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# Drug release from silicone elastomer through controlled polymer cracking: an extension to macromolecular drugs

V. Carelli, G. Di Colo, C. Guerrini and E. Nannipieri

*Pharmaceutical Technology Laboratory, Institute of Pharmaceutical Chemistry, University of Pisa, Pisa (Italy)*

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## Summary

An attempt to promote macromolecule release at controlled rates from a polydimethylsiloxane elastomer (Silastic Q7-4840) through osmotically induced polymer cracking is presented. Matrices of the monolithic type are loaded with 15%, 20% or 28% of osmotically active granules in the 40–106, 106–150 or 150–212 μm size range, composed of bovine serum albumin (BSA) and sodium chloride in a 35 : 65 or 70 : 30 w/w ratio. The latter granule composition was found to be unsuitable, due to an inadequate level of osmotic agent. With the 35 : 65 w/w BSA–NaCl ratio in granules protein release to normal saline is of zero-order in the matrix swelling stage. The stationary release rate and time scale are modulated through matrix geometry and granule load and size. With disk-shaped devices and 106–150 or 150–212 μm granule size the release rate and granule load are linked by a log–log correlation. The release pattern is determined by the rate of polymer cracking. The solutes are carried through cracks by a composite convective–diffusive flux.

## Introduction

Macromolecular drugs are known to be degraded or poorly absorbed in the GI tract, and to have short therapeutic half-lives. For these reasons these drugs are currently being considered as candidates for administration by implantable polymer matrices, which are intended both to protect the drug from the body and sustain the drug delivery to the body. The release of polypeptide drugs from matrices of ethylene–vinyl acetate copolymers has been studied extensively (Brown et al., 1986; Cohen et al., 1984; Langer et al., 1980; Peppas and Flosenzier, 1986; Rhine et al., 1980). In order to obviate the virtual impermeability of polymer to polypeptides, matrices were loaded with polypeptide doses high enough to allow the formation of interconnecting aqueous pores upon matrix hydration. Protein release from polydimethylsiloxane, another biocompatible polymer, was equally well achieved by the use of high drug loadings (Hsieh et al., 1985), although in some cases release was promoted by admixing water carriers, such as glycerol (Hsieh et al., 1985) or polyethylene glycol derivatives (Kim, 1985). In some instances the release kinetics was controlled to a zero-order by making up special geometries and coatings (Siegel and Langer, 1984), but no

*Correspondence*: G. Di Colo, Istituto di Chimica Farmaceutica, Università di Pisa, Via Bonanno 6, 56100 Pisa, Italy.

time-constant release could be obtained from matrices of the simple monolithic type. The present and other authors have shown that a zero-order drug delivery from monolithic matrices can be achieved with osmotically active drugs if the progressive polymer cracking secondary to water swelling of matrix is properly controlled (Carelli et al., 1987; Carelli et al., in press; Gale et al., 1980; Roorda et al., 1986).

The aim of the present work was to test the applicability of such a controlled polymer cracking concept to producing simple monolithic devices capable of delivering proteins at time-constant and modulatable rates. Although proteins, even the freely water-soluble ones, are not themselves effective osmotic agents, they can in principle be made into particles of controlled size and osmotic competence by granulating with an appropriate water-carrier. In this study, bovine serum albumin (BSA), taken as representative of polypeptide drugs, was granulated with sodium chloride, and the granules were loaded into monoliths of silicone elastomer. The possibility of controlling the kinetics of BSA release to normal saline through granule size, load and osmotic competence, and matrix geometry was investigated and attempts to gain a better understanding of the release mechanism were made.

## Materials and Methods

### *Materials*

Bovine serum albumin (BSA) (Fraction V, Sigma, St. Louis, MO, U.S.A.) and sodium chloride (RPE, Carlo Erba S.p.A., Milan, Italy) were used as received. The polydimethylsiloxane (PDS) elastomer (Medical Grade Silastic Q7-4840) was a gift from the Dow Corning (Midland, MI, U.S.A.). It was used as received.

### *Preparation and sizing of granules*

BSA and NaCl powders in the desired ratio were dissolved in the minimum amount of water, and the mix was vigorously stirred in a mortar, under an air stream, until a near-dry coarse granulate was obtained. This was further dried overnight under vacuum at room temperature, then ground by a pestle and wet-sieved with petroleum ether (100–140 °C) to obtain mechanically strong granules in the 40–106, 106–150 and 150–212 $\mu$m size ranges. Virtual absence of neat crystals and undersize granules in each range resulted from microscopic examination. The BSA content in each granule size range was checked by spectrophotometrically analyzing aqueous solutions of samples at 280 nm. No important deviations from the established BSA–NaCl ratios in granules (35 : 65 or 70 : 30 w/w) were ever observed.

### *Preparation of matrices*

Granules of specified composition and size range were uniformly dispersed into the parts A and B of the elastomer, Silastic Q7-4840, by repeatedly spreading a film of the mix onto a glass plate and re-collecting with a spatula, with care to avoid air entrapment. Next the mixture was pressed into sheets of 0.1 cm thickness, or added to a plastic mold to form cylindrical pellets of 0.6 cm diameter and 0.3 cm height, then allowed to cure 24 h at 37 °C. Disks of 1 cm diameter were cut from the vulcanized sheets. All matrices were apparently elastic. Their surfaces were smooth, non-tacky and hydrophobic. The air content in matrices, as calculated for 50 samples from knowledge of matrix volume, weight and composition, and densities of ingredients was $5.3 \pm 2.8\%$ v/v.

### *Kinetic measurements*

The procedure for determination of solute release and matrix swelling kinetics was reported elsewhere (Di Colo et al., 1982). Each matrix was shaken in 5 ml of solvent, usually normal saline, at 37 °C. The BSA concentration in the receptor was determined spectrophotometrically at 280 nm. In some experiments isotonic phosphate buffer (0.13 N, pH 7.4) was used as the receptor, and both BSA and NaCl concentrations in this medium were determined, the former spectrophotometrically, the latter through titration of the chloride ion with 0.01 N mercuric perchlorate. For titration, 4 ml samples were made to pH 3 with perchloric acid, then added with 10 ml ethanol and 2 drops of 1% ethanolic diphenylcarbazone. The absence of any interference with the titration from BSA was demonstrated. Where the plot of

cumulative amount released versus time showed apparently linear portions, these were separately analyzed by linear regression. Analysis was extended to data points in the portion of plot that gave the best fit. All regressions were highly significant ($P < 0.001$). Each of the reported release rates resulted from the averaged slopes for at least 3 runs carried out with separate batches of identical formula.

## Results and Discussion

*Studies with granules of BSA–NaCl (35:65 w/w) composition*

Representative matrix swelling and BSA release data for disk matrices loaded with 15%, 20% or 28% granules (5.2%, 7.0% or 9.8% of BSA, respectively) of 3 different size ranges are plotted in Figs. 1–3. Each of all matrices showed a significant swelling and a zero-order release kinetics over the time to reach its maximum swelling degree, after which the release rate tapered off. Since the present hydrophobic silicone polymer is supposed to be impermeable to BSA, release of the protein must have occurred through aqueous pathways having formed in the polymer network. Parallel experiments with papaverine-HCl, a drug having a fair aqueous solubility but low osmotic

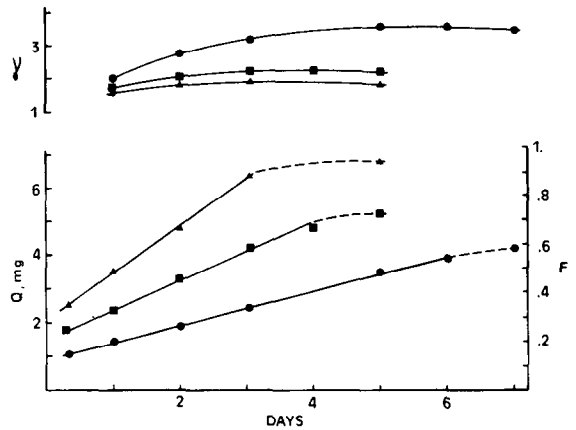


Fig. 2. Typical profiles of BSA release ($Q$, amount released; $F$, fraction released) and matrix swelling ($\gamma$, ratio of swollen-to-dry matrix weights) for disk matrices loaded with 20% granules of BSA–NaCl (35:65 w/w) composition and 40–106 μm (●), 106–150 μm (■) or 150–212 μm (▲) size range. The full portion of each release profile represents the linear regression line.

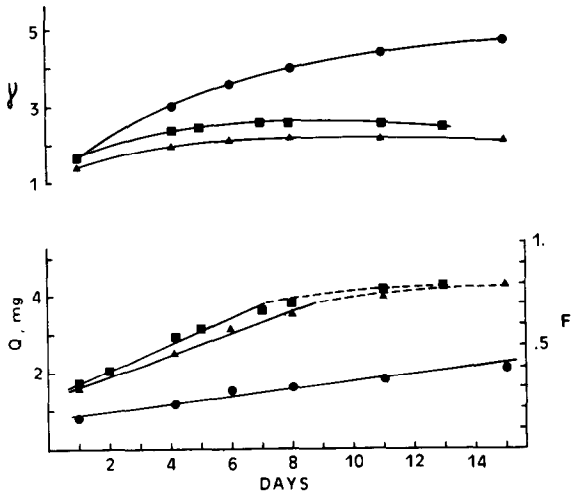


Fig. 1. Typical profiles of BSA release ($Q$, amount released; $F$, fraction released) and matrix swelling ($\gamma$, ratio of swollen-to-dry matrix weights) for disk matrices loaded with 15% granules of BSA–NaCl (35:65 w/w) composition and 40–106 μm (●), 106–150 μm (■) or 150–212 μm (▲) size range. The full portion of each release profile represents the linear regression line.

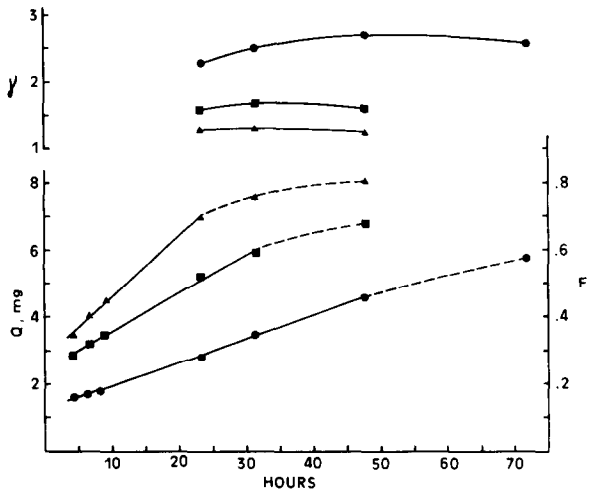


Fig. 3. Typical profiles of BSA release ($Q$, amount released; $F$, fraction released) and matrix swelling ($\gamma$, ratio of swollen-to-dry matrix weights) for disk matrices loaded with 28% granules of BSA–NaCl (35:65 w/w) composition and 40–106 μm (●), 106–150 μm (■) or 150–212 μm (▲) size range. The full portion of each release profile represents the linear regression line.

power and permeability through PDS, have shown that loads up to 30% of neat drug particles in the same size ranges as the present granules cannot be released to any significant extent from Silastic Q7-4840 (Carelli et al., in press). Hence it is reasoned that BSA release from the present systems was elicited by the osmotic activity of granules, and that the rate-controlling pathways for such a release were not formed from just free dissolution of granules, but rather from cracking of the polymer walls separating them. Cracks were expected to be developing during the swelling period and to stop forming at the end of it. The BSA release profiles ought to be determined by the pattern of polymer cracking. With the present matrix shape and granule composition such a pattern must have been appropriate for zero-order release kinetics. In fact, variations of granule size and load were allowed without the release pattern being disturbed. These variables, nevertheless, influenced the stationary release rate, the drug fraction released at a constant rate and the initial burst effect, as it is seen in Figs. 1–3. The effects of granule size and load on the zero-order rate are quantified in Table 1. For the 106–150 $\mu$m and 150–212 $\mu$m size ranges the logarithmic plot of rate versus granule load, shown in Fig. 4, is significantly linear ($P < 0.001$) in the load range explored. A similar relationship was reported for

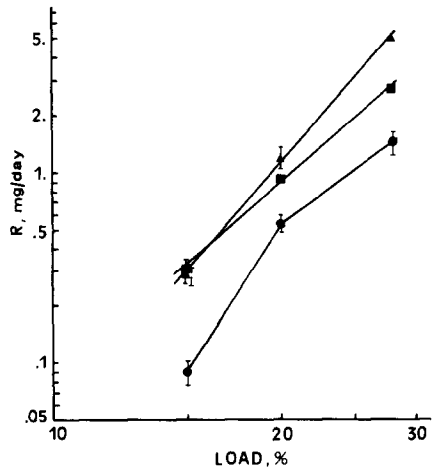


Fig. 4. Log–log plot of $R$ values of Table 1 for the disks plotted against load of granules in the 40–106 $\mu$m (●), 106–150 $\mu$m (■) or 150–212 $\mu$m (▲) size range.

osmotically active matrices of clonidine-HCl based on silicone elastomer (Carelli et al., 1987). For the 40–106 $\mu$m range the points relative to the 20% and 28% loads show a trend consistent with the

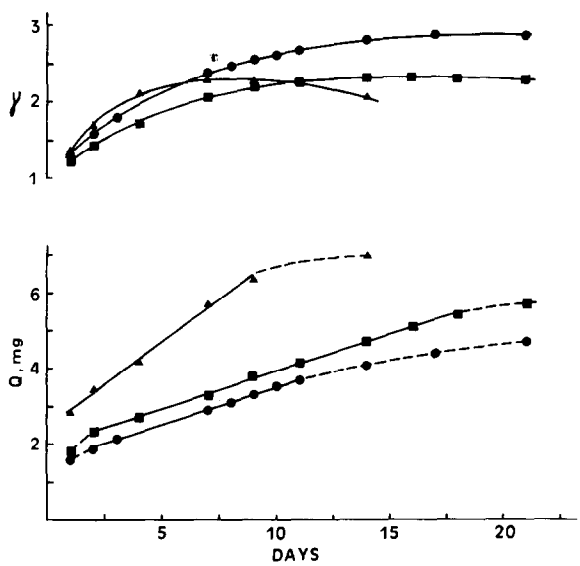


Fig. 5. Typical profiles of BSA release ($Q$, amount released) and matrix swelling ($\gamma$, ratio of swollen-to-dry matrix weights) for cylindrical matrices loaded with granules of BSA–NaCl (35 : 65 w/w) composition. Key: ●, 20% load, 106–150 $\mu$m size range; ■, 20% load, 150–212 $\mu$m size range; ▲, 28% load, 106–150 $\mu$m size range. The full portion of each release profile represents the linear regression line.

TABLE 1

*Influence of matrix geometry and granule load and size range on stationary release rate (R) for matrices loaded with granules of BSA–NaCl (35 : 65 w/w) composition*

| Matrix geometry | Granule load (%) | Granule size range ($\mu$m) | $R$ (S.D.) ($\mu$g/day) |
|---|---|---|---|
| Disk | 15 | 40–106 | 90 (13) |
| | | 106–150 | 303 (43) |
| | | 150–212 | 286 (32) |
| | 20 | 40–106 | 548 (60) |
| | | 106–150 | 927 (25) |
| | | 150–212 | 1198 (142) |
| | 28 | 40–106 | 1437 (196) |
| | | 106–150 | 2775 (48) |
| | | 150–212 | 5008 (75) |
| Cylinder | 20 | 106–150 | 179 (20) |
| | | 150–212 | 190 (8) |
| | 28 | 106–150 | 510 (38) |

higher size ranges, whereas the point relative to the 15% load deviates remarkably from such a trend.

The matrix surface–volume ratio was decreased in an attempt to prolong the duration of the zero-order period. The matrix swelling and BSA release profiles for cylinders of approximately the same weight as the disks discussed so far are typified in Fig. 5. As expected, the matrix swelling and constant drug release times for the cylinders were much longer than those for disks of corresponding formula and granule size. With the cylinders, however, the release pattern in the swelling period was not independent of granule load and size, as shown by the constant release regime ending well before the attainment of maximum matrix swelling in the case of 20% load and 106–150 $\mu$m size range. It is worthwhile noticing that the stationary release rates for cylinders loaded with 20% or 28% granules in the 106–150 $\mu$m range were in about the same ratio as those for disks of corresponding granule loads and size range, as can be figured out from the relevant data in Table 1.

*Studies with granules of BSA–NaCl (70:30 w/w) composition*

Typical matrix swelling and BSA release data for disk matrices loaded with 15%, 20% or 28% granules (10.5%, 14.0% or 19.6% of BSA, respectively) of 3 different size ranges are plotted in Figs. 6–8. All release profiles were apparently curvilinear. The release data points up to maximum matrix swelling were fitted by computer to the following equation:

$$Q = a + bt^n \qquad (1)$$

to obtain the regression curve for each case. The fit was always very good ($r > 0.997$, $P < 0.001$) The exponent of time in Eqn. 1 gauges the curvature of the release profile. The effects of granule load and size on such a curvature as appear from the $n$ values, listed in Table 2, show no clear correlations, which means that the release pattern was difficult to control through these variables, probably because of an inadequate osmotic competence of granules with the present composition.

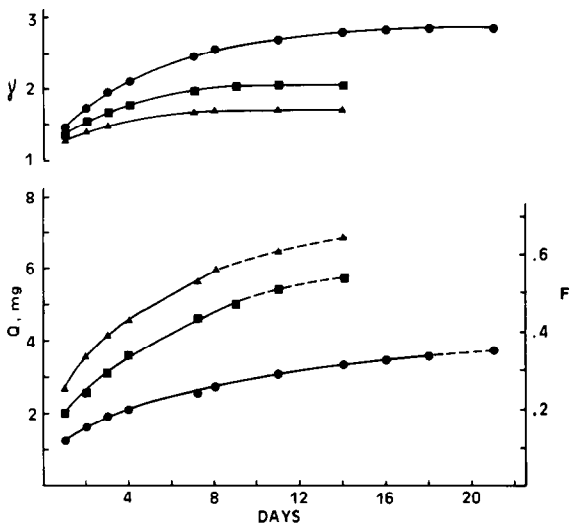


Fig. 6. Typical profiles of BSA release ($Q$, amount released; $F$, fraction released) and matrix swelling ($\gamma$, ratio of swollen-to-dry matrix weights) for disk matrices loaded with 15% granules of BSA–NaCl (70:30 w/w) composition and 40–106 $\mu$m (●), 106–150 $\mu$m (■) or 150–212 $\mu$m (▲) size range. The full portion of each release profile represents the regression curve as calculated through Eqn. 1.

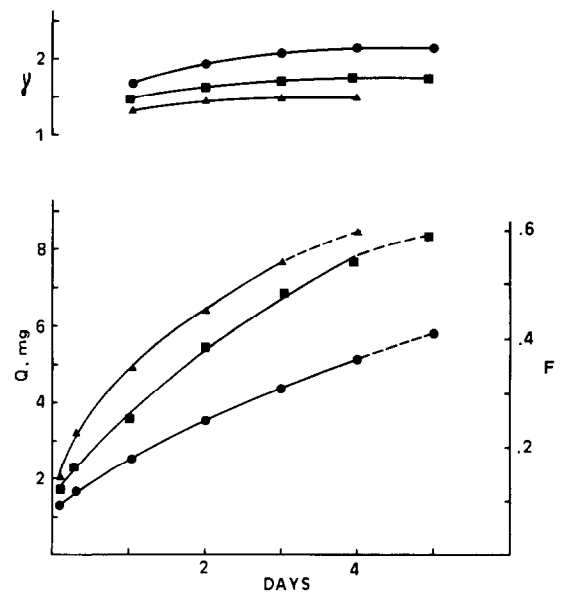


Fig. 7. Typical profiles of BSA release ($Q$, amount released; $F$, fraction released) and matrix swelling ($\gamma$, ratio of swollen-to-dry matrix weights) for disk matrices loaded with 20% granules of BSA–NaCl (70:30 w/w) composition and 40–106 $\mu$m (●), 106–150 $\mu$m (■) or 150–212 $\mu$m (▲) size range. The full portion of each release profile represents the regression curve as calculated through Eqn. 1.

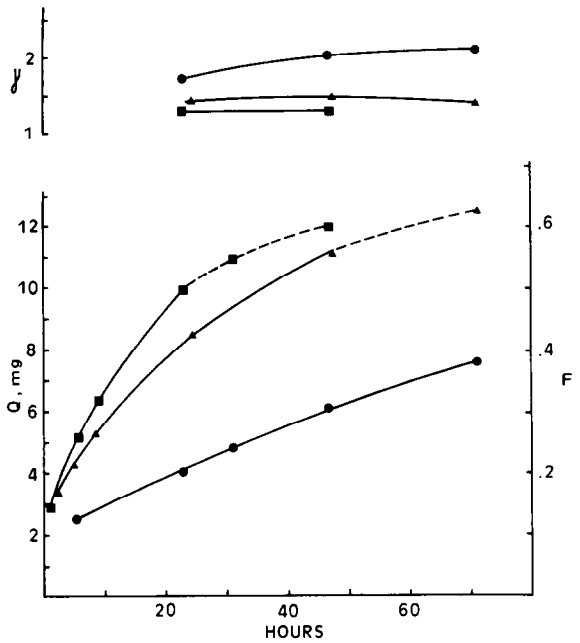


Fig. 8. Typical profiles of BSA release ($Q$, amount released; $F$, fraction released) and matrix swelling ($\gamma$, ratio of swollen-to-dry matrix weights) for disk matrices loaded with 28% granules of BSA–NaCl (70:30 w/w) composition and 40–106 $\mu$m (●), 106–150 $\mu$m (■) or 150–212 $\mu$m (▲) size range. The full portion of each release profile represents the regression curve as calculated through Eqn. 1.

*Studies of release mechanism*

Because of the intrinsic clearness of the polymer, the dissolution of the embedded solids by the penetrating solvent could be inspected visually. The matrices became completely clear in a short time compared to the entire swelling time, in accordance with the high water solubility of both granule components and the previously reported comparatively high penetration rate of water into osmotically active silicone rubber matrices of similar type as the present ones (Carelli et al., 1987). The point made in that report that the matrix fluid should be pumped out through cracks developing in the polymer can also be taken for the present systems. However, a contribution to solute transport from solute diffusion in such a fluid cannot be ruled out a priori. In order to elucidate this point and to evaluate the actual relevance of the nature of solute flux through cracks, whether convective or diffusive, to the overall release kinetics the rates of BSA and NaCl release from the same matrix were put to comparison at even times. The underlying concept was that if diffusion were uninfluent, then the solutes should travel the aqueous pathways in matrix at virtually the same rate, otherwise the NaCl flux would be faster than the BSA flux, due to the exceedingly higher diffusivity of the former. Accordingly, the BSA and

TABLE 2

*Values of parameter n, as calculated through fit of Eqn. 1 to release data from disk matrices loaded with granules of BSA–NaCl (70:30 w/w) composition*

| Granule load (%) | Granule size range ($\mu$m) | $n$ (S.D.) [a] |
|---|---|---|
| 15 | 40–106 | 0.33 (0.02) |
| | 106–150 | 0.46 (0.03) |
| | 150–212 | 0.31 (0.01) |
| 20 | 40–106 | 0.75 (0.01) |
| | 106–150 | 0.62 (0.06) |
| | 150–212 | 0.38 (0.07) |
| 28 | 40–106 | 0.79 (0.05) |
| | 106–150 | 0.53 (0.07) |
| | 150–212 | 0.53 (0.06) |

[a] Mean and standard deviation from 3 runs carried out with distinct preparations of identical formula.

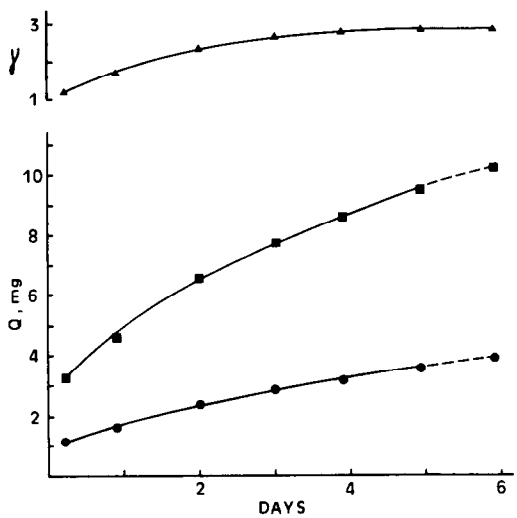


Fig. 9. Data on simultaneous BSA (●) and NaCl (■) release ($Q$, amount released) and matrix swelling (▲) ($\gamma$, ratio of swollen-to-dry matrix weights) for a disk matrix loaded with 20% granules of BSA–NaCl (35:65 w/w) composition and 106–150 $\mu$m size range. The full portion of each release profile represents the regression curve as calculated through Eqn. 1.

NaCl release from a disk matrix loaded with 20% granules of BSA–NaCl (35 : 65 w/w) composition and 106–150 $\mu$m size range was determined up to maximum matrix swelling, using isotonic pH 7.4 phosphate buffer as a receptor medium allowing no interferences with the titration of the chloride ion. This medium was previously reported to increase the silicone polymer resistance to cracking (Carelli et al., 1987). This could explain why the drug release and matrix swelling data obtained, plotted in Fig. 9, were different from those reported in Fig. 2 for a matrix equal to the one being discussed, but eluted with isotonic NaCl. Both BSA and NaCl release profiles of Fig. 9 were curvilinear, so the data were fitted to Eqn. 1 to obtain the respective regression curves. The ratio of NaCl-to-BSA release rates, as calculated by differentiation of Eqn. 1 towards time, varied from 3.0 through 2.3 over the time interval of the regression curve, i.e. it was always greater than the NaCl–BSA ratio formulated within matrix. This

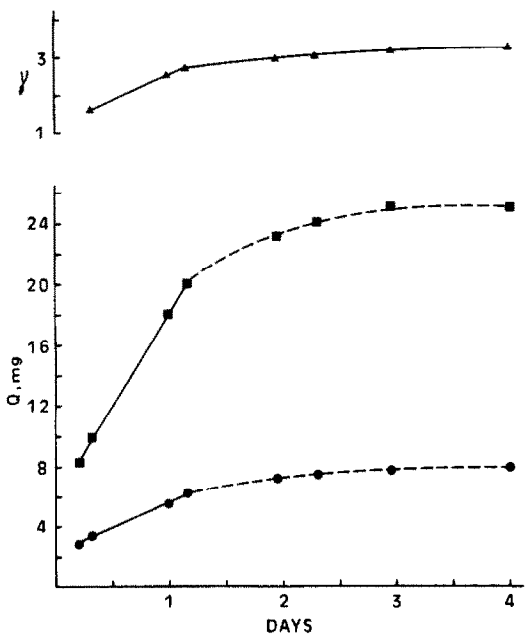


Fig. 10. Data on simultaneous BSA (●) and NaCl (■) release ($Q$, amount released) and matrix swelling (▲) ($\gamma$, ratio of swollen-to-dry matrix weights) for a disk matrix loaded with 40% granules of BSA–NaCl (35:65 w/w) composition and 150–212 $\mu$m size range. The full portion of each release profile represents the regression curve as calculated through Eqn. 1.

could not have been the case if solutes had been transported totally by convection. In a further experiment the extent of polymer cracking was augmented by increasing both granule load and size to 40% and 150–212 $\mu$m, respectively. The data for this matrix, seen in Fig. 10, show a period of constant release of both solutes with a NaCl–BSA release rate ratio of 3.8, a value much higher than the ones from the preceding matrix. Since the two solutes had to travel the same pathways in either matrix, such an increased rate ratio could only be ascribed to an increased contribution of diffusion to the overall pore transport. This type of transport can therefore be concluded to have occurred by parallel convection and diffusion, the latter being the more influent the lower the solute molecular weight and the larger the cross-sectional area of the openings available for liquid flow. In light of the discussion so far, the linear portion of the NaCl profile in Fig. 10 suggests that release to be of apparent zero-order may not require solute flux being entirely convective.

## Conclusions

The principle of using an osmotically induced rupturing of polymer to control release of macromolecular drugs from polymer matrices has proved applicable with the silicone elastomer, Silastic Q7-4840, as the matrix material. With an adequate osmotic agent fraction in granules the release kinetics was of zero-order and the release rate and time scale could be modulated through matrix geometry and granule load and size. The release pattern was rather controlled by the rate than the extent of polymer cracking. As a consequence, the zero-order regimen could last at most as long as the time for matrix to reach its maximum swelling degree. The solutes were carried through cracks by a composite convective–diffusive flux. The role of diffusion was more important with the low molecular weight osmotic agent than with the macromolecular drug. The former, therefore, leached from matrix at a higher rate than the latter. This is an inherent fault with the present release systems in so far as that it limits the drug fraction released

at a constant rate by limiting the matrix swelling period.

## Acknowledgements

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