Pharmaceutical Research, Vol. 10, No. 7, 1993

Swelling and Dissolution Kinetics During Peptide Release from Erodible Anionic Gel Beads

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Received October 13, 1992; accepted February 3, 1993

The transient dynamic swelling and dissolution behavior during the release of a growth hormone releasing peptide, [D-Trp^2-D-Phe^5]GHRP, from erodible, non-cross-linked poly(methyl methacrylate-co-methacrylic acid) (PMMA/MAA) beads has been investigated at pH 7.4 as a function of buffer concentration. Although the swelling front penetration shows a ionization-limited behavior similar to that of nonerodible cross-linked PMMA/MAA beads, the normalized diameter of the polymer beads exhibits a brief initial rise followed by an extended linear decline due to establishment of the polymer dissolution process. This is consistent with the general kinetic scheme of dissolution of glassy polymers originally predicted for the slab geometry. In all cases, the initial gel thickness increases as a result of the ionization and swelling of the glassy PMMA/MAA beads. This is followed by an extended period of constant gel thickness due to the onset of polymer dissolution and the synchronization of movement of the swelling and dissolution fronts. The resulting constant gel layer thickness as well as the onset and duration of front synchronization shows an increasing trend with decreasing buffer concentrations. As a result, the corresponding peptide release is slower and the release duration longer at lower buffer concentrations. This is believed to be the first time that a synchronization of swelling and dissolution fronts has been documented for a *spherical* erodible sample. Although such synchronization of fronts does not result in a constant rate of peptide release due to the spherical geometry, some non-Fickian release characteristics have been observed.

KEY WORDS: swelling and dissolution kinetics; front synchronization; poly(methyl methacrylate-co-methacrylic acid); spherical erodible beads; growth hormone releasing peptide release.

INTRODUCTION

Bioerodible polymers are becoming increasingly important in the design of controlled-release drug delivery systems, particularly for the delivery of protein/peptide drugs (1,2). One of the major advantages associated with such delivery systems is the avoidance of the need for device removal after the exhaustion of drug therapy. In addition, erodible systems exhibiting surface-erosion characteristics are capable of producing time-varying patterns of drug release not achievable by the diffusion mechanism alone, thus affording a better release rate modulation (3,4). The latter aspect is particularly important to the rate-programmed delivery of protein/peptide drugs.

Two distinctive processes, namely, swelling and true dissolution, generally occur during the overall erosion of these polymers. This is characterized by the formation of an erosion/dissolution front at the device surface and a diffusion/swelling front at the gel/core interface (5). In glassy polymers, the latter front is usually accompanied by a glassy/rubbery transition. A schematic diagram is shown in Fig. 1 to illustrate the two moving fronts involved during such erosion process. The synchronization of movement of these two fronts has been shown to be necessary for zero-order drug release from surface-erodible polymer matrices with a near-constant surface area such as slabs (6). This aspect has also been confirmed experimentally in pharmaceutical matrix tablets undergoing restricted one-dimensional erosion (7,8). Despite the growing interest in such bioerodible systems for drug delivery, the kinetics of the erosion process during drug release has not been studied in necessary detail, particularly with spherical samples. This is attributed primarily to the limitation of available sample geometry. The commonly employed slab geometry and granular particles are limited by the edge effect, anisotropic swelling behavior, and technical difficulties in the direct observation of swelling and dissolution boundaries. In contrast, spherical samples avoid these drawbacks and permit accurate measurement of the erosion kinetics. Although the front synchronization aspect is mechanistically important in achieving zero-order drug release for surface erodible polymer slabs, its role in the drug release from spherical samples has not been examined experimentally or theoretically. In fact, it is not immediately clear whether the front synchronization would occur in an erodible sphere because of a continuous decrease in surface area at both the swelling and the dissolution fronts.

In this paper, we report for the first time the complete swelling/dissolution kinetics during the release of a growth hormone releasing peptide from *spherical* erodible poly(methyl methacrylate-co-methacrylic acid) beads. The effect of buffer concentration on the peptide release and the swelling/dissolution behavior is also examined.

EXPERIMENTAL

Synthesis of Erodible Polymer Beads. Based on the modification of a previously described process (9), erodible poly(methyl methacrylate-co-methacrylic acid) (PMMA/MAA) beads were synthesized by free-radical suspension polymerization of a mixture (54/46 mol%) of freshly distilled methyl methacrylate (MMA) and inhibition-free methacrylic acid (MAA) *without* the addition of any cross-linking agent. The polymerization was carried out in a concentrated $CaCl_2$ solution at 70°C and 150 rpm for 5–6 hr under nitrogen, using freshly precipitated hydroxyapatite [$3Ca_3(PO_4)$ $Ca(OH_2)$] as the suspending agent and 2,2′-azobisisobutyronitrile (Vazo 64, DuPont) as the initiator. The relative amount of monomer to water in the polymerization mixture was 1:5 by weight. After exhaustive extraction in a Soxhlet with methanol, the beads were vacuum-dried and fractionated. The fraction of PMMA/MAA beads with a dry diameter of 0.1–0.118 cm was used for this study. The intrinsic viscosity of the PMMA/MAA in tetrahydrofuran (THF) was measured on a Ubbelohde viscometer at 25°C.

Erosion and Drug Release. The erosion experiments were carried out in a cuvette immersed in a constant-

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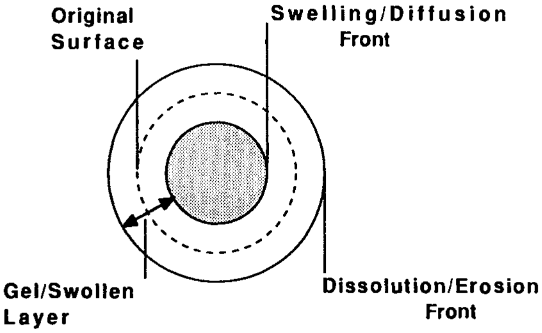

Fig. 1. Schematic diagram of moving fronts during polymer erosion.

temperature water bath (Haake D8-G; accurate to ±0.02°C). The swelling and dissolution fronts were observed with a Wild M-420 stereomicroscope equipped with camera attachments and a digital optical measuring accessory (Wild MMS-235; accurate to ±0.001 mm). A growth hormone releasing peptide (GHRP), Tyr-D-Trp-Ala-Trp-D-Phe-NH_2 ([D-Trp^2-D-Phe^5]GHRP or Momany peptide), which was shown to release growth hormone (GH) from rat pituitary *in vitro* (10), was used as a model drug. The loading of the peptide was achieved by equilibrating the PMMA/MAA beads for 2 days in a 0.65 wt% peptide solution prepared in an acidic ethanol/water mixture (1:1 ethanol:0.1% acetic acid). After filtering and drying, the peptide-loaded beads were then used for swelling and release studies in Sorensen phosphate buffer (pH 7.4). The *in vitro* peptide release at 37°C under perfect sink condition was monitored continuously at 280 nm in a thermostated and stirred cuvette (at 200 rpm) on a Hewlett Packard 8452A diode-array UV-vis spectrophotometer. The perfect sink condition was maintained at all times by having a large buffer solution-to-sample volume ratio (>6000).

RESULTS AND DISCUSSION

The PMMA/MAA beads studied here are non-cross-linked and therefore erodible upon ionization. These beads are almost identical in composition to the commercially available enteric polymer, Eudragit L (54/46 vs 50/50 mol% of MMA/MAA); however, the molecular weight of the present suspension polymerized PMMA/MAA is much higher. Eudragit polymers are described in USP XXI/NF XVI in the monograph on Mathacrylic Acid Copolymers. We have determined the intrinsic viscosities of the present polymer and Eudragit L to be 0.906 and 0.302 dL/g (at 25°C in THF), respectively. Based on the intrinsic viscosity data and the corresponding Mark-Houwink constants for PMMA/MAA from low-angle laser light-scattering data of Ouano (11), the weight-averaged molecular weight M_w is calculated to be about 500,000 for the present suspension polymerized PMMA/MAA and about 70,000 for Eudragit L. In this case, a higher molecular weight is expected to lead to a slower polymer erosion.

The model peptide, [D-Trp^2-D-Phe^5]GHRP, studied here is a pentapeptide, originally designed using structural concepts derived from conformational energy calculations (10). Although radiochemical and immunochemical methods are generally employed for peptide quantitation, the UV method employed here is an acceptable strategy for the present purpose because this model peptide contains two tryptophan units and 280 nm is the characteristic absorbing wavelength of tryptophan (12). Because peptides can be prone to intermolecular interactions leading to aggregate formation and solubility reduction, one may question the suitability of the drying step involved in the present loading process. However, this is unlikely to be a problem since aggregation in solution can be prevented by the use of a denaturing solvent system (13) such as the loading solvent ethanol/acetic acid used here. After the equilibrium loading step, the loaded peptide is essentially dissolved in the same loading solvent throughout the swollen gel bead (PMMA/MAA swells in ethanol). At the low loading level of the present study (4%), aggregation and, therefore, reduced solubility of loaded peptide would have been prevented by the shielding effect of the polymer network during drying.

The release of the model growth hormone releasing peptide from erodible PMMA/MAA beads in different concentrations of phosphate buffer (pH 7.4) is illustrated in Fig. 2 for a peptide loading level of 4%, where a prolonged release period as long as 35 hr is achieved in 0.05 *M* buffer, while shorter release durations are attained at higher buffer concentrations. The observed peptide release appears to be non-Fickian in nature, with a release rate gradually decreasing with time. Such a rate decline is generally expected in a spherical erodible matrix with a decreasing surface area, however, in the present case, the release rate decreases much more slowly than that from the geometry effect alone, most likely due to additional contributions from polymer swelling. It is also observed in Fig. 2 that the model peptide release is faster and the release duration shorter at higher buffer concentrations. This is primarily a result of the faster electrolyte uptake at higher buffer concentrations due to a more effective reduction of Donnan potential which effectively facilitates polymer ionization, resulting in faster polymer swelling and dissolution. This dependence on buffer concentration may seem to be similar to that reported for cross-linked PMMA/MAA beads (14), however, the underlying mechanisms of drug release are quite different. Thus, the non-cross-linked PMMA/MAA beads of the present study are erodible, which eventually disappear at the end of the erosion process; the drug release is controlled by both the swelling and the dissolution processes. On the other hand, the cross-linked PMMA/MAA beads studied previously are swellable but nonerodible, which remain swollen at the end of the releasing period; here the drug release is controlled by the swelling process. The transient dynamic swelling/dissolution behavior corresponding to that in Fig. 2 is illustrated in Figs. 3 and 4 for the case of 0.2 *M* buffer, where a complete time course of the erosion kinetics in a spherical sample is shown for the first time. In this case, a sharp swelling front is formed initially due to the ionization of pendant carboxylic acid groups in phosphate buffer. This leads to the formation of a swollen ionized shell surrounding a glassy nonionized core (Fig. 4). As shown in Fig. 3, the progression of this penetrating swelling front exhibits a short induction time followed by an apparent constant-rate front movement before accelerating toward the core. This front penetration kinetic is not only governed by the ionization-limited swelling process similar to that reported for the

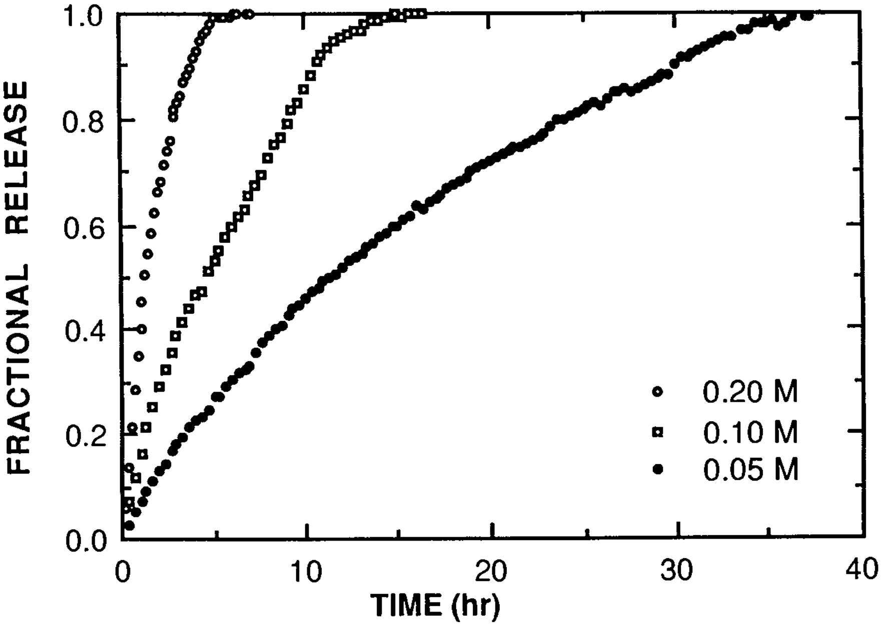

Fig. 2. Effect of buffer concentration on the release of [D-Trp^2-D-Phe^5]GHRP from erodible PMMA/MAA beads at pH 7.4 and 37°C.

cross-linked version of the present PMMA/MAA (9,14), but also affected by the rate of movement of the erosion/dissolution front (6). The front acceleration near the core observed here is a natural outcome of the spherical geometry, which has been documented for other glassy polymer beads (15).

The movement of the dissolution front is described by the observed transient changes in the overall bead diameter in Figs. 3 and 4, where, after a brief initial increase, the bead diameter exhibits an extended linear decline due to the progression of polymer dissolution as a result of the continuous disentanglement of polymer chains at the surface. Before the establishment of a critical surface concentration for such macromolecular disentanglement, the polymer continues to swell, resulting in the initial increase in bead diameter as observed in the photographs in Fig. 4. This is consistent with the general kinetic scheme for the dissolution of glassy polymers predicted originally for the slab geometry (5). Also

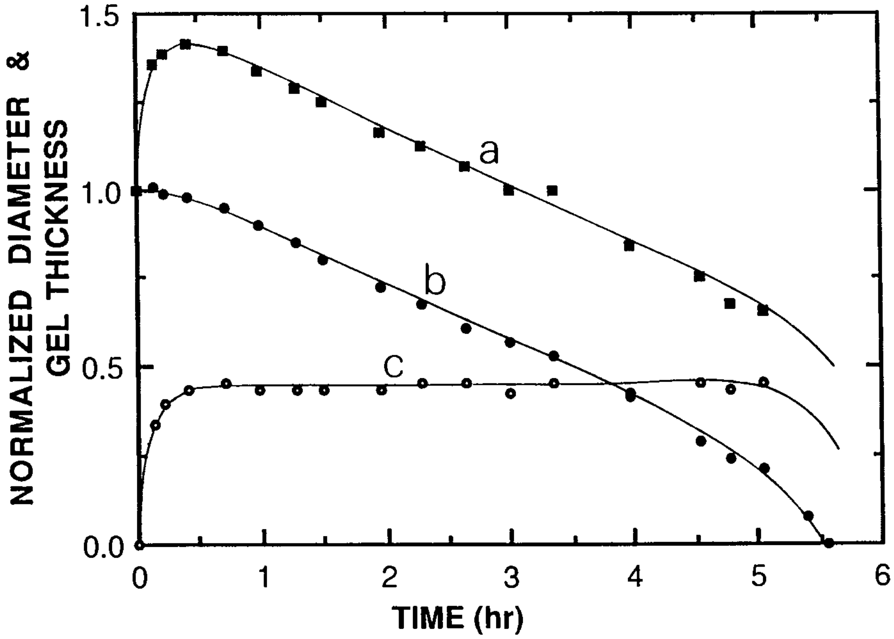

Fig. 3. Dynamic swelling/dissolution behavior during the release of [D-Trp^2-D-Phe^5]GHRP from erodible PMMA/MAA beads in 0.2 M phosphate buffer (pH 7.4) at 37°C. (a) Dissolution front; (b) swelling front; (c) gel thickness.

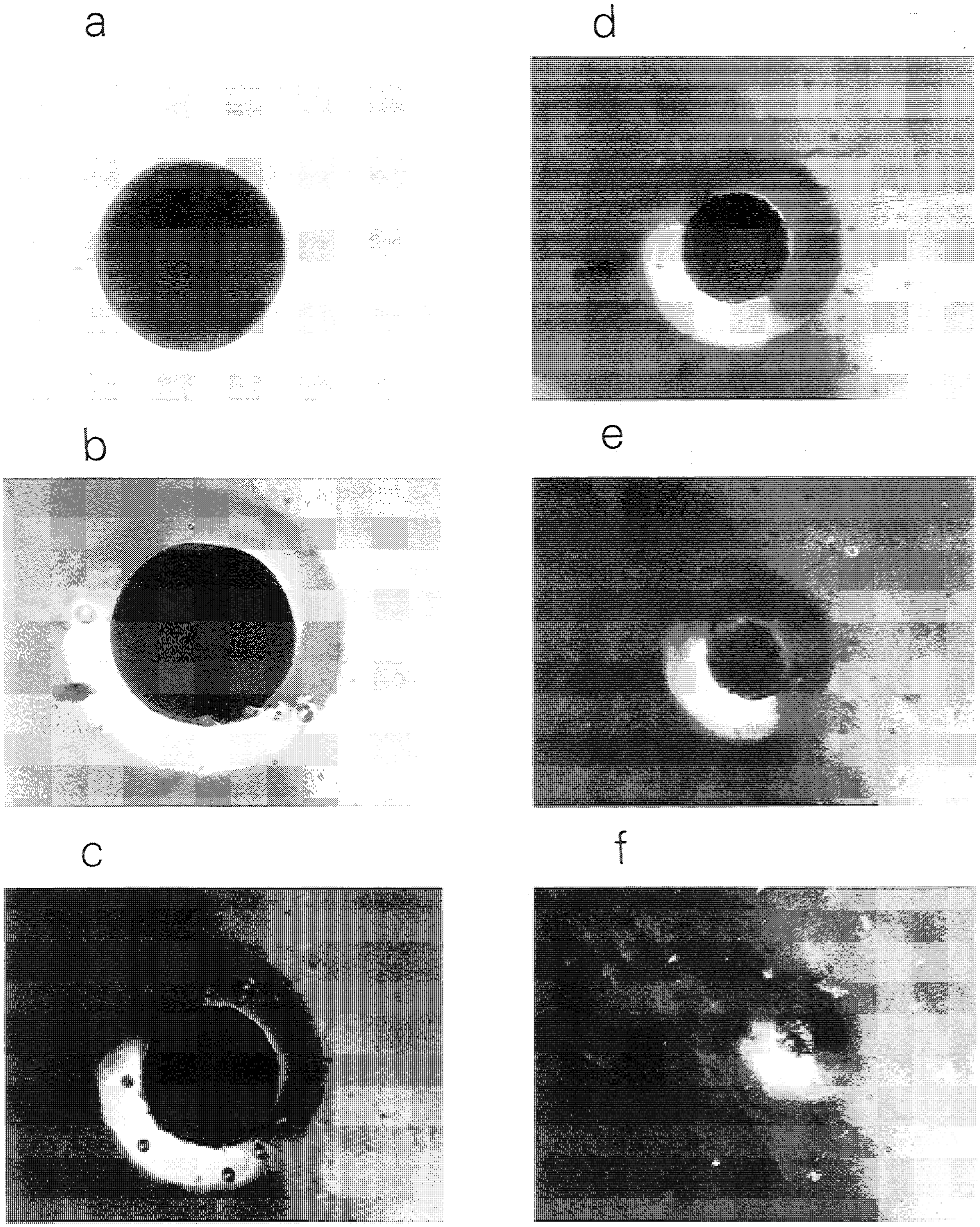

Fig. 4. Photomicrographs showing the swelling/dissolution kinetics corresponding to the system in Fig. 3: (a) 0 hr; (b) 0.5 hr; (c) 2 hr; (d) 3 hr; (e) 4 hr; (f) 5 hr.

shown in Fig. 3 is the time course of the corresponding thickness variations of the swollen gel layer. It is clear that the initial gel thickness increases as a result of ionization and swelling of the glassy PMMA/MAA. This is followed by an extended period of constant gel thickness due to the onset of polymer dissolution and the synchronization of the movement of swelling and dissolution fronts (6). Although such synchronization of fronts was originally predicted and observed in slab geometry (6,7), it becomes evident from this study that similar behavior also exists in spherical erodible samples. In the final stage of the erosion process, the glassy core disappears and the gel layer thickness decreases sharply with time. In fact, the swollen gel phase was observed to become completely disintegrated soon after the completion of swelling front penetration. The fact that the peptide release almost ends before the disintegration of the remaining gel suggests the existence of some diffusional contribution to the overall erosion-controlled release process. However, such diffusional contribution does not seem to be significant for the present peptide because of the slower diffusion rate corresponding to its molecular weight (MW 770).

Results of transient dynamic swelling/dissolution during peptide release similar to that shown in Figs. 3 and 4 have also been obtained at lower buffer concentrations. Other than the magnitude of the constant gel layer thickness and the onset and duration of front synchronization, their kinetic behavior remains identical to that described above. Table I summarizes the key features of the erosion behavior of PMMA/MAA beads during the peptide release as a function of buffer concentrations. The onset time and duration for front synchronization become longer at lower buffer concentrations. These are a result primarily of the slower polymer ionization, which diminishes the rates of polymer swelling and dissolution, due to the more effective Donnan exclusion at lower buffer concentrations. As a result, the corresponding peptide release is slower and the release duration longer at lower buffer concentrations. This trend is certainly consistent with that shown in Fig. 2. The observed increases in the constant gel thickness at lower buffer concentrations are attributed to the increase in ion osmotic pressure difference between the gel and the solution as a result of decreasing the solution osmotic pressure at lower buffer concentrations.

CONCLUSIONS

We have characterized the complete time course of swelling/dissolution during the release of a model growth hormone releasing peptide from erodible, non-cross-linked PMMA/MAA beads. The present polymer is similar in composition to the enteric polymer Eudragit L, except that our polymer has a weight averaged molecular weight about seven times larger. Although the swelling front penetration behaves similarly to that observed for cross-linked, nonerodible PMMA/MAA beads, the diameter of the eroding bead exhibits a brief initial rise followed by an extended linear decline due to establishment of the polymer dissolution process. This is consistent with the general kinetic scheme predicted for the dissolution of glassy polymers originally predicted for the slab geometry. In all cases, the continuous gel swelling develops into an extended period of constant gel thickness as a result of the synchronization of movement of the swelling and dissolution fronts. The onset and duration of such front synchronization as well as the resulting gel layer thickness exhibit an increase with decreasing buffer concentrations. Here, a synchronization of swelling and dissolution fronts has been documented for the first time in a spherical sample. Although such synchronization of fronts does not result in a constant rate of peptide release due to the spherical geometry, some non-Fickian release characteristics are evident. The slowness of the swelling and dissolution of the present erodible PMMA/MAA beads at the physiological pH and ionic strength have resulted in a prolonged release period, which can be adjusted to suit various potential drug delivery applications. One obvious approach to adjust the release period is to employ a bead size different from the present average diameter of 1 mm; smaller for shorter, and larger for longer, release periods.

Table I. Effect of Buffer Concentration on Front Synchronization Behavior in Erodible PMMA/MAA Beads During Peptide Release

Buffer concentration (M)[a]	Time to front synchronization (hr)	Normalized gel thickness	Duration of front synchronization (hr)
0.2	0.5	0.45	5
0.1	1.0	0.62	11
0.05	4.5	1.25	24

[a] Sorensen phosphate buffer (pH 7.4).

ACKNOWLEDGMENTS

This work was supported by Grant DG-377 from the Medical Research Council of Canada. The technical assistance of C.-J. Kim is also acknowledged.

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