DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 12(11-13), 1767-1775 (1986)



# THE EFFECT OF A RATE CONTROLLING MEMBRANE ON RELEASE FROM POLYHEMA HYDROGELS

E.J.PYWELL, S.H.YALKOWSKY* and J.H.COLLETT
Department of Pharmacy, University of Manchester, Manchester, M13 9PL.
*Department of Pharmaceutical Sciences, University of Arizona, Tucson, Arizona 85721.

## ABSTRACT

The possibility of laminating a non-permeable, perforated membrane onto a polymer matrix providing zero-order drug release kinetics has been reported. The work we have undertaken involves an assessment of the suitability of poly(2-hydroxyethylmethacrylate) (polyHEMA) as the matrix in such a system. PolyHEMA hydrogels were prepared by the radiation polymerization of HEMA monomer solutions of different initial water contents. Membranes were laminated during the polymerization process. *In vitro* release rates of substituted benzoic acids from laminates were determined.

## INTRODUCTION

Transdermal drug delivery devices generally comprise a drug filled matrix from which release is controlled by a porous membrane. The reliability of some of these devices has yet to be proven and, to date, they are not suitable for the release of macromolecules.



 0363-9045/86/1211-1767$3.50/0

Kuu and Yalkowsky[1] have given the theoretical rationale for obtaining zero-order drug release by laminating a non-permeable membrane, with multiple circular perforations at specific separation, onto a matrix. Zero-order release kinetics is anticipated due to a hemispherical receding front of drug dissolution in the matrix occurring by diffusion through each circular perforation. The diffusion of drug from a suspension through a single hole has been described in detail by Hsieh *et al*[2] and has been shown to be applicable to both low molecular weight compounds and macromolecular systems[2]. However, the role of matrices in diffusion control is not known.

The work we have undertaken involves an assessment of the suitability of poly(2-hydroxyethylmethacrylate) (polyHEMA) as the matrix in a delivery system with a perforated, non-porous, laminated membrane.

## MATERIALS

2-hydroxyethylmethacrylate (HEMA) (Aldrich Chemical Company), salicylic acid and benzoic acid (BDH Chemicals Ltd.) were used as received. Waterproof 'Band-Aid' (Johnson and Johnson Ltd.) was employed as the non-permeable, perforated release controlling membrane.

## METHODS

Monomer solutions were prepared containing known amounts of water and 2-hydroxyethylmethacrylate. Prepared solutions were poured between glass plates into moulds of diameter 5.5 cm and depth 5mm. The monomer was $\gamma$-irradiated using a 2000 Ci $^{60}$Co

source and given a dose of 450 kRad. The polymerization was carried out at ambient temperature. Membranes were laminated during the polymerization process.

*In vitro* release rates of substituted benzoic acids from laminates were determined. The dissolution cell comprised a 500 ml Perspex cylinder, 9.5 cm in diameter. A central cavity 2.5 cm in diameter and 5 mm deep was cut into the Perspex base of the cylinder. Stirring was established using a Perspex three bladed paddle driven by a Synchronous Motor (Crouzet Ltd.) at 100 rpm. The distance between the paddle and the base of the dissolution cell was kept constant. The dissolution cell was suspended in a water bath maintained at 37° C by a Rotax mercury thermostat.

Sample discs for dissolution (2.5 cm x 5 mm) were cut from polyHEMA. Dissolution was allowed to occur from one face only into 300 ml 0.1N HCl. Automated sampling was achieved using a Cecil CE 202 UV spectrophotometer with flow through attachment connected to a Watson-Marlow peristaltic pump (flow rate 5 ml/min). Transmittance readings were recorded on a Philips PM 8251 chart recorder (chart speed 10 mm/hr). Salicylic acid was assayed at 298 nm and benzoic acid at 232 nm.

## RESULTS AND DISCUSSION

The effect of initial hydrogel water content on the release of salicylic acid is shown in figure(1). There is a sigmoidal relationship between the release rate ($mg.ml.^{-1}t^{-\frac{1}{2}}$) and the initial hydrogel water content. The initial hydrogel water

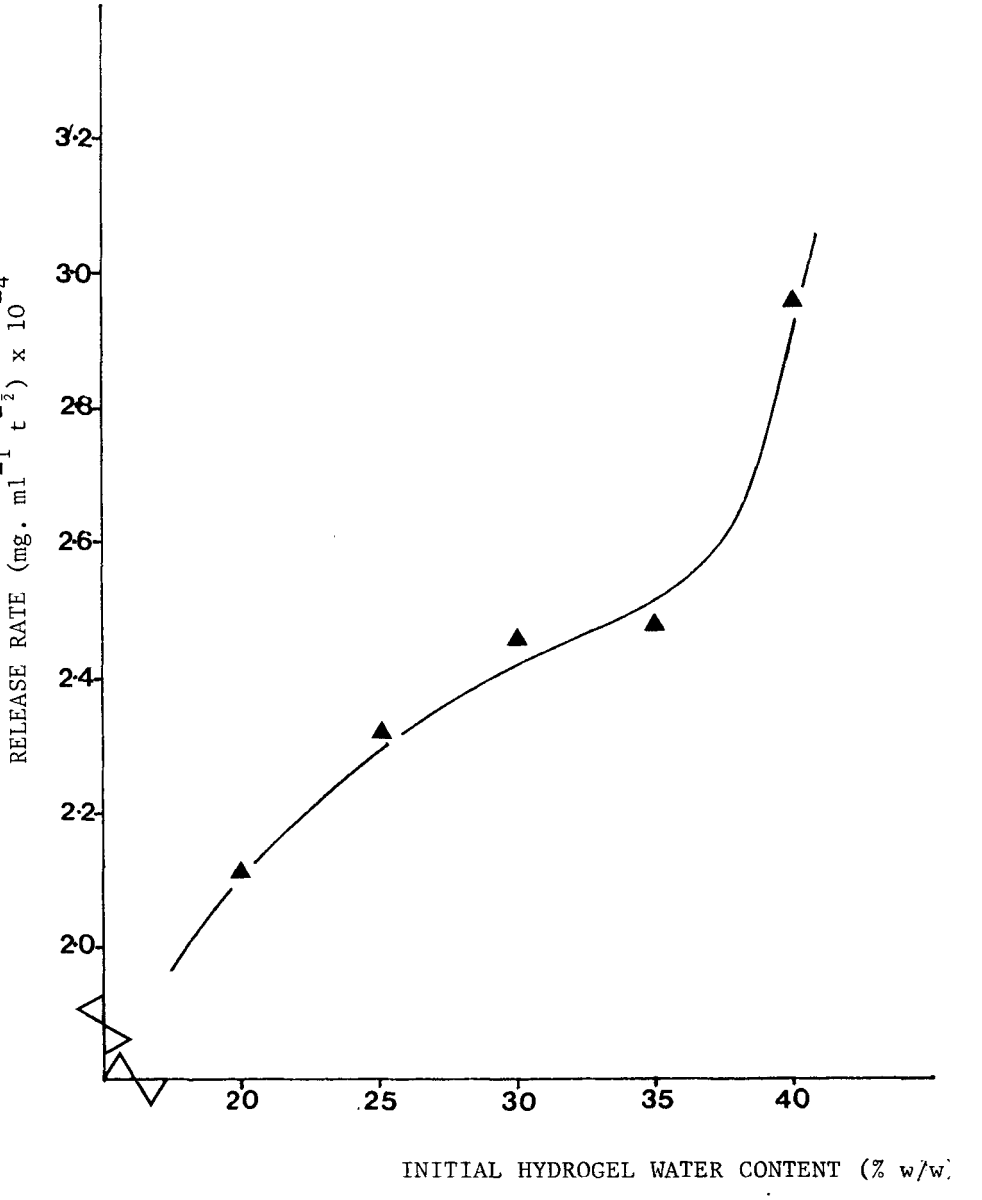


FIGURE 1

Release rates of Salycylic acid from poly HEMA hydrogels with different initial water contents.

content has similarly been shown to affect markedly the release of added solute[3]. The relationship between release rate and initial hydrogel water content can be equated with the nature of the water within hydrogels proposed by Lee *et al*[4].

However, the presence of a rate controlling membrane (figure 2) is seen to have an overiding influence on release;- its effect being greater than that of initial water content. This control is reflected in a linear relationship between release rate ($mg.ml^{-1}t^{-1}$) and initial hydrogel water content (linear correlation coefficient, 0.9916).

Release from swellable hydrogels can be described by the equation $Mt/M_\alpha = kt^n$ where Mt is the amount released at time t, $M_\alpha$ is the initial drug loading and k and n are constants. When n = 1 zero-order release kinetics are achieved and n = 0.5 corresponds to diffusion controlled release kinetics[5]. The values of n obtained for the release of salicylic acid from polyHEMA hydrogels without the non-permeable, perforated rate controlling membrane are given in Table I.

A mean value for n of 0.492 obtained for the release of salicylic acid from polyHEMA hydrogels of different initial water content implies diffusion controlled release kinetics.

Release from an homogenous matrix occurring by simple diffusion from a planar surface has been described by the following equation where release follows square root of time dependent kinetics[6].

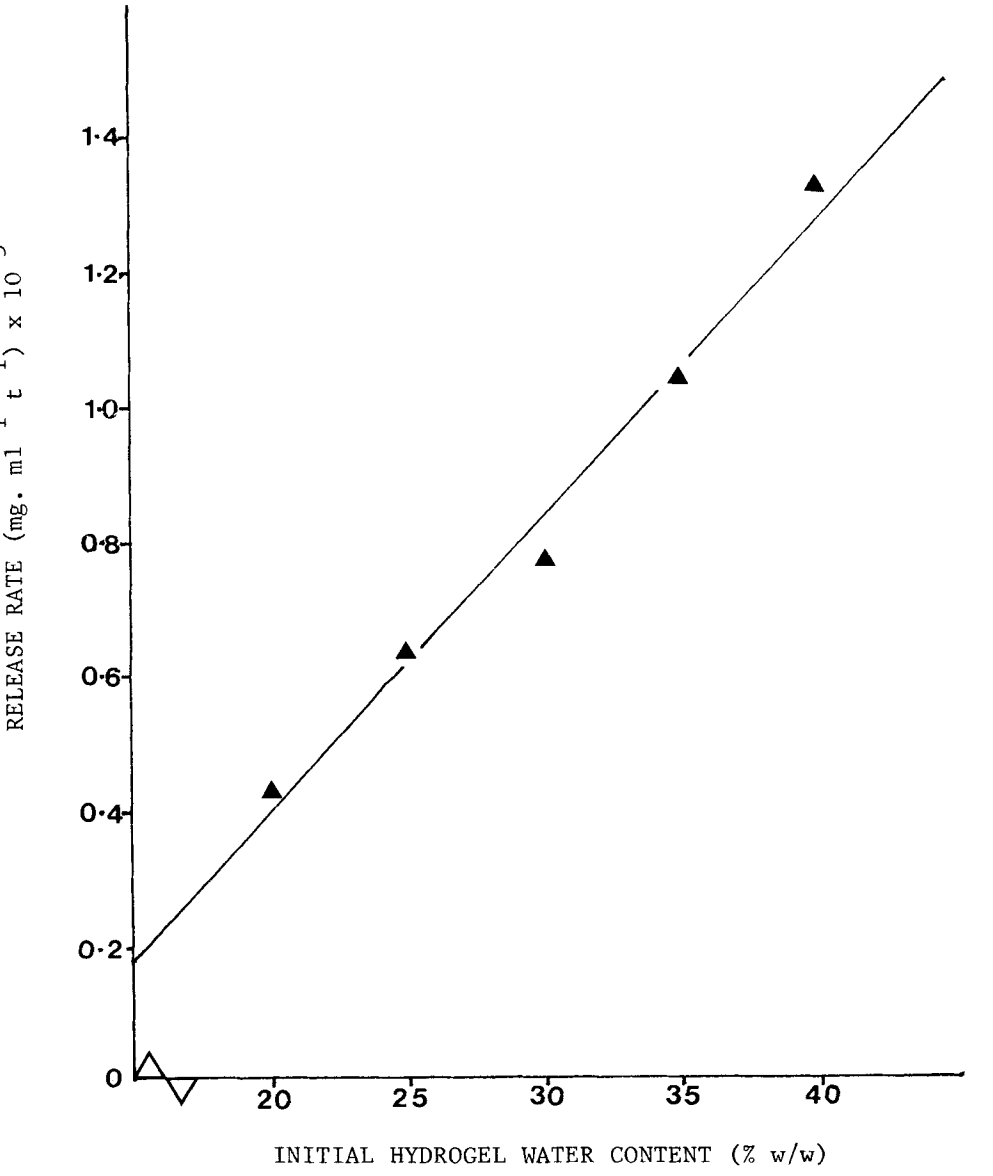


FIGURE 2

Release rates of salicylic acid from polyHEMA hydrogels laminated with a perforated, non-permeable membrane.

TABLE I

Release Rate ($mg.ml^{-1}t^{-\frac{1}{2}}$) and n Values for PolyHEMA Hydrogels Without Rate Controlling Membrane

| INITIAL HYDROGEL WATER CONTENT (%w/w) | n | Rate ($mg.ml^{-1}t^{-\frac{1}{2}}$) | r |
|---|---|---|---|
| 20 | 0.47 | $2.113 \times 10^{-4}$ | 0.9972 |
| 25 | 0.52 | $2.330 \times 10^{-4}$ | 0.9818 |
| 30 | 0.50 | $2.457 \times 10^{-4}$ | 0.9998 |
| 35 | 0.49 | $2.475 \times 10^{-4}$ | 0.9999 |
| 40 | 0.48 | $2.954 \times 10^{-4}$ | 0.9971 |

$$Q = \sqrt{D(2A - Cs)\ Cst}$$

Where Q is the amount released after time t per unit area, D is the diffusion coefficient of the drug in the matrix, A is the total amount of drug present per unit volume and Cs is the solubility of the drug in the matrix.

The values for release rate ($mg.ml^{-1}t^{-\frac{1}{2}}$) for salicylic acid from polyHEMA hydrogels of different initial water content are shown in Table I, assuming square root of time dependent release kinetics.

Table II shows the values of n for release from polyHEMA hydrogels of different initial water content when a non-permeable, perforated membrane is laminated to the matrix. A mean value for n of 0.922 is obtained indicative of zero-order release. The values for rates of release ($mg.ml^{-1}t^{-1}$) and show zero-order release kinetics.

TABLE II

n Values, Rate ($mg.ml^{-1}t^{-1}$) and Linear Correlation Coefficients for PolyHEMA Hydrogels with Release Controlled by Rate Controlling Membrane

| INITIAL HYDROGEL WATER CONTENT ($\%^{w}/w$) | n | Rate ($mg.ml^{-1}t^{-1}$) | r |
|---|---|---|---|
| 20 | 0.92 | $4.313 \times 10^{-6}$ | 0.9976 |
| 25 | 0.90 | $6.394 \times 10^{-6}$ | 0.9990 |
| 30 | 0.91 | $7.718 \times 10^{-6}$ | 0.9994 |
| 35 | 0.98 | $1.0396 \times 10^{-5}$ | 0.9989 |
| 40 | 0.90 | $1.3211 \times 10^{-5}$ | 0.9992 |

TABLE III

$t_1$ (Time to 1% Release) for Release of Benzoic Acid and Salicylic Acid from PolyHEMA Gels with a Laminated Membrane

| INITIAL HYDROGEL DRUG LOADING ($\%^{w}/w$) | $t_1$ (benzoic acid) (mins) | $t_1$ (salicylic acid) (mins) |
|---|---|---|
| 1 | 40 | 60 |
| 2 | 60 | - |
| 4 | 60 | - |
| 5 | - | 65 |
| 10 | 70 | 60 |
| 20 | 65 | 70 |

It has been shown previously that the chemical structure of added solute affects release from polyHEMA hydrogels[3]. However, values for t, (time to 1% release) for benzoic acid and salicylic acid obtained for release from laminates were similar (Table III) which would suggest that the influence of the membrane is greater than the solute.

## CONCLUSION

It has been shown that the presence of a perforated, non-permeable membrane has a greater influence upon release rate than initial hydrogel water content and than the nature of added solute. The presence of a perforated, non-permeable membrane has been shown to give a good approximation to steady state release kinetics. The application of this technique to transdermal drug delivery will be investigated.

## REFERENCES

1. W.Y.Kim and S.H.Yalkowsky, J. Pharm. Sci., 74, 926 (1985)

2. D.S.T.Hsieh, W.D.Rhine and R.Langer, J. Pharm. Sci, 72, 17 (1983)

3. J.H.Collett, D.Attwood and J.M.Wood., J. Pharm. Pharmacol., 33, 60P (1981)

4. H.B.Lee, M.S.Jhon and J.D.Andrade, J. Coll. Interface Sci., 51, 225 (1975)

5. R.W.Korsmeyer, R.Gurny, E.Doelker, P.Buri and N.A.Peppas., Int. J. Pharm., 15, 25 (1983)

6. T.Higuchi., J. Pharm. Sci., 50, 874 (1961)