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INFLUENCE OF DRUG LOADING AND GEL STRUCTURE ON IN-VITRO RELEASE KINETICS FROM PHOTOPOLYMERIZED GELS

E.O. Akala* and J.H. Collett**

**Department of Pharmacy,
University of Manchester,
M13 9PL, U.K.

*Department of Pharmaceutics,
Faculty of Pharmacy,
University of Ife,
Ile-Ife,
Nigeria.

ABSTRACT

Precious work has shown that stabls and homogenous polyHEMA gels can be prepared using a visible light sensitive initiator system. Gels were prepared from solutions of water and poly-2-hydroxyethyl methacrylate monomer. At concentrations of water greater than 10% $^{v}/_{v}$, translucent gel resulted. However, polymerization solvents such as glycerol and tertiary butyl alcohol (T.B.T.A) gave transparent, flexible gels over a wider range of concentrations. Subsequent work showed that changes in polymerization solvent and monomer concentration brought about changes in the mechanical and structural properties of the gels.

In this work, the effects of drug loading and polymerization solvents on *in vitro* drug release rate from the photopolymerized polyHEMA gels were studied. Polymerization solvents used included glycerol and tertiary butyl alcohol. Results indicated that the

release rate *in vitro* was a diffusion-controlled process except at high drug concentrations in polyHEMA - T.B.T.A. gels when a departure from root-time kinetics occurred. PolyHEMA T.B.T.A. gels presented greater hinderance to the mobility of the drug than polyHEMA - glycerol gels. Higuch's model for release from incoluble homogenous matrices containing dispersed solute was found to be inappropriate for the analysis of the release of the drug from the gels. A simple equation based on the modelling of desorption in diffusion was found more appropriate. Estimates of drug release rates *in vitro* may be made from measurements of the physical crosslinking density of the polymer (if matrix-diffusion controlled release is operative). Quantitative drug loading was achieved in the gels as evidenced from variation in crosslinking density and *in vitro* release rate with drug loading.

INTRODUCTION

The development and assessment of controlled release drug delivery systems are aided by the determination of release rates *in vitro*. It has been pointed out that the *in vitro* release studies provide an estimate of the delivery capability of a particular drug delivery device and may be used to screen materials worthy of inclusion as a drug carrier[1].

The rate of diffusion and hence release rate of a solute through a medium depend, among other factors, on the resistance to molecular movement presented by the medium[2]. Our previous work has shown that increase in monomer concentration and changes in polymerization solvents resulted in polyHEMA gels of different mechanical and structural properties (3). Therefore we considered it desirable to investigate the effect of polyHEMA gel structure on drug release rate. Moreover, in the preparation of a controlled release drug delivery system, varying amounts of a therapeutic agent have to be incorporated into the device for varying lengths of treatment. We have reported the effect of variation in drug concentration on the mechanical properties of

these photopolymerized gels (3). Another objective of the present work is to investigate the effect of drug concentration on release rate and correlate the pattern observed with the effect of drug concentration on the structural property of the gels (i.e., crosslinking density).

EXPERIMENTAL

MATERIALS

The following compounds were used as received: 2-Hydroxyethylmethacrylate (HEMA) (>95%) (Fluka); dl-camphoroquinone (99%) (Aldrich), Glycerol (BP) (McCarthys), Tertiarybutylalcohol (T.B.T.A) (Lab. grade) (M & B) and Salicylic acid (Analytical grade) (BDH).

METHODS

a) Preparation of Gels

The monomer solution was added to the required amount of dl-camphoroquinone and N,N-dimethylethanolamine and shaken. The appropriate amounts of diluent (polymerization solvent) and salicylic acid were added and shaken. The polymerization solution was deaerated and purged free of oxygen by bubbling oxygen-free Nitrogen (OFN, BOC). The solution was poured into a mould and placed on a platform approximately 28 cm from a light source for 6 hours.

b) Determination of Release Rates

Discs (2.32 cm diameter) were cut from the gel and thus placed in the centre of a dissolution vessel [4], containing 300 ml 0.1 NHCl at 37° C. This volume was chosen to ensure that sink conditions would prevail over the course of the course of the experiment. Drug release occurred from one

surface only. The dissolution vessel was immersed in a water bath maintained at 37° C with a rotax thermostat unit. The dissolution medium was stirred at 80 r.p.m. (crouzet a synchronous motor). 5 ml samples were remoed at intervals and replaced by 5ml dissolution medium maintained at the same temperature as the sample. Samples were assayed by U.V. spectrophotometry (Pye Unicam, SP6-450 UV/vis spectrophotometer.

Value of λ_{max} for salicylic acid = 300 nm and $E^{1\%}_{1cm}$ = 250

c) Stress-Strain Test

Gels of thickness 0.35 cm and in the shape of dumb-bells were prepared for the tensile tests. The tests were carried out using a (J.J.Lloyd Instruments) and a chart plotter (J.J. Lloyd Instruments, type PL4). The strain rate was kept constant at 16 mm min^{-1} The tests were carried out at 23± 1° C.

RESULTS AND DISCUSSION

(A) Effect of Solute Concentration and Polymerization Solvents on Release Rate In Vitro

Gels were prepared containing 60% $^{v}/_{v}$ HEMA, 1% $^{v}/_{v}$ N,N-dimethylethanolamine, 60 mg % dl-camphoroquinone, 0 - 250 mg/ml salicylic acid and selected amounts of either glycerol or T.B.T.A. to make 100% $^{v}/_{v}$ solutions (equimolar amounts of N,N-dimethylethanolamine relative to the concentration of salicylic acid was added as an excess).

The release of drugs from monolithic devices has been investigated extensively and equations that describe the release rate, mostly based on Fick's laws of difussion, have been developed for several monolith geometries. For a planar monolithic device (matrix system) containing suspended drug, the

following equations have been used to model drug release data (from polyHEMA gels) (5,6,7):

$$Q_t = [C_s D_p (2A - C_s)t]^{\frac{1}{2}} \quad \ldots \text{(Eq.1)}$$

where Q_t is the amount released per unit surface area at time t, D_p is the diffusion coefficient of the drug in the polymer matrix, and A and C_s are the initial concentration and equilibrium solubility of the drug in the matrix respectively. When $2A \gg C_s$, equation 1 reduces to equation 2:

$$Q^t = (2AC_s D t)^{\frac{1}{2}} \quad \ldots \text{(Eq.2)}.$$

Release from homogenous monolithic devices containing suspended drug has also been described by equation 3:

$$Q_t = \frac{2D_p^{\frac{1}{2}} A t^{\frac{1}{2}}}{\Pi^{\frac{1}{2}}} \quad \ldots \text{(Eq.3)}.$$

In equation 3, the equation for release medium uptake was adapted to solute release (7).

Peppas (8) has presented an analysis of Fickian and non-Fickian drug release from polymers. He proposed equation 4 for use with systems where drug diffusion occurs through the polymer structure (network).

$$\frac{Mt}{M_\infty} = K t^n \quad \ldots \text{(Eq.4)}.$$

where M_t/M_∞ is the fraction of drug released at time t, and K is a constant incorporating structural and geometric characteristics of the controlled release device. The term n is the release exponent indicating the kinetics and mechanism of release. It is not difficult to see that diffusion by a Fickian mechanism in monolithic devices, as has been modelled by equations 2 and 3, is a particular case of equation 4 with n = 0.5. The implication is that square root of time kinetics is predicted by equations 2 and

3 (i.e. the amount of drug released is propotional to the square root of time).

The results obtained for polyHEMA-glycerol and polyHEMA - T.B.T.A. gels containing different concentrations of salicylic acid are shown in figures 1 and 2 respectively. Plots of the amount of salicyclic acid released per unit surface area of the device *versus* square root of time show a linear relationship, indicating a matrix-controlled release process [9]. However, since the factors determining drug release rates are of particular importance in the formulation and production of controlled release preparations, it is necessary to determine the appropriate equation for the release pattern observed in any polymeric device. It is often difficult to distinguish between diffusion controlled process (in which the amount released is linear with $t^{\frac{1}{2}}$) and first-order release process (in which the amount released is linear with log t) on the basis of the linearity of the plot [10]. When the data obtained from formulations containing 50 mg/ml of salicylic acid in polyHEMA - glycerol gel and polyHEMA - T.B.T.A. gel were plotted according to a first-order equation, linearity was obtained, though the correlation coefficients of the diffusion-controlled model were slightly higher than those of the first-order equation.

We obtained further evidence for the relative validity of the two models (diffusion controlled process and first-order process) by utilizing the differential forms of their rate equations [11,12,13]. Linearity is predicted if the rates (amount released per time) are plotted versus the reciprocal of the amount released for the diffusion-controlled process; first-order release process predicts a linear relationship between the rate of release and the amount released. Results show that the plot of release rate *versus* the reciprocal of the amount released is linear while the plot of release rate *versus* the amount released is not, indicating that the release process is diffusion-controlled.

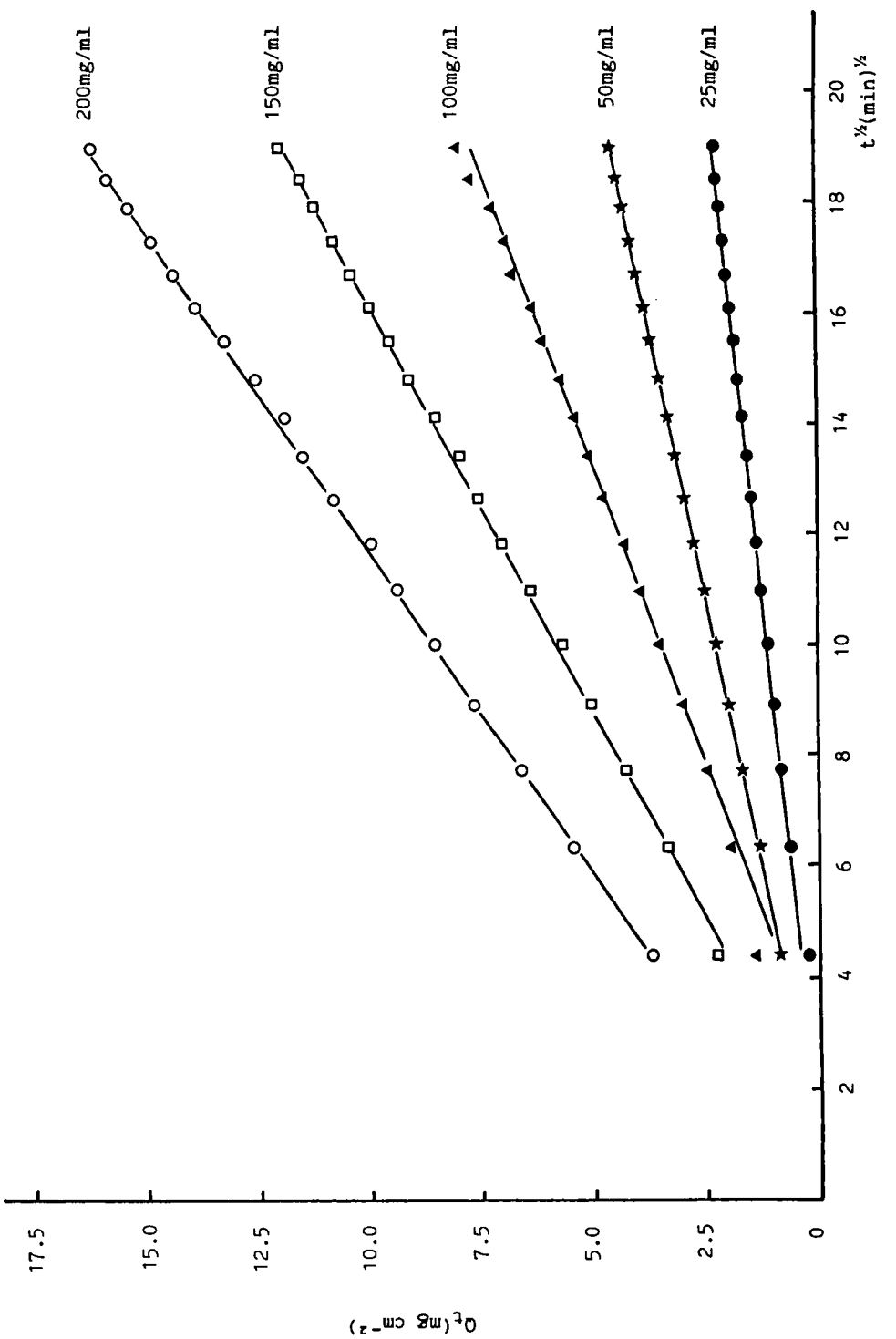

Fig 1. Influence of salicylic acid concentration on the amount released as a function of square root of time (polyHEMA-glycerol hydrogels).

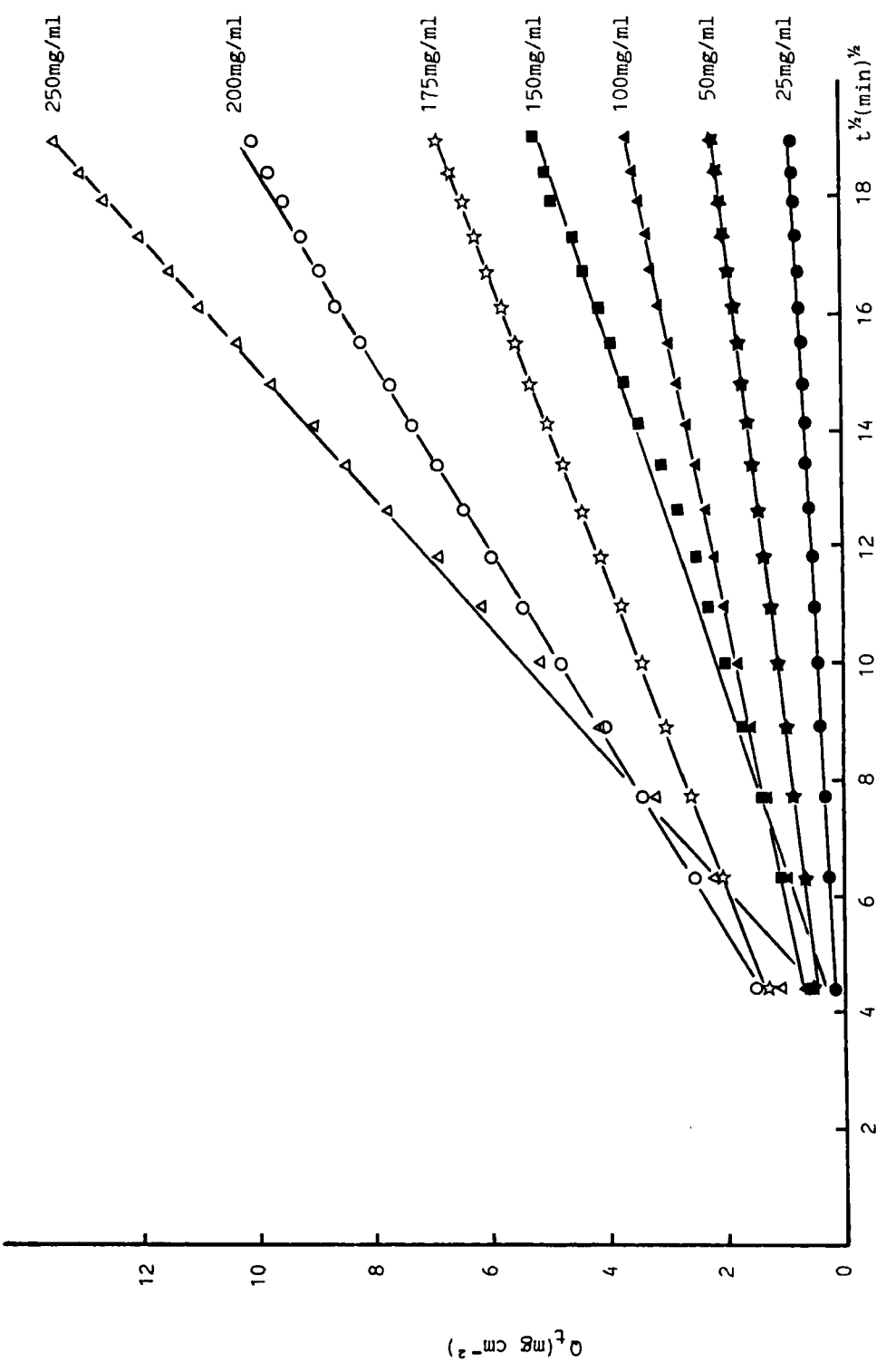

Fig. 2. Influence of salicylic acid concentration on the amount released as a function of square root of time (polyHEMA-T.B.T.A. hydrogels).

The diffusion-controlled model can be expressed by equation 5:

$$M_t = K\, t^{\frac{1}{2}} \quad \ldots\ldots\ldots\ldots\ldots \text{(Eq.5)}.$$

where M_t is the amount released.

The suitability of the diffusion-controlled model was substantiated by determining the exponent of t in equation 5 as shown in equation 6.

$$\log M_t = \log K + \tfrac{1}{2} \log t \quad \ldots\ldots \text{(Eq.6)}.$$

Values of the exponents of t for polyHEMA - glycerol and polyHEMA - T.B.T.A. gels are respectively 0.467 (± 0.008) and 0.488 (± 0.026) (number in parentheses are 95% confidence intervals). These values are of the order of 0.5, confirming that the diffusion-controlled mechanism is operative.

Homogenous polyHEMA matrix systems containing dispersed or suspended solute can give release rates that are directly proportional to the square-root of the initial drug concentration (equations 1 and 2) or to the initial drug concentration (equation 3) [7]. The exponents of A (the initial drug concentration) were determined from a log - log plot of the amount of salicyclic acid released [$M_t = Q_t \times S$ where S is the surface area of the device) and the initial drug concentration (A)] [7]. For polyHEMA - glycerol system, the plot yielded an exponent of 0.93 ± 0.005 in A. The same plot for polyHEMA - T.B.T.A. system yielded an exponent of 1.13 ± 0.15 in A. These exponents are close to 1, showing the applicability of equation 3 rather than equation 1 or 2.

The release rate per unit surface area ($Q_t/t^{\frac{1}{2}}$) was plotted *versus* the initial drug concentration (A) as shown in figure 3. Linearity was obtained for polyHEMA - glycerol system. Furthermore, linearity was obtained for polyHEMA - T.B.T.A. system until a concentration of about 200 mg/ml of salicyclic acid where a positive deviation from linearity was obtained. A

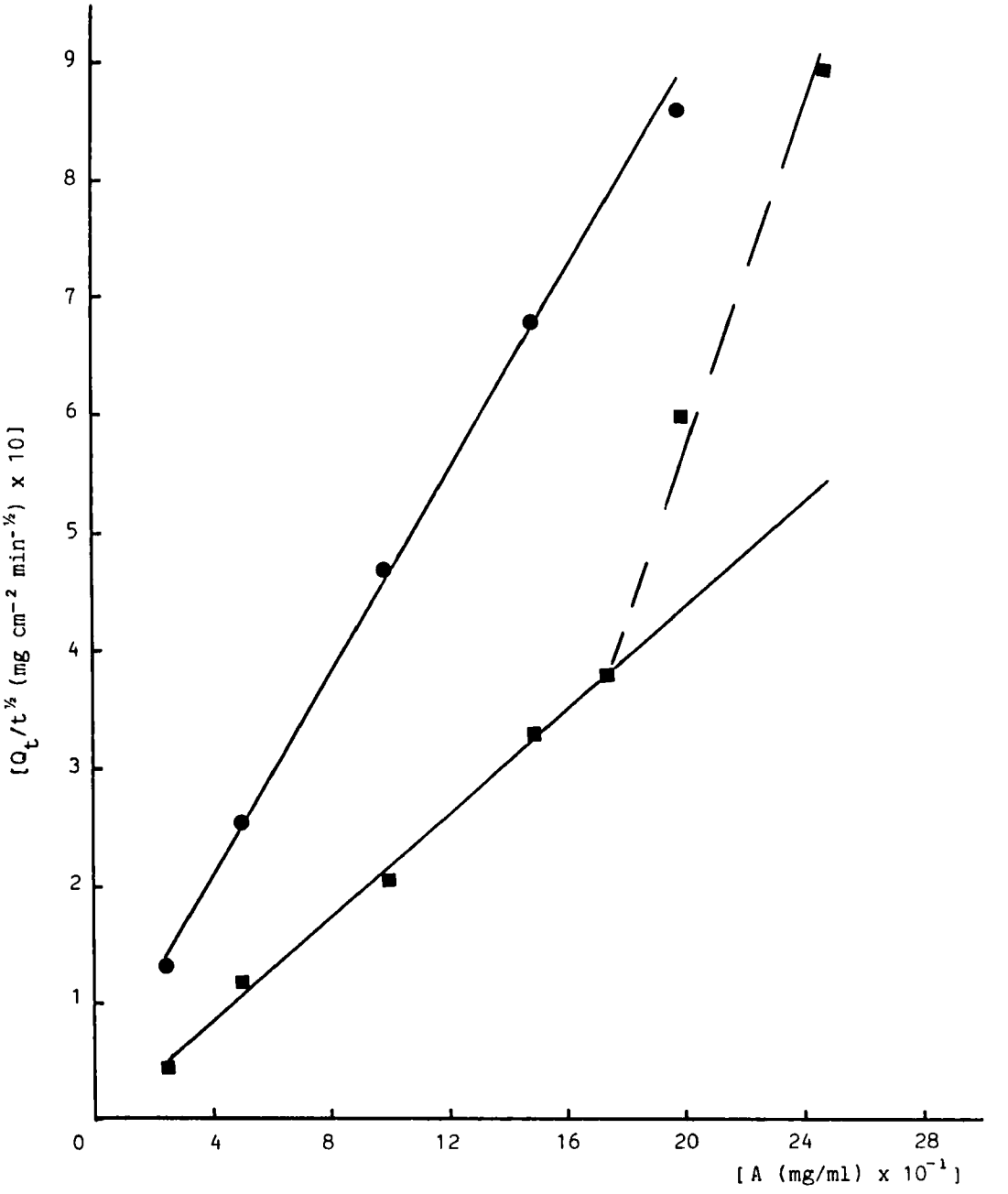

Fig. 3. Effect of salicylic acid concentration (A) impregnated in polyHEMA-glycerol (●) and polyHEMA-T.B.T.A. (■) hydrogel devices on drug release rate ($Q_t/t^{\frac{1}{2}}$).

log - log plot of the amount released (M_t) and initial drug concentration (A) in the linear part of polyHEMA - T.B.T.A. curve (figure 3) (0 - 175 mg/ml of salicyclic acid) also yielded an exponent of 1.02 ± 0.15 in A, further showing the applicability of equation 3 to polyHEMA - T.B.T.A. system. The exponent of 1 in A rather than 0.5 in A for homogenous matrix system containing suspended soluts has been reported for polyHEMA - tartaric acid system [7] and like our results, it appears to contradict the prediction of Higuchi's equation (14) (equation 1). There are conditions under which the exponent of 0.5 in A in Higuchi's equation can become 1. These conditions have been described as follows [7,14]: the initial porosity is small or the volume fraction of the drug in the matrix is very large; the drug is the sole extractable component and the matrix is granular.

These conditions for an exponent of 1 in A are believed to be absent in polyHEMA - tartaric acid system because polyHEMA - gel cannot be considered a granular matrix and ergotamine (embeded in the gel) and tartaric acid are extractable [7]. The photoinitiated polymerized polyHEMA - glycerol and polyHEMA - T.B.T.A. hydrogel systems also cannot be considered granular matrices. Moreover, as found in the swelling properties of these gels [22] glycerol and T.B.T.A. are extractable, though the amount leached out might be small during the six-hour drug release period of this work. The leaching out of tritiated glycerol from silicone elastomer (not as hydrophilic as polyHEMA) has been reported - the leaching out followed a matrix-diffusion controlled mechanism ([15]). Thus, the applicability of equation 3 rather than equation 1 may be characteristic of polyHEMA gels containing water soluble additives and suspended solutes and are capable of water uptake to effect drug release.

The positive deviation from linearity obtained in polyHEMA - T.B.T.A. system at high drug concentrations when release rate was plotted as a function of initial drug concentration (figure 3) may be attributed to the following factors:

a) Possible formation of continuous pores or channels within the matrix as drug is released at high drug concentrations. These pores might result in an increase in free-volume for diffusion and a change in the effective diffusion coefficient in the matrix. The tendency for the formation of such pores or channels is believed to occur at about 10% $^{w}/_{w}$ drug loading [16]. Song *et al* [17] reported that the diffusion coefficient of progesterone in polyHEMA hydrogels increased as the initial drug load was increased.

b) The leaching out of T.B.T.A. might also contribute to increase in the internal porosity created by the leached drug at high drug concentrations in a manner analogous to the effect of polyethyleneglycol 4000 on the release of salicylic acid and tripelennamine from ethylcellulose film [11].

Samuelov *et al* [11] reported that the presence of two leachable components could give rise to more than one mechanism of release and could increase the release rate abruptly at a critical porosity value. Moreover, heavily loaded polymer films might ultimately show structure breakdown leading to rapid dissolution-controlled drug release. Consequently, the exponents of t in polyHEMA - T.B.T.A. systems containing 200 mg/ml and 250 mg/ml of salicyclic acid (figures 2 and 3) were determined from equation 6 and were found respectively to be 0.648 (±0.025) and 0.854 (±0.034) (numbers in parentheses are 95% confidence intervals). This result indicates a gradual increase in the exponent of t with drug concentration, reflecting a departure from a matrix-diffusion-controlled release mechanism (which is characterised by root-time kinetics).

The straight line obtained in the plot of release rate *versus* drug concentration in polyHEMA - glycerol system (figure 3) suggests lack of structure breakdown and that the rate of leaching of glycerol was probably low. It might be a consequence of its higher viscosity and higher molecular weight than T.B.T.A.

The linear portions of the graphs (figure 3) indicate regions where the diffusion coefficient is concentration

independent. The apparent diffusion coefficient of salicylic acid in polyHEMA glycerol and polyHEMA - T.B.T.A. systems were calculated to be 2.270 x 10^{-7} cm^2/sec and 0.636 x 10^{-7} cm^2/sec respectively using equation 3.

The Effect of Polymer Structure as Modified by Polymerization Solvents on Release Rate and Diffusion Coefficient of Salicylic Acid:

Results shown in figure 3 indicate that the release rates of salicylic acid are lower in polyHEMA - T.B.T.A. system than polyHEMA - glycerol system. This is also the case for the diffusion coefficients as shown above. The pattern observed may be attributed to the following:

i) The results of the mechanical properties and characterization of the network structure of the photopolymerized polyHEMA gels (reported in details in ref. 3 and shown in part in figures 4,5 and 6) show that polyHEMA - T.B.T.A. systems, in the absence and presence of different amounts of salicylic acid, have higher values of physical crosslinking density and Young's modulus than polyHEMA - glycerol systems. Consequently, the difference in release rate and diffusion coefficient may be due to a greater hinderance to the mobility of salicylic acid in polyHEMA - T.B.T.A. system than in polyHEMA - glycerol system.

ii) The effect observed may also be due to the different rates of water penetration thereby resulting in different rates of hydration of the polymer and dissolution of salicylic acid which then diffused out through the hydrated matrix.

iii) The different rates of release of salicylic acid from the two polyHEMA hydrogel systems may also be due to the modifying effect of the solvents on the solubility of salicylic acid in the polymer.

The results of the effect of polymer structure as modified by the polymerization solvents on the release rate and apparent

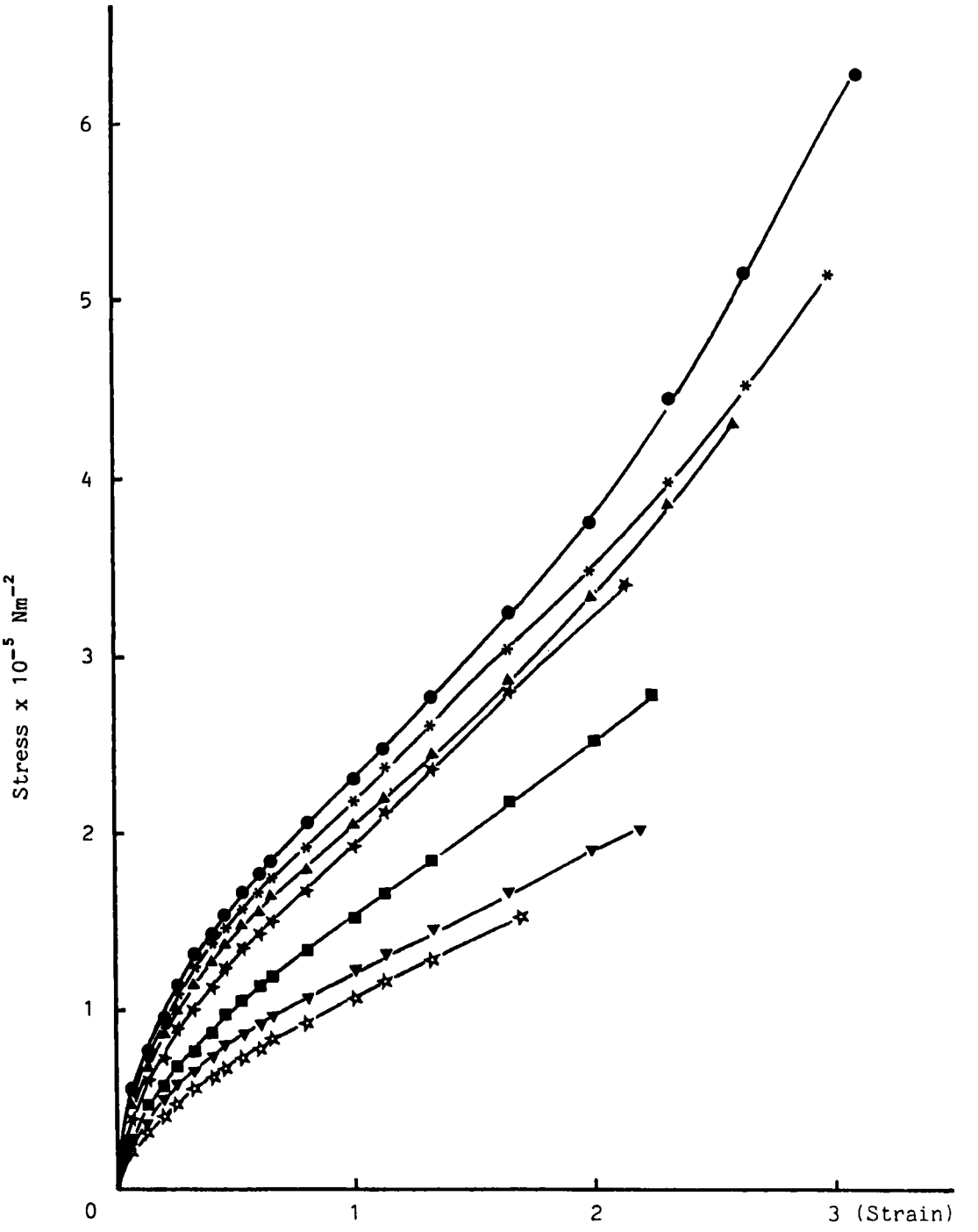

Fig. 4. Stress-strain curves for polyHEMA-glycerol hydrogels containing different concentrations of salicylic acid. (●) 0% $^{v}/_{v}$ (✱) 0.706% $^{v}/_{v}$ (▲) 1.764% $^{v}/_{v}$ (✱) 3.529% $^{v}/_{v}$ (■) 7.057% $^{v}/_{v}$ (▼) 10.586% $^{v}/_{v}$ (☆) 14.114% $^{v}/_{v}$

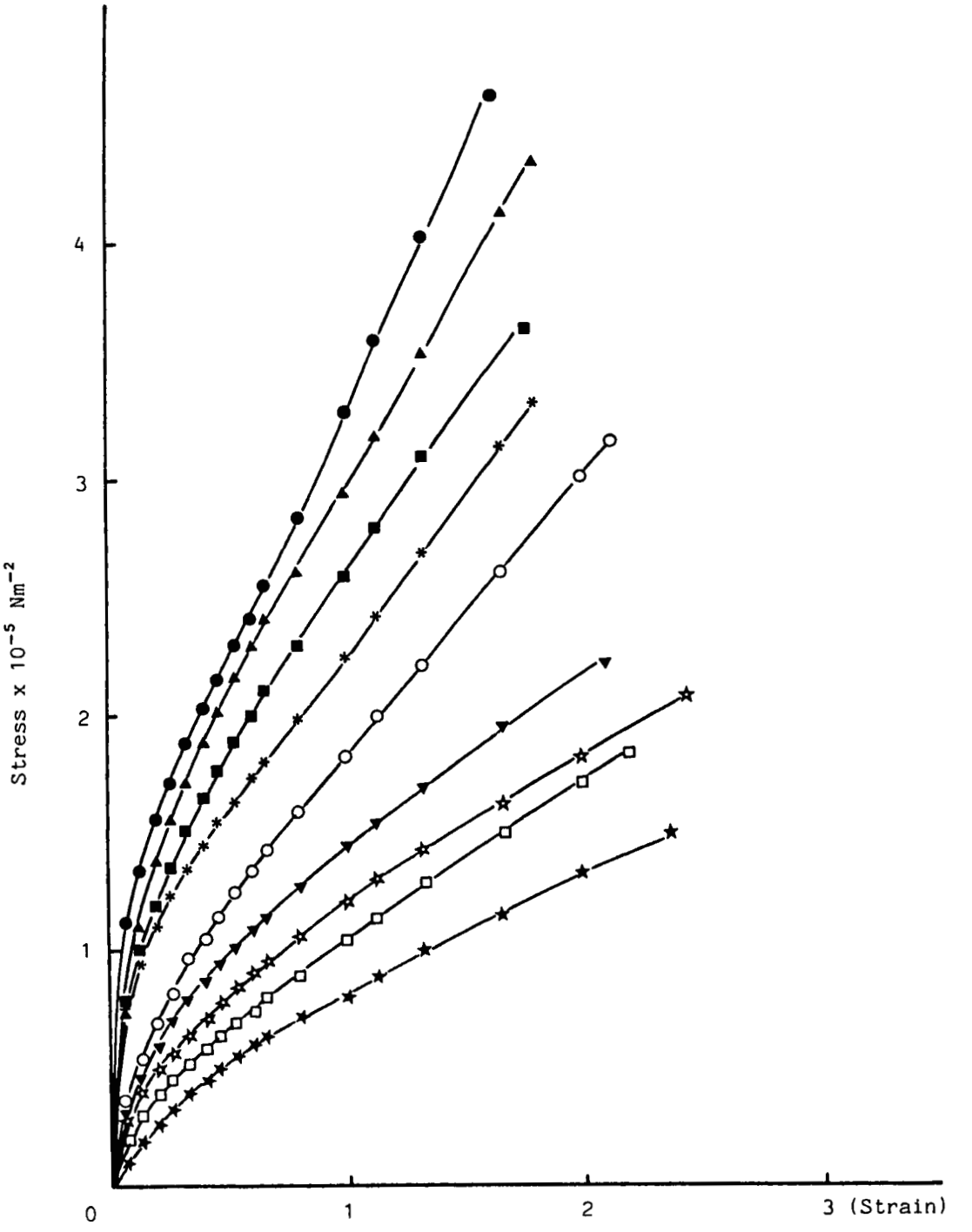

Fig. 5. Stress-strain curves for polyHEMA-T.B.T.A. hydrogels containing different concentrations of salicylic acid
(●) 0% $^{V}/_{v}$ (▲) 0.706% $^{V}/_{v}$ (■) 1.764% $^{V}/_{v}$
(*) 3.529% $^{V}/_{v}$ (○) 7.057% $^{V}/_{v}$ (▼) 10.586% $^{V}/_{v}$
(☆) 12.350% $^{V}/_{v}$ (□) 14.114% $^{V}/_{v}$ (★) 17.643% $^{V}/_{v}$

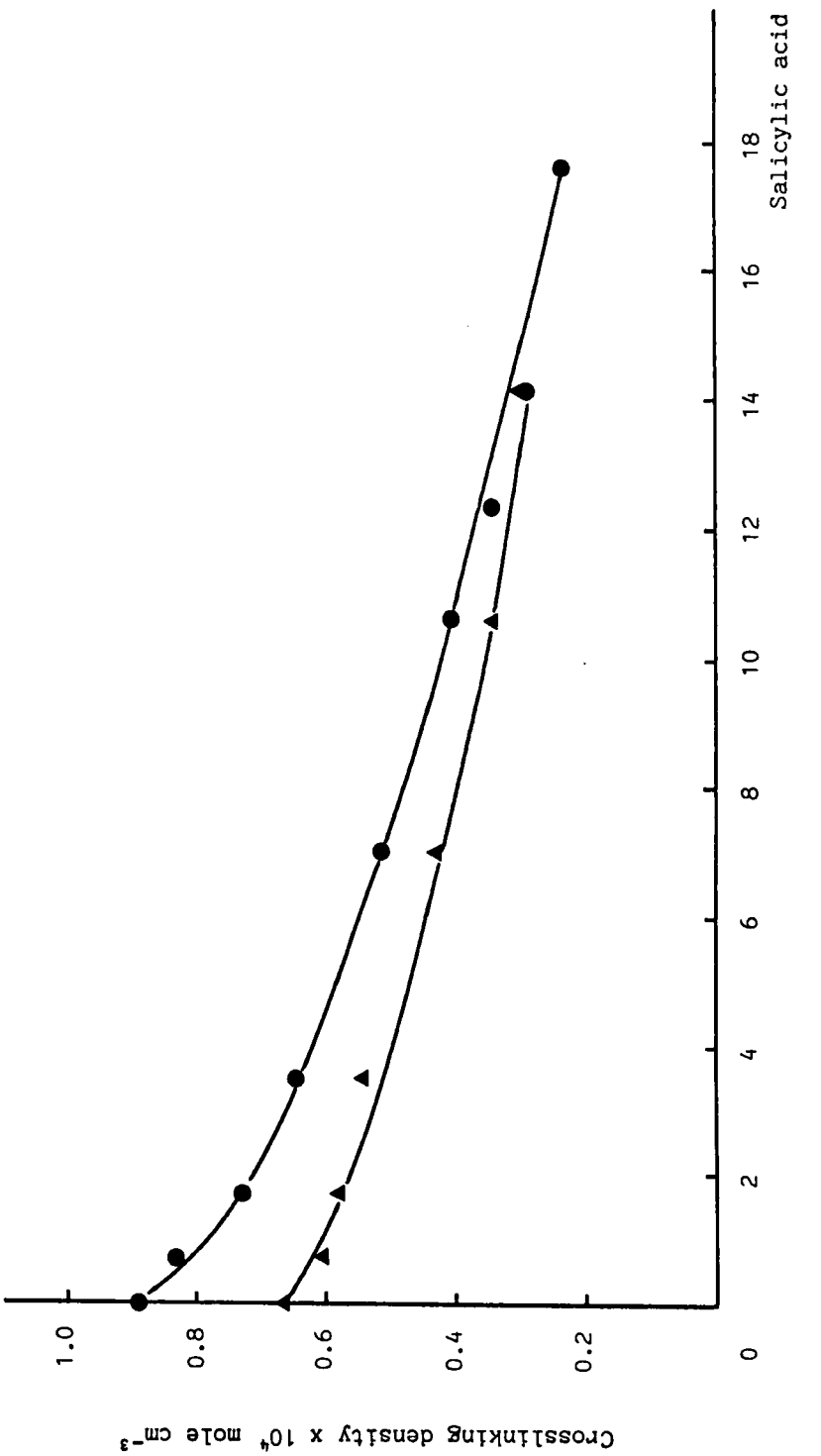

Fig. 6. Crosslinking density of polyHEMA hydrogels as a function of salicylic acid concentration.

(●) polyHEMA-T.B.T.A. hydrogels

(▲) polyHEMA-glycerol hydrogels

diffusion coefficient of salicylic acid reported in this work are different from the report of Zentner *et al* [18] that the permeability and partition coefficient of progesterone in polyHEMA were independent of the nature and concentration of the solvents employed [water, ethanol and tertiarybutylalcohol (T.B.T.A.]. However, one should take cognizance of the fact that they employed polyHEMA gels swollen to equilibrium in water in their studies.

Correlation of PolyHEMA Network Structure With Drug Release

The formulations are the same as described under release rates. Figures 4 and 5 show that the stress-strain curves of polyHEMA - T.B.T.A. gels respectively containing known concentrations of salicylic acid. The concentrations are expressed as percentage-volume-in-volume using the density of salicylic acid (1.417 g cm^{-3}) [3]. The mechanical properties of the gels have been analysed [3] using the models for filler (drug) - polymer matrix interactions and will not be discussed again here. The crosslinking density (V) was calculated from equation 7 [19,20,21]:

$$V = \frac{2\,(C_1 + C_2\,\alpha^{-1})}{V_2^{2/3}\,RT} \quad \text{.....(Eq. 7)}$$

where R is the gas constant, T is the temperature, V_2 is the volume fraction of the polymer in the gel, α is the elongation ratio (L/Lo where L is the stretched length and Lo is the initial length of the specimen) and C_1 and C_2 are the Mooney-Rivlin constants. The relationship of equation 7 to the theory of rubber elasticity has been discussed in one of our reports on these photopolymerized gels [3].

The effect of drug concentration on the crosslinking density of PolyHEMA - glycerol and PolyHEMA - T.B.T.A. gels is shown in figure 6. The linear increase in release rates with increase in

drug concentration (figure 3) is similar to the linear decrease in crosslinking density (figure 6) with increase in drug concentration for polyHEMA - glycerol and polyHEMA - T.B.T.A. gels, except at high drug concentrations where deviations from linearity was obtained in polyHEMA - T.B.T.A. gels. The results are of significance for two reasons: firstly, quantitative drug loading was achieved in the gels which is very important to mathematical modelling of drug release rate and the expected performance of the controlled release drug devices fabricated from the gels; secondly, it is possible to make an approximate prediction of the release rate characteristics of drug *in vitro* from the results obtained during the determination of the mechanical and structural properties of the gels provided the release is matrix-controlled.

CONCLUSION

In summary, the results reported in this study indicate that *in vitro* release from monolithic polyHEMA-glycerol and polyHEMA - T.B.T.A. gels containing different concentrations of a suspended drug followed root-time kinetics and was a diffusion-controlled process, except at high drug concentrations in polyHEMA - T.B.T.A. gels when a departure from root-time kinetics was found. PolyHEMA - glycerol gels showed a higher capacity for the drug in terms of the linear variation of drug release rate with initial drug concentration. PolyHEMA - T.B.T.A. gels presented greater hindrance to the mobility of the drug than polyHEMA - glycerol gels as reflected in the lower values of release rates and diffusion coefficient in polyHEMA - T.B.T.A. gels. Higuchi's model for insoluble homogenous matrices containing dispersed solute was found to be inappropriate for the analysis of the release of the drug from photopolymerized polyHEMA gels. A simple equation based on how desorption is treated in diffusion was found more appropriate. Estimates of drug release rates *in vitro* may be made from measurements of the physical crosslinking

density of the polymer (matrix-diffusion-controlled mechanism is assumed). Quantative drug loading was achieved in the gels.

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