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SWELLING AND RELEASE CHARACTERISTICS OF POLY(SULFOPROPYL METHACRYLATE POTASSIUM-*co*-HYDROXYETHYL METHACRYLATE) GELS

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ABSTRACT

A new polyelectrolyte gel consisting of sulfopropyl methacrylate potassium and 2-hydroxyethyl methacrylate has been synthesized and characterized in terms of swelling and drug release. The swelling of the drug-free gel is influenced by the salt concentration, ranging from a swelling ratio of 44.0 in the absence of NaCl to 3.6 in 2 M NaCl. The degree of swelling does not fluctuate significantly in a variation of swelling ratios from 23.4 to 26.4 with the pH of the swelling medium ranging from 3.0 to 9.8 in 0.01 M NaCl. Even at pH 1.2 the swelling ratio is 10.7 in 0.01 M NaCl. The release of oxprenolol HCl and diphenhydramine HCl, highly water-soluble drugs, are independent of both buffer concentration (0.01 to 0.1 M) and the pH (1.4 to 7.4) of the dissolution medium. However, the release of less water-soluble drugs, such as propranolol HCl and labetalol HCl, slows down as the pH decreases.

INTRODUCTION

Ionic polymeric materials, crosslinked or noncrosslinked, have been extensively investigated for enteric coating [1], ion-exchange processes [2], drug delivery systems [3], and artificial arms [4]. Drug delivery systems using ionic polymers are

one of the oldest processes: ion-exchange resins were used to sustain the release of drugs [5]. Commercially available cationic exchange resins are highly crosslinked sulfonated polystyrene or crosslinked methacrylic acid. Ion-exchange resins may be classified morphologically as gel and microporous. Drug release from microporous ion-exchange resins takes place very fast in the porous space of the resins as soon as the drug molecules bounded in the resins are dissociated. In addition, highly crosslinked gel-type resins (negligible swelling) significantly retard the diffusion of drug in the gel matrix, which yields an unfavorable release kinetics with a tailing. To modify the release kinetics from ion-exchange resins, several methods have been developed, such as coacervation [6] and interfacial polymerization, for encapsulation [7].

Recently, swellable polyelectrolyte gel matrices have been extensively investigated for drug delivery systems. By varying the ionic pendant groups carrying monomer composition and the degree of crosslinking of the polymer chains, the degree of swelling of charged polyelectrolytes may be tailored. In recent reports [8–11], cationic hydrophobic polymers containing tertiary amine groups and anionic hydrophobic gels containing methacrylic acid groups have been investigated for the release of drugs. The release of drug from both cationic and anionic polymer gels deviated from the Fickian diffusion principle and showed a quasi-linear or zero-order rate. Those studies indicated that drug release from the ionizable polymer matrix was governed by protonation or ionization of pendant groups in the polymer chain.

However, due to the swelling characteristics of charged polymers containing tertiary amine or carboxylic acid pendant groups, these ionic gels may not be suitable to be employed as oral drug delivery systems in which the pH condition changes as the dosage forms travel along the gastrointestinal tract. Methacrylic-acid-based hydrophobic gels have a minimal swelling below pH 6.0 due to the un-ionization of pendant groups at this pH. Even though acrylic-acid-based gels exhibit high swelling and reasonable release characteristics [12, 13] in a weak acid, the release of drugs from these matrices is severely retarded by the gastric fluid with negligible swelling. On the other hand, the polyelectrolyte gel matrix possessing sulfonate groups showed that the degree of swelling was not influenced by the pH condition of the swelling medium [14].

In this paper the synthesis of a highly swellable polyelectrolyte gel consisting of sulfopropyl methacrylate potassium (SPMK) and 2-hydroxyethyl methacrylate (HEMA), its swelling characteristics, and its drug release kinetics are presented.

EXPERIMENTAL

Synthesis of SPMK/HEMA Polymer

Polymer gels were prepared by free-radical polymerization of sulfopropyl methacrylate potassium salt (Polysciences) (SPMK) (17.4 wt%) and 2-hydroxyethyl methacrylate (99.5% optical grade, Polysciences) (HEMA) (82.6 wt%) in water which was 11.9 wt% of the total solution. An additional crosslinking agent (ethylene glycol dimethacrylate) was not used except for a small quantity present in the HEMA monomer. The mixture of monomers with the initiator (tertiary butyl peroctoate) (Elf Atochem N.A.) was degassed by nitrogen bubbling for 1 hour followed

by in vacuo for 10 minutes. The mixture was discharged into a glass ampule (11 mm i.d.) and sealed with a cork stopper. The polymerization was carried out in an oil bath at 70°C for 5 hours. The glass ampule was broken and a polymer rod was sliced by a glass-cutting machine knife. The polymer disks were equilibrated in water for several days with frequent water replacement to remove residuals left after polymerization. Swollen PSPMK/HEMA gels were cut by a cork borer (size 9) before being dried. Dried polymer disks were approximately 1.4 mm thick and 4 cm in diameter. Conversion was determined gravimetrically, and polymer composition was determined by converting potassium sulfonate into its sulfonic acid form by adding HCl and then backtitrating with 0.2 M NaOH.

Swelling and Drug Release Studies

For equilibrium swelling, the dried polymer disks were immersed in 0.01 M NaCl solutions of various pHs and in various NaCl concentrations for 24 hours at 37°C. The polymer disks were removed from the solution, and the weight gain was determined after blotting the surface water with a Kimwipe. The swelling of polyelectrolyte gels is expressed by

$$\text{Swelling ratio, } Q = \text{g of swollen polymer gel/g of dry polymer gel}$$

For the drug release experiments, the dried polymer disks were equilibrated with approximately 3% aqueous solutions of each drug for 3 days before being dried in vacuo for 2 days. The release kinetics from dry drug-loaded disks were carried out at 37°C in phosphate buffers and a simulated gastric fluid (pH 1.4, 0.46 M NaCl) in a jacketed tempering beaker (250 mL) thermostated with a water circulator by vigorous magnetic stirring. Drug release was monitored for oxprenolol HCl, diphenhydramine HCl, propranolol HCl, and labetalol HCl on a HP 8451A diode-array spectrophotometer at 272, 222, 272, and 244 nm, respectively.

RESULTS AND DISCUSSION

Sulfoalkyl- or sulfoxyalkyl-methacrylate copolymers have been investigated as new biomaterials for medical purposes, especially the development of blood-compatible polymer surfaces [15, 16]. To our knowledge, these polymers have not been evaluated for controlled drug release systems. The conversion of copolymerization was 95.3% with 13.1 wt% of SPMK in the polymer chain. The resulting polymers were highly swellable and disintegrated, which are of no value for drug delivery systems due to the surface stress instability when the SPMK composition is higher than 13.1 wt%.

Equilibrium swelling of PSPMK/HEMA gels in different pHs ranging from 1.2 to 9.8 in 0.01 M NaCl is shown in Fig. 1(A). The disk gels swell even at very low pH due to the low pK_a of sulfonic acid compared to carboxylic acid groups (pK_a 4–6) in the polymer chain [5]. The swelling ratio varies from 10.7 to 26.4 g swollen polymer/g dry polymer. Researchers [15] have prepared a copolymer of HEMA and sulfohexyl methacrylate sodium (PHEMA/SHMNa) and reported a swelling ratio of 18 in water. Our polymer is more loosely crosslinked as compared to PHEMA/SHMNa. However, in pHs higher than 3.0, the degree of swelling be-

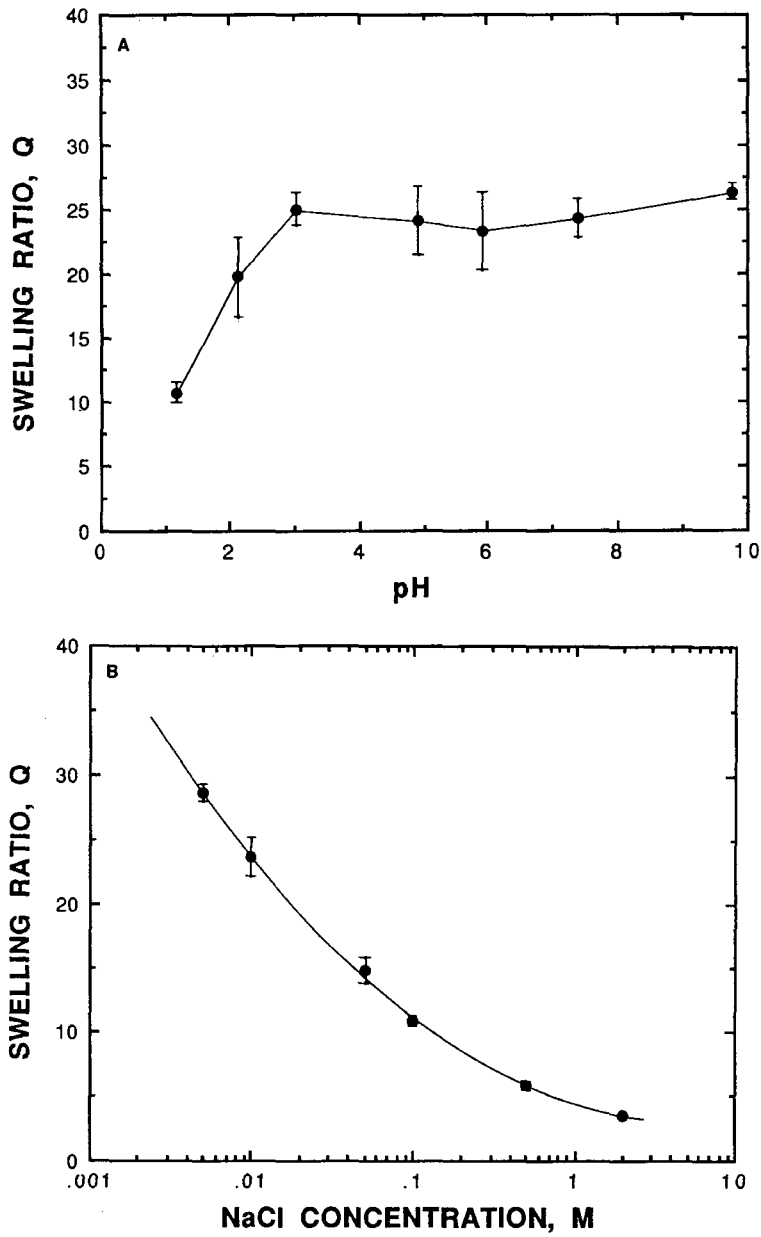

FIG. 1. Swelling of PSPMK/HEMA gels: pH (A) and NaCl (B).

comes relatively constant with an average Q of 24.7 (23.4–26.4). This lack of sensitivity of PSPMK/HEMA gels to the pH of the surrounding medium indicates that the PSPMK/HEMA gel is a good candidate for oral drug carriers, because the pH varies along with the gastrointestinal tract (being acidic in stomach to weak basic in the intestine). The effect of an electrolyte concentration on equilibrium swelling of

PSPMK/HEMA is shown in Fig. 1(B). Upon addition of sodium chloride, the equilibrium swelling is depressed from a Q of 44.0 in the absence of NaCl (not shown in Fig. 1B) to 3.6 in 2 M NaCl due to the smaller osmotic pressure difference between the internal and external gel and less expansion of a charged coil [17]. The extent of swelling (Q = 23.7) in 0.01 M NaCl is comparable to the degree of swelling observed in the different pH levels in 0.01 M NaCl. During the time course of swelling, the disk samples present a surface-driven instability as has been reported for other synthetic polymers [18, 19].

During the drug-loading process, drugs (secondary amine HCl's) diffuse into the polyelectrolyte gels to form a drug/polymer complex. When fully swollen disk gels are discharged into an aqueous drug-loading solution, the swollen gels start to shrink because the drug complex chain formed is less swellable. The complex surface formed is distorted or cracked due to the instability of the surface of the complex chain formed, which was not observed in other moderately swellable ionic hydrogels [11]. In order to avoid the breaking/cracking of disk gels by surface instability, dry disk gels are used to load drugs. Upon contact with an aqueous drug solution, dry gels start to swell and drugs diffuse in slowly, with a white drug/polymer complex forming a moving boundary behind which a clear gel layer is left.

The effect of buffer concentration on the release of oxprenolol HCl from PSPMK/HEMA is presented in Fig. 2. Release data are normalized with respect to the thickness of the disk (1.4 mm). The release of highly water-soluble drug (oxprenolol HCl, solubility in water = 77%) is not affected by the buffer concentrations (0.01 to 0.1 M) used in this study. We observed the same insensitivity to buffer concentration on drug release from carboxylate-based polyelectrolyte gels [13, 20]. Unlike

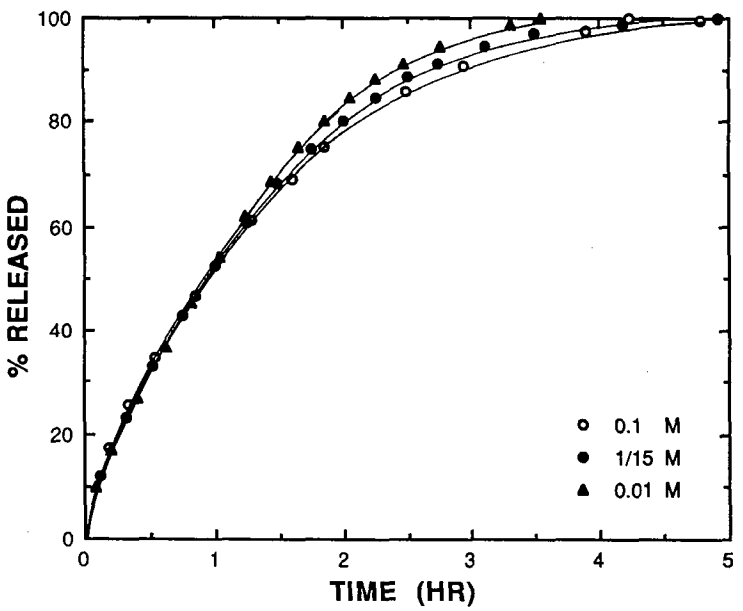

FIG. 2. Effect of buffer concentration on the release of oxprenolol HCl from PSPMK/HEMA gels at pH 7.4.

carboxylate-based gels, however, the release of drug is not influenced by the pH variation of the dissolution medium, as illustrated in Figs. 3(A) and 3(B) for oxprenolol HCl and diphenhydramine HCl (solubility in water = ~50%), respectively. Even at pH 1.4, drug release maintains the same kinetics without retardation. On the other

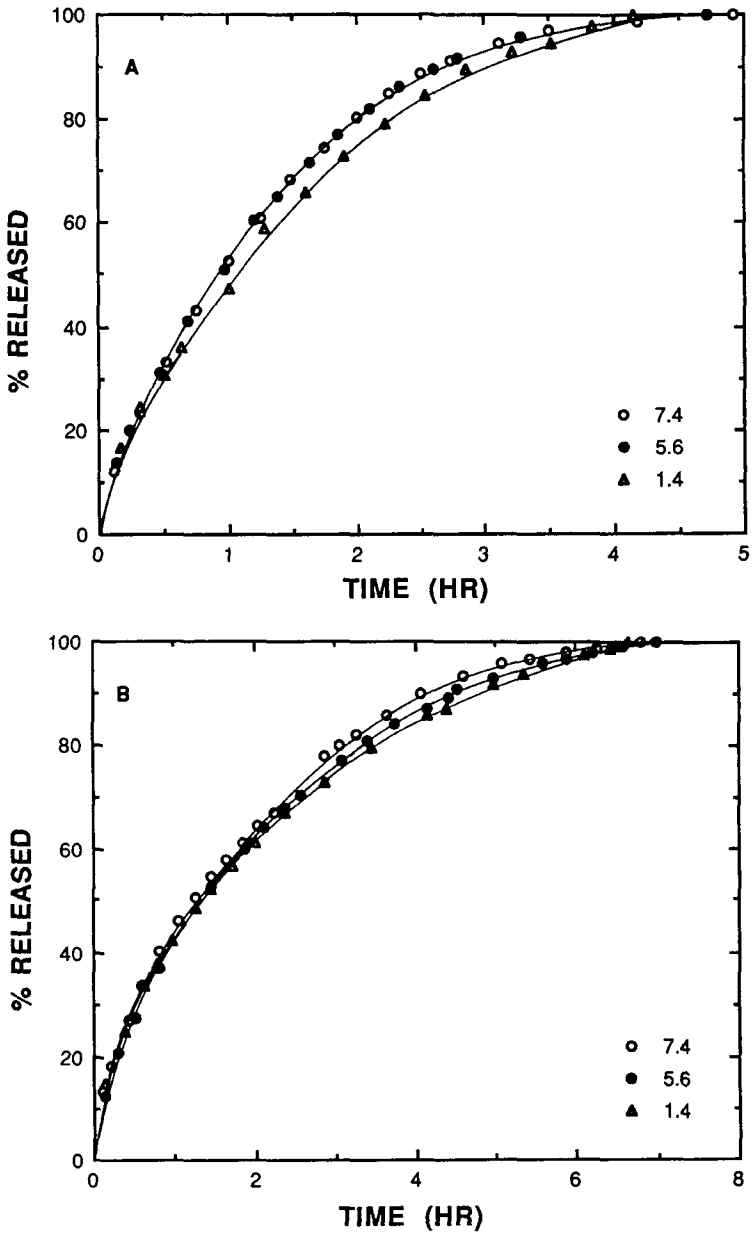

FIG. 3. Effect of pH on the release of drug from PSPMK/HEMA gels in 1/15 M buffer concentration: oxprenolol HCl (A) and diphenhydramine HCl (B).

hand, no drug release occurred in the acidic condition for PMMA/MANa gel beads [20]. At a low pH, the degree of swelling is depressed significantly compared with that at weak and neutral pHs, but it still allows enough swelling for the drug to diffuse

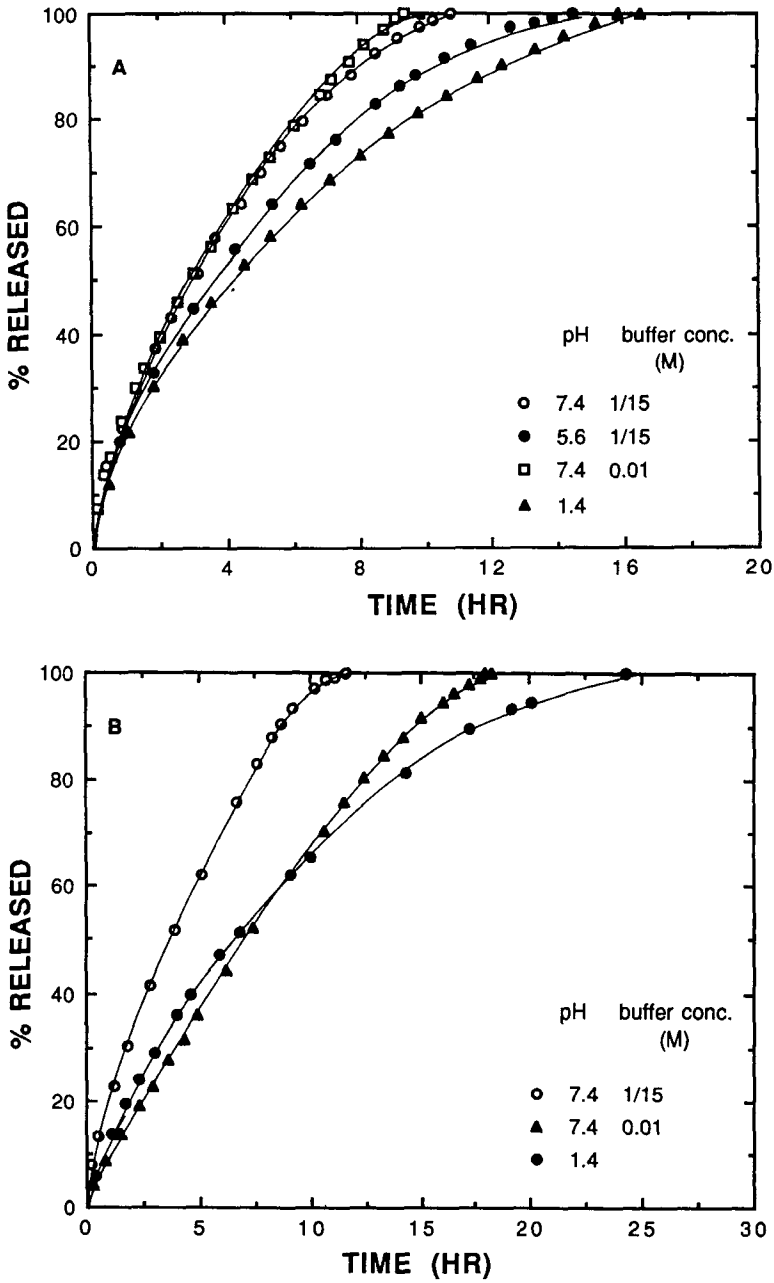

FIG. 4. Effect of pH and buffer concentration on the release from PSPMK/HEMA gels: propranolol HCl (A) and labetalol HCl (B).

out of the matrix. Until now, cation-exchange resins (sulfonated polystyrene) with minimal swelling have been used for sustained release dosage forms. Since the PSPMK/HEMA gel's drug release is characteristically less dependent on the pH of the dissolution medium, it is promising for oral drug delivery systems.

On the other hand, as drug solubility decreases, the drug release from PSPMK/HEMA gels starts to deviate from that observed with highly soluble drugs. As shown in Figs. 4(A) and 4(B) for propranolol HCl (water solubility = ~5%) and labetalol HCl (water solubility = ~1.5%), respectively, drug release behavior changes when the pH of the dissolution medium changes to weak acidic and acidic conditions. Release of propranolol HCl, presented in Fig. 4(A), is not affected by the buffer concentration ranging from 0.01 to 1/15 M as observed in Fig. 2 for highly water-soluble drugs (oxprenolol HCl). However, release of labetalol HCl is retarded significantly as the buffer concentrations decrease from 1/15 to 0.01 M. This retardation of the release of labetalol HCl in 0.01 M buffer was also reported earlier for poly(methyl methacrylate-*co*-potassium acrylate) beads [12, 13]. This suggests that at lower buffer concentrations the dissociation of the drug/polyelectrolyte complex occurs at a fractional order of the dissociation reaction of other drugs used in this study [12, 13]. We would like to point out, however, that compared with the release of labetalol HCl from PMMA/A-K beads [13], drug release kinetics from PSPMK/HEMA disk gels is less favorable for linear release than from PMMA/A-K beads. Even though spherical geometry has a disadvantage in exhibiting declining surface area as release time proceeds, PMMA/A-K beads present a more linear release rate than PSPMK/HEMA disk gels. The total release time is increased with a decrease in drug solubility, as expected.

In the time course of drug release, a phenomenon opposite to the drug loading process takes place in the drug-loaded disk gels while releasing drugs. Upon contact with the buffer solution, the drug/polymer complex is dissociated by counterions and drug is liberated. However, the surface of the drug-free gel layer is formed with numerous line curved segments (surface instability) as mentioned in the swelling of drug-free PSPMK/HEMA gels. Upon more drug release, this phenomenon grows and finally disappears. The initial disk shape changes slowly to a dumbbell shape, which changes back to a disk shape close to the end of drug release. The drug/polyelectrolyte complex dissociating front moves slowly toward the center of the gel. This moving front is distinctive as drug solubility in water decreases.

This study shows that the high swelling of polyelectrolyte gels consisting of sulfonate functional groups may be beneficial for drug release kinetics because one can obtain the complete release (exhaustion) of drug with less pH dependence. On the contrary, conventional cationic-exchange resins containing sulfonate groups, highly crosslinked and with minimal swelling, exhibit a tailing behavior toward complete release due to the slow diffusion of the drug through a tight gel matrix [3].

CONCLUSIONS

We have synthesized and characterized poly(sulfopropyl methacrylate potassium-*co*-hydroxyethyl methacrylate) in terms of the effects of pH and salt concentration on the equilibrium swelling of drug-free gels, and buffer concentration and pH on drug release in drug-loaded gels. The equilibrium swelling is not affected by the

pH of the swelling medium above pH 3.0, whereas the degree of swelling decreases as the salt concentration increases due to less expansion of the charged coil and less osmotic pressure difference between the internal and external gel. Generally speaking, drug release for highly water-soluble drugs (oxprenolol HCl and diphenhydramine HCl) is independent of the buffer concentration and the pH of the dissolution medium. Surprisingly, even at a low pH (1.4), drug release retains the same kinetics as that at other pH conditions, suggesting that highly swellable and sulfonate-containing polymer such as PSPMK/HEMA may be good candidates for oral drug delivery systems. However, as drug solubility in water (propranolol HCl and labetalol HCl) decreases, drug release slows down as pH decreases to weak acid (5.6) or acidic conditions (1.4). At a low buffer concentration (0.01 M), release kinetics of labetalol HCl (very low solubility) are more linear, as we reported for the release of labetalol HCl from poly(methyl methacrylate-*co*-potassium acrylate) beads [13].

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