# *In Vitro* Drug Release Profile of Bioerodable Citric Acid–Glycerol Copolymer

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## Synopsis

The incorporation and release of sulfadiazine, paracetamol, diazepam, quinine hydrochloride, and doxycycline hydrochloride in and from rectangular slabs of highly crosslinked citric acid–glycerol copolymer matrix have been described. The release of the drugs in phosphate buffer of pH 7.4 and at 37°C was followed spectrophotometrically. After an initial burst, the first three drugs were released up to 4 days and the last two drugs up to 7 days at almost constant rates. The erosion profile of the drug-free matrix and the release characteristics of the drug-loaded slabs under physiological conditions indicate hydrolytic erosion of the slab from the surface as well as from the bulk. It has been suggested that the zero-order release of the drugs was possible due to a balance between the decreasing release rate by diffusion through the matrix and the increasing release rate because of increasing polymer permeability resulting from gradual crosslink cleavage.

## INTRODUCTION

Controlled release of biologically active agents to a local environment by the erosion or chemical degradation of a polymer matrix containing the active agent is becoming an advantageous method of drug administration. Starting from poly(lactic acid)[1,2] and poly(glycolic acid)[3] matrices in the early seventies, a number of polymers such as homo- and copolymers of $\epsilon$-caprolactone[4] and DL-lactic acid,[3] glutamic acid/leucine copolymers,[5] partial esters of methyl vinyl ether/maleic anhydride copolymers,[6,7] polyanhydrides,[8] and so on have been used as drug delivery matrices. We have developed a novel biodegradable citric acid–glycerol copolymer (CGC) that releases the incorporated drug (methyl dopa) in vitro at an approximately constant rate (zero order) for about a week. The details of the synthesis, characterization and microbiological degradation of the polymer have been published elsewhere.[9] This communication reports the release profile of five drugs *in vitro* under physiological condition from this novel bioerodable polymer matrix.

## EXPERIMENTAL

**Materials.** Citric acid, glycerol, and *p*-toluene sulfonic acid (catalyst) were Merck analytical reagent grade materials. Ethylene carbonate, the medium for

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swelling, was a guaranteed reagent from Fluka. Quinine hydrochloride, doxycycline hydrochloride, and diazepam were obtained as tested samples from West Bengal Pharmaceutical and Phytochemical Development Corporation (a government of West Bengal undertaking). Paracetamol was a gift from Burroughs Wellcome (India Ltd.). Sulfadiazine was also a gift from May and Baker (India Ltd.).

**Polymer Matrix.** Preparation of CGC from citric acid and glycerol has been described[9] in detail. Here we will describe the incorporation and release of five drugs in and from the copolymer matrix having the highest crosslink density, namely the one prepared[9] from the acid to glycerol mole ratio 0.88, together with the erosion profile of the drug-free matrix under physiological condition. The CGC lumps were cut into slabs of suitable dimensions having face areas 12–15 $mm^2$ and thickness 2–3 mm. The slabs were vacuum dried and stored in a vacuum desiccator.

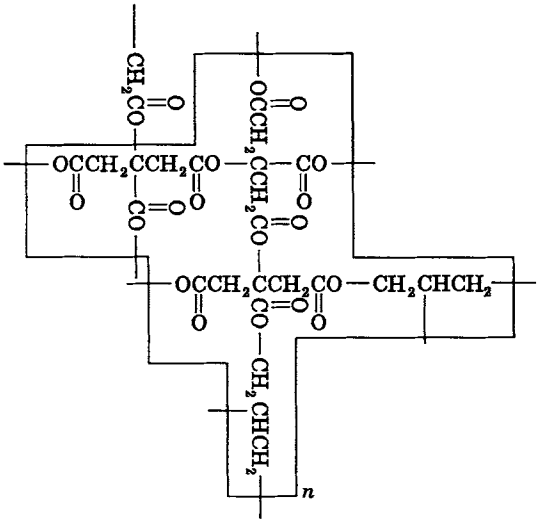
**Matrix Erosion.** A drug-free CGC slab was placed in 250 mL of 0.2*M* phosphate buffer of pH 7.4 at 37°C, and the erosion of the CGC slab in the buffer under unstirred condition was followed by observing the UV absorption of the buffer solution from time to time.

**Drug Incorporation.** The dry slabs were allowed to swell in a concentrated solution of each drug in ethylene carbonate. When swelling equilibrium was reached, the slab was taken out of the drug solution, and the solvent was removed from the slab by vacuum drying at ambient temperature retaining the drug homogeneously distributed in the polymer matrix.

**In Vitro Drug Release.** Drug release was studied by placing the drug-impregnated and dried down slabs weighing 25–55.3 mg and containing drugs between 5.5 and 22.6 wt %, each in 250 mL of 0.2*M* phosphate buffer (pH 7.4) at 37°C under unstirred condition. A 0.5-mL aliquot portion of the buffer solution was removed from time to time, and its absorbance (after suitable dilution where necessary) was measured on a Hitachi UV spectrophotometer at the appropriate wavelength. Concentrations of the released drugs were then obtained by comparison with standard curves prepared for each of the pure drugs in the buffer in the appropriate concentration region. Three samples of each matrix were tested in this way and the concentrations of the released drugs were then averaged, the variations in the concentration values being within 2%.

## RESULTS AND DISCUSSION

**The Polymer Matrix.** The CGC prepared from citric acid to glycerol mole ratio 0.88 has the highest crosslink density[9] having its glass transition temperature of 22°C. The structure of the totally crosslinked product obtainable from the acid to triol mole ratio of 3 : 2 (stoichiometric amounts) is expected to be as follows.



The CGC we prepared, however, not totally crosslinked as discussed in detail elsewhere.[9]

**Matrix Erosion under Physiological Condition.** Immersed in phosphate buffer of pH 7.4 at 37°C, a drug-free CGC slab under unstirred condition was found to maintain its shape and physical integrity while decreasing in size during the first 4 days. Thereafter the slab began to disintegrate into small pieces, which completely dissolved in the buffer within the next 3 days. The *in vitro* CGC degradation by the hydrolysis of the ester bonds in the network structure is expected to produce carboxylate and hydroxyl chromophores as endgroups. The carboxylate ($COO^-$) chromophores are known[10] to absorb near 200 nm as ester chromophores but with a larger extinction coefficient ($\epsilon_{COO^-}/\epsilon_{COOR} \sim 20$). It is also known[11] that a carboxylate group attached to a longer carbon chain absorbs at a relatively higher wavelength. Hence as the slab erodes into the medium by the hydrolytic degradation of the ester bonds and as the ester bonds of the dissolved parts are further converted into carboxylate endgroups, a gradual increase in the absorbance of the medium is expected. Table I shows the changes in UV absorption of the buffer medium with time.

In the early stages of polymer erosion, the buffer medium has a peak at 217 nm and the absorbance at this wavelength ($\lambda$) increases gradually indicating a gradual erosion of the slab by the cleavage of the ester bonds. At the 46th hour another peak appears at 210 nm, and the absorbance at this $\lambda$ also goes on increasing with time. At the 70th hour, the second peak shifts further to 208 nm, and the absorbance at this $\lambda$ continues to increase up to 132 h ($5\frac{1}{2}$ days). The appearance of a second peak at a lower $\lambda$ and the gradual shifting of the second peak toward lower wavelengths indicates the generation of smaller oligomers with $COO^-$ endgroups. After 132 h the second peak tends to shift to a still lower wavelength, which could not be detected because of the large absorbance of the buffer solution in this region. This experimental shortcoming prevents us from following further hydrolysis of the ester bonds leading to smaller molecules by observing UV absorption. However, the gradual erosion of the disintegrated particles and their ultimate dissolution forming a clear

TABLE I
Erosion of CGC in pH 7.4 Buffer at 37°C

| Time (h) | λ (nm) | Optical density |
|---|---|---|
| 12 | 217 | 0.190 |
| 22 | 217 | 0.239 |
| 36 | 217 | 0.322 |
| 46 | 217 | 0.428 |
| | 210 | 0.437 |
| 60 | 217 | 0.699 |
| | 210 | 0.735 |
| 70 | 217 | 0.964 |
| | 208 | 1.028 |
| 84 | 217 | 0.972 |
| | 208 | 1.037 |
| 108 | 217 | 0.986 |
| | 208 | 1.047 |
| 132 | 217 | 0.989 |
| | 208 | 1.051 |

solution suggests the continuation of the hydrolytic degradation process, although we cannot adduce any experimental evidence in support of our suggestion.

**Drug Incorporation and Release Characteristics.** Ethylene carbonate was chosen as the medium for swelling because CGC swells more in this medium than in water, and the drugs used also have a good solubility in it. The amount of drug incorporation in the CGC matrix could be varied by varying the concentration of the drug solution within the solubility limit of the drug in this solvent. By the swelling procedure it was possible to incorporate 5.5–23 wt % of different drugs in the CGC matrix. The release profile of five drugs is shown in Figures 1 and 2 and is discussed below.

*Sulfadiazine.* The matrix dimension was $4 \times 3 \times 2.3$ mm$^3$ and 32.8 mg, with a drug incorporation of 5.5 wt %. Curve 1 in Figures 1 and 2 show, respectively, the total release and the release rate of the drug with time. After an initial burst during the first day, an almost constant release rate was obtained up to the fourth day, by which time about 99% of the drug was released.

*Paracetamol.* The matrix dimension was $4 \times 3 \times 2$ mm$^3$ and 25 mg, with a drug incorporation of 10.8 wt %. Curve 2 in Figures 1 and 2 show, respectively, the release of paracetamol from the CGC matrix and its release rate with time. On the first day about 40% of the drug was released. Then the release rate became steady and continued to remain so up to the fourth day, by which time about 92% of the drug was released.

*Diazepam.* The CGC matrix dimension was $5 \times 3 \times 3$ mm$^3$ and 55.3 mg, with a drug incorporation of 22.6 wt %. Curve 3 in Figures 1 and 2 show, respectively, the total release and the release rate of the drug from the matrix with time. About 47% of the drug was released on the first day. This was followed by an almost constant release rate on the second and third day. On the fourth day the release rate increased to some allowable extent when 99% of the drug was released in the buffer.

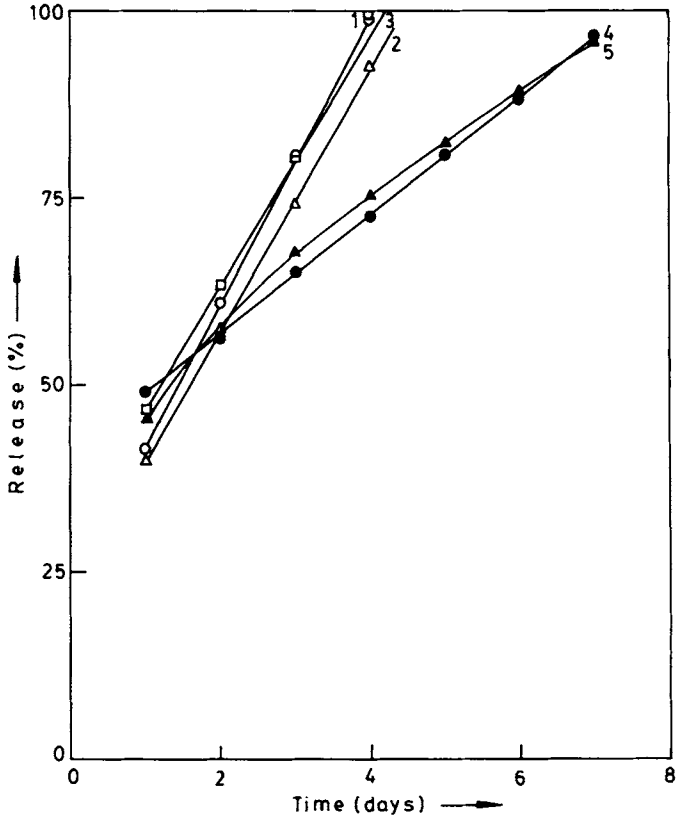



Fig. 1. Drug release study from the drug-loaded CGC matrix: Total release (%). (1) Sulphadiazine (○), (2) paracetamol (△), (3) diazepam (□), (4) doxycycline hydrochloride (●), (5) quinine hydrochloride (▲).

*Doxycycline Hydrochloride.* The matrix dimension was 4 × 3 × 2 $mm^3$ and 39.2 mg, with a drug incorporation of 8 wt %. Curve 4 in Figures 1 and 2 show, respectively, the total release of the drug from the matrix and the release rate with time. About 48% of the drug was released on the first day. This was followed by a period of constant release rate up to the seventh day, when about 96% of the drug had been released.

*Quinine Hydrochloride.* In this case matrix dimension was 4 × 3 × 3 $mm^3$ and 33.1 mg, with a weight percent of 10.5. Curve 5 in Figures 1 and 2 show, respectively, the total release of the drug from the matrix and the release rate with time. On the first day about 45% of the drug was released. This was followed by a period of constant release rate up to the seventh day, when about 95% of the drug had been released.

**Mechanism of Drug Release.** Since the CGC slab in phosphate buffer (pH 7.4) at 37°C maintains its shape and physical integrity up to 4 days, it appeared to us initially that the erosion of the matrix takes place from the surface. However, the fact that the polymer swells considerably in water shows that it is hydrophilic and largely permeable to water. Hydrolytic degradation of such polymers occurs on the surface as well as in the bulk. Only when a

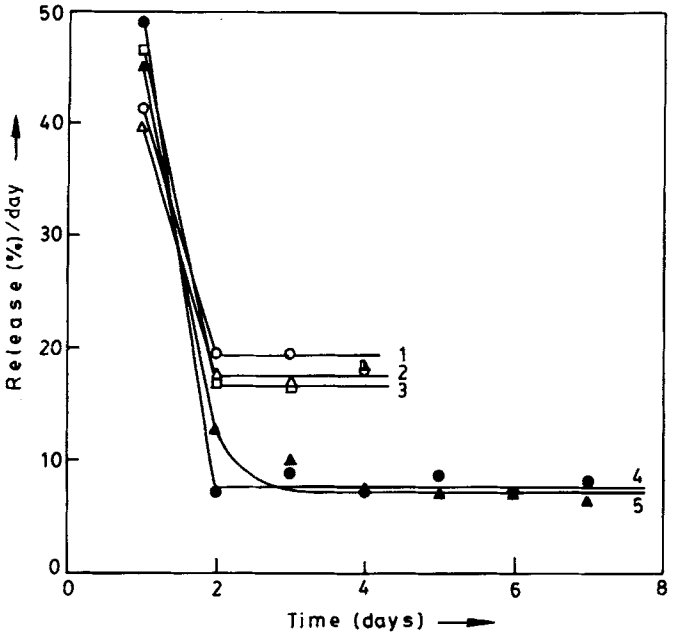



Fig. 2. Drug release study from the drug-loaded CGC matrix: Release rate (%/day). (1) Sulphadiazine (○), (2) paracetamol (△), (3) diazepam (□), (4) doxycycline hydrochloride (●), (5) quinine hydrochloride (▲).

critical number of crosslinks in the bulk are lost by hydrolysis, as after the fourth day, does the matrix collapse into smaller particles, which continue to suffer further hydrolysis and disappear completely by the next 3 days forming a clear solution. Release of a drug from such hydrophilic polymers should take place by diffusion through the matrices following the well-established relation[12]

$$\frac{Q_t}{Q_\infty} = K\frac{(Dt)^{1/2}}{\pi l^2}$$

where $Q_t$ is amount of drug released at time $t$, $Q_\infty$ is the amount released at $t = \infty$, $D$ is the apparent diffusion coefficient of the drug through the swollen polymer, $l$ is the half thickness of the slab, and $K$ is an integer of value 2, 4, or 6. The fractional release with time should thus be proportional to $t^{1/2}$, and the desirable constant release rate is apparently not obtainable. However, it has been found that devices that swell during drug release are capable of providing a more uniform rate of release. Our method of drug incorporation leaves the devices completely dried up, and we have obtained a nearly constant rate of release up to 4 days for three drugs (sulfadiazine, paracetamol, and diazepam) and up to 7 days for the two drugs (doxycycline hydrochloride and quinine hydrochloride). This desirable occurrence may be due to a balance between the decreasing release rate by diffusion through the matrix and the increasing release rate due to increasing polymer permeability resulting from gradual crosslink cleavage. This nearly constant release rate may also be the result of

the semicrystallinity of these crosslinked polymers, which provides a profile of release similar to that suggested by Hopfenberg[13] for bioerodable polymers. The increased duration of constant release rate in the case of doxycycline hydrochloride and quinine hydrochloride loaded matrices may reasonably be attributed to the comparatively larger molecular sizes of these two drugs, which offer greater resistance to their diffusion out of the matrix. A larger amount of drug release on the first day in all the five cases may arise from the fact that the free drug particles on the surface go into solution as soon as the device is placed in the medium. Besides, in the case of such hydrophilic polymers the initial rate of swelling and hence the penetration of the swelling interface into the matrix is very high, releasing a large amount of drug into the aqueous environment. Such high initial rate of release from hydrophilic polymer matrices has been observed by others[3,14] also. At present work is under way in this laboratory for synthesizing novel bioerodable polymers from naturally occurring polyfunctional acids and polyols having less hydrophilicity with a view to extending the duration of constant release period.

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