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Novel Approach to Zero-order Drug Delivery *Via* Immobilized Nonuniform Drug Distribution in Glassy Hydrogels

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Abstract □ A novel approach to zero-order drug delivery from glassy hydrogel matrices *via* an immobilized, sigmoidal, initial drug distribution has been developed. The method utilizes a controlled-extraction process on initially dry, drug-loaded hydrogels to generate an inflection-point-containing drug concentration profile followed by a vacuum freeze-drying step to rapidly remove the swelling solvent and immobilize *in situ* a nonuniform drug distribution. The drug release from such a system generally exhibits typical zero-order characteristics similar to that of a membrane-reservoir device. However, a saturated reservoir of active ingredient as in the membrane-reservoir device is not required because the constant release is achieved *via* an initially nonuniform concentration distribution instead of the constant activity in a reservoir. The applicability of the present concept and process has been demonstrated experimentally with the release of oxprenolol hydrochloride from hydrogel beads based on 2-hydroxyethyl methacrylate polymerized with a polymeric cross-linking agent.

Keyphrases □ Glassy hydrogels, oxprenolol hydrochloride—nonuniform drug distribution □ Oxprenolol hydrochloride—glassy hydrogels, nonuniform drug distribution □ Drug delivery systems—oxprenolol hydrochloride, glassy hydrogels

Diffusion-controlled polymeric delivery systems are finding increasing applications in the area of controlled release of pharmaceuticals (1–3). To achieve optimal therapeutic effects, especially for drugs with short physiological half-lives, it is often desirable to have a zero-order (or constant-rate) drug delivery (4). Unlike membrane-reservoir devices, monolithic systems where the drug is uniformly dissolved or dispersed in a polymer matrix generally do not exhibit zero-order release behavior. Instead, a release rate that continuously diminishes with time is observed (5, 6). This is a consequence of the increased diffusional distance and decreased area at the penetrating diffusion front. In addition to geometry factors (7), methods that approach zero-order release from monolithic matrices generally involve the introduction of either a constant rate of surface erosion much larger than the drug diffusion rate in the polymer matrix (8–10) or a constant rate of solvent front penetration (the so-called case II swelling) much smaller than the drug diffusion rate in the swollen region (11, 12). The applicability of these systems may be further limited by the need to maintain a constant surface area at the erosion or penetrating solvent front.

An important concept which has not been explored is the approach to zero-order drug release from a glassy polymer matrix having a specific nonuniform initial drug concentration distribution. Hydrogel polymers are unique for this application in that they are glassy in the dry state and capable of immobilizing any nonuniform drug distribution introduced prior to the dehydration step. In the presence of water, hydrogels can absorb a significant amount of water to form an elastic gel and, at the same time, release the dissolved drug by diffusion through the swollen region (13, 14).

This paper reports a method for immobilizing such a nonuniform drug concentration distribution in glassy hydrogel beads and the resulting zero-order drug release behavior. A

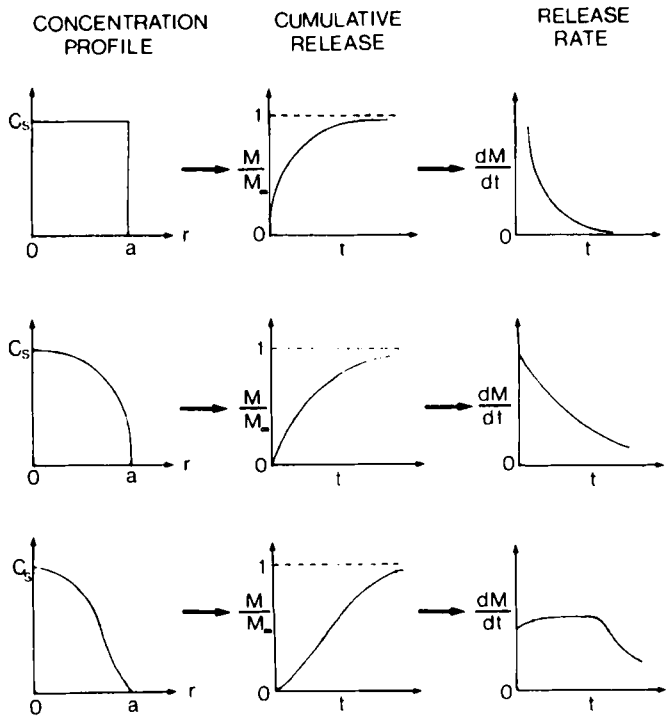

Figure 1—*Theoretical profiles illustrating the characteristics of drug release from spherical matrices as a function of the initial drug concentration distribution.*

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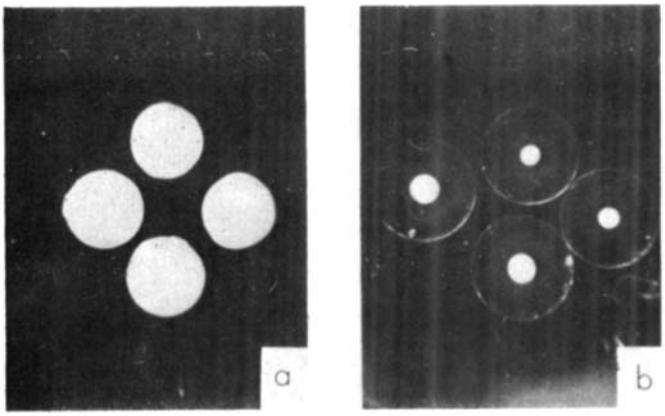

Figure 2—*Photographs showing typical solvent penetration behavior in drug loaded glassy hydrogel beads. Key: (a) original; (b) solvent penetrqted.*

detailed kinetic study of such release systems will be published elsewhere[1].

EXPERIMENTAL SECTION

Spherical hydrogel beads containing purified 2-hydroxyethyl methacrylate[2] (70%) and a polymeric cross-linking agent (30%), which was derived from poly-*n*-butyleneoxide (mol. wt. 2000)[3] by end-capping with 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl-isocyanate[4] followed by reaction with excess 2-hydroxyethyl methacrylate, were synthesized by free-radical suspension polymerization in a saturated salt solution using 0.1% *tert*-butyl peroxy-2-hexanoate[5] as the initiator (15). The fraction of beads with a mean dry diameter of 0.115 cm and a mean swollen diameter of 0.13 cm was used for the release study. These hydrogel beads exhibit a major glass transition temperature (T_g) of ~110°C (as determined by differential scanning calorimetry[6]), an equilibrium ethanol swelling of 49%, and an equilibrium water swelling of 25%.

Oxprenolol hydrochloride[7], a β-blocker with water solubility as high as 77% at room temperature, was used as the model drug. A drug loading of 34.4% was achieved by equilibrating the hydrogel beads in an excess amount (5:1 ratio) of a 50% oxprenolol hydrochloride solution prepared in ethanol–water (60:40). After filtration and a brief rinse, the swollen loaded beads were dried at 50°C in a vacuum oven. These dry, loaded beads were then divided into several portions and subjected to a controlled-extraction process in an excess volume of water under vigorous stirring at 23°C for 5, 15, 20, and 30 min, respectively. The extraction process was controlled so that the extraction time was shorter than the time required for the penetrating solvent fronts to meet at the center to ensure that there would always be an inner glassy core surrounded by a swollen, partially extracted region. Immediately after separation of the extracting solvent, the controlled-extracted beads were freeze-dried under reduced pressure (0.025 mm Hg) for 15 h to rapidly remove the swelling solvent and to immobilize the drug, which was distributed in a nonuniform sigmoidal manner, decreasing from the core to the surface.

The oxprenolol hydrochloride release (under perfect sink diffusion conditions at 37.5°C) was followed continuously on a spectrophotometer[8] at 272 nm using a flow-through cell. The storage stability tests were conducted in capped vials under room conditions.

RESULTS AND DISCUSSION

The release characteristics of matrix devices containing uniformly dissolved or dispersed drug are well known (10, 16–18). However, the effect of nonuniform initial drug distribution on the release behavior has not been reported in the literature. Figure 1 illustrates the characteristics of drug release from spherical matrices as a function of the initial drug distribution[1]. Based on solutions to the diffusion equation, these theoretical curves show that both the uniform and parabolic initial concentration distributions result in an initially high rate of release followed by a rapid decline; the latter distribution exhibits a reduced initial rate of release compared with the former. In contrast, a sigmoidal initial drug distribution is capable of introducing a characteristic inflection point and, therefore, considerable linearity into the cumulative release curve. The duration of the constant-rate release region in such systems generally depends on the slope at the inflection point in the concentration distribution. Although Fig. 1 describes the drug release from spherical matrices, similar results are expected for planar and cylindrical geometries.

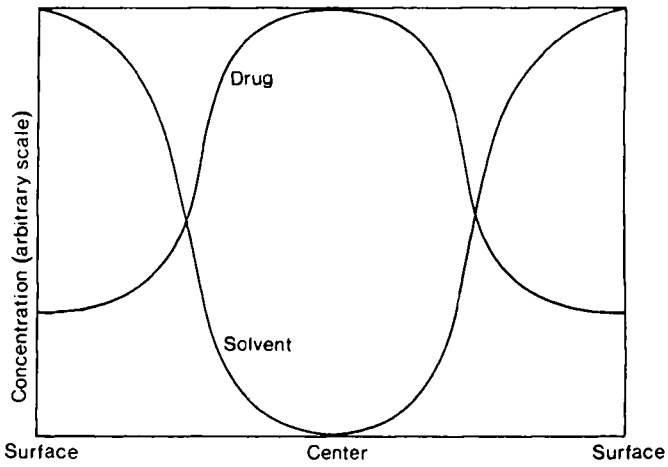

Figure 3—*Idealized solvent and drug distributions during solvent penetration in a drug-loaded glassy hydrogel matrix.*

The parabolic type of concentration distribution described above is characteristic of Fickian diffusion in rubbery polymers (19, 20), whereas the sigmoidal distribution is characteristic of glassy polymers partially penetrated by a swelling solvent undergoing non-Fickian diffusion. As a swelling solvent (in this case, water) penetrates a glassy hydrogel matrix having uniform drug loading, a clear discernible boundary separating an outer, rubbery, swollen region from an unpenetrated glassy core is usually observed (Fig. 2) (14). Such penetration and swelling generally do not follow Fickian diffusion. The existence of some molecular relaxation process in addition to diffusion is believed to be responsible for the observed non-Fickian behavior (12, 21). As a result, an inflection point is built into both the concentration profile of the penetrating solvent and the corresponding drug distribution, as shown in Fig. 3. This is similar to the solvent profiles reported for the partial penetration of organic swelling solvent in glassy polymers (22–24). The physical situation depicted in Fig. 3 is believed to reflect the solvent and drug distributions generated by the controlled-extraction process described in the *Experimental Section*. The subsequent vacuum freeze-drying step is intended to reduce the polymer segmental mobility by lowering the temperature and, at the same time, rapidly remove the swelling solvent to immobilize the drug *in situ* in a sigmoidal distribution in the hydrogel matrix.

As shown in Figs. 4A and B, scanning electron microscopy[9] X-ray microprobe chlorine scans for oxprenolol hydrochloride across the cross sections of the hydrogel beads confirm that the combination of controlled-extraction and freeze-drying steps has immobilized the drug *in situ* with a sigmoidal concentration profile in the 20-min extracted sample compared with the uniform concentration distribution in the unextracted control. The corresponding *in vitro* release of oxprenolol hydrochloride from the controlled-extracted beads is compared with that of the unextracted control in Fig. 5. It is evident that an inflection point and a zero-order release region of up to 60% of the total are introduced by the present process. With the increase in controlled-extraction time, the constant-rate release region extends, and the release half-life more than doubles. The constant-release region also shows a progressively decreasing slope with increased controlled-extraction time. In addition, release time-lags similar to that of membrane-reservoir devices are developed. Inevitably, a certain amount of drug will be lost during the controlled-extraction process. However, as shown in Fig. 6, where the oxprenolol hydrochloride loading is plotted as a function of controlled-extraction time in water, only ~10% of the drug is removed with an extraction time of 30 min.

In the absence of moisture, the sigmoidal drug concentration distribution generated by the present process can be preserved indefinitely in the glassy hydrogel matrix. The release of the entrapped drug should not occur until the hydrogel matrix is swollen at the time of usage. This is illustrated by a comparison of oxprenolol hydrochloride release rates from both the unextracted control and controlled-extracted beads at 0 and 59 d of storage as shown in

[1] Submitted to *Polymer*.
[2] White Chemical Co., Bayonne, N.J.
[3] Polymeg 2000; Quaker Chemical Co., Chicago, Ill.
[4] Veba Chemie, Gelsenkirchen-Buer, West Germany.
[5] Pennwalt Co., Philadelphia, Pa.
[6] DuPont Model 910 differential scanning calorimeter.
[7] Ciba-Geigy Co., Summit, N.J.
[8] ACTA C-III UV-visible; Beckman Instruments, Fullerton, Calif.
[9] Cambridge Stereoscan 180 scanning electron microscope.

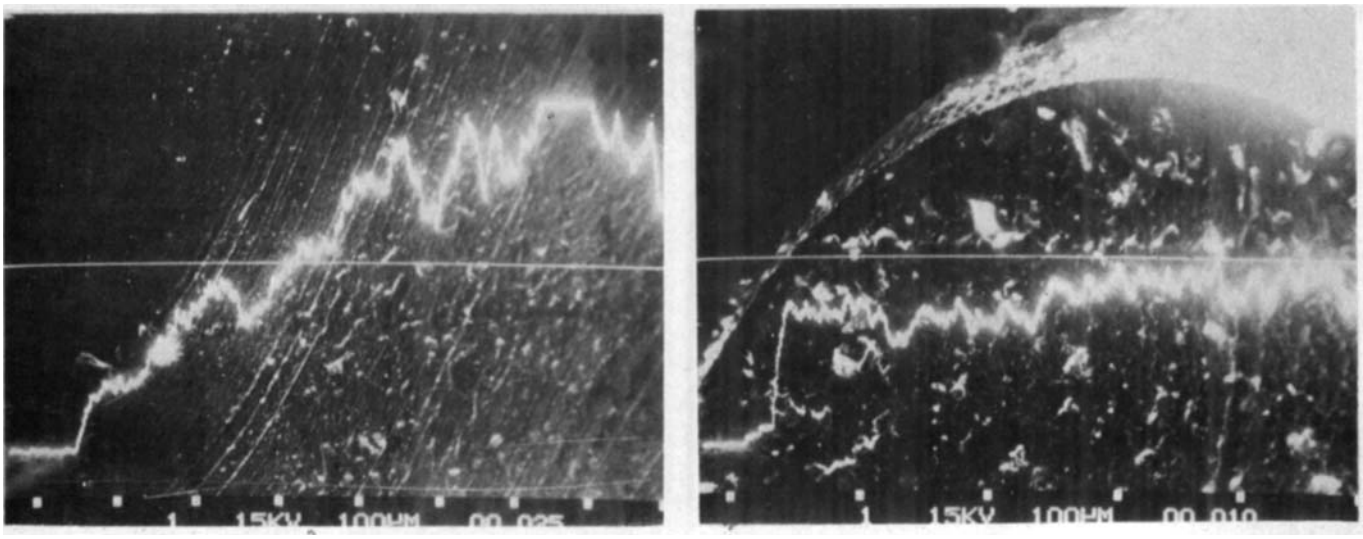

Figure 4—*Scanning electron microscope X-ray microprobe chlorine scans for oxprenolol hydrochloride on the cross section of hydrogel beads. Key: (A) controlled-extracted in water for 20 min; (B) unextracted control.*

Figs. 7A and B. In addition to the specific feature of prolonged zero-order release from controlled-extracted samples compared with the rapid decay of release rate in the unextracted control, there is very little change in the release rates after nearly 2 months of storage.

In summary, a novel appraoch to zero-order drug delivery from glassy hydrogel beads *via* an immobilized sigmoidal drug distribution is described. The combination of controlled-extraction and freeze-drying process is critical in the *in situ* immobilization of such a nonuniform concentration distribution.

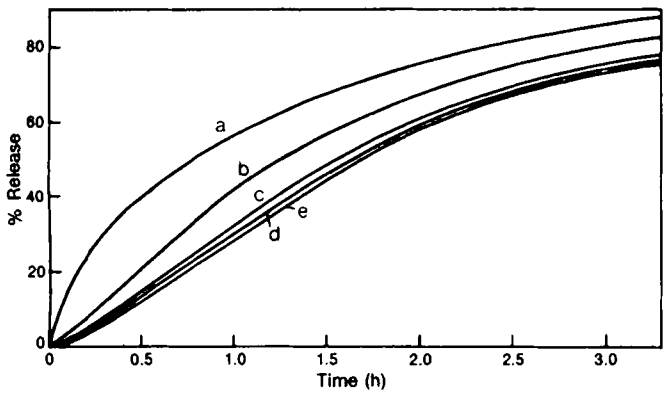

Figure 5—*Effect of controlled-extraction time in water on the* in vitro *release of oxprenolol hydrochloride. Key: (a) control; (b) 5 min; (c) 15 min; (d) 20 min; (e) 30 min.*

The evidence indicates that when the extraction process is carried out on drug-loaded beads in the fully swollen state instead of the dry glassy state, or when the drying is done at an elevated temperature instead of freeze-drying, no inflection point or constant-release region will be observed in the cumulative drug release profiles. Apparently, a parabolic type of drug concentration distribution, characteristic of Fickian diffusion in the rubbery state, does not lead to a zero-order release (Fig. 1). Other parameters such as the hydrogel composition and the extracting solvent also play important roles in determining the resulting release characteristics.

The concept and process described here have several distinct advantages

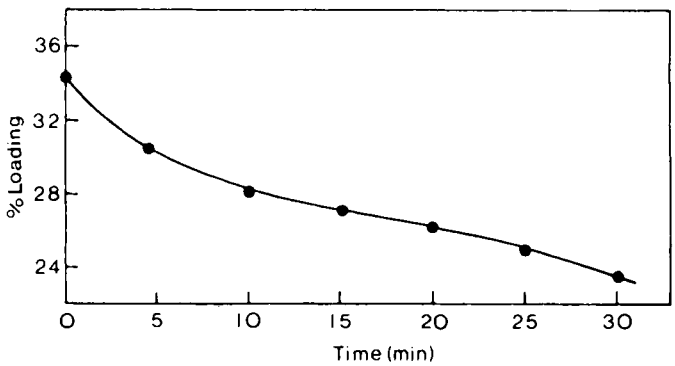

Figure 6—*Oxprenolol hydrochloride loading as a function of controlled-extraction time in water.*

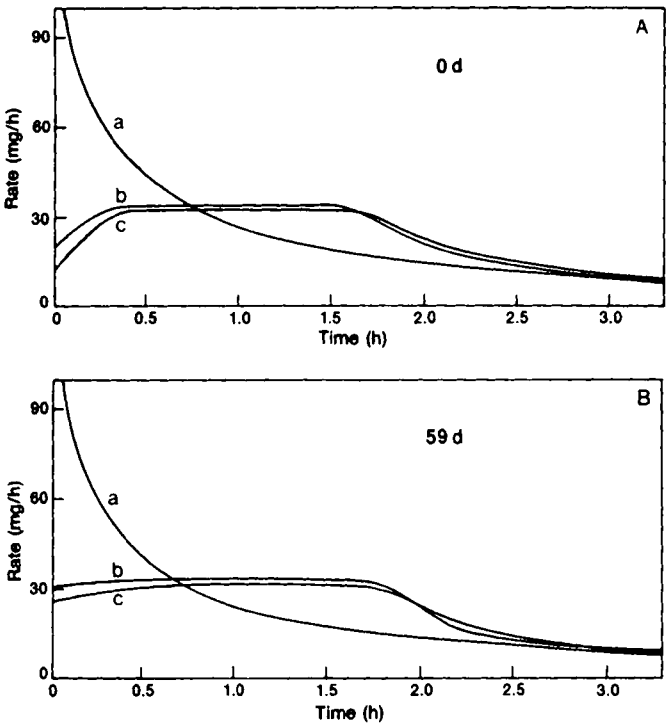

Figure 7—*Effect of storage time on the rate of oxprenolol hydrochloride release. Key: (A) 0 d; (B) 59 d; (a) loaded control; (b) controlled-extracted in water for 20 min; (c) controlled-extracted in water for 30 min.*

in addition to the zero-order release characteristics: (*a*) it is applicable to glassy hydrogels of any geometry including granules, beads, and sheets; (*b*) the burst-effect generally associated with membrane-reservoir devices is eliminated; and (*c*) a saturated reservoir of active ingredient (as in the membrane-reservoir device) is not required because the constant release is achieved by a nonuniform concentration distribution instead of the constant activity in a reservoir. This is particularly suitable for drugs with high water solubility.

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