, in order to determine whether a change in release mechanism can be achieved by changing the nature of the para-substituent.

PolyHEMA gel discs containing a known amount (A) of suspended para-substituted benzoic acid were prepared by γ irradiation. Drug release rates into 300 ml of an aqueous elution medium at pH 1.7 and 37° C were measured. Saturation solubilities of the drug in the monomer solution at 37° C were determined. Partition coefficients (K) were obtained by placing known weights of gel in appropriate solutions and assaying the solutions at equilibrium. K was calculated from the ratio of the amount of solute in the gel to that in the aqueous phase.

Table 1

Release rates ($Q/(At)^{\frac{1}{2}}$) of para-substituted benzoic acids of different polymer solubilities (Cs) and apparent partition coefficients (K).

R	H	OH	F	CH_3	OCH_3	Cl	Br	I
$Q/(At)^{\frac{1}{2}}$	1.61	1.10	0.79	0.50	0.40	0.23	0.20	0.13
Cs(mg ml^{-1})	235.7	134.7	65.6	32.2	14.3	8.2	6.2	11.0
K	127	13	2	13.5	18	25	34.5	77.5

Plots of the amount of drug released from the gel disc (Q) against time (t) were linear in the initial period of release (up to 1 hour) for Cl, Br and I-benzoic acids, indicating partition controlled release during this period. These compounds have high values of K, suggesting that they have a much higher affinity for the gel matrix than for the elution medium. In agreement with a partition controlled mechanism, the release rates decreased as K increased. Benzoic acid has the highest value of K but did not show a period of constant release and has the highest rate of release of all compounds (Table 1). The high rate of diffusion of benzoic acid into and out of the gel is attributed to the absence of a polar group in the para position on the molecule which may facilitate its transport through the hydrophilic matrix. Plots of Q against root time were found to be linear for each compound, excluding the constant release periods mentioned above, suggesting matrix controlled release. Table 1 shows the release rates of the acids as a function of the nature of the para-substituent (R). Further evidence of matrix controlled release was a linear relationship between $Q/(At)^{\frac{1}{2}}$ and $Cs^{\frac{1}{2}}$, and the lack of correlation between K and $Q/(At)^{\frac{1}{2}}$.

It is apparent that the release mechanism can be changed by minor modifications in the molecular structure of the solute. This approach provides an alternative method of achieving zero order kinetics to that of using laminated devices.

Chien, Y.W., Lambert, H.J. (1974) J. Pharm. Sci. 63: 515-519
Roseman, T.J., Higuchi, W.I. (1970) Ibid. 59: 353-357

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