

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.

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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, proxiphylline, 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.

formulations listed in Table 1. In order to compare the effects of pH on the release of lidocaine from carbopol hydrogels, the pH values of those hydrogels (CP14–CP17) were adjusted with TEA to 4.02, 5.96, 7.47, and 9.44 with an insignificant increment in the volume to maintain the added amount of lidocaine at the desired level.

A 1% chitosan stock solution was prepared by dissolving chitosan with different molecular weights (C10, C100, C500, and C1000) in a 0.5% v/v acetic acid aqueous solution. Then the above solutions were mixed with an appropriate amount of a 0.5% acetic acid solution to achieve the desired concentration (0.3%, 0.5%, and 1%), followed by adding different concentrations (0.5 to 4 mg/mL) and types (B or S) of lidocaine to produce the finished chitosan hydrogels. The compositions of the chitosan hydrogel formulations are listed in Table 2.

2.2.2. In vitro release studies and theoretical considerations

To simulate the release conditions from a local implant packed in a post-extraction socket, an in vitro release study was conducted with Franz diffusion cells (with a membrane surface area of 2.84 cm² and a cell volume of 0.8 mL) using regenerated cellulose membranes (with a MW cutoff of: 6000–8000) as the interface that provides the least resistance to the diffusion of drug [18]. Carbopol hydrogels (CP1–CP21), and chitosan hydrogels (CS1–CS10) were placed on the donor side, and a 0.9% NaCl solution was used as the receptor medium that was maintained at 37 °C with stirring at 300 rpm. At predetermined time intervals (1, 2, 3, 4, 6, 8 and 12 h), 200-μL aliquots were withdrawn from the receptor compartment and replaced with an equal volume of fresh medium. The concentration of lidocaine in the receptor samples was determined by HPLC analysis.

In the release studies using Franz diffusion cells interfaced with regenerated cellulose membranes that are freely permeable to drug molecules with molecular weights lower than 6000–8000, the gel matrix of both hydrogels was potentially considered to be the main barrier for the release of a drug molecule such as lidocaine (LB and LS). Therefore, since the amount of drug added (C_0) to the hydrogel was in excess of the drug solubility (C_s), the Higuchi equation expressed below, which

describes the matrix-controlled release under this condition, was applied to theoretically elucidate the determinant factors responsible for controlling the release of lidocaine from both hydrogels:

$$M_t = S[DC_s(2C_0 - C_s)t]^{1/2}$$

where M_t is the release amount at time t , S is the surface area for the release, D is the diffusion coefficient of drug in the gel matrix, and C_0 and C_s were defined above. If C_0 is much larger than C_s , the Higuchi equation can be further simplified as follows:

$$M_t = S[2DC_sC_0t]^{1/2}$$

Based on this equation, the plot of the cumulative amount of drug released versus the square root of time is linear with the slope being correlated with both the square root of the amount of drug added (C_0) and the diffusion coefficient (D). The slope so calculated was designated as the release rate constant (K).

2.2.3. HPLC analysis and assay validation

HPLC analysis was conducted using a Dynamax (Jasco, Japan) model SD-200 solvent delivery pump with a UV–VIS detector (model UV-1). An Inertsil silica (5 μm, 4.6 × 150 mm) column (Merck) was applied. The silica gel column was initially preserved in hexane. Before analysis, the column was serially reconditioned by eluting it with solvents of gradually increasing polarity from *n*-hexane, tetrahydrofuran, methanol, and then water in the final elution (the volume for each solvent was approximately 100 mL). Thereafter, this silica gel column was eluted with reverse-phase eluents. The mobile phase consisted of a mixture of solvents (methanol: water, 7:3, v/v) that contained 0.01% (v/v) triethylamine and 0.01% (v/v) acetic acid. The flow rate was 1.0 mL/min, the injection volume was 100 μL, and detection was at λ_{max} of 230 nm. The assay method was validated using the precision and accuracy of intra- and inter-day assays. Results demonstrated that both the precision and accuracy of the inter- and intra-day assays in the linear concentration range of 0.5–50 μg/mL for the model drug of lidocaine were within the acceptable range of <5%.

3. Results and discussion

The release profiles of basic drug (LB) from hydrogels with anionic characteristics containing various concentrations (0.1%, 0.3%, and 0.5%) of carbopol were examined, and the cumulative amounts of drug released plotted against the square root of time are shown in Fig. 1 (1A: 0.1%; 1B: 0.3%; 1C: 0.5%). A linear relationship between the cumulative amount and the square root of time was observed in the range of the added amount of LB from 0.25 to 2.5 mg/mL for the 0.1% carbopol hydrogel and from 0.25 to 0.75 mg/mL for both the 0.3% and 0.5% carbopol hydrogels. This indicates that the Higuchi model adequately describes the release of LB from carbopol hydrogels. The slope of the linear portion of the plot of the cumulative amount versus the square root of time, designated as the release rate constant (K), was calculated and is

Table 2

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

Formulation	CS ⁽¹⁾ type	CS ⁽¹⁾ conc. (w/w)	[L] ⁽²⁾	Form ⁽³⁾	K (r^2) ⁽⁴⁾
CS1	10	0.5	0.5	B	45.90 (0.9372)
CS2	100	0.5	0.5	B	46.86 (0.9945)
CS3	500	0.5	0.5	B	45.45 (0.9798)
CS4	1000	0.5	0.5	B	44.15 (0.9934)
CS5	1000	0.5	0.75	B	65.33 (0.9968)
CS6	1000	0.5	1	B	85.72 (0.9967)
CS7	1000	0.5	2	B	194.3 (0.9839)
CS8	1000	0.3	4	B	304.2 (0.9881)
CS9	1000	1	4	B	263.3 (0.9989)
CS10	1000	1	4	S	269.7 (0.9895)

⁽¹⁾[CS], chitosan.

⁽²⁾[L], lidocaine concentration (mg/mL).

⁽³⁾B and S, B: lidocaine free base; S: lidocaine HCl.

⁽⁴⁾ r^2 , correlation coefficient.

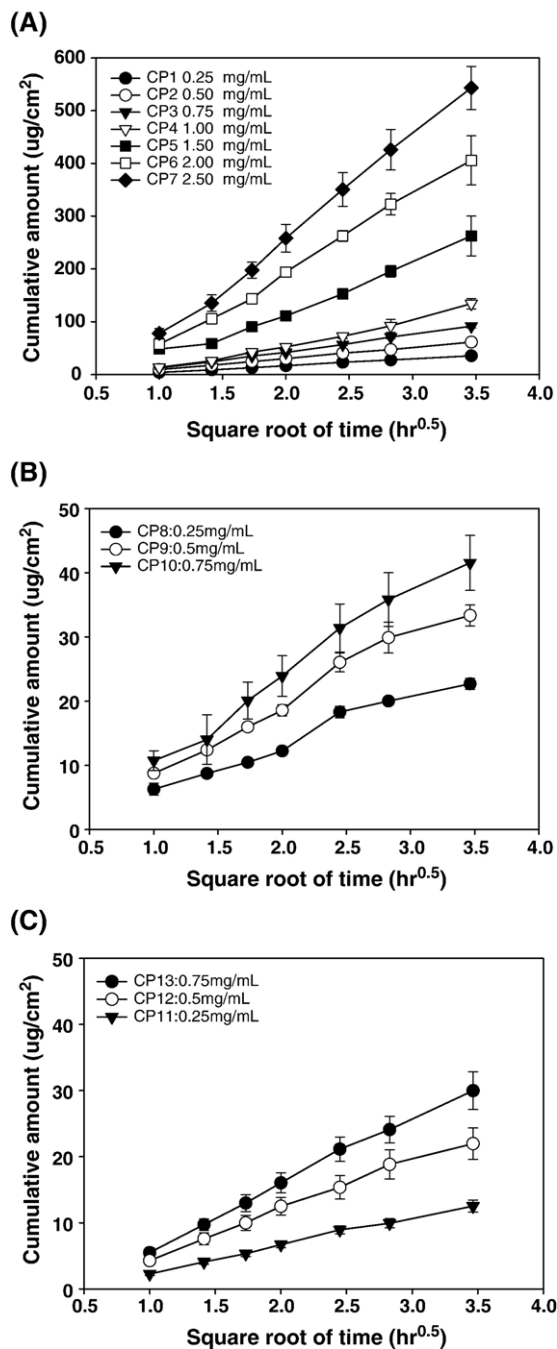


Fig. 1. Release profiles of lidocaine base through a regenerated cellulose membrane from hydrogels with various concentrations of carbopol. (A) 0.1%; (B) 0.3%; (C) 0.5%.

summarized in Table 1. Results clearly revealed that the K value increased with increasing LB concentration at the three same carbopol levels of the hydrogel, whereas it increased with a decreasing level of carbopol for the same concentration of LB in these hydrogels.

Based on the Higuchi model, a linear relationship between the release rate constant (K) and the square root of the added amount of LB was expected. This was only valid for the lower range of the added amount of LB (0.25–0.75 mg/mL) at the three different carbopol concentrations (0.1%, 0.3%, and 0.5%)

as shown in Fig. 2. However, a non-linear curve (with increased K values) was observed between the release rate constant (K) and the square root of the added amount of LB when the latter was extended to as high as 2 mg/mL in the 0.1% carbopol hydrogel. Since the acidic groups of carbopol can be neutralized by the basic drug (LB), the fraction of neutralized LB should decrease with an increasing added amount of LB at the same level of carbopol. The diffusion coefficients of the two (neutralized and free) forms of LB in the gel matrix of carbopol were expected to be lower for the former and higher for the latter due to the difference in the ionic complexing effect with the carboxylic groups of carbopol. Therefore, the non-linear relationship was attributed to the diffusion coefficient of the dominant fraction of the neutralized form of LB in the lower range of the amount of LB added having a lower value, whereas the diffusion coefficient of the dominant fraction of the free form of LB in the higher range of the amount of LB added had a higher value.

Similarly, when comparisons were made among the three levels of carbopol in the same lower range of the amount of LB added as shown in Fig. 2, the slopes of the corresponding plots for each level of carbopol were parallel to both the square root of the diffusion coefficient and drug solubility as theoretically predicted by the Higuchi equation. Assuming that drug solubility (the free drug portion that is not neutralized by carbopol and is available for diffusion) was constant at the three carbopol concentrations when lidocaine was added in an excess amount, the increase in the corresponding slope with respect to the decrease in the carbopol level was attributed to the increase in the diffusion coefficient of the hydrogel, which was due to the lower viscosity (after complete neutralization with lidocaine base) with a decreasing carbopol concentration, causing an increase in the diffusion coefficient as predicted by the Stokes–Einstein equation. Because of this, the influence on the diffusion coefficient predicted by the Higuchi equation can appropriately be applied to describe the release characteristics of LB from the three levels of the carbopol hydrogels.

The effects of different pH values of carbopol hydrogels at a 0.5% concentration on the release of LB were examined at the

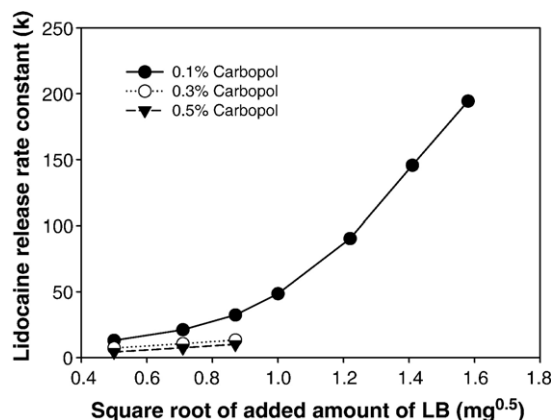


Fig. 2. Lidocaine release rate constant through a regenerated cellulose membrane versus the square root of the amount of lidocaine added to hydrogels with various concentrations of carbopol.

same amount (1 mg/mL) of LB added. The plots of the cumulative released amounts of LB versus the square root of time are illustrated in Fig. 3A and the release rate constants (K) calculated from the slopes are summarized in Table 1. The plot of the release rate constant versus the pH value of the hydrogel is shown in Fig. 3B. Results demonstrated that the Higuchi model can appropriately describe the release mechanism of LB from 0.5% carbopol hydrogels with different pH values. A minimum in K was observed at a pH of 6, whereas non-neutral pH environments increased K .

The minimum in K as a function of pH values of hydrogels containing the same carbopol concentration and amount of LB added can be attributed to two influencing factors: first, the viscosity of the carbopol hydrogel (anionic polymer) significantly increases with increasing pH values of 4 to 6, after which it gradually reaches a plateau [20] resulting in the corresponding influence on the diffusion coefficient of the drug through the hydrogel matrix; and second, the influence on the diffusion coefficient by the ionic complexing effect of un-neutralized acidic groups of carbopol with the un-ionized form of lidocaine (pK_a 7.9) decreases with increasing pH values of the respective hydrogel. When the pH value of the hydrogel is lower than 6, the viscosity of the hydrogel increases so profoundly with an

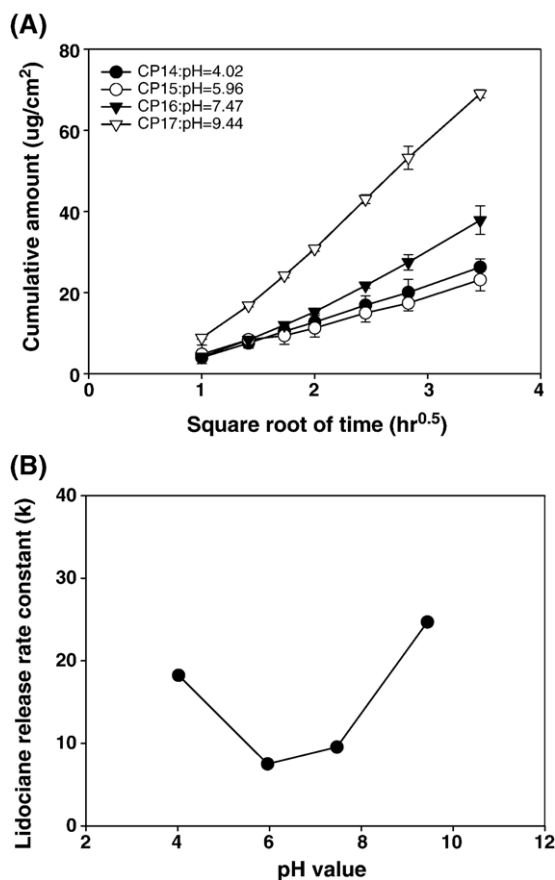


Fig. 3. (A) Release profiles of lidocaine through a regenerated cellulose membrane from 0.5% carbopol hydrogels prepared with different pH values; (B) Relationship of the lidocaine release rate constant (K) and various pH values in 0.5% carbopol hydrogels.

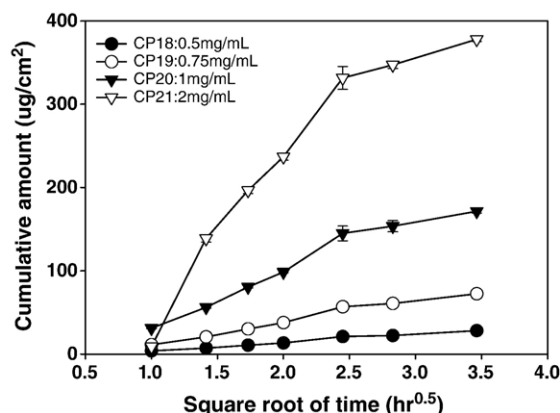


Fig. 4. Release profiles of lidocaine HCl through a regenerated cellulose membrane from 0.5% carbopol hydrogels.

increase in the pH value that a significant decrease in the diffusion coefficient of lidocaine through the matrix of the hydrogel occurs. In this pH range, although the un-neutralized acidic groups of carbopol gradually decrease, the ionized form of lidocaine is the dominant fraction in the hydrogel, and it shows similar ionic complexing effects on the diffusion coefficient. Taken together, the release rates of LB from the hydrogels having pH values lower than 6 are determined by the viscosity of the carbopol hydrogel, which shows a decreasing K value with increases in the pH value of the hydrogel. When the pH of the hydrogel exceeds 6, the viscosity of the hydrogel gradually increases with increasing pH values which only causes a minor influence on the diffusion coefficient. However, most of the acidic groups of carbopol were neutralized, and the un-ionized form of lidocaine was the dominant fraction causing the ionic complexing effect to influence the diffusion efficiency to decrease with increasing pH values of the hydrogel in this pH range. Therefore, the release rates of LB from hydrogels with pH values exceeding 6 are determined by the extent of ionic complexation between the acidic groups of carbopol and the un-ionized form of lidocaine which produce an increase in the K value as the pH of the hydrogel increases.

For the 0.5% carbopol hydrogels, the release of lidocaine was measured at the concentration range of 0.25–2 mg/mL using lidocaine HCl (LS) instead of LB. The release rate constant (K) calculated from the linear portion of the Higuchi plot was compared to examine the influence of the added amount of LS on its release kinetic from the same carbopol concentration of 0.5%, and results are summarized in Table 1 and Fig. 4. The same tendency as that at the same carbopol levels of hydrogels containing LB was demonstrated, showing that the release rate constant increases with an increasing concentration of LS in the hydrogels. However, the release rate constant (K) at the same concentration of lidocaine was larger for those using the salt form compared to the base form. This can be explained by both the effects of increasing the C_0 and diffusion coefficient (D) for LS than for LB due to a higher solubility of LS than LB at the same amount added and less of an ionic complexing effect of LS than LB with the carboxylic groups of the carbopol hydrogel.

The release of the basic drug (LB) from 0.5% chitosan hydrogels with cationic characteristics was examined at four different amounts (0.5, 0.75, 1, and 2 mg/mL) of LB added, and the cumulative amount of drug released was plotted against the square root of time as shown in Fig. 5A. The release rate constants calculated from the slope of the linear portion of the plot are summarized in Table 2. Results reveal that the release rate constant (K) increased with an increase in the amount of LB added in chitosan hydrogels with the same 0.5% concentration of C1000. This indicates that the Higuchi model is appropriate for describing the release mechanism of LB from chitosan hydrogels. This was further proven by the linear relationship of the plot of the K value versus the square root of the added amount of LB as shown in Fig. 5B based on the Higuchi equation. Therefore, the increase in the release rate constant with an increasing amount of LB added was mainly due to the increasing concentration of LB in the gel matrix when the amount of LB added to the chitosan hydrogel was increased. The diffusion coefficient of LB in the gel matrix containing the same concentration of C1000 was minimally affected by the increasing amount of LB added.

The release of LB from chitosan hydrogels prepared with different MWs (designated C10, C100, C500, and C1000) at the

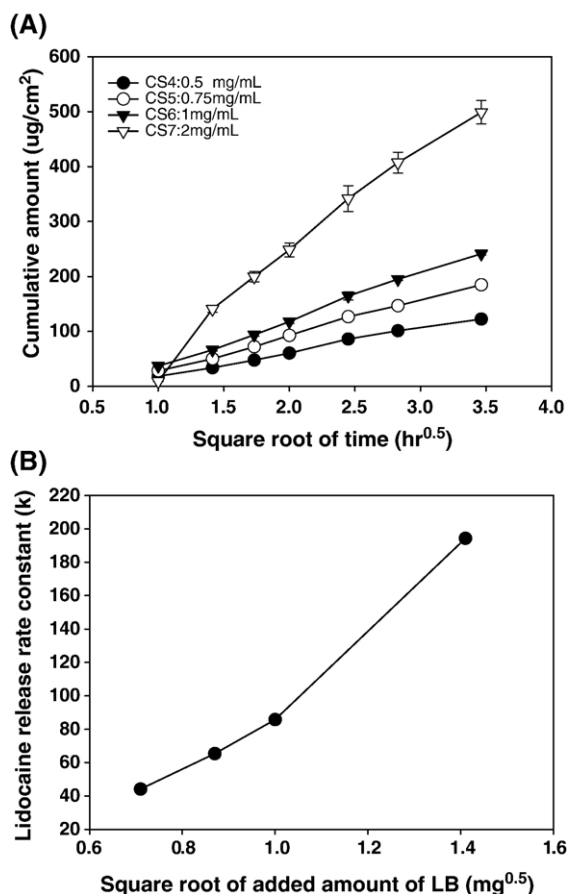


Fig. 5. (A) Release profiles of lidocaine through a regenerated cellulose membrane from 0.5% chitosan hydrogels with various concentrations of lidocaine free base; (B) Lidocaine release rate constant through a regenerated cellulose membrane versus the square root of the amount of lidocaine added to 0.5% chitosan (C1000) hydrogels.

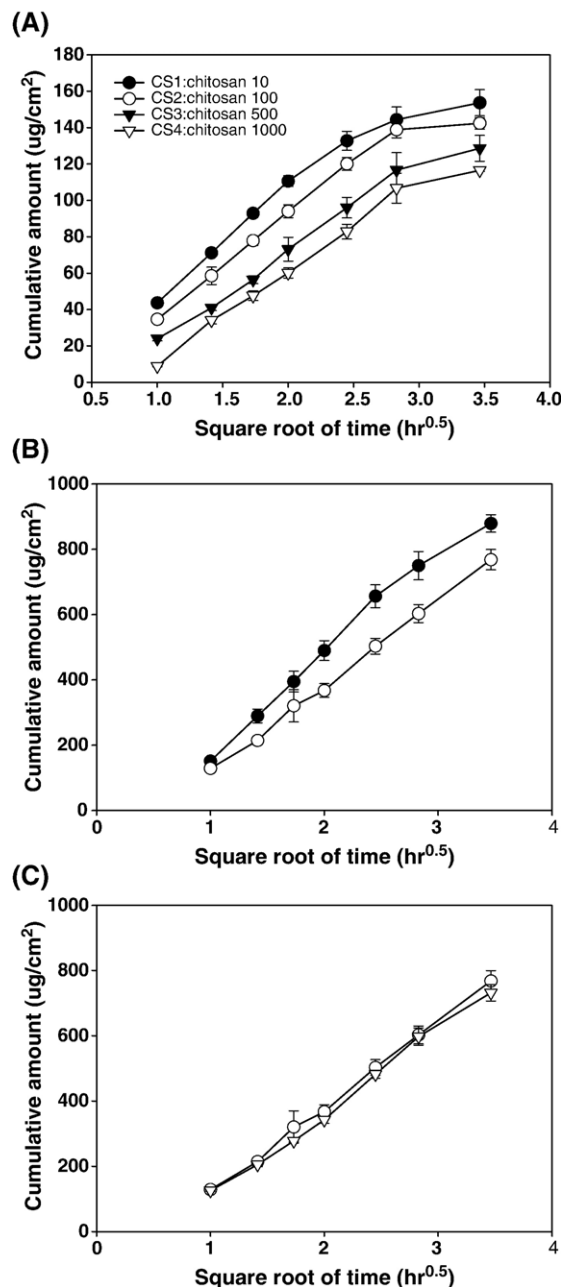


Fig. 6. Release profiles of lidocaine through a regenerated cellulose membrane from 0.5% hydrogels (A) with chitosan of various molecular weights; (B) with two (●CS8: 0.3% chitosan hydrogel; ○CS9: 1% chitosan hydrogel) concentrations of chitosan; and (C) from 1% chitosan hydrogels using two (○: CS9; ▽: CS10) lidocaine forms.

same level and concentration of the acetic acid solution and with the same amount of LB added was examined. Results illustrated by plotting the cumulative amount of LB released versus the square root of time are shown in Fig. 6A, and the release rate constant (K) calculated from the slope of the linear portion is summarized in Table 2. It demonstrates that a linear relationship as predicted by the Higuchi model was observed for all chitosan hydrogels with different MWs examined, and the K value increased with a decrease in the MW of chitosan. This can mainly be attributed to an increase in the diffusion coefficient of

the same form of LB as a result of the decreasing viscosity of the gel matrix of chitosan hydrogel with decreasing MW of chitosan, since the same amount of LB was added and chitosan was prepared at the same level in an acetic acid solution of the same concentration. On the other hand, the influence of viscosity on the release profile of lidocaine was further demonstrated using the same viscosity grade of chitosan (C1000) at two different concentrations (0.3% vs. 1%). As shown in Fig. 6B, the release profiles of lidocaine from chitosan hydrogels at two different levels followed the same pattern as predicted by the Higuchi model. The slopes calculated from the linear portion of the respective plots indicate that the release rate constant was lower for the release from chitosan hydrogels prepared at a lower level than with a higher level. Obviously, the lower viscosity of chitosan hydrogels prepared at a lower level resulted in a higher diffusion coefficient for lidocaine which was released at a faster rate.

Fig. 6C compares the influence of the salt and base forms of lidocaine on the release profiles of lidocaine from chitosan hydrogels prepared with C1000 at the 1% level. The release profiles of lidocaine for both forms of lidocaine had linear relationships between the cumulative amounts of lidocaine released as predicted by the Higuchi model. However, a similarity in the release profiles between the two forms (LB and LS) of lidocaine was observed, which demonstrates that no significant effect of the different forms of lidocaine on the release rate existed. This can be explained by the fact that the LB added to chitosan hydrogels prepared from an acetic acid solution was converted to the salt form which is the same as LS. Therefore, similar release profiles were shown when adding both forms of lidocaine to chitosan hydrogels. This also explains that the release of lidocaine from chitosan hydrogels is faster than that from carbopol hydrogels at the same concentration level (Fig. 1A versus Fig. 5A) as a result of formation of lidocaine salt in chitosan hydrogels.

4. Conclusions

In conclusion, the release mechanism of lidocaine in its salt and base forms from a local implant composed of either an anionic carbopol hydrogel or a cationic chitosan hydrogel was appropriately and simply described by the Higuchi model. Based on the Higuchi equation, the influence of the amount of LB added, the polymer levels, the pH values of the resulting hydrogels on the release rate constant (K) were all attributed to their effects on the diffusion coefficient of the diffusant in the gel matrix. The viscosity of the gel matrix increased with increasing viscosity grade and with an increasing level of polymer leading to a decrease in the diffusion coefficient. The ionic complexing effect between anionic acid groups of the hydrogel polymer and basic groups of the basic drug also resulted in a lower diffusion coefficient for the diffusant, and

this effect was applicable to describe the influence of different forms of lidocaine and the pH values of anionic hydrogels on the release profiles.

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