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Drug release from injectable depots: two different in vitro mechanisms

Liwei Wang[a], Subbu Venkatraman[a,*], Lothar Kleiner[b]

[a]School of Materials Engineering, Nanyang Technological University, N4.1-1-30 Nanyang Avenue, Singapore 639798, Singapore
[b]Guidant Corporation, 3200 Lakeside Drive, Santa Clara, CA 95054-2807, United States

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Abstract

Certain poly (lactide-*co*-glycolide) (PLGA)/benzyl benzoate (BB) solutions can form gels when injected into buffer (depot formation) as well as upon ageing under ambient conditions. When evaluating various PLGAs in benzyl benzoate, we have found that only those that gel upon ageing also form gel depots in buffer. This indicates that depot formation in this system may be fundamentally different from the phase inversion depot formation that has been observed for PLGA in water-miscible solvents. The drug release kinetics in vitro is controlled both by diffusion and erosion, with the base form of the drug being always released faster than its salt form. This is due to base-catalyzed hydrolysis. While gel permeation chromatography (GPC) measurements show a continuous decrease in molecular weight, the rheological properties upon buffer injection show maxima, for the base drug and the salt drug. The location of the viscosity maximum with time is dependent on the nature of the drug and its concentration.

Keywords: Poly (lactide-*co*-glycolide) (PLGA); Benzyl benzoate (BB); Gelation; Metoclopramide; In vitro

1. Introduction

A recent series of patents [1–3] and publications [4–12] has disclosed a novel delivery approach to prolonged drug release over a 2 week to 6 months duration. These innovative systems, which are easier to administer and better accepted by patients than existing delivery solutions, are prepared by dissolving biodegradable polymers in biocompatible organic solvents. Drug is added into the polymer solution, where it forms a homogenous solution or a suspension depending on its solubility. The drug suspension or solution is injected subcutaneously, forming an "in situ implant", which slowly releases the drug over time. Atrix Laboratories has pioneered this approach [13].

Several formulations have been studied using polymers such as polylactide, poly (lactide-*co*-glycolide) (PLGA), or poly (ε-caprolactone) [15] in solvents such as *N*-methyl-2-pyrrolidone (NMP) [5,6,10,14], dimethyl sulfoxide (DMSO) [4,10,16], glycofurol

* Corresponding author. Tel.: +65-6790-4259; fax: +65-6790-9081.
E-mail address: assubbu@ntu.edu.sg (S. Venkatraman).

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[polyethylene glycol monotetra-hydrofurfuryl ester] [7,8] and triacetin [9,17]. These solvents are fully or partially water-miscible, and hence the in situ gels or implants were formed by a nonsolvent induced phase separation (NIPS) mechanism. The mass transportation (drug release) kinetics is associated with the phase inversion rate and the gel/implant morphology. Due to this mechanism, many of these systems display an initial burst. The initial burst can be problematic with potent drugs that have a narrow therapeutic window, such as many chemotherapeutics (5-FU, carbamazepine), and certain hormones, such as human growth hormone.

Researchers at ALZA have refined the system to minimize the "burst effect," which is accomplished through control of the internal depot morphology and constant drug dissolution rates. These workers also reported that solutions of low molecular weight PLGA polymers (M_w=12,000 to 20,000; L/G=50/50) in benzyl benzoate (BB) provide stabilization of macromolecules and a long-lasting delivery profile without initial burst [14]. The PLGA/BB system is claimed to be a slow phase inversion system, and the slower phase inversion kinetics leads to membranes that are very smooth and have much smaller pore sizes than with solvent-miscible systems (the NMP membranes are spongelike in comparison). This morphological difference may account for the observed lower burst effect in the PLGA/BB system.

We have previously found that the PLGA/BB solution forms a three-dimensional structure during ageing [18]. In this paper, we extend the study of the structure formation (gelation) to drug-containing systems upon injection into buffer, as well as to the in vitro drug release kinetics. Both the base and salt forms of metoclopramide were used as low molecular weight model drugs. Their release kinetics were investigated and compared.

2. Materials and methods

2.1. Materials

Poly (D,L-lactide-*co*-glycolide)s used in this experiment were purchased from different companies, as listed in Table 1. The molecular weights were determined by gel permeation chromatography (GPC) using an Agilent series 1100 GPC. Reagent grade benzyl benzoate (BB) from Aldrich was used as solvent. Metoclopramide monohydrochloride (salt) was purchased from Sigma-Aldrich, and the base form was made in our laboratory as follows: the salt form is reacted stoichiometrically with NaOH, and the resulting precipitate is washed repeatedly until constant pH is attained; this solid is then recrystallized from DCM solution. The phosphate buffer (pH 7.0) was purchased from Merck.

2.2. Preparation of PLGA solutions

The PLGA was mixed with BB at a mass ratio of 50/50. The mixture was stirred periodically and kept at

Table 1
Copolymers/homopolymer used for the preparation of formulations

Polymer PLGA/PDLA	Manufacturer	L/G[a] ratio	Inherent viscosity[b] (dl/g)	M_w (GPC)[c]
Resomer RG502[d]	Boehringer Ingelheim	52/48		17,000
Resomer RG502H		53/47		14,460
A137-28	Absorbable Polymer Technologies	100/0	0.20	15,000
A137-29		75/25	0.19	15,000
A137-31		54/46	0.22	11,150
APT071603-1		53/47	0.19	16,000
PURASORB PDLG	PURAC Biochem bv.	52/48	0.13	10,080
PURASORB DL 655FK		53/47	0.47	45,000

Resomer RG502 is terminated with $-COOC_2H_5$.
A137-31 is terminated with lauryl ester.
All others terminated by –COOH.
[a] As specified in certificate analysis.
[b] Inherent viscosity of as-received raw polymer, in chloroform, 25 °C.
[c] Molecular weight as determined by GPC in lab.
[d] Polymer as a present from ALZA, Palo Alto, CA.

37 °C overnight, until a slightly amber, transparent solution was achieved. This solution was then capped and heated to 65 °C to remove trapped air bubbles. For in vitro release and degradation experiments, metoclopramide salt and base was mixed into the PLGA/BB solution. The drug was milled and sieved to a diameter less than 100 μm, dispersed in the PLGA/BB solution, and homogenized. Since the ageing process led to structure formation and the structure formation may be minimized or eliminated by storing PLGA/BB solutions at low temperatures, the PLGA/BB solution is stored at 10 °C prior to experimentation.

2.3. In vitro study

Polymer solutions with/without drug (total solution weight ~500 mg) were homogenized and injected after removing bubbles into 20-ml vials into which 10 ml pH 7.00 phosphate buffer would be added thereafter. The vials were kept at 37 °C using a Grant Sub14 water bath. Receptor solution was replaced at proper intervals in order to maintain pH and a sink condition for drug release. A series of measurements were carried out. Tests were carried out at least in duplicate in order to estimate the repeatability of operation. Average values of at least two consistent results were plotted.

2.3.1. In vitro degradation in buffer

The degradation of PLGA in this report was characterized by molecular weight change. The samples in vitro were taken out at various time points, dried under vacuum at ambient temperature immediately and then dissolved in appropriate solvents subjected to gel permeation chromatography (GPC) analysis. The following conditions were adopted: the mobile phase was an 80:20 solvent mixture of tetrahydrofuran and dichloromethane at a flow rate of 1 ml/min and a temperature of 35 °C. Average molecular weights were calculated using a series of polystyrene standards that ranged from 162 to 5,000,000 in their molecular weight.

2.3.2. Liquid–liquid demixing

PLGA solutions (about 500 mg) without drug were injected into buffer solution, the amount of solvent released into the buffer was analyzed by reversed-phase HPLC. The chromatographic analysis is performed on an Agilent 1100 Series instrument equipped with a VW detector and a ZORBAX 300SB-C18 column. Acetonitrile/water (60/40 v/v) with 80 mM trifluoroacetic acid (TFA) is used as mobile phase and the eluent absorbance was monitored at 278 nm.

The water content and its distribution in the PLGA/BB depots were also monitored. A Mitsubishi moisture meter model CA-06 Karl Fisher titration was used to determine the moisture in solvents and the in vitro samples from different time points. The in vitro samples were dissolved in a water-miscible solvent, such as NMP, in order to ensure the water inside the samples is completely titrated. The moisture content of the NMP and its solutions was determined.

2.3.3. Rheological properties of PLGA/BB solution

For this study, in vitro PLGA/BB samples were periodically removed and analyzed for rheological properties using a ThermoHaake Rheostress 300 rheometer designed to measure relatively high-viscosity samples. The strain amplitude (γ=0.005–0.02) or the stress amplitude (τ=10 Pa) was kept low enough that structures formed, if any, were not disrupted by measurement. For those samples containing drug, the experiments were performed on a cone-and-plate fixture having a diameter of 20 mm and a cone angle of 4° while a cone angle of 1° was used for drug-free samples.

2.3.4. Drug release

Drug concentration in receptor solution at proper intervals was determined by ultraviolet (UV) absorbance spectrophotometer (UV-2501, SHIMADZU). A pure solution without drug was also analyzed at the same time point for comparison.

3. Results and discussion

3.1. Degradation process of PLGA/BB solutions: ageing effects and after injection into buffer

Fig. 1a shows the changes of PLGA (RG502)/BB solutions by weight average molecular weight after injection into pH 7.00 buffer kept at 37 °C. The molecular weight of all the solutions decreased immediately after placement in buffer and continued to decrease throughout the time course of the study. The solution with metoclopramide base displayed the

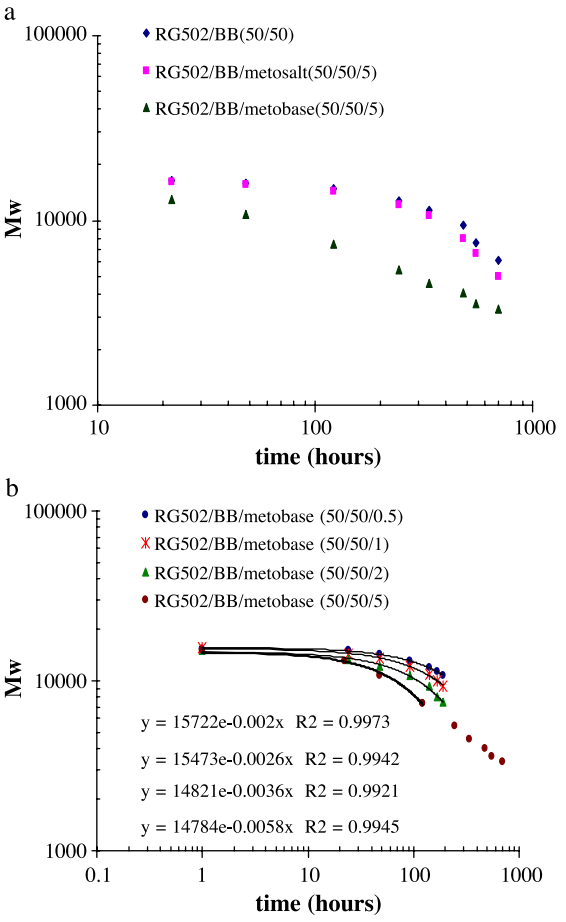

Fig. 1. (a) In vitro degradation of PLGA (RG502)/benzyl benzoate solution with/without drug, where drugs are metoclopramide salt and base, and the formulation is PLGA/BB/drug=50/50/5 by weight. (b) Effect of metoclopramide base loadings on the degradation of PLGA (RG502)/benzyl benzoate formulations: the pseudo first-order kinetics analysis is shown for different drug loadings concentration within the first 200 h.

fastest degradation, followed by solutions with metoclopramide salt and the solution without drug. For solutions with different metobase loadings, the degradation rate increased with the drug loading (Fig. 1b). The degradation rate constant (within the initial 200 h) is proportional to the drug loading suggesting the coexistence of catalyzed reaction and noncatalyzed reactions, where

$$r = r_0 + r_c = (k_0 + k_c[C])[A] = k[A]$$

$$k = k_0 + k_c[C]$$

Table 2a
GPC results for PLGA/BB solutions aged at 10 °C

Ageing conditions	Samples	M_w
Fresh preparation	PLGA/BB	17,006
Aged at 10 °C for 43 days	PLGA/BB	16,810
	PLGA/BB/metoclopramide salt	17,093
	PLGA/BB/metoclopramide base	15,694

where r and k are total reaction rate and rate constant, r_0 and k_0 are reaction rate and rate constant without catalysis, r_c and k_c are reaction rate and rate constant of catalyzed reaction, and $[A]$ and $[C]$ are concentrations of reactant and catalyst, respectively. A plot of the overall rate constant against base drug concentration $[C]$, gives a straight line: k=0.0017+0.02$[C]$, indicating that $k_c \gg k_0$.

This catalytic effect apparently contributes more to the overall rate constant than auto-catalysis by terminal end groups, which exist in the case of the salt drug, and for drug-free polymer. In other words, the base drug accelerates the hydrolysis much more than other factors.

The same samples, when aged at different temperatures in closed vials (no injection into buffer) also show similar decreases in M_w. This set of data is shown in Tables 2a and 2b. The trends parallel those observed in Fig. 1, in the sense that the base drug-containing formulation shows faster degradation in ageing as well as after buffer injection. This general phenomenon of base catalysis of PLGA degradation has been observed in our labs using films with the same drug or lidocaine salt/base and elsewhere [19–21]. For example, Li et. al. reported that basic additives have two opposite and different effects, i.e. base catalysis of ester bond cleavage when the drug is in excess with respect to acid chain ends, and decrease of degradation rate when base drug is not in excess [19].

The results shown in Tables 2a and 2b also suggest a temperature effect on the hydrolysis of PLGA, which is substantial for the formulation containing base drug. The relationship between rate of degrada-

Table 2b
GPC results for PLGA/BB solutions aged at 25 °C

Ageing conditions	Samples	M_w
Fresh preparation	PLGA/BB	17,006
Aged at 25 °C for 43 days	PLGA/BB	16,970
	PLGA/BB/metoclopramide salt	16,873
	PLGA/BB/metoclopramide base	12,871

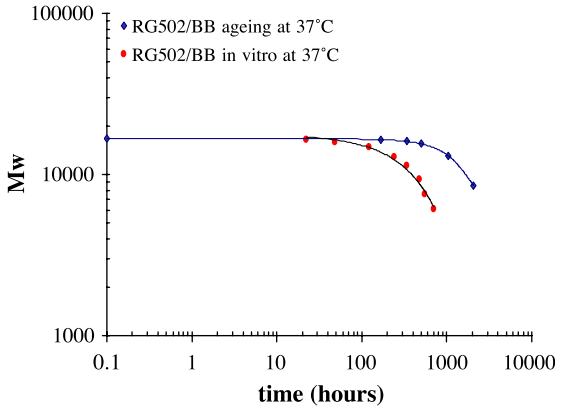

Fig. 2. The change of PLGA mass molecular weight, PLGA (RG502)/benzyl benzoate (50/50) solution aged and in vitro at 37 °C.

tion and temperature has been discussed in our previous study [18].

Theoretically, hydrolysis would not occur if there were no water in the system. However trace amounts of moisture present in the polymer and solvent can initiate the hydrolysis. Even extensive drying is unable to get rid of this residual moisture. The extent of degradation is much less during the ageing process than in the in vitro experiment (Fig. 2), as expected from the relative amounts of water available in the two experiments.

3.2. Liquid–liquid demixing

It is well known that PLGA solutions may be used as an injectable system that forms drug depots in situ.

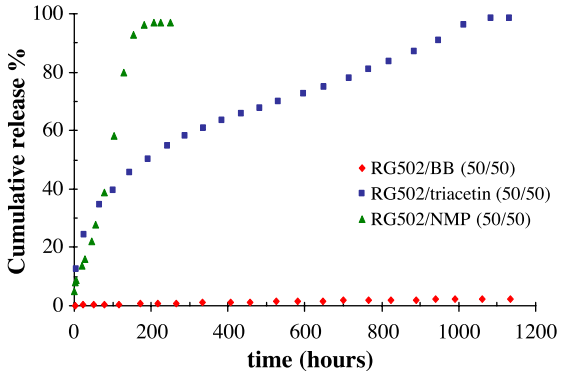

Fig. 3. The amount of solvent released into the buffer as a function of time, PLGA (RG502) solutions in vitro in pH 7.0 buffer at 37 °C: the formulation is PLGA/solvent=50/50 by weight.

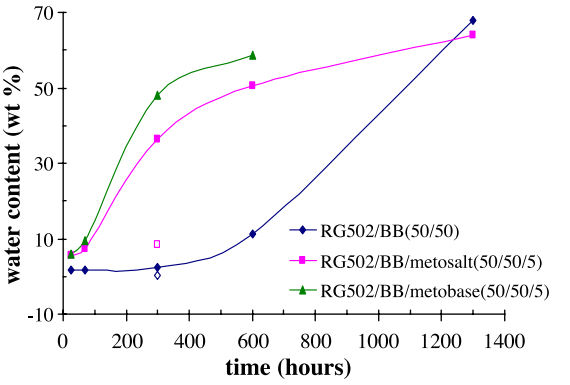

Fig. 4. Water content in RG502/BB depots with/without drugs during in vitro: filled legends represent the water content in the whole depot (including core and surface), while unfilled □ represents the water content in the core of RG502/BB/metosalt system, unfilled ◇ represents the water content in the core of RG502/BB system (only at one time point).

The depot formation is based on the mechanism of nonsolvent induced phase separation (NIPS), similar to that involved in membrane formation. The basic NIPS concept requires a polymer that does not dissolve in the bath side liquid, and polymer solvent that is fully or partially miscible with the bath side liquid. Liquid–liquid demixing is a necessary process that is responsible for initiation and growth of the solidified structure.

We show the release of solvent into buffer, as a measure of liquid–liquid demixing, in Fig. 3. It can be seen that NMP, a water-miscible solvent, showed the fastest release kinetics. The NMP released completely within 200 h. Triacetin migrated into buffer phase more

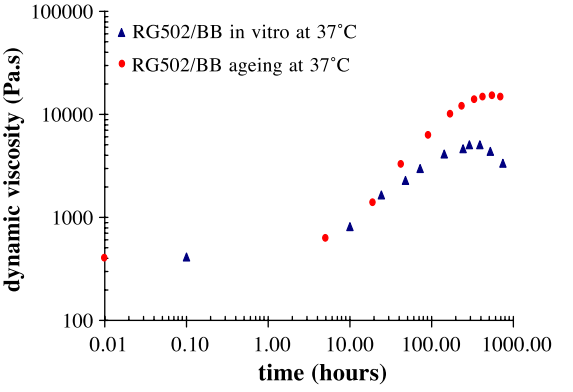

Fig. 5. The flow properties of PLGA (RG502)/benzyl benzoate solution during in vitro and upon ageing at 37 °C: the formulation is PLGA/BB=50/50 by weight.

Table 3
Gel formation kinetics

Samples	Composition	Injection into buffer, $t_{\eta max.}$ (h)	Ageing, $t_{\eta max.}$ (h)
RG502/BB	50/50	330	520
RG502/BB/metosalt	50/50/1	300	
RG502/BB/metosalt	50/50/5	300	
RG502/BB/metobase	50/50/1	90	
RG502/BB/metobase	50/50/5	75	
RG502H/BB	50/50		≈900; η^* increased slowly, but system has not gelled
APT071603-1	50/50	90	590
A137-28	50/50	*	*
A137-29	50/50	*	*
A137-31	50/50	*	*
DL655FK (Purac)	50/50	*	*

*Does not gel either upon ageing or upon injection into buffer.

slowly; for benzyl benzoate, due to its limited solubility in water, the total release was less than 3% after 1100 h.

We also monitored the water content and its distribution in the PLGA (RG502)/BB depots. The results in Fig. 4 show the estimation of water content in the depot after buffer injection. Although the data are subject to some error, certain features may be inferred. Water mainly locates at the surface layer of the depot, especially during the early stages. Water penetrates the depot later as a result of leaching out of drugs or degraded polymer products from the depot, and exists mostly as macrophase separated water vesicles. Very little water diffuses into the core of the depot. The presence of drugs undoubtedly increased the rate of water ingress into the core of the depots. For the depot containing base drug, the interface between surface layer and core disappeared early from about 250 h, which is consistent with the aforementioned base-catalyzed degradation effects.

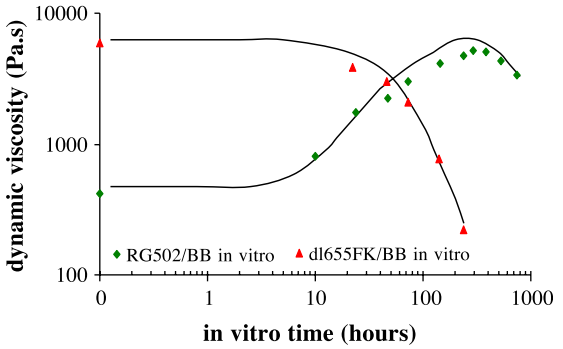

Fig. 6. Viscosity change of PLGA/benzyl benzoate (50/50) solutions during in vitro: different polymers compared.

From above results, we may infer that NMP and triacetin systems form depots via a NIPS mechanism. In the case of BB system, the amount of BB diffused-out is limited. At the same time, the influx of water leads to hydrolysis of PLGA that results in reduced viscosity. Thus, the PLGA/BB system may not form a "depot" upon injection into buffer via a NIPS mechanism which requires macroscopic phase separation. However, certain PLGA/BB systems do form gels upon buffer injection, and lead to a different kind of in situ implant.

3.3. Gelation properties of PLGA/BB (50/50) solutions observed by rheological measurement

The PLGA/BB system has been claimed to be a slow phase inversion system when used as an

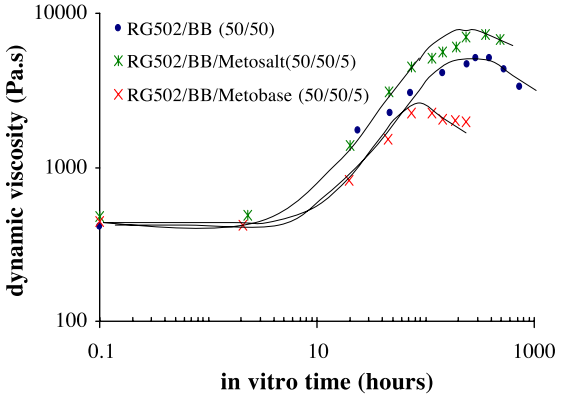

Fig. 7. The flow properties of PLGA (RG502)/benzyl benzoate solution with/without drug during in vitro: the formulation is PLGA/BB/drug=50/50/5 by weight.

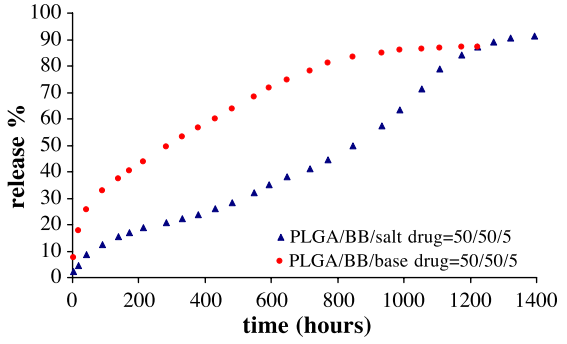

Fig. 8. Release kinetics of metoclopramide salt and base from PLGA (Resomer 502)/benzyl benzoate system: the formulation is PLGA/BB/drug=50/50/5 by weight.

injectable depot. Among the different systems we investigated, all NMP solutions of PLA/PLGA can form semisolid depots after injection into buffer; this is certainly due to a nonsolvent induced phase separation mechanism. Triacetin solutions also behave similarly. However, in the case of the PLGA/BB system, not all PLGAs are capable of forming a semisolid depot upon buffer injection. Such nongel forming solutions were fluid (observed by simply tilting the vials) during the whole period of experiment, while the gel formers produced depots but without a solidified skin as in the case of the NMP solutions. The gel formation can be conveniently monitored using the viscosity.

Fig. 5 shows an increase of dynamic viscosity over time for RG502/BB solution in vitro at 37 °C in pH 7.0 buffer. The amount of BB remains fairly constant, throughout the time scale of this experiment, as measured by HPLC. The viscosity increases, and reaches a maximum before decreasing. This behavior parallels the rheological behavior observed upon ageing [18] (no buffer injection), except for a shift on the time scale to longer time.

We compare the dynamic flow properties of different PLGA (PDLA)/BB solutions after buffer injection and during ageing as shown in Table 3. We attribute the viscosity increase upon ageing to three-dimensional structure formation (gelation) that is thermoreversible [18], and believe a similar mechanism is causing gel formation upon injection into buffer, except that the gel forms more rapidly after the buffer injections. The structure formation leads to a viscosity increase, which is eventually negated by molecular-weight decrease, so that a maximum is observed in the viscosity–time plots.

In contrast to the gelation behavior of the above polymer, we find that those polymers that do not form gel during ageing such as PLGA 53/47 (DL655FK from Purac), initial M_w=45,000, also do not exhibit gel formation upon injection into buffer, from BB solutions. See Fig. 6. For this polymer, the viscosity decreases continuously over time, as would be expected of degrading polymers that do not form structures (or gels).

The flow properties of RG502/BB solutions with drug (metoclopramide salt and base) are shown in Table 3 and Fig. 7. For the solutions with drug, the dynamic viscosities of these solutions show an initial increase followed by an eventual decrease. The onset of this decrease occurs earlier when base drug is used, indicating accelerated hydrolysis kinetics.

Evaluating the structural parameters of these polymers and others listed in Table 1 by ^{1}H and ^{13}C NMR, we find that the gel formation (and hence depot formation) is predominantly dependent on local stereo-regularity or the "blockiness" of the GA units in the copolymer. Details of this work have been

Table 4
Calculation of drug release kinetics by linear regression based on: $Q(t) = a + k\sqrt{t}$

Samples	Composition	Time (h)	k Value		R^2
			Experiment	Theoretical	
RG502/BB/metosalt	50/50/1	24–500	68.384		0.994
RG502/BB/metosalt	50/50/1.82		110.05	91.88	0.987
RG502/BB/metosalt	50/50/5		228.68	149.97	0.996
RG502/BB/metosalt	50/50/10		533.01	207.21	0.985
RG502/BB/metobase	50/50/1	100–900	102.59		0.998
RG502/BB/metobase	50/50/5		643.03	224.99	0.997
RG502/BB/metobase	50/50/10		2002.2	310.86	0.998

submitted as a separate paper, but we explain the blockiness as follows: it is the number-average glycolide sequence length, and is related to the probability of finding glycolyl units on the glycolide–lactide copolymer. For a perfectly random copolymer, this sequence length is unity. The ordered gel structure is found to form only for polymers that have glycolide block lengths above about 2.9 (number average). For polymers with glycolide lengths below this value, no gel formation is observed. This may imply that a certain amount of local stereo-regularity is necessary for structure formation, which is similar to what is observed in the atactic polystyrene/solvent system [22].

Gelation upon ageing correlates well with in vitro depot formation, thus indicating that the depot formation mechanism is fundamentally different from phase inversion, which is observed for the same polymer in a water-miscible solvent such as NMP. Depot formation in the BB system appears to be due entirely to the formation of an ordered three-dimensional structure, and not due to phase inversion.

The above discussion focused on the properties of PLGA solutions in a pure solvent. A solution of PLGA in BB may form a depot via the NIPS mechanism, under some conditions, e.g., injection into a water/triacetin mixture [6], or using a mixed solvent of BB and a water-miscible solvent as NMP [23] at proper ratios. Both these conditions lead to rapid solvent-solvent demixing kinetics.

3.4. Release of metoclopramide salt/base from PLGA/BB solutions in vitro

Fig. 8 shows the release kinetics of the salt and base form of metoclopramide into buffer. The release kinetics is affected by several factors that change the permeation parameter and permeation routes. Interestingly, the base drug shows a faster overall release kinetics compared to the salt drug, indicating that the degradation rate has a substantial influence on the drug release kinetics. From another point of view, the drug solubility (in the polymer and/or the gel) is an important factor for diffusion-controlled kinetics [24]. In the PLGA/metobase system, the drug is both dissolved and dispersed (high drug solubility in PLGA/BB), whereas in the metosalt case, the drug is almost completely dispersed in PLGA/BB (low drug solubility). Higuchi [25] and Paul and McSpadden [26] developed different expressions for the amount of drug release at time t, M_t:

$$M_t = A\sqrt{DC_s(2C_d - C_s)t} \quad \text{by Higuchi} \tag{1}$$

and

$$M_t = \frac{2C_sA}{\operatorname{erf}\xi^*}\sqrt{\frac{Dt}{\pi}} \quad \text{by Paul and McSpadden} \tag{2}$$

where

$$\zeta = \frac{x^*}{2\sqrt{Dt}} \tag{3}$$

and

$$\sqrt{\pi}\zeta\exp\left(\zeta^{*2}\right)\operatorname{erf}\zeta^* = \frac{C_s}{(C_d - C_s)} \tag{4}$$

Both models predict that the amount of drug release is proportional to the saturated concentration (solubility) of the drug, and from this viewpoint, the base drug would be released faster than the salt form in the diffusion-controlled phase if the diffusion coefficient of the two drugs is same.

As shown in Fig. 8, the release of salt follows the classical two-phase release profile, which is an indication of early diffusion control, followed by erosion control. The onset of erosion control occurs at around 500 h that corresponds to the onset of viscosity decrease (Table 3).

The diffusion-controlled phase may be further confirmed by plotting against square root of time (not shown), and by a regression analysis of the resulting plot. Table 4 shows the results of such an exercise for both the salt and base drug release.

The onset of erosion for the base drug happens between 100 and 150 h, far earlier than the case for the salt drug. However, in the period from 100 to 900 h, we still see a $t^{1/2}$ dependent release pattern, which we postulate as due to diffusion through a predominantly water-filled pore structure. The pores are caused by erosion of low molecular weight species and/or of solvent.

If the Higuchi equation were applicable, increased drug loading would increase the diffusion rate constant, k, by a factor of $\sqrt{C_{d2}/C_{d1}}$. Instead, we observe a higher-than-expected increase (see Table 4). This is true of both forms of the drug. In fact, we find

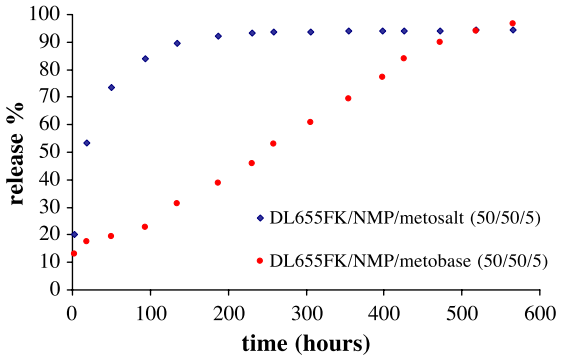

Fig. 9. Release kinetics of metoclopramide salt and base from PLGA (DL655FK)/NMP solution system: the formulation is PLGA/BB/drug=50/50/5 by weight.

the diffusion rate constant is proportional to the degradation rate constant, in the case of the metobase. This suggests that the extent of "connectedness" of the microchannels is related to the degradation kinetics.

As stated above, the polymers studied here do form depots when injected into buffer from NMP solutions, presumably via phase inversion. For example, the polymer DL655FK (PLGA 53/47) does indeed form a depot and releases metoclopramide with a burst effect, as shown in Fig. 9. As expected, the PLGA/NMP system releases salt drug much faster than the base drug, since water-NMP exchange is rapid and the more hydrophilic version of the drug diffuses out faster, presumably through water-filled channels. In contrast to the BB system, where most of the drug release appears to be degradation-controlled and hence leads to faster release of the base drug, the NMP system has fast phase inversion kinetics in vitro and releases the more hydrophilic drug faster. However, the same polymer cannot be formulated into a depot system from BB solutions, further confirming that the depot formation pathways are quite different for NMP and BB solutions. It appears that gel formation is a prerequisite for depot formation in the PLGA/BB system.

4. Conclusions

Certain PLGA/BB systems that form in situ implants also undergo gelation upon ageing under ambient conditions or at 37 °C. We believe that the gel formations upon ageing and upon buffer injection are due to similar mechanisms. In conjunction with data on the "blockiness" of the PLGAs measured by ^{1}H and ^{13}C NMR, however, it appears that the local stereo-regularity or "blockiness" is necessary for structure formation. As emphasized earlier, gelation upon ageing correlates well with in vitro depot formation, indicating that the depot formation mechanism is fundamentally different from phase inversion, as observed for the same polymer in a water-miscible solvent such as NMP.

Rheological measurements show that the dynamic viscosity of these systems show an initial increase followed by an eventual decrease. The onset of this decrease occurs earlier when base drug is used, indicating accelerated hydrolysis kinetics. Thus, the overall drug release profile in vitro includes a diffusion phase, followed by an erosion phase. The so-called burst effect, when present, accounts for less that 10% of the total drug loading.

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