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The effects of drug physico-chemical properties on release from copoly (lactic/glycolic acid) matrix

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Abstract

A study on the effect of physico-chemical properties of drugs on their release behavior from copoly (L-lactic/glycolic acid) (PLGA) matrix was performed. PLGA and drugs of acidic, neutral or basic nature were mixed and molded by heat compression method into a cylindrical matrix. The release rate of drugs from the rod depended on their physico-chemical properties. Basic drugs were found to show high PLGA/aqueous medium partition coefficients (K_{app}), implying a strong ionic interaction with the polymer. This interaction kept these drugs dissolved in the matrix during the release studies. The interaction shielded the polymer terminal carboxyl residues resulting in the slower matrix erosion, and made the matrix less swellable, thus diminishing drug diffusion through the matrix. Consequently, K_{app} could be regarded as the determinant parameter to evaluate the release rate of basic drugs. In contrast, acidic and neutral drugs had only weak interaction with PLGA, so that the drugs quickly precipitated out as crystals in the matrix during the release studies. In this case, the drugs did not affect the matrix erosion, and hence the solubility of each drug in the hydrated matrix became the predominant parameter affecting drug diffusion.

Keywords: Biodegradable polymer; Copoly (lactic/glycolic acid); Controled release; Release mechanism; Drug physico-chemical properties; Polymer/drug interaction

1. Introduction

In recent years, much attention has been paid to biodegradable polymers as implantable reservoirs for sustained-release drug delivery, as these polymers do not require surgical removal after completion of drug release. Among these polymers, poly (lactic acid) (PLA) and copoly (lactic/glycolic acid; PLGA) have been used as surgical sutures for the past 30 years and are known to be non-toxic and perfectly biocompatible (Kulkarni et al., 1966). In addition, the properties of these polymers can be controled by their molecular

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weight and monomer composition. Therefore, there are numerous investigations underway on the use of these polymers with sustained-release bioactive agents (Wise et al., 1980; Wakiyama et al., 1981; Sanders et al., 1984; Jalil and Nixon, 1990). Nowadays, several parenteral dosage forms using these polymers are commercially available (e.g. Leuprin® (Takeda), Zoladex® (Zeneca); Ogawa et al., 1988; Furr and Hutchinson, 1992). However, designing a suitable formulation for a new drug using these polymers is a challenge, as drug release is affected by not only molecular weight and monomer composition, but also by the matrix shape, preparation method and polymer crystallinity (Ogawa et al., 1988; Jalil and Nixon, 1990; Wada et al., 1990; Aso et al., 1993; Jeyanthi et al., 1996; Mandal et al., 1996; Miyajima et al., 1997).

Furthermore, it has been reported that the physico-chemical properties of the incorporated drug in the polymer matrix are important factors in polymer degradation and drug release (Maulding et al., 1986; Cha and Pitt, 1989; Kishida et al., 1989; Bodmeier and Chen, 1991). Therefore, the interaction between drug and polymer can be critical with respect to sustained-release characteristics (Li et al., 1996; Takada et al., 1997). As PLA and PLGA have terminal carboxyl residues, basic drugs are anticipated to interact with the polymer and affect their own release profiles from the polymer matrix. In this case, two results are possible:

1. Drug release can be accelerated. Basic drugs behave as a base catalyst acting on the ester bonds in polymer chains; this behavior enhances the polymer degradation and, hence, drug release (Maulding et al., 1986; Cha and Pitt, 1989; Kishida et al., 1989).
2. Drug release can be suppressed. Basic drugs neutralize the polymer terminal carboxyl residues, so that the autocatalytic effect of acidic chain ends on polymer degradation is minimized (Bodmeier and Chen, 1991; Mauduit et al., 1993).

Therefore, the dissociation property of the incorporated drug seems of importance to the drug release manner. Kishida et al. (1989) reported that the higher the pK_a of the basic drug, the faster the drug release. In contrast, Cha and Pitt (1989) reported that the drug release rate did not correlate with pK_a nor with the octanol/water partition coefficient (log P) of drugs. Accordingly, it remains to be clarified how the ionic properties of the incorporated drug influence their release rates.

The purpose of this paper is to ascertain the relationship of the ionic property of drugs to their release profiles from the PLGA matrix. Generally, microspheres are the preferred dosage form for implants. However, drug release from microspheres is significantly affected by preparation conditions (Jalil and Nixon, 1990; Wada et al., 1990; Jeyanthi et al., 1996; Mandal et al., 1996), which can vary depending on the drug to be incorporated. Consequently, microspheres are not suitable for studying the effect of drug properties on release. In order to minimize the effect of preparation, we prepared a cylindrical drug-dissolved PLGA matrix by heat compression method from a low molecular weight PLGA with relatively rapid degradability and investigated the release mechanism of five basic, one acidic and two neutral drugs. We estimated the interaction between the drug and polymer by measuring the apparent partition coefficient of the drug between hydrated polymer and aqueous medium. The crystallinity of the drugs was observed using powder X-ray diffraction patterns. From these results, the qualitative influence of the physico-chemical properties of drugs on the release process is discussed.

2. Materials and methods

2.1. Materials

PLGA (PLG1600HL; 70:30 weight ratio of L-lactic acid to glycolic acid, 1500 number average molecular weight and 4500 weight average molecular weight) was purchased from Kokusan Chemical (Tokyo, Japan). Papaverine HCl was obtained from Iwaki Pharmaceutical (Tokyo, Japan). Diltiazem HCl and nicardipine HCl were obtained from Sigma (St. Louis, MO). Chlorpheniramine maleate and verapamil HCl were purchased from Wako Pure Chemical Industries

Table 1
Some physico-chemical parameters of drugs and UV detection wavelength using HPLC

Drug	Molecular weight	Log P[a]	pK_a	Solubility (mg/ml) at pH 7.3 at (37°C)	λ (nm)
Acid					
Naproxen (NP)	230.3	3.2	4.2	2.6	240
Neutral					
Testosterone (TES)	288.4	3.3	—	0.031	240
Griseofulvin (GF)	352.8	2.0	—	0.010	235
Base					
Chlorpheniramine (CP)	274.8	4.5	4.0,9.2	>100	260
Papaverine (PAP)	339.4	3.0	6.4	0.027	240
Diltiazem (DIL)	414.5	2.7	7.7	0.39	240
Verapamil (VP)	454.6	3.8	8.6	>1.2	230
Nicardipine (NC)	479.5	4.3	7.2	0.010	235

[a] P: octanol/water partition coefficient.

(Osaka, Japan). All basic drugs were used as free bases. The free bases of papaverine (PAP), diltiazem (DIL), chlorpheniramine (CP), verapamil (VP) and nicardipine (NC) were prepared as detailed below. Each drug salt was dissolved in water, except for NC, which was dissolved in 90% methanol. All solutions were neutralized with sodium hydroxide and the drugs converted to the free base form. Precipitated PAP was collected on a paper filter, washed with water and dried under vacuum (Miyajima et al., 1997). The other drugs were extracted with benzene (DIL) or dichloromethane (CP, VP, NC) from the above basic aqueous solutions. Crystallized DIL was obtained by evaporation of its benzene solution, followed by recrystallization in isopropylether. CP, VP and NC were obtained as oily compounds in dichloromethane by solvent evaporation. The acidic drug naproxen (NP) was obtained from Sigma (St. Louis, MO). The two neutral drugs testosterone (TES) and griseofulvin (GF) were purchased from Tokyo Kasei Kogyo (Tokyo, Japan) and Wako Pure Chemical Industries (Osaka, Japan), respectively. Some of the physico-chemical properties of these drugs are listed in Table 1. All other chemicals used were reagent grade.

2.2. Preparation of PLGA rods

Each PLGA rod, 1 mm in diameter and 10 mm in length, was prepared using the heat compression method as described in the previous paper (Miyajima et al., 1997). PLGA (500 mg) and each drug (5 or 10% of PLGA) were dissolved in dichloromethane (5 ml). Dichloromethane was evaporated from the solution, and the resultant mass was further dried in vacuum. The dried powder (10 mg) was compressed (100 kg/cm^2) into 1 mm diameter rods at 40–50°C, which is above the glass transition temperature (T_g) of the PLGA used. T_g for each of the rods was determined with a DSC (DuPont 2000, DE).

2.3. Release study

The release of a drug from a rod was examined in 10 mM phosphate buffered saline at pH 7.3 (PBS). A rod was placed in 50–200 ml of buffer in a flask that was shaken in a 37°C water bath at a frequency of 20 strokes/min. The release test performed on a drug-containing rod was repeated at least once. Five milliliters of the release medium was withdrawn periodically and replaced with an equivalent volume of fresh buffer. The amount of drug released was determined by HPLC (L6000 series, Hitachi, Japan). HPLC was used under the following condition: column, YMC-Pack ODS AM-312 150×6.0 mm I.D. (YMC, Tokyo, Japan); column temperature, 40°C; mobile phase, 10 mM KH_2PO_4/acetonitrile

(CP, PAP, DIL, VP: 6/4; NP, TES, GF, NC: 4/6); flow rate, 1.5 ml/min; detection, UV wavelength for each drug is listed in Table 1.

2.4. PLGA/PBS drug partition coefficient

PLGA is a biodegradable polymer, whose molecular weight decreases gradually with time in aqueous medium. As a result, the number of polymer carboxyl residues and the water content of the rod increases, and consequently the PLGA/aqueous medium partition coefficient of each drug is expected to vary with time. Therefore, for convenience, the partition at a fixed time point was selected as a representative value. This fixed time was determined based on the conditions that the polymer is hydrated sufficiently and the degradation of polymer is insignificant. The apparent partition coefficient (K_{app}) between hydrated polymer and aqueous phase was determined by the method given below.

About 10 mg of PLGA powder (W) was immersed in 20 ml of drug PBS solution (PAP, DIL, CP, VP, NP and TES: 20 μg/ml; NC and GF: 10 μg/ml) for 19.5 h at 37°C. K_{app} was determined from the initial and equilibrium drug concentration (C_0 and C_e, respectively) in the medium using Eq. (1).

$$K_{app} = \frac{20 \times (C_0 - C_e)}{W \times C_e} \quad (1)$$

2.5. Weight loss of PLGA rods

PLGA rods ($n = 3$) were immersed in PBS at 37°C for a predetermined time, then wiped and dried in a vacuum. Rod weight was measured in wiped and dried states. The water content in the rods was then determined from the wet and dried weight, and the weight loss was calculated from the difference between the dried weight and the original weight before immersion.

2.6. Drug crystallinity in PLGA rods during immersion in aqueous medium

The crystallinity of the drugs in the PLGA rods was examined using a powder X-ray diffractometer (RINT2000, Rigaku Denki, Japan). The X-ray source was copper Kα (40 kV, 40 mA), and the scanning speed was 4 degrees/min.

3. Results and discussion

3.1. PLGA rods

The PLGA rods prepared were transparent. Fig. 1 shows the powder X-ray diffraction patterns of PLGA rods containing PAP, TES or NP. No crystalline forms for any of the drugs were detected before immersion. These results suggest that the drugs completely dissolved in the PLGA matrix for rods containing up to 10% drugs (Miyajima et al., 1997). It has been reported that high molecular weight PLGA of L-lactic and glycolic acid (75/25) is intrinsically amorphous, but transforms to a semicrystalline state during immersion in aqueous medium (Therin et al., 1992). However, the PLGA used here had low molecular weight, so it retained its amorphous state throughout the release study. This was confirmed by X-ray diffraction analysis (Fig. 1).

3.2. Influence of basic drug property on their own release

As shown in Fig. 1(A), the powder X-ray diffraction pattern shows the absence of any PAP crystals even at the end of the release study. The PLGA rods containing the other basic drugs provided the same diffraction patterns as the rod containing PAP. These results indicate that the basic drugs remained dissolved in the matrix throughout the release study. Release profiles of CP, PAP, DIL, VP and NC from the PLGA rods are shown in Fig. 2, and the released percentage for 1 day is shown in Table 2. It is apparent that the release rate of these basic drugs does not exhibit any relationship to their log P, pK_a and solubility in PBS (Table 1). This result is consis-

tent with observations by Cha and Pitt (1989) but not with Kishida et al. (1989).

Incorporation of the various basic drugs raised the T_g of the PLGA rods (Table 2), presumably due to interactions between the carboxylic group of the polymer and the drugs as reported (Okada et al., 1994; Miyajima et al., 1997; Takada et al., 1997).

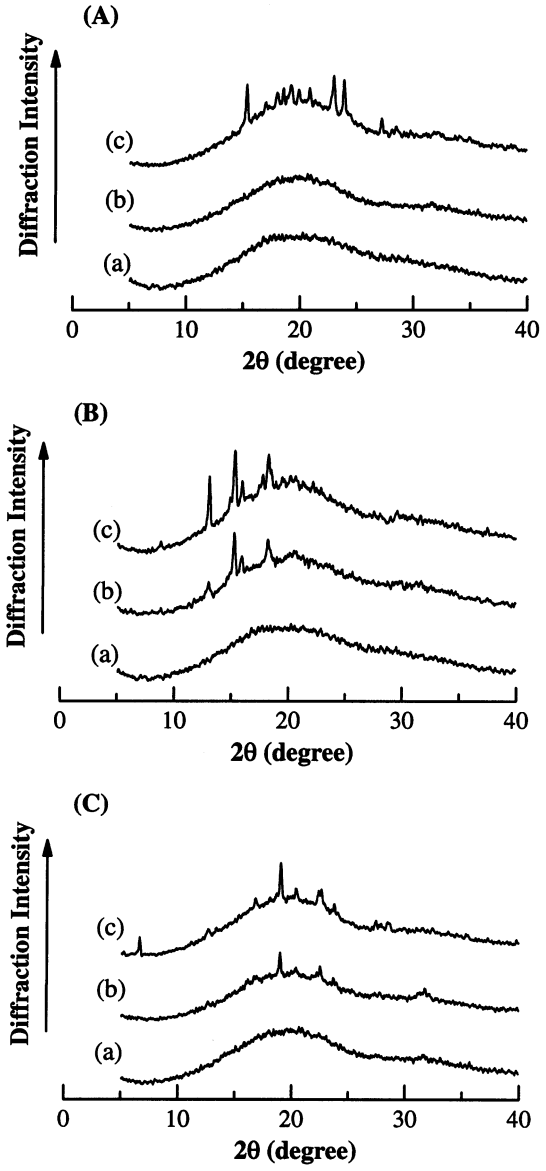

Fig. 1. Powder X-ray diffraction patterns of PLGA rods containing 10% (A) PAP, (B) TES and (C) NP; (a) before immersion, (b) after 7 days (A) or 1 day (B and C) immersion in PBS at 37°C, and (c) physical mixture of PLGA and drugs.

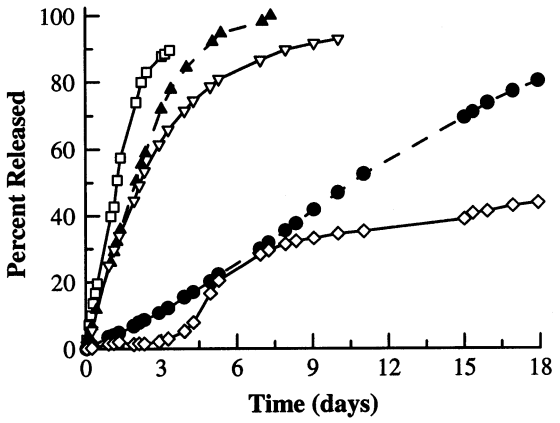

Fig. 2. Drug release profiles from PLGA rods containing 10% basic drugs in PBS at 37°C: (□) CP, (▲) PAP, (▽) DIL, (●) VP and (◇) NC.

However, the differences in the T_g of each matrix were not very significant, and it was difficult to correlate T_g with the drug release rate (Fig. 2 and Table 2).

We then evaluated the strength of the interaction between the polymer and the drugs more precisely using K_{app} values (Table 2) instead of T_g. K_{app} values is a factor expressing not only the ionic interactions between the polymer carboxyl residues and basic drugs, but also the weak interactions such as van der Waals forces, hydrogen bonds or hydrophobic interactions between the polymer main chains and the drugs. The order of K_{app} (Table 2) was found to be CP < PAP < DIL < VP < NC; this order was the same as the order of the drug release rate from the matrix (Fig. 2 and R_1 in Table 2). Therefore, K_{app} is apparently a determi-

Table 2
K_{app} of drugs; T_g of PLGA rods; and water content (H_1), weight loss (W_1) and drug released (R_1) of the PLGA rods after 1 day of immersion in PBS at 37°C

Drug	K_{app}	T_g (°C)	H_1 (%)	W_1 (%)	R_1 (%)
None	—	29.9	831	28.1	—
CP	624	42.2	237	15.0	39.9
PAP	818	45.3	277	13.7	26.5
DIL	1418	44.5	164	10.0	25.1
VP	3543	41.5	85	4.4	6.9
NC	6409	44.6	70	3.8	1.1

nant parameter of release rate of the basic drugs, and this correlation is presumably based on the interaction between the polymer and the basic drugs.

Generally speaking, in a low molecular weight PLGA matrix such as the one used here, both erosion of matrix and diffusion through the hydrated matrix are responsible for the drug release (Jalil and Nixon, 1990). In the following section, we discuss the effect of the polymer/drug interaction on both erosion and diffusion in detail.

It is known that the polymer degradation is affected by the incorporated drug (Maulding et al., 1986; Cha and Pitt, 1989; Kishida et al., 1989; Bodmeier and Chen, 1991). We investigated the effect of the polymer/drug interaction on the erosion of the PLGA rods. The weight loss (W_1) of the rods after 1 day of immersion in PBS is shown in Table 2. It is apparent that the W_1 value for a rod containing a basic drug is smaller than that for the drug-free rod. This result indicates that these drugs do not behave as base catalysts, but neutralize the polymer terminal carboxyl acid residues to suppress the autocatalytic effect on the polymer degradation (Bodmeier and Chen, 1991; Mauduit et al., 1993). For almost all drugs K_{app} is inversely proportional to W_1.

The interaction between the polymer and basic drugs is thought to be mainly based on ionic attraction. Accordingly, the ionic terminal of the polymer is shielded and the hydrophilicity of the matrix is reduced, so that the water content (H_1) in the rod is decreased (Table 2). In a hydrated matrix, drug diffuses through water channels between polymer chains. Therefore, the lower content of water in the polymer matrix causes slower diffusion of the drug through the matrix, as Yasuda et al. (1969) reported. Though the intrinsic diffusion coefficient of drugs in water is decreased with increasing drug molar volume (Flynn et al., 1974), the estimated diffusion coefficient of NC, which has the largest molar volume, is as far above 0.7 as that of CP, which has the smallest molar volume. Consequently, our results can be considered to show that drug release by diffusion becomes much slower for a basic drug with larger K_{app}.

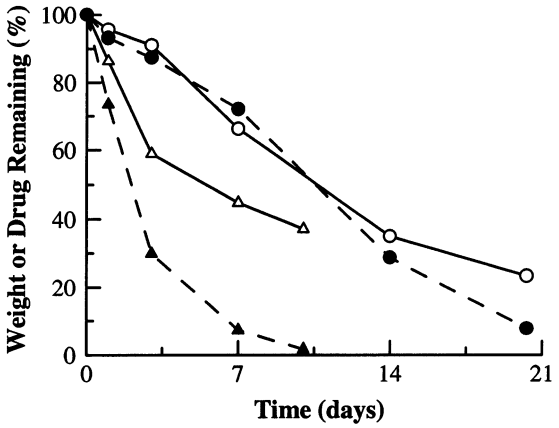

Fig. 3. Changes in rod weight (△, ○) and drug remaining in the rods (▲, ●) in PBS at 37°C: (△, ▲) containing 10% of PAP, (○, ●) containing 10% of VP.

In the extreme case of drugs with the strongest polymer/drug interaction, such as VP and NC, the drug release is predominantly governed by matrix erosion (Table 2). Fig. 3 shows the decreasing trends of rod weight and drugs remaining in the rod containing VP and PAP. In the rod containing VP, there is no significant difference in the relative change of rod weight to matrix-fixed drug for 14 days. In contrast, a difference is obvious in the rod containing PAP, which has weaker interaction with the polymer. From these results, it is concluded that the release of VP from the rod is predominantly controled by matrix erosion, but the release of PAP is controled by both erosion and diffusion through the matrix.

3.3. Effect of basic drug content on release profile

Fig. 4 shows the profiles of the fraction of drug released from rods containing either 5 or 10% of the basic drugs PAP or VP. In both drugs, the percent release rate from the 5% rod was larger than that from the 10% rod.

The H_1 and W_1 of the rod after 1 day of immersion in PBS at 37°C are shown in Table 3. A higher drug content resulted in smaller H_1 and W_1, as expected. This relationship indicates that in the 10% rod a larger fraction of the polymer carboxyl residues are held by the interaction with the basic drug, slowing the release.

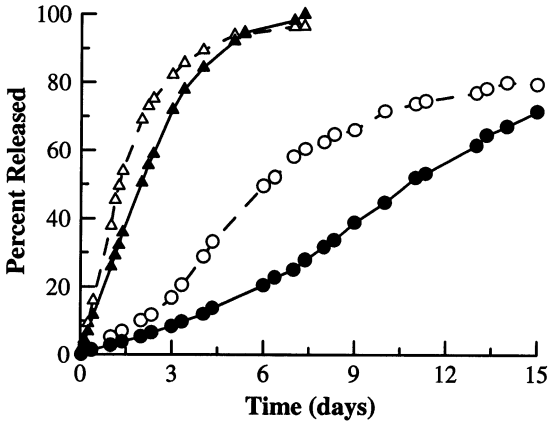

Fig. 4. Effect of drug content on release profiles from the PLGA rods containing basic drugs. PAP content: 5% (△) and 10% (▲), VP content: 5% (○) and 10% (●).

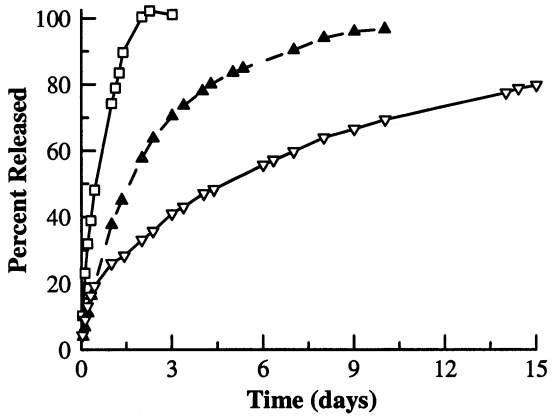

Fig. 5. Drug release profiles from PLGA rods containing 10% of acidic or neutral drugs in PBS at 37°C: (□) NP, (△) TES and (▽) GF.

As shown in Table 3, the T_g of the 10% rod is higher than that of the 5% rod. The significantly larger number of polymer/drug interactions due to increased drug content are likely reflected in the rise of T_g as these interactions made the matrix more rigid. By implication, the effect of drug content on the release is a function of the T_g of the rod. These results are consistent with Okada et al. (1994), who reported an increase in T_g of the PLGA microspheres with increasing basic drug content, resulting in a depression of the initial burst of drug release.

3.4. Influence of acidic and neutral drug property on their own release

The basic drugs remained dissolved in the matrix throughout the release study (Fig. 1(A)). In contrast, NP and TES precipitated in the matrix as crystals within 1 day of immersion in the release medium as shown in Fig. 1(B, C). These drugs were dissolved in the PLGA matrix before immersion (a). However, drug crystals appeared in the matrix after 1 day of immersion (b), as shown by the diffraction pattern that was nearly identical to that for a physical mixture of PLGA and these drugs (c). The PLGA rods containing GF provided similar results (data not shown). Therefore, it was revealed that the PLGA rods containing these drugs transformed into a drug-dispersed matrix due to water penetration into the matrix.

Fig. 5 shows the drug release profiles from PLGA rods containing 10% of each drug. The K_{app} of the drugs and T_g of the PLGA rods as well as the water content in, weight loss of and amount of drug released from the rods after 1 and 7 days immersion in PBS at 37°C are shown in

Table 3
T_g of PLGA rods; and H_1, W_1 and R_1 of the rods after 1 day of immersion in PBS at 37°C

Drug	Content (%)	T_g (°C)	H_1 (%)	W_1 (%)	R_1 (%)
None	—	29.9	831	28.1	—
PAP	5	39.7	670	22.0	44.6
	10	45.3	277	13.7	26.5
VP	5	34.4	131	7.4	8.7
	10	41.5	85	4.4	6.9

Table 4
K_{app} of drugs; T_g of PLGA rods; and water content (H_1), weight loss (W_1, W_7) and drug released (R_1, R_7) of the rods after 1 and 7 days of immersion in PBS at 37°C

Drug	K_{app}	T_g (°C)	1 day			7 days	
			H_1 (%)	W_1 (%)	R_1 (%)	W_7 (%)	R_7 (%)
None	—	29.9	831	28.1	—	54.2	—
NP	4	26.6	442	22.4	74.2	58.2	100
TES	23	32.6	691	32.7	40.4	56.1	88.1
GF	325	38.2	629	22.6	26.0	47.1	52.2

Table 4. Apparently, the K_{app} values of the acidic and neutral drugs are smaller than those of basic drugs (Tables 2 and 4). The low K_{app} values of the acidic/neutral drugs are attributable to the absence of drug-polymer carboxyl group ionic interactions. Among these drugs, GF had the largest K_{app} value, corresponding to the highest T_g value (Table 4). This observation suggests that the interaction between the polymer main chain, not the carboxyl residue, and the drug is the strongest for GF. In contrast to the basic drugs, for acidic and neutral drugs, no clear general correlation between K_{app} and either the water content or the weight loss existed (H_1, W_1 and W_7 in Table 4). This is because the rod containing acidic or neutral drugs converts to a drug-dispersed matrix within a day. Hence, it is implied that the K_{app} is not a determinant factor which can be used to predict the release profile from a PLGA rod containing an acidic or a neutral drug.

Considering the release mechanism, both erosion rate of the matrix and diffusion through the hydrated matrix vary depending on the basic drug contained, as described previously. However, rates of erosion for the rods containing NP, TES and GF were almost the same as their similar weight loss values shown in Table 4. This intimates that among these rods are no significant differences in the drug release by matrix erosion; therefore, the diffusion component must be different. Higuchi (1961) developed the well-known theory for drug release controled by Fickian diffusion; his theory can be applied to drug-dispersed matrices. According to his theory, the higher the drug solubility in the matrix, the greater the release rate of the drug. In this study, the water content of the rods containing the acidic or neutral drugs is considerable (H_1 in Tables 2 and 4) because of the lack of ionic interaction between the polymer and these drugs. Thus, the drug solubility in PBS should represent that in the hydrated matrix. The solubilities of NP, TES and GF in PBS at 37°C were 2.6, 0.031 and 0.010 mg/ml, respectively (Table 1). This order of solubility agrees with the order of the drug release rate given in Fig. 5. Therefore, it can be supposed that the release from the drug-dispersed rod containing these acidic or neutral drugs is controled by the drug solubility in the hydrated matrix.

4. Conclusion

In conclusion, the properties of the incorporated drugs in the drug-dissolved PLGA matrix are responsible for the time variation of the drug release profile as all rods were prepared in the same manner and matrix preparation was therefore not a contributing factor. It is clarified whether the polymer/drug interactions exist or not is a critical factor in drug release. Basic drugs strongly interact with and shield the polymer carboxyl residues, with the result that the matrix becomes more rigid and less hydrophilic. Consequently, both processes of drug release—erosion of the matrix and diffusion through the matrix—are suppressed. Hence, the release rate of a basic drug can be qualitatively estimated based on the strength of the interaction represented by K_{app}. On the other hand, the acidic and neutral drugs have weaker interactions with the polymer due to the absence of ionic interactions with the terminal

carboxyl residues. Therefore, these drugs precipitated out as crystals in the matrix within a day after immersion in PBS, transforming the rods into a drug-dispersed matrix. In this case, the erosion rate of the matrix is not affected by the incorporated drugs. Hence, the solubility of the drug in the highly hydrated polymer matrix is the decisive factor for the release rate and this solubility can be evaluated from the aqueous solubility of the drug.

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