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Controlled release of nalbuphine prodrugs from biodegradable polymeric matrices: influence of prodrug hydrophilicity and polymer composition

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Abstract

The objective of this work was to assess the effects of nalbuphine prodrug hydrophilicity and lactide/glycolide copolymer ratio on drug release from lactide/glycolide based polymeric matrices. A panel of four nalbuphine prodrugs with various ester chains were incorporated into poly (D,L-lactide) based matrices by using the solvent evaporation method. Drug release rates for the matrices were found to be a function of prodrug hydrophilicity, with higher drug release rates for matrices with more hydrophilic prodrugs. Data analysis using the Higuchi expression indicated that the release of various prodrug from poly (D,L-lactide) based matrices was consistent with a diffusion mechanism. The prodrug release rate constants derived from the Higuchi expression correlated well with prodrug solubilities. In the second part of the study, the effect of lactide/glycolide copolymer ratio on nalbuphine propionate release was studied. The drug release rate and matrix hydration rate were found to be a function of copolymer ratio, with faster drug release and matrix hydration for matrices with lower lactide/glycolide ratio copolymers. The nalbuphine propionate release profiles fit well to the Higuchi expression, indicating that drug release from the Poly (D,L-lactide-co-glycolide) based matrices was consistent with a diffusion mechanism. The drug release rates correlated well with matrix hydration rates, suggesting that different polymer compositions may attribute to various matrix hydration and therefore affect drug release from the PLGA matrices.

Keywords: Controlled release; Diffusion; Nalbuphine prodrugs; Poly (D,L-lactide); Poly (D,L-lactide-co-glycolide)

1. Introduction

Biodegradable polymers have received considerable attention in the design of drug delivery

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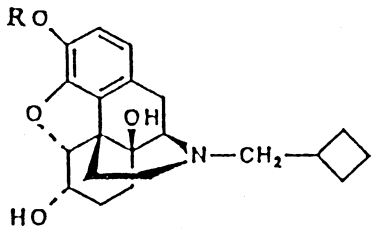
devices. The major advantage of using biodegradable polymers in drug delivery is that it enables the site-specific or systemic administration of pharmaceutical agents without the need for subsequent retrieval of the delivery system. Among various biodegradable polymers, the aliphatic polyesters based on lactide/glycolide are most widely used and investigated. Various therapeutic agents, such as antibiotics, anti-inflammatory drugs, anticancer drugs, steroids, peptides and proteins have been incorporated in the lactide/glycolide copolymer systems (Sanders et al., 1986; Ike et al., 1992; Mauduit et al., 1993; Niwa et al., 1993; Zhang et al., 1993; Aso et al., 1994; Lambert et al., 1995; Chandrashekar et al., 1996). Since the pharmacokinetic properties of those therapeutic agents are different, drug release rates from the lactide/glycolide-based systems should be varied in order to achieve the optimum blood drug concentration and therapeutic effect.

The drug release mechanism from poly (D,L-lactide) (PLA) or poly (D,L-lactide-co-glycolide) (PLGA)-based matrices have been described by several authors (Hutchinson et al., 1990; Jalil et al., 1990; Yamakawa et al., 1990; Fitzgerald et al., 1996; Hsu et al., 1996a). Drug release from such matrix systems is governed by both diffusion of drugs in the matrix as well as the matrix erosion resulting from degradation and dissolution of smaller molecular weight polymer at the surface. The mechanism indicates that drug release may be influenced by physicochemical properties of the polymer and the drug, such as polymer molecular weight, lactide/glycolide copolymer ratio, drug loading percentage, drug solubility as well as matrix fabrication method (Sanders et al., 1986; Sato et al., 1988; Asano et al., 1989; Fitzgerald et al., 1996; Hsu et al., 1996a,b). Despite that the drug hydrophilicity may have impact on release kinetics of the matrix devices, it's effect on drug release from PLA and PLGA matrices has not yet been fully explored in a systematic way. Therefore, it is desirable to characterize the effect of drug hydrophilicity on drug release from the matrices using a series of chemically related compounds with various hydrophilicity.

Nalbuphine is a narcotic analgesics used effectively in the treatment of both acute and chronic pain. It has quite potent analgesic effects and relatively low side effects. Due to its short elimination half-life and low oral bioavailability, frequent injection is needed. It is obvious that the patient compliance and therapeutic effectiveness in pain management can be improved by maintaining the blood nalbuphine concentration. As a result, a series of nalbuphine prodrug, including nalbuphine propionate, nalbuphine pivalate, nalbuphine enanthate and nalbuphine decanoate have been synthesized (Fig. 1) (Wang, 1992). Various nalbuphine prodrug formulations such as suspension and microsphere have also been developed (Wang, 1992). The use of biodegradable implants such as PLA or PLGA matrices incorporating those prodrugs may provide a constant



	R
nalbuphine decanoate	$CH_3(CH_2)_8\overset{O}{\overset{\|}{C}}-$
nalbuphine enanthate	$CH_3(CH_2)_5\overset{O}{\overset{\|}{C}}-$
nalbuphine pivalate	$CH_3-\underset{CH_3}{\overset{CH_3}{\overset{\|}{\underset{\|}{C}}}}-\overset{O}{\overset{\|}{C}}-$
nalbuphine propionate	$CH_3CH_2\overset{O}{\overset{\|}{C}}-$

Fig. 1. Structure of nalbuphine prodrugs

drug release rate, resulting in both patient comfort and a reduced total amount of analgesics. The series of nalbuphine prodrug may also be used as model compounds to study the effect of drug hydrophilicity and polymer composition on drug release from the lactide/glycolide-based matrices.

In the present study, a series of nalbuphine prodrug matrices based on PLA and PLGA were developed. The various PLA and PLGA matrices were used to characterize the effect of prodrug hydrophilicity and copolymer ratio on drug release kinetics. The drug release data, prodrug solubility as well as matrix hydration data were utilized to explore the release mechanism of nalbuphine prodrugs from the PLA and PLGA-based matrices.

2. Materials and methods

2.1. Materials

PLA and PLGA were purchased from Medisorb Technologies (Cincinati, OH, USA). Two different ratios of PLGA were used in the study, including 75/25 and 50/50. The manufacturer reported molecular weight range of the polymers was 40000–100000 (weight average molecular weight). The nalbuphine hydrochloride and four nalbuphine prodrugs, including nalbuphine propionate, nalbuphine pivalate, nalbuphine enanthate and nalbuphine decanoate were synthesized and supplied by the National Defense Medical Center, Taipei, Taiwan. All the other chemicals were purchased from the Sigma (St. Louis, MO) and used as-received.

2.2. Preparation of implants

The drug-containing polymeric matrices used in the fabrication of implants were cast from polymer-drug solutions. The solutions were composed of 50 mg of drug and 100 mg of polymer as well as 20 ml of methylene chloride. The solution were poured onto glass plate and the solvent was allowed to evaporate at room temperature for approximately 24 h. The drug containing polymeric matrices were peeled off and micronized by a cutting mill (YU2S, Tai-Shin Machinery Works, Taiwan) to obtain fine granules. The granules were sieved and heated to 50°C for 20 min before they were compressed by a manual single-punch tablet machine (Chen-Tai Machinery Works, Taiwan). The diameter and thickness of the resulting implants were approximately 8 and 1.5 mm, respectively. The final weight of the implants were 112 ± 8.80 mg.

2.3. In vitro release study

The release studies were conducted in 500 ml stopped Erlenmeyer flasks containing 250 ml of phosphate buffer (pH = 7.4, 0.025M) as the release medium. The flasks were incubated in a shaking bath, with temperature and shaking rate of 37°C and 40 rpm, respectively. Five hundred microliter samples were removed from the flasks on sampling times of 0, 0.25, 1, 2, 4, 7, 10, 14 and 28 day. The medium removed from the flask was immediately replaced with fresh buffer. The collected samples were then subjected to further HPLC analysis.

2.4. Matrix hydration study

In the hydration study, polymer matrices in triplicate were immersed into drug release medium at 37°C. Periodically, the polymer matrices were withdrawn from the medium and weighed on an electronic balance (Mettler Model AE 240) after removal of surface water by light blotting with a laboratory tissue. The hydration ratio of the matrix (H) was defined as:

$$H = \frac{(\text{partially hydrated matrix weight} - \text{dry matrix weight})}{(\text{dry matrix weight})}$$

2.5. Measurement of solubility

An excess amount of drug was added to 5 ml of deionized water and was shaken in a water bath (37°C). The supernatant was assayed periodically for drug concentration until the drug concentration kept at a constant level. This drug concentration was designated as the drug solubility.

2.6. HPLC Analysis

Nalbuphine and its prodrug concentrations were analyzed using high performance liquid chromatography. The chromatographic system consisted of a pump (HITACHI 655-A40), an autosampler (HITACHI L6000), a UV detector (HITACHI L4000) and an integrator (HITACHI D2500). A normal phase silica column (μ porasil, 3.9mm*300mm, 10μm, Waters) was utilized for drug separation, while an acetonitrile-pH 3.5 acetate buffer system (80:20) was used as the mobile phase. The flow rate and the UV wavelength were 1.5 ml/min and 210 nm, respectively. The injection volume was 10 μl. Under these conditions, the retention times of nalbuphine hydrochloride, nalbuphine propionate, nalbuphine pivalate, nalbuphine enanthate and nalbuphine decanoate were approximately 9.8, 8.1, 7.4, 6.9 and 6.3 min, respectively. The drug concentrations were determined by measuring the peak area and comparing with the peak area of known standards. Further details concerning the assay are available elsewhere (Wang, 1992).

3. Results and discussion

3.1. Effect of prodrug hydrophilicity on drug release kinetics

The effect of nalbuphine prodrug hydrophilicity on drug release kinetics is shown in Fig. 2. The rate controlling polymer was PLA. According to Fig. 2, the fastest drug release was observed for matrices loaded with nalbuphine hydrochloride; with all drug released in two days. The release of nalbuphine enanthate and nalbuphine decanoate was relatively slow, with only less than 14% and 4% of drug released in 28 days, respectively. For the release of four nalbuphine prodrugs, a greater drug release rate was observed for matrices loaded with more hydrophilic prodrug (i.e. prodrug with shorter ester chain). For example, after 10 days, around 45.3, 31.3, 8.26 and 1.97% of drug have released from the matrices loaded with nalbuphine propionate, nalbuphine pivalate, nalbuphine enanthate and nalbuphine decanoate,

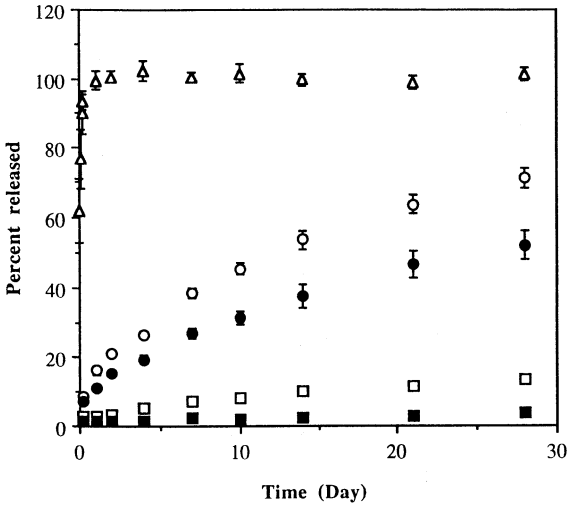


Fig. 2. The percent drug released vs. time profiles for matrices loaded with various drugs: (△) nalbuphine hydrochloride; (○) nalbuphine propionate; (●) nalbuphine pivalate; (□) nalbuphine enanthate and (■) nalbuphine decanoate. Mean ± standard error are presented ($n = 3$).

respectively. The instantaneous drug release rates decreased with time for all the formulations, which is reflected in the curvature of percent drug release profiles.

For a drug incorporated in an undissolved polymeric matrix, the Higuchi expression describing Fickian drug release from single face of a non-swelling tablet is frequently used to describe the drug release profiles of matrix extended-release dosage forms (Ford et al., 1985; Doelker, 1987; Sung et al., 1996). According to this model, a straight line is expected for the percent drug released versus square root of time plot if drug release is based on a diffusion mechanism. Since the bulk degradation of PLA is trivial during the initial period (Shih, 1995; Hsu et al., 1996a); moreover, the drug release time (28 days) in this study is considerable shorter than the degradation lifetime of PLA and PLGA (Lewis, 1990; Hsu et al., 1996a), the Higuchi model can be applied here to study drug release mechanism (Yamakawa et al., 1990; Fitzgerald et al., 1996). Fig. 3 shows the percent drug released versus square root of time plots (up to 60% of total drug released) for matrices loaded with various prodrugs. It is notable that the r^2 values of the linear regressions were

greater than 0.99 and the residuals were randomly distributed for all the formulations studied, indicating that the data fit the Higuchi model well. The results demonstrate that, within the 28 days of experiment time, the release of nalbuphine prodrug from those matrices is consistent with a diffusion mechanism. The results also confirm that PLA does not degrade appreciably during the experiment and therefore is essentially inert with respect to release.

For a drug release from matrix systems via a diffusion mechanism, the solubility of drug inside hydrated matrices is an important factor to determine drug release rate (Ford et al., 1985; Doelker, 1987; Sato et al., 1988). The more hydrophilic drug, which is often more water soluble, may have higher solubility inside the hydrated polymeric environment and result in faster drug release. This phenomenon was observed in the present study. Fig. 4 shows the relationship between the Higuchi release rate constants (% released/day$^{1/2}$) and aqueous solubilities of various prodrugs. This linear relationship ($r^2 = 0.990$) demonstrates that the prodrug release rate correlates well with prodrug solubility; the positive slope indicates that the prodrug release rate increases with prodrug solubility. These results suggest that the different prodrug release rates can be attributed to various prodrug hydrophilicity. This empirical relationship can also be used to predict the prodrug release rate for matrix with known prodrug solubility.

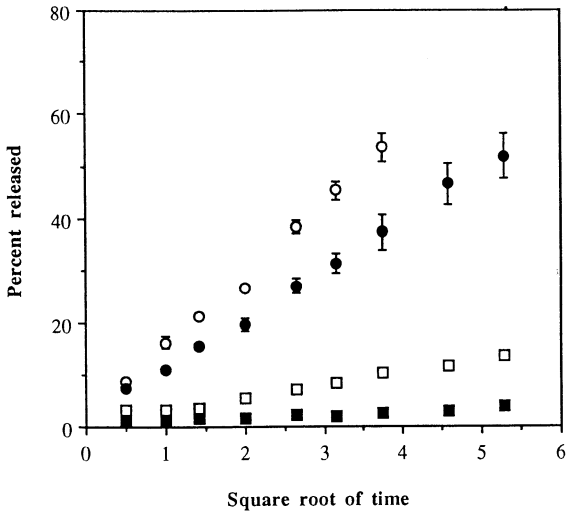


Fig. 3. The percent drug released vs. square root of time (day$^{1/2}$) plots for matrices loaded with various nalbuphine prodrugs: (○) nalbuphine propionate; (●) nalbuphine pivalate; (□) nalbuphine enanthate and (■) nalbuphine decanoate. Mean ± standard error are presented ($n = 3$).

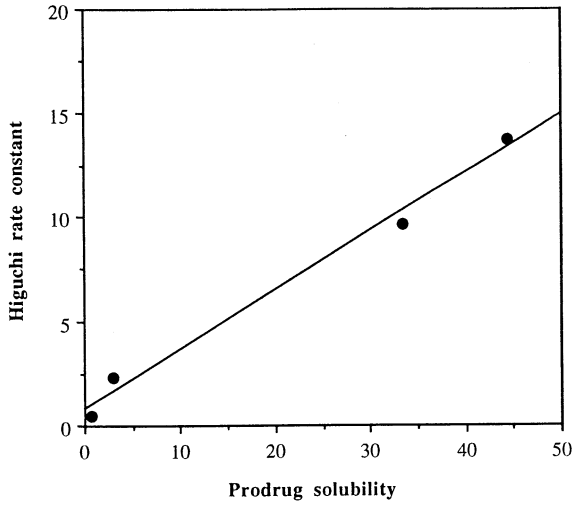


Fig. 4. The relationship between Higuchi rate constants (% released /day$^{1/2}$) and aqueous solubilities (μg/ml) of various prodrugs. The slope and intercept of the regression line are 0.283 and 0.790, respectively. The r^2 of the linear regression is 0.990.

3.2. Effect of lactide/glycolide copolymer ratio on drug release kinetics

The effect of lactide/glycolide copolymer ratio on nalbuphine propionate release from PLGA matrices is shown in Fig. 5. A greater drug release rate was observed for matrices with lower lactide/glycolide ratio copolymer. The results are consistent with previous reports on similar systems (Sanders et al., 1986; Ogawa et al., 1988) and demonstrate that the changes in lactide/glycolide ratio can be used to manipulate drug release rates. For example, after 10 days, around 60.8, 50.7, and 38.9% of drug have released from the matrices with copolymer ratio of 50/50, 75/25 and 100/0, respectively. The concave release profiles of those matrices indicate that the drug release rates decreased with time.

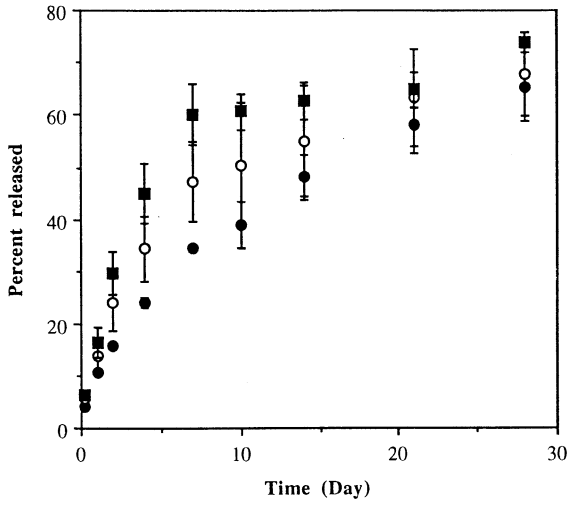


Fig. 5. The percent nalbuphine propionate released vs. time profiles for matrices with various lactide/glycolide ratio copolymers: (■) 50/50; (○) 75/25 and (●) 100/0. Mean ± standard error are presented ($n = 3$).

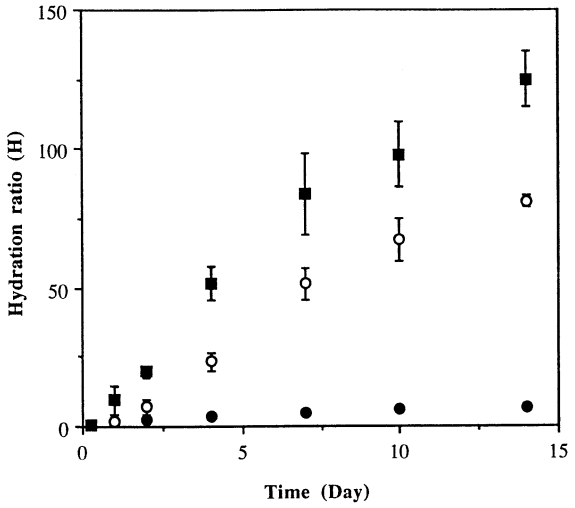


Fig. 7. The hydration ratio vs. time profiles for matrices with various lactide/glycolide ratio copolymers: (■) 50/50; (○) 75/25 and (●) 100/0. Mean ± standard error are presented ($n = 3$).

Fig. 6 shows the percent drug released (up to 60% of total drug released) versus square root of time plots for matrices with various lactide/glycolide ratio copolymers. Linear relationships were observed for all the formulations tested, with r^2 greater than 0.99. The results indicate that the release of nalbuphine propionate from those matrices is consistent with a diffusion mechanism; the results also confirm that the matrix integration does not change appreciably during the drug release.

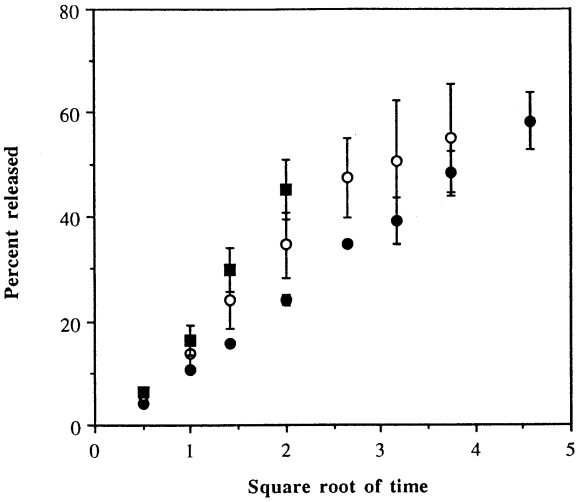


Fig. 6. The percent nalbuphine propionate released vs. square root of time ($day^{1/2}$) plots for matrices with various lactide/glycolide ratio copolymers: (■) 50/50; (○) 75/25 and (●) 100/0. Mean ± standard error are presented ($n = 3$).

The effect of matrix hydration on drug release from polymeric matrices has been described in several literature (Peppas et al., 1980; Ranga Rao et al., 1988; Vergnaud, 1993; Gao et al., 1996). Matrix hydration may affect drug release rate via increasing drug diffusional pathlength and drug diffusion rate inside the hydrated polymeric matrix as well as increasing matrix release surface area. As a result, polymeric matrices with various hydration rates may result in different drug release kinetics. Fig. 7 shows the hydration kinetics of the matrices with various lactide/glycolide ratio copolymers. Since the matrices with 50/50 ratio copolymer absorbed appreciable amount of water and the hydration ratio could not be measured accurately after 14 days of immersion, only 14 days of hydration data were presented. It can be observed from Fig. 7 that the matrices with more hydrophilic copolymers (i.e., the matrices with lower lactide/glycolide ratio copolymers) have faster hydration. For example, after 10 days, the

hydration ratio were 98.1, 67.1 and 5.82 for matrices with 50/50, 75/25 and 100/0 ratio copolymers, respectively.

According to the model describing the absorption of liquid into polymeric matrices via diffusion, a straight line is expected for the amount of liquid absorbed (matrix hydration) versus square root of time plot (Vergnaud, 1993). That is, the slope of matrix hydration versus square root of time plot represents the hydration rate constant (hydration ratio/time$^{1/2}$). Table 1 shows the hydration rate constant for matrices with various lactide/glycolide ratio copolymers. The magnitudes of hydration rate constant in Table 1 matched with Fig. 7 and the r^2 values were higher than 0.96, indicating that the hydration kinetics of those matrices fit reasonable well to the diffusional absorption model. Table 1 demonstrates that matrices with 50/50 ratio copolymer (the more hydrophilic matrices) has the highest hydration rate constant of 40.4 and the constants decrease as the lactide/glycolide ratios increase.

In order to examine the relationship between drug release and matrix hydration, the Higuchi release rate constants were plotted against the hydration rate constants (Fig. 8). The linear relationship ($r^2 = 0.961$) indicates that the drug release rate correlates well with matrix hydration rate; the positive slope also indicates that drug release rate increases with matrix hydration rate. These results suggest that the various matrix hydration rates contribute to different drug release rates. Therefore, it can be concluded from the drug release data and matrix hydration data that the different polymer compositions may attribute to various matrix hydration kinetics and then result in different drug release kinetics.

Table 1
The hydration rate constants (hydration ratio/day$^{1/2}$) and r^2 values of matrices with various lactide/glycolide ratio copolymers.

Lactide/glycolide ratio	Hydration rate constant	r^2
100/0	1.91	0.998
75/25	27.5	0.962
50/50	40.4	0.985

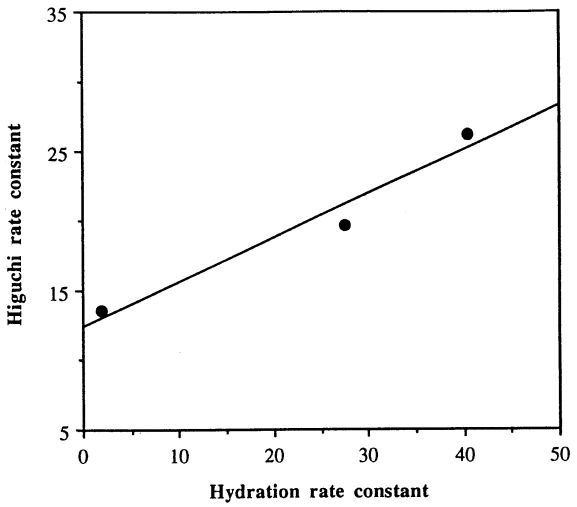


Fig. 8. The relationship between Higuchi rate constants (% released/day$^{1/2}$) and hydration rate constants (hydration ratio/day$^{1/2}$) for matrices with various lactide/glycolide ratio copolymers. The slope and intercept of the regression line are 0.319 and 12.4, respectively. The r^2 of the linear regression is 0.961.

In summary, the effects of prodrug hydrophilicity on drug release from PLA-based matrices were studied. Higher release rates were observed for matrices loaded with more hydrophilic prodrugs. The release data fit well to the Higuchi model, indicating the drug release was consistent with a diffusion mechanism. The prodrug release rates correlated well with prodrug solubilities, suggesting that the different prodrug release rates were attributed to various prodrug hydrophilicity. The effects of lactide/glycolide copolymer ratio on nalbuphine propionate release were also investigated. Higher drug release rates were observed for matrices with lower lactide/glycolide ratio copolymers. The drug release data can be described well by the Higuchi model, indicating that the release of nalbuphine propionate from those matrices was also consistent with a diffusion mechanism. Faster matrix hydration was observed for matrices with lower lactide/glycolide ratio copolymer. The drug release rates correlated well with matrix hydration rates, suggesting that different polymer compositions may attribute to various matrix hydration and therefore affect drug release from the PLGA matrices.

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