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Release characteristics of lidocaine from local implant of polyanionic and polycationic hydrogels

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Abstract

In this study, the release characteristics of lidocaine conveyed in base (LB) and salt (LS) forms from an anionic hydrogel composed of carbopol and a cationic hydrogel composed of chitosans were examined for optimizing hydrogel formulation as a sponge filler to stop the bleeding and as a carrier for delivering lidocaine to relief pain after a tooth extraction. A Franz cell was used to simulate the in vivo environment and evaluate the drug release kinetics. It was confirmed that the release profiles of LB and LS from both the carbopol and chitosan hydrogels were best described by the Higuchi model, and values of the release rate constant (K) calculated from the slope of the linear portion of the plot were compared. Results demonstrated that the K value increased with increasing LB concentration at the same three carbopol levels of the hydrogels, whereas it increased with a decreasing level of carbopol for the same concentration of LB in the hydrogels. A minimum in the value of K was observed near neutral pH, which was attributed to two influencing factors of the viscosity and the complexing effect of carbopol gel. However, K values at the same concentration of lidocaine were larger for those formulations using the salt form compared to those using the base form. Results further revealed that the K value increased with an increasing amount of LB added to chitosan hydrogels with the same 0.5% concentration of C1000 (Chitosan, viscosity 1000 cps). K values increased with a decreasing MW of chitosan at the same level in the same concentration of an acetic acid solution with the same amount of LB added. K values for the release from chitosan hydrogels prepared at a lower level were lower than those of hydrogels prepared at a higher level. However, similarities in the release profiles between LB and LS were observed. In conclusion, the viscosity of the gel matrix and the ionic complexing effect between the anionic acid groups of hydrogels and basic groups with lidocaine were two main factors influencing regulation of the diffusion coefficient for controlling drug release.

Keywords: Lidocaine; Carbopol; Chitosan; Release characteristics; Hydrogel

1. Introduction

Hydrogels are very versatile materials and have attracted significant attention recently as drug delivery systems [1,2]. In addition to their inertness and good compatibility, the ability of hydrogels to release an entrapped drug in an aqueous medium and the ease of regulating such drug release make hydrogels particularly suitable as drug carriers for the controlled release of pharmaceuticals [3]. For many years, hydrogels have been engineered to control the release of low-molecular weight (MW) drugs as well as large molecules such as proteins that had not been considered feasible candidates because they were too large to slowly diffuse through most hydrogel networks [4]. The amount of water in a hydrogel, i.e., the volume fraction of water, and its free vs. bound water 'character' determine the absorption (or partitioning) and diffusion of solutes through hydrogels [5].

Using the pH-sensitive anionic copolymer of 2-hydroxyethyl methacrylate with acrylic acid or methacrylic acid to prepare controlled-release systems of theophylline, proxyphylline, and oxprenolol HCl, the initial release rates and drug release mechanisms were found to be dependent upon the pH and ionic strength of the buffer solution as well as its salt composition [6].

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The pH-modulated swelling behavior is the underlying mechanism for controlling drug release from anionic hydrogels of poly(methacrylic acid) (p(MAA)) or poly(acrylic acid) (p(AA)) and poly(hydroxyethyl methacrylate) (p(HEMA)) [7,8] and for interpenetrating cationic networks of chitosan and poly (ethylene oxide) [9]. Permeability studies of a pH-sensitive hydrogel made of hydroxyethyl methacrylate/methacrylic acid for drugs with different water solubilities showed a water content-dependent or pore-dependent diffusion mechanism for ephedrine HCl (a water-soluble drug), whereas a partition- or solute diffusion-dependent mechanism for indomethacin (water-insoluble drug) was observed [10].

In addition to being capable of swelling with water absorption, ionic groups linked to the molecular network of polyelectrolyte hydrogels allow interactions with oppositely charged proteins through formation of a polyelectrolyte complex for different biomedical applications. The release can be sustained for positively charged lysozymes when incorporated in a negatively charged fibrin film [11]. It was reported that the amount of complexed lysozyme reached 1.7 g/g dry hydrogel, when a high content of a phosphate-carrying monomer with five ethylene glycol units was incorporated into a hydrogel, and the lysozyme could be released by immersion in a phosphate-buffered solution at pH 7.4 [12]. A spontaneous loading technique for encapsulating positively charged molecules in negatively charged alginate microcapsules was developed for drug delivery applications [13]. In order to localize cisplatin application to tumors, a polymeric hydrogel with carboxylic groups was used for complexation, thus providing sufficient interactions between cisplatin and polyacrylic acid residues that reduce the burst effect, prolonging the release of cisplatin and further reducing its systemic toxicity [14].

In the field of pharmaceutical formulation, polyelectrolytic hydrogels carrying acidic groups have been applied as carriers of basic drugs [15–17]. A detailed mechanism for the release of lidocaine from carbomer–lidocaine (C–L) polyelectrolyte complex hydrogels has been elucidated, and it was concluded that C–L hydrogels behave as a reservoir that releases the drug at a slow rate, and the dissociation of [R–COO^-LH^+] is the slow step that controls release rates [18]. On the contrary, in vitro release of lidocaine HCl through a positively charged chitosan membrane from a chitosan gel reservoir was found to be proportional to the swelling index of chitosan membranes; a higher swelling index was determined for chitosan membranes with a lower extent of deacetylation [19].

Pain is the chief complains of patients after tooth extraction and the main cause of patient revisits. For a long time, gauze soaked with an anesthetic drug, such as lidocaine, was used to pack the post-extraction socket, but it needs to be removed at some future time. In this study, hydrogels were developed as sponge filler to stop the bleeding after a tooth extraction and as a carrier for delivering a local anesthetic. Lidocaine was selected as the model drug with local anesthetic activity. Since the ionic characters of hydrogel (affects its adherence to tooth cavity at extraction site) and in vitro release characteristics of drug from hydrogels are two most critical factors, the in vitro release characteristics of lidocaine from two types of hydrogels, an anionic hydrogel composed of carbopol and a cationic hydrogel composed of chitosans, were examined for the purpose of in vitro formulation optimization for subsequent in vivo application. Lidocaine with cationic characteristics was conveyed in the polyelectrolytic hydrogel in salt and base forms at different concentrations.

2. Experimental section

2.1. Materials

Lidocaine base (LB), lidocaine HCl (LS), and carbopol 934p were from Sigma Chemical (St Louis, MO, USA). Chitosans with different molecular weights having various viscosities designated as C10 (10 cps), C100 (100 cps), C500 (500 cps), and C1000 (1000 cps), were purchased from Wako (Japan). Methanol, *n*-hexane, triethylamine (TEA), and tetrahydrofuran were provided by Merck (Darmstadt, Germany).

2.2. Methods

2.2.1. Preparation of carbopol and chitosan hydrogels

A carbopol stock solution of 1% (w/w) was prepared by dissolving carbopol 934p in an aqueous solution without neutralization, from which carbopol concentrations of 0.1%, 0.3%, and 0.5% were prepared by mixing with deionized water at the respective ratios of 10/90, 30/70, and 50/50. Then, various added amounts (0.25 to 1.0 mg/mL) and types of lidocaine (free base: B; salt form: S) were added according to the designed

Table 1
Composition of carbopol hydrogel formulations and their values of K (the release rate constant) for the release of drug calculated according to Higuchi's equation

Formulation	[CP](1)	[L](2)	Form(3)	pH(4)	K (r^2)(5)
CP 1	0.1	0.25	B	–	13.03 (0.9980)
CP 2	0.1	0.5	B	–	21.16 (0.9994)
CP 3	0.1	0.75	B	–	32.34 (0.9984)
CP 4	0.1	1	B	–	48.50 (0.9854)
CP 5	0.1	1.5	B	–	90.36 (0.9807)
CP 6	0.1	2	B	–	145.70 (0.9968)
CP 7	0.1	2.5	B	–	194.40 (0.9975)
CP 8	0.3	0.25	B	–	7.21 (0.9700)
CP 9	0.3	0.5	B	–	10.50 (0.9795)
CP 10	0.3	0.75	B	–	13.30 (0.9864)
CP 11	0.5	0.25	B	–	4.20 (0.9958)
CP 12	0.5	0.5	B	–	7.34 (0.9933)
CP 13	0.5	0.75	B	–	10.04 (0.9958)
CP 14	0.5	1	B	4.02	18.24 (0.9983)
CP 15	0.5	1	B	5.96	7.50 (0.9964)
CP 16	0.5	1	B	7.47	9.54 (0.9981)
CP 17	0.5	1	B	9.44	24.7 (0.9895)
CP 18	0.5	0.25	S	–	10.32 (0.9832)
CP 19	0.5	0.5	S	–	26.25 (0.9764)
CP 20	0.5	1	S	–	61.00 (0.9565)
CP 21	0.5	2	S	–	147.5 (0.9050)

(1)[CP], carbopol concentration (w/w).
(2)[L], lidocaine concentration (mg/mL).
(3)B and S, B: lidocaine free base; S: lidocaine HCl.
(4)pH, carbopol hydrogel adjusted using TEA.
(5)r^2, correlation coefficient.