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RESEARCH PAPER

Preparation and Release of Ibuprofen from Polyacrylamide Gels

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ABSTRACT

The conditions of preparation of polyacrylamide (polyAC) gels, the incorporation of ibuprofen (IB), and the kinetics of IB release under various conditions have been evaluated. Transparent, opaque, or elastic gels were prepared depending on the concentration of acrylamide (AC) and the cross-linking agent, N,N′*-methylenebisacrylamide (BIS). Release studies in media below pH 5.0 resulted in opaque gels. The kinetics of IB release was a function of the AC, BIS, and the pH of the medium, but the optimum composition, in terms of gel integrity and release characteristics, was 7% AC cross-linked with BIS at a 50:1 ratio. Modulation of the release rate was possible with the incorporation of 10% of certain polymers. The amount of IB that could be incorporated per gram of transparent gel was a function of the amount of polymer initiator* N,N,N′,N′*-tetramethylene diamine (TEMED) used per gram of gel. More than 200 mg of IB could be incorporated per gram of transparent gel by using 100 μl of TEMED. The release of IB obeyed matrix/swelling-controlled kinetics and 70–80% of the IB was released from gels containing 10 to 40 mg IB per gram of gel in 5 hr at pH 7.4 and 37°C.*

INTRODUCTION

Polymer formulated drug delivery systems are becoming important approaches to the improved therapeutic administration of drugs because of the possibilities of attaining controlled rates of delivery for extended time periods (1). Anti-inflammatory drugs, such as ibuprofen (IB), could benefit from controlled-release and sustained-release modalities because of their rapid elimination kinetics (2), particularly for the treatment of arthritic con-

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ditions. In this regard, bioerodible polymers would be advantageous at implant sites. Localized delivery of therapeutic agents useful for adjuncts to surgery, delivery of polypeptides, and very-long-term delivery of contraceptives are some additional benefits to be derived (3).

Polyacrylamide (polyAC) gels have received considerable attention as bioerodible polymers (4). However, in the range of the monomer acrylamide (AC) concentration commonly used, significant erosion of the gel does not occur. Only gels containing less than 1% *N*,*N*′-methylenebisacrylamide (BIS) as cross-linking agent are reported to degrade significantly (5). Nevertheless, sustained delivery of enzymes, proteins, and drugs from polyAC gels have been described (6–10). Others have observed that the effectiveness of these therapeutic gels was dependent on the solubility and loading of the active ingredient and the porosity of the gel (related to the AC and BIS concentration) (5,8,9).

PolyAC gel is chemically inert and nontoxic (11–13) and does not itself induce any immune reaction in the rabbit (11). The gel implants did not cause any overt pathological changes in hamsters either in the area of implants or in the organs removed at autopsy (8). Gin et al. (14) studied the biocompatability of implanted polyAC microcapsules in the peritoneal cavity of rats. After 20 weeks, they found that the microcapsules remained isolated and free in the peritoneal cavity. The microcapsules did not enhance inflammatory responses as determined by in vitro chemiluminescence and interleukin-1 level. The low gel/water interfacial tension minimizes protein adsorption and cellular adhesion and proliferation. This was further proved by the fact that, in vitro, the surface of the polyAC gel is a poor support for attachment and growth of human fibroblast (14).

In the present study, the conditions for the preparation of polyAC gels of low AC content are described. The IB was incorporated into these cylindrical gels, and its release characteristics were evaluated under various conditions of loading and pH at 37°C.

MATERIALS AND METHODS

The AC, BIS, ammonium persulfate (AP), and *N*,*N*,*N*′,*N*′-tetramethylene diamine (TEMED) were obtained from Sigma Chemical Company (St. Louis, MO). The IB powder was a gift from Upjohn Company (Don Mills, Ontario, Canada). All other reagents were analytical grade.

Preparation of the Gels

Stock solutions of AC, BIS, and AP were prepared in distilled water. Calculations were done to give 1 g equivalent of the gel (excluding the weight of IB). The required amount of IB was weighed into a glass vial (4.5 cm × 1.3 cm id) and dissolved in 20 μl of TEMED (unless mentioned). Aliquots of the stock solutions of AC and BIS, along with the required amount of water, were added, and the solution was thoroughly mixed. Ammonium persulfate solution (200 μl, 2%) was then added and mixed; after 10–15 min standing at room temperature, gel formation was complete. When polymers were added, an equivalent weight of water in the gel was replaced. In separate experiments, the effect of TEMED concentration on the amount of IB that could be incorporated in the polyAC gels was determined.

Swelling Studies

PolyAC gels (7% AC and AC:BIS 50:1 weight ratio) containing 30 mg of IB were used to determine the changes in weight and volume after soaking them at 37°C in 100 ml of buffers (pH 7.4 and pH 2.0). The weight, diameter, and height of the gels were measured for up to 21 days. The volume of the gel was calculated as ($\pi r^2 h$, where r is the radius and h is the height of the gel cylinder.

Drug Release Studies

Release studies were carried out on the freshly prepared gels containing IB using the USP dissolution test apparatus (Type I) operated at 100 rpm and 37°C in 900 ml Sorrensen's phosphate buffer solution at pH 7.4. Studies also were made at pH 2.0 (Clark and Lubs's KCl/HCl) and pH 9.0 (Sorrensen's sodium borate/HCl). Drug release behavior of polyAC gels containing various polymers was also investigated. At various time intervals, 100 μl of the release medium were withdrawn for high-performance liquid chromatographic (HPLC) analysis. Equal volumes (20 μl) of release medium and flurbiprofen solution (5 μg/ml as internal standard) were combined, and the mixed solution was injected into a 20-μl loop of a Rheodyne injector connected to a Waters model 501 solvent delivery system. Chromatographic separation was carried out on a Novapak C_{18} reverse-phase column (15 cm, 5 μm) and a mobile phase of water:acetonitrile:acetic acid:triethylamine (55:45:0.1:0.02) was pumped at 1.5 ml/min. Solute concentrations were determined

Table 1

Characteristics of PolyAC Gels

AC Concentration (% w/w)	BIS Concentration (% w/w)	AC:BIS (Weight Ratio)	Appearance
1.5	0.05	30:1	Clear liquid
3.0	0.10	30:1	Viscous liquid
4.0	0.50	8:1	Opaque
6.0	0.20	30:1	Transparent, thin jelly
7.0	0.17	40:1	Transparent
7.0	0.14	50:1	Transparent
8.0	0.20	40:1	Transparent
8.0	2.00	4:1	Opaque
9.0	0.22	40:1	Transparent
9.0	0.18	50:1	Transparent

from spectrophotometric detection at 230 nm (Waters model 481 UV detector).

RESULTS

Gel Characteristics

PolyAC gels prepared at different AC concentrations and AC:BIS weight ratios are described in Table 1. Both conditions are seen to influence the appearance of the gels, with the AC concentration having the strongest influence on the apparent consistency, and the AC:BIS ratio having the greatest effect on the clarity of the gels. For instance, at an AC:BIS 30:1 weight ratio, compositions containing AC concentrations from 1.5% to 6% w/w were clear, viscous liquids, whereas at an AC:BIS 40:1 or 50:1 ratio, transparent gels formed over the range 7% to 9%% AC. In comparison, at AC:BIS 4:1 ratios, the gels were opaque. Transparent gels formed within 10–15 min, whereas the opaque gels formed within 3 min. Although an opaque liquid resulted at an AC:BIS 8:1 weight ratio and 4% w/w AC concentration, a gel could be formed by storing it at 4°C for 12 hr.

The Effect of Ibuprofen Incorporation on the Gels

Gels selected for this study had an AC:BIS 50:1 weight ratio and contained 7% AC. Initially, 20 μl of TEMED was used as an initiator for formation of the gels. Gels containing 30 mg of IB per gram of gel were transparent. Gels containing more than 35 mg of IB were opaque, but when 50 mg IB were incorporated, the gel consistency was thin. A slow rate of dissolution of 50 mg of IB in 20 μl of TEMED may have contributed to this result. Increasing the amount of TEMED dissolved the IB more rapidly, resulting in the immediate formation of transparent gels. Table 2 presents the results of the concentration-dependent study of TEMED on the incorporation of IB into 7% AC gels with an AC:BIS 50:1 weight ratio. It is observed that transparent gels were formed only if the weight ratio of IB:TEMED was less than 2:1. At a 2:1 weight ratio of IB and TEMED, the gels are opaque; at higher ratios (e.g., 2.5:1), the gels took a longer time to form.

Swelling Studies

All gels gained weight and increased volume after exposure to buffers at pH 2.0 and pH 7.4. Swelling was a fairly slow process that increased up to day 7; the weight of the gel increased from 1.04 ± 0.01 to 2.79 ± 0.02 g at pH 7.4. There were no significant differences between the weight gain of the gel in pH 2.0 and pH 7.4 buffers. After 7 days of soaking, some weight loss/shrinking of the gel occurred, and erosion of the gel became apparent.

Kinetics of Release of Ibuprofen from Gels

The release profiles of 10-mg-loaded IB gels as a function of AC concentration at an AC:BIS 40:1 ratio are shown in Fig. 1. Approximately 50% IB was released within 1 hr from gels containing 7% or 8% AC, and the profiles were identical; this was delayed for 2.5 hr from 9% AC gels, after which release of IB was considerably slower. However, at an AC:BIS 50:1 weight ratio of

Table 2

Effect of the Amount of TEMED on the Formation of 7% PolyAC Gel (AC:BIS 50:1) and Incorporation of IB per Gram of the Gel

IB (mg/g gel)	TEMED (μl)	IB:TEMED	Appearance
30	20	1.5:1	Transparent
35	20	1.7:1	Opaque
40	20	2:1	Opaque
50	20	2.5:1	Opaque, thin jelly
50	30	1.7:1	Transparent
75	40	1.9:1	Transparent
100	40	2.5:1	Opaque
125	50	2.5:1	Opaque
150	50	3:1	Opaque
175	60	3:1	Opaque
200	80	2.5:1	Opaque
200	100	2:1	Slightly cloudy

cross-linked gels, the rate of release of IB was almost independent of concentration of AC (Table 3). Also, the kinetics of IB released from polyAC gels were essentially independent of IB content from 10 to 40 mg IB (Fig. 2). About 80% IB was released after 5 hr.

The release of IB as a function of the pH of the dissolution medium from a gel composition of AC:BIS 50:1 with 7% AC and an initial loading of 20 mg IB is shown in Fig. 3. The percentage of IB released was plotted as a function of $t^{1/2}$ according to the Higuchi model (15) and showed linear relationships, at least at early time periods (Fig. 4).

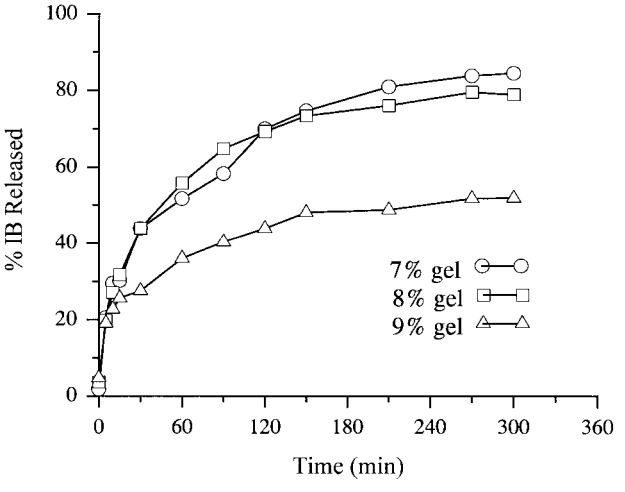

Figure 1. Effect of AC concentrations on the release of IB from polyAC gels (40:1 AC:BIS weight ratio) containing 10 mg IB per gram of gel at pH 7.4 and 37°C.

Since the gels are transparent, it is assumed that IB is dissolved in the gel, in which case the kinetics can be described by the model of $t^{1/2}$ kinetics up to about 40% released and by exponential release from 60% released, according to Baker and Lonsdale (16) for dissolved solute in a matrix cylinder system. The fraction of drug released F is given by

$$F = 4\left[\frac{Dt}{r\pi^2}\right]^{1/2} - \frac{Dt}{r^2} \quad (1)$$

at early times, and

$$F = 1 - \frac{4}{(2.405)^2}\exp\left[-\frac{(2.405)^2\, Dt}{r^2}\right] \quad (2)$$

at late times. A plot of F versus $t^{1/2}$ should be linear up to 40% released, and a plot of log F versus t should be

Table 3

Percentage Release of IB from PolyAC Gels at 10-mg Loading After 5.0 Hours at pH 7.4 and 37°C as a Function of AC Concentration and Degree of Cross-Linking

AC:BIS (Weight Ratio)	% w/w AC		
	7	8	9
40:1	83.2	79.0	51.8
50:1	89.3	84.2	83.2

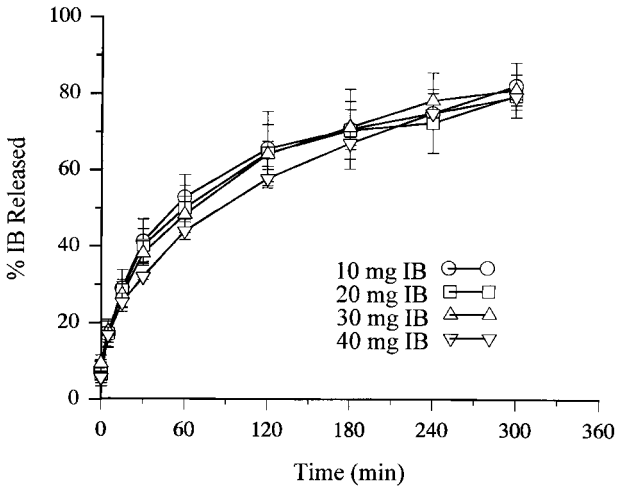

Figure 2. Effect of varying loading concentrations of IB per gram of gel on IB release from 7% polyAC gels (50:1 AC:BIS weight ratio) at pH 7.4 and 37°C.

linear above 60% released. It is apparent that the release of IB from transparent gels at pH 7.4 and 9.0 followed this pattern, but opaque gels at pH 2.0 or containing 40 mg IB exhibited different release profiles, in particular, reduced fractions of drug released during the initial period. Table 4 shows the mean slopes of release profiles fitted to the Baker and Lonsdale model (16) with their corresponding correlation coefficient at each drug loading and pH.

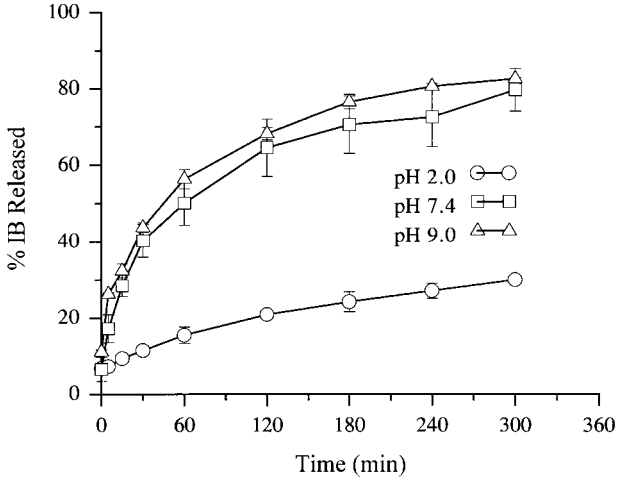

Figure 3. Effect of the pH of the dissolution medium on the release of IB from 7% polyAC gels (50:1 AC:BIS weight ratio) at 37°C and 20 mg IB per gram of gel.

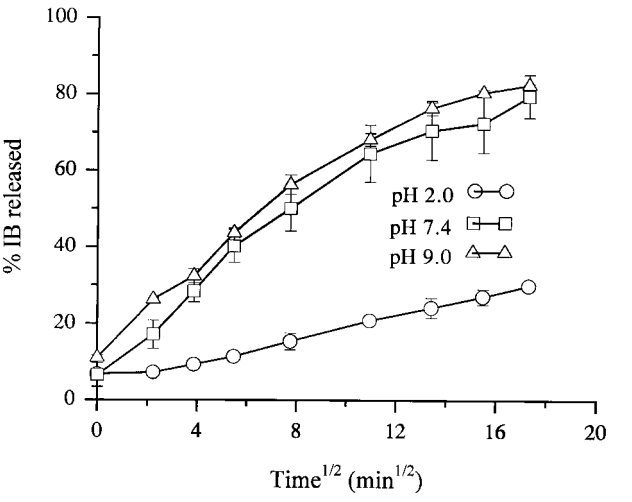

Figure 4. Release of IB from 7% polyAC gels (50:1 AC:BIS weight ratio) as a function of $t^{1/2}$ at different pHs (20 mg IB per gram of gel and at 37°C).

Incorporation of polymers such as poly(ethylene glycol) (PEG) (400, 1000, and 4000), poly(vinyl pyrrolidine) (PVP) (10,000 and 40,000), poly(vinyl alcohol) (PVA) (10,000 and 40,000), dextran (66,300), carboxy methyl cellulose (CMC), sodium alginate, pectin, and gelatin in the concentration range up to 10% of the gel did not adversely affect gel formation and consistency. The addition of 10% PVA to the polyAC gel (7%, AC:BIS 50:1) decreased the percentage release of IB from the gel after 5 hr compared to the control gel (76.7% vs. 82.8%), while addition of 10% PEG, PVP, dextran, and CMC increased the release of IB compared to the control gel (90.0%, 86.9%, 96.9%, and 90.3% vs. 82.8%, respectively). Sodium alginate, pectin, and gelatin in the same concentration had no influence on the release of IB from polyAC gel.

DISCUSSION

The formation of polyAC gels is dependent on several factors, including the concentration of AC, the AC:BIS weight ratio, and the presence of additives or solvents other than water used to prepare the gels (17). Thus, it is important to understand the physical properties of the gels and the influence of an additive such as a drug on the gel properties in considerations of polyAC gels as drug delivery systems.

The process of gel formation involves formation of a free-radical initiator of TEMED by reaction with AP.

Table 4

Comparison of IB Release Kinetics from 50:1 AC:BIS, 7% PolyAC Gels According to Baker and Lansdale Model of Early-Time and Late-Time Release

IB (mg/g of gel)	pH	Slope ± SD (% $min^{-1/2}$)	Correlation Coefficient (r)	Slope ± SD ($\times 10^3$) (min^{-1})	Correlation Coefficient (r)
10	7.4	6.11 ± 0.49	0.9932	0.54 ± 0.19	0.9744
20	7.4	5.85 ± 1.02	0.9951	0.49 ± 0.17	0.9879
30	7.4	5.22 ± 0.79	0.9920	0.58 ± 0.10	0.9842
40	7.4	4.91 ± 0.35	0.9978	0.77 ± 0.13	0.9784
20	9.0	5.78 ± 0.39	0.9963	0.46 ± 0.04	0.9544
20	2.0	1.44 ± 0.09	0.9903	—	—

Reaction between the free radical and the AC monomer occurs, producing an activated AC monomer that subsequently reacts with another AC monomer. This sequence of events continues until the monomer concentration is reduced to near zero, with the reaction product being the polyAC gel. The addition of the cross-linking agent, BIS, strengthens the gel in a manner dependent on the AC concentration and the AC:BIS ratio, as shown in Table 1.

It might be expected that the addition of substances that interfere with the polymerization process would result in a product having altered properties or, indeed, would prevent polymerization entirely. Ibuprofen is an arylpropionic acid derivative that, at alkaline pH, is ionized and water soluble. At concentrations up to 30 mg IB, the gels remained transparent, and only slight changes in gel consistencies were observed (Table 2). At 35 mg IB, the gel became opaque, although its integrity was maintained, suggesting that the solubility of IB in the gel had been exceeded. However, at 50 mg IB, the gel did not properly form; from this, it may be concluded that, at this level, IB interfered with the free-radical formation of TEMED or its reaction with AC monomer and, thus, the polymerization process. As the amount of TEMED was increased, incorporation of IB into the gel increased.

Cross-linking not only strengthened the gels, but also reduced porosity and increases tortuosity of the gel matrix (17). This resulted in reduced release of IB at an AC concentration of 9% and an AC:BIS 40:1 ratio, but not at a 50:1 ratio, suggesting that, at the higher degree of cross-linking, the porosity and tortuosity of the gel for IB diffusion reached a threshold level.

The release of IB from polyAC gels at pH 7.4 containing from 7% to 9% AC is generally characterized by an initial fast-release phase for about 1 hr, followed by a slower-release phase for up to 5 hr (Fig. 1). A change in drug loading from 10 mg to 30 mg of IB per gram of gel had only a small effect on the dissolution profiles (Fig. 2 and Table 4). Formulations containing 10 to 30 mg IB were transparent, whereas the gel containing 40 mg was opaque, and the kinetic behavior was somewhat different. The initial release rate of IB from gels containing 40 mg of IB was slower compared to that of gels containing 10 to 30 mg of IB.

Transparent gels of IB followed the release kinetics of diffusion-controlled monolithic devices with dissolved drug. In this system, the release occurs according to a $t^{1/2}$ law for about the first half of the device life, and then the release rate falls exponentially. For monolithic devices with a large amount of excess dispersed drug, the release follows the $t^{1/2}$ law essentially throughout the life of the device (16). At a pH of 7.4 or 9.0, IB is ionized (pK_a 4.5) and possesses a substantial water solubility of 34.2 mM at pH 7.4 (18). Therefore, the release of IB is efficient and similar at these two pH (Figs. 3 and 4 and Table 4). On the other hand, at pH 2.0, the solubility of IB is 0.043 mM (18) and is suspended rather than being dissolved in the gel matrix, resulting in a much slower and gradual release over the 5-hr period. In this case, release of drug is preceded by a dissolution process that causes less IB in the medium, but for a longer period of time. All transparent gels containing IB in release media at a pH less than 5.0 became opaque, whereas blank gels remained transparent.

In comparison to other means of administration of IB, such as the tablet for oral delivery, the polyAC gels described here offer a means of delivering drugs that are released slowly over a prolonged time period. The percentages of AC and BIS in the gel are dependent on the intended use of the gel. If the gel is designed to deliver its active ingredient(s) for a relatively long period of time, its porosity may be reduced by utilizing a high concentration of AC. Davis et al. prepared polyAC gels with

25% and 40% AC and 2% BIS for releasing insulin in rats for 21 days (7); the gels were only very slowly bioerodible. Furthermore, the polyAC gels may be formed in a variety of shapes and sizes for convenient administration. At the levels of AC and the cross-linking agent BIS used in this study, complete biodegradability can be expected within a reasonable period of time. However, even under these conditions, it would appear that the gel dosage forms could be exhausted of IB before any significant erosion has taken place. This implies that the release kinetics are not necessarily complicated by changes in the surface area of the dosage form during the release period; therefore, the dosage form is more predictable in its behavior. This aspect of development could facilitate regulatory approval.

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