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Partition-controlled progesterone release from waterborne, in situ-gelling materials

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Abstract

The primary goal of this work was to evaluate the long-term constant zero-order release of progesterone from a waterborne, in situ-gelling, injectable material. The motivation for this is to develop an intrafallopian tube embolization system for contraception. Poly(ethylene glycol) diacrylate (PEGDA, 575 g/mol) or poly(propylene glycol) diacrylate (PPODA, 540 g/mol) as a Michael-type addition acceptor was combined with pentaerythritol-tetrakis (3-mercaptopropionate; a Michael-type addition donor) to create a 75 wt.% emulsion solution in 0.1 M PBS (pH 7.4 for PEGDA and pH 12 for PPODA) that gels in minutes by the Michael-type reaction to form a hydrophobic solid. Samples, with ~5.5 or 25 wt.% progesterone, were formed in Tygon tubing. Samples (1.6 mm × 1.0 cm cylinders) showed constant, partition-controlled release of progesterone for a prolonged period (time dependent on the mass of progesterone). Cylinders with ~25 wt.% load of progesterone exhibited constant release (~40 μg per day) for more than 50 days in both the PEGDA and PPODA systems. This type of release is normally associated with preformed hydrophobic matrix systems. In contrast, these in situ-gelling materials reported here can be used to provide zero-order, partition-controlled release of progesterone and enhance the efficiency of an intrafallopian tube embolization system through progesterone release in an injectable, in situ-forming system.

Keywords: Drug delivery systems; Progesterone; In situ-gelling; Contraception; Controlled release; Michael-type addition

1. Introduction

The difficulty of achieving constant (zero-order release) from monolithic drug-dispersed delivery systems has been recognized for some time (Paul, 1976). This type of release can be achieved for hydrophobic drugs from more hydrophobic matrices by the partition-controlled mechanism (Roseman and Yalkowsky, 1976). In the early 1970s, release of progesterone from silastic matrix systems was reported by several groups (Chien, 1976; Flynn et al., 1976). The need for hydrophobic matrices to achieve this zero-order release has previously precluded use of waterborne, injectable, in situ-forming materials due to their hydrophilicity.

A popular method for permanent contraception is tubal ligation, a surgical procedure where the fallopian tubes are cut and often removed, cauterized or sutured closed (MacKay et al., 2001). As with any surgery, there are medical risks associated with this kind of procedure. In addition, the financial cost is high, making it economically unavailable to a significant part of the population. Another disadvantage is the permanent damage done to the fallopian tube. An alternative (less invasive) solution has been the use

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of intrauterine devices. These can be highly effective for long-term contraception, with a low failure rate of 0.2–0.5% reported over 10 years worldwide (Bilian, 2002). However, there are a number of potential risks associated with the traditional types of intrauterine devices available on the market today. Some of the more serious risks include pelvic inflammatory disease (Bilian, 2002), ectopic pregnancy (Dunn et al., 2002), perforation of the wall of the uterus by the device (Wynter et al., 2002), expulsion of the device (Bilian, 2002), as well as permanent infertility (Fraser and Weisberg, 1982). An additional potential side effect of copper IUDs is an increase in bleeding and cramping during the menstrual cycle, particularly during the first year of insertion (Bilian, 2002).

Due to the complications and disadvantages associated with tubal ligation and intrauterine devices, in situ-gelling materials for fallopian tube embolization are being pursued for simpler, safer permanent contraception (Maubon et al., 1996; Abdala et al., 2001). Embolization with collagen plugs was found to be ineffective for contraception but phase inversion polymers were found to be effective (Maubon et al., 1996). Phase inversion polymers however use water miscible organic solvents for delivery. Although these are FDA approved for application, waterborne embolization systems without these solvents would be advantageous if they are effective in contraception.

Here it is proposed that a waterborne, in situ-gelling, self-reactive material, previously developed for repair of ruptured intravertebral discs (Vernon et al., 2003), should be investigated as a potential fallopian tube embolization material for tubal sterilization. This class of in situ-gelling material is based on a Michael-type reaction between thiols and acrylates (Hurd and Gershbein, 1947). Within the fallopian tube, the material converts from a liquid emulsion to a hydrophobic solid as the result of a self-reactive chemical cross-linking. Physical presence of the material in the fallopian tube would act to inhibit conception. If the release can be controlled, the addition of progesterone would increase the efficacy of the tubal device. It is hypothesized that the release will be partition-controlled (true zero-order) giving constant release because the system is delivered as a waterborne hydrophobic emulsion (suspension) that sets up into a hydrophobic solid matrix with dispersed drug.

To obtain partition-controlled release of the hydrophobic steroid progesterone, hydrophobic materials such as silicone have been used to release dispersed drug (Chien, 1976; Flynn et al., 1976). These systems however, require more invasive application because they are not in situ forming, having to be implanted in their final shape. Erosion-controlled delivery of progesterone from a polymer system has also been documented but not in an in situ-forming system. Jameela et al. (1998) were able to use smooth, spherical, cross-linked chitosan microspheres to deliver progesterone in rabbits. In that study, the progesterone was mixed with the chitosan and dispersed in a mixture of liquid paraffin and petroleum ether.

The immediate goal of this work, therefore, was to investigate the release mechanisms for progesterone from waterborne in situ-gelling materials. This type of delivery than could be used to enhance the efficacy of the intrafallopian tube-gelling material for contraception. This work would also show the potential of zero-order partition-controlled release from a waterborne, injectable, in situ-gelling material for numerous other applications with other hydrophobic drugs.

2. Materials and methods

2.1. Materials

Pentaerythritol-tetrakis (3-mercaptoproprionate; QT), poly(ethylene glycol) diacrylate (PEGDA) having an average molecular weight of 575, poly(propylene glycol) diacrylate (PPODA) having an average molecular weight of 540, sodium chloride, sodium hydroxide (1.005N, volumetric standard), and progesterone were obtained from Aldrich company (Milwaukee, USA) and used as received. Sodium phosphate (dibasic), sodium phosphate (monobasic), and methanol were from Sigma Chemical Company (St. Louis, USA). Tygon tubing (1/16 in. i.d., 1/32 in. thickness) was obtained from VWR International, So. (Plainfield, NJ, USA).

2.2. Sample preparation

Progesterone loaded cylinders (1.6 mm × 1.0 cm) were prepared using the reaction outlined in Fig. 1 for PEGDA and PPODA systems. For the PEGDA sam-

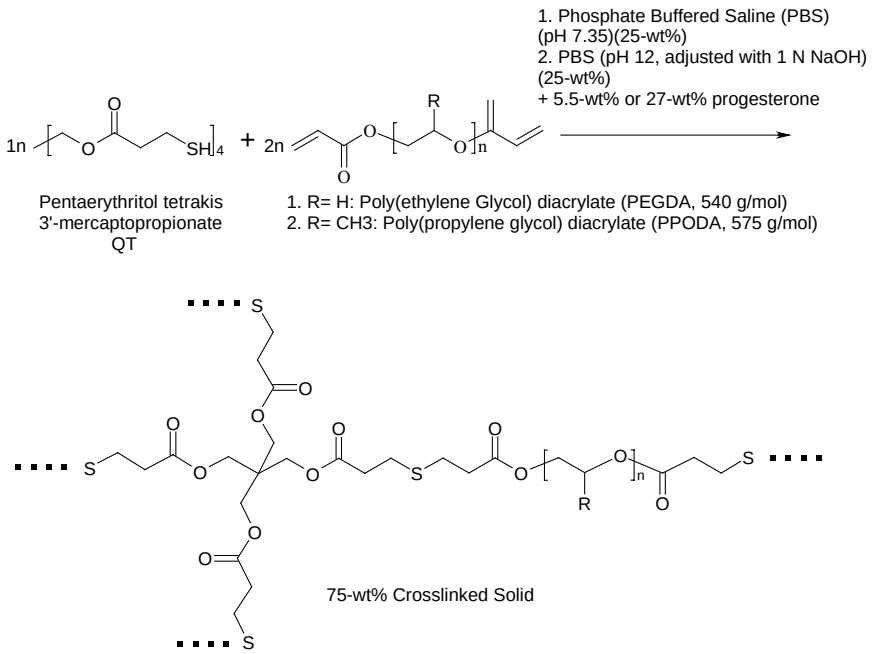

Fig. 1. In situ-gelling, self-reactive materials using pentaerythritol-tetrakis (3-mercaptopropionate) and either (1) poly(ethylene glycol) diacrylate (PEGDA, 540 g/mol) and Phosphate Buffered Saline (PBS, pH 7.35) or (2) poly(propylene glycol) diacrylate (PPODA, 575 g/mol) and PBS (pH 12) with 5.5 or 27 wt.% progesterone.

ples, 33 mg (5.5 wt.%) or 165 mg (27 wt.%) of progesterone (in powder form, 9.1–36.1 μm particle size distribution, 21±4 μm average, determined at 50× optical magnification and 4× digital magnification, three fields with 17 ± 4 particles/field) was first weighed into a 1.8 ml cryovial. Following the progesterone, 288 mg of PEGDA was then added and the PEGDA and progesterone were mixed by vortexing the vial on a VWR standard mini Vortexer. Next, 122 mg of pentaerythritol-tetrakis (3-mercaptoproprionate) (QT) was added and the resulting mixture was vortexed for 90 s to premix. Following the last vortex, 136.7 mg of 0.1 M Phosphate Buffered Saline (PBS, pH 7.35) was added and the solution was vortexed for 2 min to ensure thorough mixing. Following this, the mixture was injected into a 6–8-cm long Tygon tube having an inner diameter of 1.6 mm. The ends of the tube were sealed with parafilm and the gelling mixture was allowed to cure overnight. The tubing was then cut away and the intact gel was cut into 1-cm long samples.

For the PPODA samples, 32 mg (5.8 wt.%) or 160 mg (23 wt.%) of progesterone was weighed into a 1.8 cm cryovial. Next, 270 mg of PPODA was added and mixed. Following this, 122 mg of QT was added and the entire mixture was premixed by vortex. Next, 130.7 mg of 0.1 M PBS (pH 12 adjusted with 1N NaOH) was added and the mixture was vortexed for 2 min. The mixture was injected into a Tygon tube, cured, and cut into 1-cm long samples.

Weighing the samples and calculating the fraction of the volume in each sample compared to the total mixture volumes approximated drug loading. The drug loading was confirmed by UV spectroscopy (Pharmacia Biotech, Ultrospec 3000 UV-Vis Spectrophotometer) at 247 nm after the release experiments by extracting the remaining progesterone in 10 ml of methanol for 2 weeks ($\varepsilon = 0.0549$ ml/(μg cm), mass extinction coefficient for progesterone in methanol, $R^2 > 0.99$).

2.3. Progesterone release

All the drug-loaded samples (three each for PEGDA and PPODA at each drug loading) were placed individually into labeled 50 ml centrifuge tubes. PBS (50 ml, pH 7.35, 0.1 M) was added to each tube. The tubes were capped and placed inside a rocker-incubator set

at 37 °C, 75 rpm. In order to measure progesterone release, 1 ml aliquots were taken from each centrifuge tube after 24 h. The concentration of the drug in solution was determined by UV absorbance at 247 nm ($\varepsilon = 0.0341$ ml/(μg cm), mass extinction coefficient for progesterone in PBS). The remaining PBS in each centrifuge tube was discarded and replaced with 50 ml of fresh PBS. Sink conditions were maintained by replacing the PBS at sufficient intervals to keep the concentration below 20% of the saturation limit in the buffer (every 24–72 h, on average).

2.4. Analysis

To investigate whether these injectable delivery systems could be used for long-term progesterone release within the Fallopian tubes and to evaluate for zero-order release, the release profiles were analyzed to determine dependence of the release on drug loading and time. The profiles were analyzed using Eq. (1):

$$\frac{M_t}{M_\infty} = kt^n \tag{1}$$

where M_t/M_∞ is the fraction of total progesterone released at time t, t is the release time, k is a kinetic constant dependent on the system geometry and diffusion coefficients (Korsmeyer et al., 1983), n is the exponent of the power function. The n-values from Eq. (1) were calculated for the progesterone release profiles by linear regression of Eq. (2) using least squares estimates.

$$\log\left(\frac{M_t}{M_\infty}\right) = n\log t + \log k \tag{2}$$

2.5. Swelling

The swelling of these materials was evaluated gravimetrically using a Mettler Toledo Analytical Balance (±0.1 mg). PEGDA and PPODA samples were prepared as outlined in the sample preparation section but without progesterone and with a diameter of 2.4 mm. The cut samples (~1 cm in length) were then placed in PBS (0.002 M) at pH 7.4 and weighed at regular intervals. Lengths and diameters were measured using calipers. Following equilibrium, the samples were dehydrated completely under vacuum at 70 °C. The swelling ratio, q, was calculated as $q = (w_w - w_d)/w_w$, where w_w is the wet weight and w_d is the dry weight. This data was obtained to calculate the flux of the drug from the samples by having an accurate surface area.

2.6. Partition coefficient

The partition coefficient between these materials, PEGDA and PPODA gels, and PBS were determined by evaluating the equilibrium polymer concentration for various equilibrium solution concentrations (Kuu et al., 1992). Samples were prepared for both the PEGDA system and the PPODA system as described in the sample preparation section but without loaded progesterone. Three polymer samples of each material type (1 cm in length and 4 mm in diameter) were placed in 10 ml PBS with either 2, 4, and 6 μg/ml progesterone in solution. The concentration in solution was determined by UV spectroscopy until equilibrium. The amount of progesterone uptake by the polymer was then calculated using the volume of the initial volume of the polymer.

2.7. Scanning electron microscopy

PEGDA and PPODA samples were prepared as described in the sample preparation section. The cut surfaces of the PEGDA and PPODA samples were imaged using scanning electron microscopy (1000× magnification on a JOEL 840 scanning electron microscope).

2.8. Statistics

The n, Eq. (1) exponent, values are reported as the mean ± standard error from least squares linear fit of Eq. (2). The goodness of the fit for the n-values was evaluated and reported using R^2 values. All other results are reported as the mean of at least three samples with standard deviation. Difference comparisons between sample sets were accomplished using the Student's t-test ($P < 0.05$ are considered statistically significant).

3. Results

3.1. Release

Progesterone was released from new waterborne in situ-gelling, self-reactive materials. Fig. 2 represents

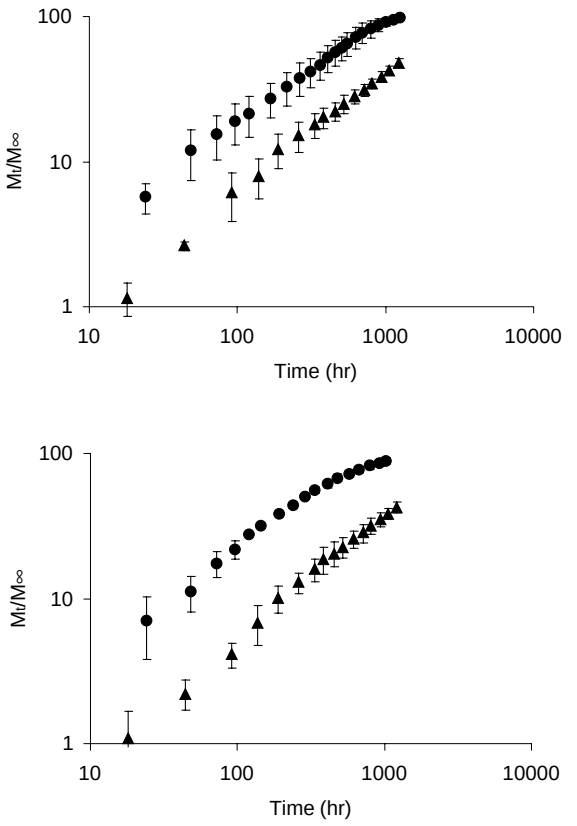

Fig. 2. Log M_t/M_∞ vs. log time for progesterone released from PEGDA samples (top) loaded with 5.5 wt.% (●) and 27 wt.% (▲) progesterone and for PPODA samples (bottom) loaded with 5.8 wt.% (●) and 23 wt.% (▲) progesterone. The higher loading of progesterone provided an extended period of sustained delivery (error bars indicate standard deviation for $n = 3$ for all data sets).

the release of progesterone from the PEGDA system loaded at 5.5 and 27 wt.% progesterone and from the PPODA system loaded with 5.8 and 23 wt.% progesterone, respectively. The release rate per day is presented in Fig. 3 for both material systems at both loading levels.

3.2. Analysis

The release profile was analyzed using Eq. (1). Table 1 presents the exponent of the power function and *k*-values from Eq. (1) for the overall release profile for the poly(ethylene glycol) (PEGDA) and poly(propylene glycol) (PPODA) systems. The steady-state phase (phase 'B') of these release profiles were determined from the daily release rate (see Fig. 3) and the exponent for this phase of the release was reanalyzed (nonlinear regression using Datafit software from Oakdale Engineering) using Eq. (1) modified to eliminate the burst, $M_t/M_\infty = kt^n + c$. Table 1 also presents values for *n*, *k*, and *c* found at steady state.

3.3. Swelling

Equilibrium swelling was determined for the PEGDA and PPODA systems gravimetrically and is presented in Fig. 4. The final water content for the PEGDA systems was 34.2 ± 0.1% obtained within 10 h in PBS. The final water content for the PPODA system was 25.7 ± 0.6 %. The drug flux, calculated using the change in surface area calculated in the swelling studies, was 0.69 ± 0.17 μg/(day mm^2) and 0.71 ± 0.20 μg/(day mm^2) at low and high drug loading, respectively, for the PEGDA system and 0.66 ± 0.09 μg/(day mm^2) and 0.68 ± 0.14 μg/(day mm^2) at low and high drug loading, respectively, for the PPODA system. In contrast to the drug release rate per device at steady state, the flux (release rate normalized to surface area) is no longer statistically different between the PEGDA and PPODA systems ($P = 0.83$ and 0.84 at low and high loadings, respectively).

3.4. Partition coefficient

The partition coefficient between these materials, PEGDA and PPODA gels, and PBS were determined by evaluating the equilibrium polymer concentration for various equilibrium solution concentrations. The partition coefficient, *K*, for the PEGDA and PPODA systems, at the concentrations describe above, were 481 ± 9.7% and 2090 ± 12.7%, respectively.

3.5. Scanning electron microscopy

Exposed progesterone particles at the cut surfaces of both materials were confirmed using scanning electron microscopy. Fig. 5 shows progesterone particles resident on the cut surface of both the PEGDA (top) and the PPODA (bottom) samples. The images also further support morphological differences between the materials, as reported earlier (Vernon et al., 2003).

Table 1
The exponent 'n' from Eq. (1) and steady-state release rates for the poly(ethylene glycol) (PEGDA) and poly(propylene glycol) (PPODA) systems

Material	Overall				At steady state				
	Drug loading (wt.%)	$n \pm$ S.E.	$k \times 100 \pm$ S.E.	R^2	Release rate $\pm$ S.E. (μg per day)	$n \pm$ S.E.	$k \times 100 \pm$ S.E.	$c \pm$ S.E.	R^2
PEGDA	5.5	0.64 ± 0.02	1.1 ± 0.1	0.99	40.9 ± 7.3*	1.0 ± 0.1	0.1 ± 0.1	0.11 ± 0.04	0.999
	27	0.74 ± 0.02	0.24 ± 0.04	0.999	42.6 ± 8.4**	1.03 ± 0.07	0.1 ± 0.1	0.11 ± 0.05	0.998
PPODA	5.8	0.55 ± 0.03	2.0 ± 0.3	0.98	35.8 ± 3.1*	1.03 ± 0.08	0.1 ± 0.05	0.15 ± 0.02	1.0
	23	0.79 ± 0.02	0.2 ± 0.02	0.997	36.8 ± 5.2**	0.99 ± 0.09	0.03 ± 0.02	0.07 ± 0.2	0.999

Analysis of Eq. (1) overall and at steady state for PEGDA materials with 5.5 and 27 wt.% progesterone and PPODA materials with 5.7 and 23 wt.% progesterone reporting the exponent, 'n,' and value 'k.' The parameter, n, was obtained from a linear least squares fit of Eq. (2) for the complete release profile (n overall) and from a nonlinear regression of $M_t/M_\infty = kt^n + c$ for the steady-state (constant release) portion of the release profile (n at steady state). The steady-state release rate for the constant release portion was obtained by averaging the release rates over the portion of the profile where the parameter, n, was equal to 1 (for zero-order release). All data is the average of three release profiles reported with the standard deviation between the three profiles.

* $P = 0.006$.

** $P = 0.002$.

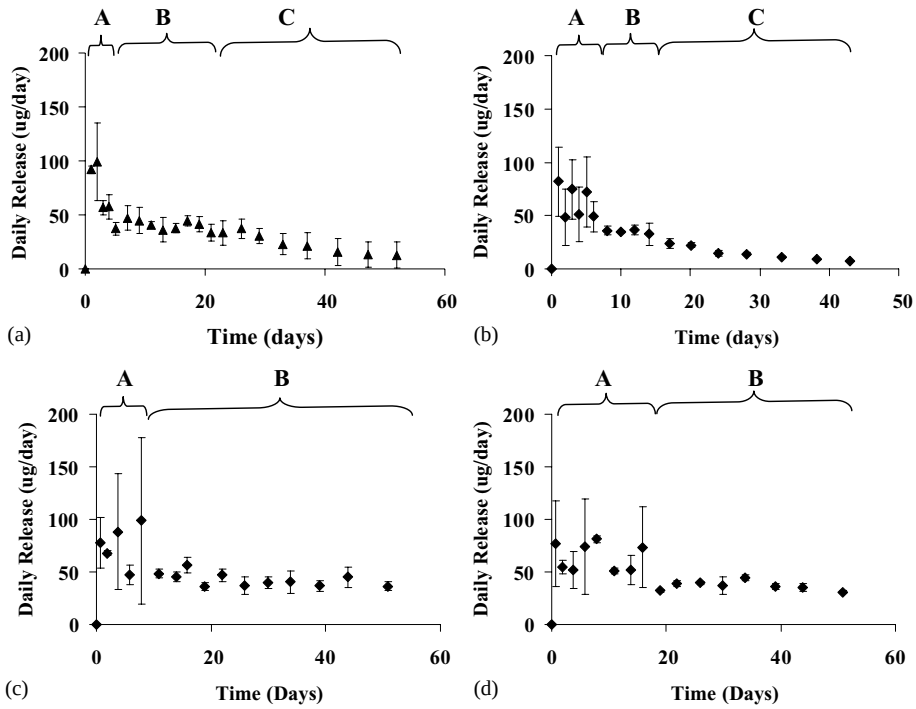

Fig. 3. Daily average progesterone release from the poly(ethylene glycol) diacrylate (PEGDA) samples loaded with 5.5 wt.% progesterone (a) and 27 wt.% progesterone (c). Period A: At the higher loading, progesterone release during the first 10 days showed fluctuations while in period B release from beyond day 10 to day 50 showed constant zero-order release. Period C: The final time period shows Fickian release as the concentration of drug in the material falls below the saturation concentration. Daily average progesterone release from the PPODA samples loaded with 5.8 wt.% progesterone (b) and 23 wt.% progesterone (d). Periods A, B, and C indicate similar release mechanisms as seen in the PEGDA materials (a and c).

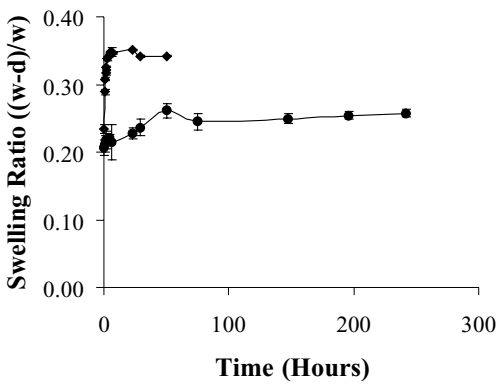

Fig. 4. Swelling ratio for poly(ethylene glycol) diacrylate 540 g/mol system (◆) and for the poly(propylene glycol) diacrylate 575 gm/mol system (●) at equilibrium was 0.342 ± 0.001 and 0.257 ± 0.006, respectively. Both systems showed little swelling and approached equilibrium in a short time frame compared to release.

4. Discussion

The rate of progesterone release was investigated from waterborne, in situ-gelling, self-reactive materials based on poly(ethylene glycol) diacrylate (PEGDA) and materials based on poly(propylene glycol) diacrylate (PPODA) versus the drug loading. These systems possessed multiphase release, similar to that found in early hydrophobic membrane systems (Paul, 1976). The first phase being some burst effect of surface drug. The second phase, most importantly, being partition-controlled, zero-order release. The final phase being the diffusion-controlled release attributed to drug depletion. It was found that changes in the drug loading, ∼5–25 wt.%, did not change the steady-state release rate from these systems. There was a marginal increase in the steady-state release rate in the PEGDA systems compared to the

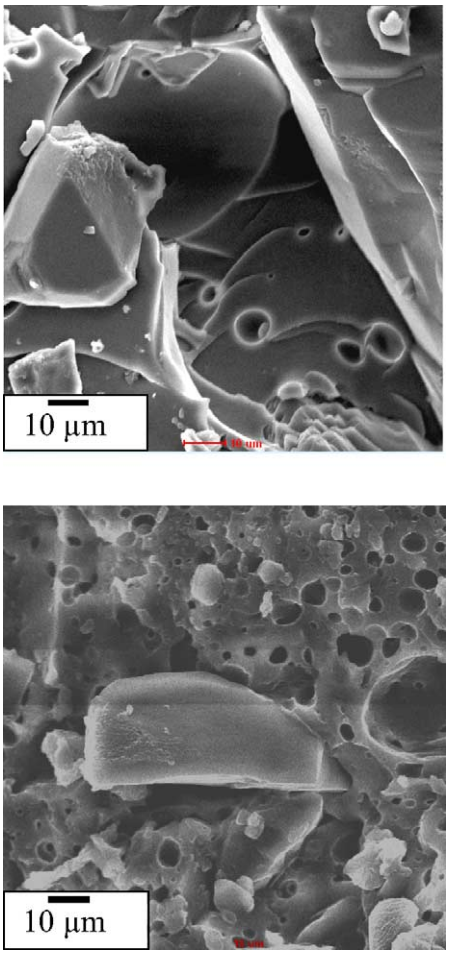

Fig. 5. Scanning electron microscopy of the surface cut between samples during experimental preparation. Poly(ethylene glycol) diacrylate (top image) and poly(propylene glycol) diacrylate (bottom image) both with pentaerythritol (3-mercaptopropionate) and ~25 wt.% progesterone showing exposed particles of progesterone. 1000× magnification on a JOEL 840 scanning electron microscope.

PPODA systems, despite the significant difference in PPODA and PEGDA hydrophobicity. This increase is accounted for by the increased surface area of the PEGDA sample compared to the PPODA sample due to the difference in swelling.

In the PEGDA system, the two loading levels showed similar release profiles for the first 200–500 h as evident in Fig. 2. At later times (beyond 500 h), the release rate decreases in the lower drug loading samples relative to the higher loaded samples. This is due to the depletion of dispersed drug and the concentration, below saturation, is no longer constant. As in the PEGDA system, the two loading levels exhibited similar release profiles in the PPODA system for the first approximately 250 h. Similarly to PEGDA, the PPODA system with the lower drug loading showed a decrease in the mass released rate after about 400 h. In both cases the actual mass release rate is not dependent on loaded concentration. This compares to early work of progesterone release from silicone in the 1970s. Silicone showed biphasic release of progesterone due to the change from partition-controlled release to diffusion-controlled release (Roseman and Yalkowsky, 1976).

The daily release from the lower drug loading exhibited three distinct release mechanisms during different time periods of the 54-day release experiment (see Fig. 3). Similar mechanisms have been reported in silastic reservoir type drug delivery systems for progesterone (Paul, 1976). The higher drug loading presented only the first two mechanisms during a 54-day release experiment, as the concentration had not been depleted sufficiently to result in diffusion-controlled release. During the first few days, period ‘A,’ there is some anomalous variable release. This anomalous release is attributed to progesterone resident at the cut surface of the samples (see Fig. 4), with higher but random direct surface contact of progesterone particles to the release media in addition to the constant release that will be seen in period ‘B.’ This phenomenon may be difficult to avoid with an in situ-gelling material. Both the higher and lower drug loaded samples showed a second time period ‘B’ when the release was constant with time. During this time period, the drug diffuses from the sample. During this time frame the concentration of drug dissolved in the device is constant (at the saturation concentration) and the release rate is only dependent on the device geometry (surface area) and stirring effects.

In order to obtain a long-term delivery system with constant progesterone delivery, a zero-order delivery system is ideal. A truly zero-order delivery system would be time-independent in respect to release. Zero-order systems based on release from a saturated reservoir would also be independent of drug loading until the concentration of the remaining drug is below the saturation concentration. The exponent value, n, found in Eq. (1) can provide indications regarding

the progesterone diffusion mechanism (Langer and Peppas, 1981). An exponent, *n*, of 0.5 suggests normal concentration-controlled Fickian diffusion while *n* of 1.0 indicates zero-order (time-independent) release. Values from between 0.5 and 1.0 indicate that there is some anomalous or Non-Fickian, diffusion occurring in the system.

As seen in Table 1, values of '*n*,' the exponent in Eq. (1), greater than 0.5 indicate that there is some anomalous release mechanism. This occurs because the overall release profile is a combination of different release mechanism including both first and zero-order release at different times. For the PEGDA samples, the exponents for the steady-state phase suggest a zero-order release mechanism during phase 'B.' The release is constant with time during this phase as seen in Table 1. The release rates between high and low drug loadings were not statistically different in either case (see Table 1). However, the release was significantly lower in the PPODA system compared to PEGDA system (see Table 1). This is partially attributed to the difference in the surface area of the two systems due to the difference in swelling. It may also be partially dependent on the higher hydrophobicity of the PPODA compared to PEGDA and the lipophilic nature of the progesterone.

As shown in Fig. 4, during the 54-day release experiments, the higher loaded samples did not show the C phase release mechanism. This was only seen in the lower drug loading. This phase corresponds to release that conforms to Fickian diffusion dependent on concentration. At this phase, the concentration within the device has fallen below the saturation concentration. At 54 days, the higher loaded samples had not been depleted to this state.

Normally, the release profile for matrix dispersed drug can be approximated with the Higuchi pseudo-steady-state model (Higuchi, 1961) where the mass of the drug released is related to the square root of time (i.e. an exponent, '*n*,' of Eq. (1) of 0.5). However, in these materials, reported in this study, the delivery behaves more like a reservoir system where the device drug concentration is constant due to the lipophilic nature of the progesterone and of the gel materials. This allows the zero-order release for these systems until the drug loading falls below the saturation concentration. The preferential solubility of the progesterone in the organic material compared to water leads to equilibrium of the drug concentration at the surface of the device allowing zero-order release. Progesterone partitions into the polymer rich phase and then is released in a zero-order, partition-controlled mechanism. In normal waterborne, injectable systems release is diffusion controlled because of the hydrophilicity of the polymer. This leads to release proportional to the square root of time ($n = 0.5$) in previous systems.

The swelling data was added to prove that the material swelling had relatively no impact on the release kinetics. The effect of swelling is only seen in the difference in volume—thus the surface area—of the PEGDA versus PPODA systems. This partially explains the difference in the flux rate seen in the two systems. The time scale that the swelling occurs is extremely short compared to the time scale of the release. For both systems the swelling has equilibrated within the first two time points of the release study. For the PEGDA system, the swelling is at equilibrium within just a few hours. For the PPODA, the swelling equilibrium is only 0.7% more water than was loaded upon mixing.

5. Conclusion

This partition-controlled mechanism has been seen previously in numerous materials with progesterone but the advantage here is that partition-controlled release has been obtained in a waterborne, in situ-gelling material. The results from these experiments provide optimism toward the development of a tubal sterilization device made from an in situ-gelling material that incorporates progesterone release. These systems provide potential long-term, zero-order release in an injectable, waterborne, in situ-gelling system.

Acknowledgements

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