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Polymer - Xerogel Composites for Controlled Release Wound Dressings

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Keywords
Composite, Wound dressing, Sol–gel, Polymer, Controlled drug release

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Polymer - Xerogel Composites for Controlled Release Wound Dressings

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Abstract

Many polymers and composites have been used to prepare active wound dressings. These materials have typically exhibited potentially toxic burst release of the drugs within the first few hours followed by a much slower, potentially ineffective drug release rate thereafter. Many of these materials also degraded to produce inflammatory and cytotoxic products. To overcome these limitations, composite active wound dressings were prepared here from two fully biodegradable and tissue compatible components, silicon oxide sol-gel (xerogel) microparticles that were embedded in tyrosine-poly(ethylene glycol)-derived poly(ether carbonate) copolymer matrices. Sustained, controlled release of drugs from these composites was demonstrated *in vitro* using bupivacaine and mepivacaine, two water-soluble local anesthetics commonly used in clinical applications. By systematically varying independent compositional parameters of the composites, including the hydrophilic:hydrophobic balance of the tyrosine-derived monomers and the poly(ethylene glycol) in the copolymers and the porosity, weight ratio and drug content of the xerogels, drug release kinetics approaching zero-order were obtained. Composites with xerogel mass fractions up to 75% and drug payloads as high as 13% by weight in the final material were fabricated without compromising the physical integrity or the controlled release kinetics. The copolymer - xerogel composites thus provided a unique solution for the sustained delivery of therapeutic agents from tissue compatible wound dressings.

1. Introduction

Polymeric wound dressings that are capable of maintaining a controlled environment at the wound site have been shown to promote healing and tissue regeneration [1,2]. To accelerate healing, active wound dressings have been developed that enable the controlled, local delivery of therapeutic agents while keeping the wound surface moist, removing exudates, inhibiting bacterial invasion and allowing oxygen permeation [3]. Ideally, the active wound dressing would deliver a nearly instantaneous initial dosage of the drug at the optimum therapeutic concentration, followed by a sustained constant delivery rate of the drug (i.e., zero-order kinetics) that maintains the local concentration at the optimum dosage level for as many days as necessary to achieve complete and effective wound healing. Many synthetic polymers and biopolymers have been used to prepare active wound dressings, including polyurethane [4], chitosan [5], poly(ethylene oxide)/ poly(vinyl alcohol) [6], alginate, cellulose [7], and collagen [8]. When such polymeric wound dressings are used for sustained release of therapeutic agents, however, they typically provide limited control of the kinetics with a burst release of drugs within the first few hours followed by much slower release thereafter [9-11]. The early burst release stage can cause drug overdose and toxicity problems while the slower release stage may be below the drug's therapeutic dosage range.

To overcome these limitations of polymeric active wound dressings, composite polymer-ceramic wound dressings have been investigated. In these composites, the continuous, organic polymer phase can provide a flexible, cohesive wound covering matrix into which the second discrete phase of drug-loaded particles is embedded. The

continuous polymeric phase can include biopolymers such as collagen [12] and chitosan [13] or synthetic polymers such as poly(lactic acid) (PLA) [14], poly(lactide-co-glycolide) (PLGA) [15], polyhydroxyalkanoates [16], polyurethanes [17], polyvinyl alcohol [18] or poly(methyl methacrylate) [19]. Certain ceramic particles, particularly sol-gel processed silicon oxide (xerogel) microparticles, can provide controlled release properties including zero-order kinetics for a broad range of therapeutic agents such as anesthetics, antibiotics and growth factors [20-31] but by themselves the ceramics do not provide for a flexible, absorbent wound covering. Polymer-ceramic composites based upon PLA and PLGA have been investigated for controlled drug delivery [32, 33] but their use is limited by the inherently acidic, pro-inflammatory polymeric degradation products and by their relatively high rigidity and lack of flexibility [34].

It is the objective of this study to demonstrate that composite active wound dressings can provide fully tunable drug delivery kinetics approaching zero-order by carefully integrating the drug binding and drug release properties of polymeric and ceramic biomaterial components that are each biodegradable and non-inflammatory. Specifically, composites of tyrosine-poly(ethylene glycol)(PEG)-derived poly(ether carbonate) copolymers [35] and silica-based sol-gel (xerogel) microparticles [26] are investigated here. These composites provide tunable drug delivery systems that can enable controlled drug delivery approaching zero-order kinetics. This is demonstrated here by analysis of the *in vitro* release of two therapeutic agents, bupivacaine and mepivacine, which are local anesthetics commonly used in clinical treatments of pain. The tyrosine-PEG derived poly(ether carbonate)s are biodegradable and have four independent compositional variables that are readily modified by established synthetic

methods to provide a wide range of physical properties, including mechanical strength, flexibility and hydrophilic:hydrophobic balance [34]. They bind and release a variety of bioactive agents and, unlike polyesters such as PLA and PLGA, they do not produce significant amounts of inflammatory degradation products [35, 36]. The silica-based xerogel particles synthesized here also display excellent local tissue response, their degradation products are safely excreted [37-39] and they allow highly tunable controlled release for a broad range of bioactive compounds [21, 24, 26, 27].

2. Materials and Methods

2.1 Xerogel synthesis

Silica xerogels containing either bupivacaine hydrochloride (BP) or mepivacaine hydrochloride (MP) (Sigma Aldrich) were prepared at room temperature via a one-step acid catalyzed sol-gel process with tetraethoxysilane (TEOS, Strem Chemicals, Newburyport, MA) as previously described [21-24]. The dried xerogel disks were then crushed into granules using mortar and pestle. The crushed silica granules were sieved using nylon meshes in order to obtain granules within the range of 20-105μm diameter. The ratio R_s of water to TEOS at which the sols were prepared was varied from 6 to 15 to control the porosity of the xerogels [26]. Our nomenclature for the drug-loaded xerogels is, for example, R_s10-100, meaning the xerogel is prepared at sol gel conditions of R_s =10 and 100 mg drug/gram of silica.

2.2 Copolymer synthesis

Pyridine 99+% was purchased from Acros (Morris Plains, NJ; poly(ethylene glycol) 1000 (PEG1K) and bis(trichloromethyl) carbonate were purchased from Fluka (Milwaukee, WI); methylene chloride HPLC grade and methanol HPLC grade were supplied from Fisher Scientific (Morris Plains, NJ); tetrahydrofurane (THF) high purity solvent stabilized with 250 ppm BHT was purchased from EMD (Gibbstown, NJ); 2-propanol, bupivacaine hydrochloride, mepivacaine hydrochloride, Dulbecco's phosphate buffer saline, acetonitrile HPLC grade and water solution containing 0.1% (v/v) trifluoroacetic acid for HPLC were purchased from Sigma Aldrich (Milwaukee, WI).

Tyrosine-PEG-derived poly(ether carbonate)s were prepared as previously described [35, 40] and their general structure is shown in **Figure 1.** The copolymers are comprised of poly(ethylene glycol) of 1,000 Da molecular weight (PEG1K) and desaminotyrosyl tyrosine alkyl ester monomers (DTR), where R is the pendent ester; DTO is desaminotyrosyl tyrosine octyl ester and DTE is desaminotyrosyl tyrosine ethyl ester. Abbreviations for the copolymers are given as: DTR- x%PEG; for example, DTO-10%PEG is poly(90%DTO-co-10%PEG1K carbonate), where the DTO and PEG 1K are in mole percent**.**

Copolymer compositions were confirmed by ^{1}H NMR (DMSO-*d6*, Varian VNMRS 400MHz spectrometer) and FTIR (Avatar 380 spectrometer, Thermo Nicolet). The molecular weights of the copolymers were measured by gel permeation chromatography (GPC) using THF as eluent [40] (see Table 1).

2.3 Copolymer and composite film preparation

Copolymer and composite copolymer-xerogel films were prepared by compression molding at temperatures 75°C above the respective T_g's on a Carver press, followed by free cooling to room temperature. The two steel plates of the press were covered with parchment paper in order to prevent the copolymers or composites from adhering to the metal surfaces. Shims with a thickness of 500 μm were used during the compression molding.

Copolymers loaded with bupivacaine or mepivacaine (i.e., without xerogel) were prepared by direct addition of 4 mg/ml drug solution in acetonitrile to a 250 mg/ml copolymer solution in THF at room temperature. The mixture was poured into a Petri dish, dried under nitrogen flow and then in a vacuum oven at 40°C overnight, and the resulting films were peeled off and compression molded to the desired film thickness. For these copolymer-drug complexes, the nomenclature is, e.g. DTO-10%PEG-50BP, which stands for poly(90% DTO-co-10% PEG1K carbonate) loaded with 50 mg bupivacaine /g copolymer.

Composites of copolymers with drug-loaded xerogels were prepared by solution blending. Approximately 200 mg copolymer was dissolved in 2 mL THF and 200mg xerogel granules containing BP or MP were added, followed by vigorous mixing for 1 min. The suspensions were then poured into small Petri dishes, dried under nitrogen flow and then in a vacuum oven at 40°C overnight. The resulting composite films were peeled off and compression molded to the desired thickness. For these composites, the nomenclature starts with the copolymer matrix used, followed by the weight % and type of xerogel and then the amount of bupivacaine loaded in the xerogel; e.g., DTO-

10%PEG-50%R_s10-100 is the composite containing 50% wt:wt poly(90% DTO-co-10%PEG1K carbonate) with 50% wt:wt of xerogel R_s10-100.

2.4 In vitro drug release

In vitro drug release rates from silica xerogel granules, copolymer films and composite films were measured for up to seven days using 30mg of samples incubated in 6 mL PBS at 37°C in a Julabo SW2 water bath shaker at 100 rpm. The incubation medium was completely withdrawn at specified time intervals and replaced with 6 mL fresh buffer. The withdrawn samples were diluted 1:1 (v/v) with acetonitrile and analyzed by HPLC. All experiments were performed in triplicates. The BP and MP concentrations were assayed by high performance liquid chromatography (HPLC) using a Waters 2695 HPLC system equipped with a Waters 2489 UV/Vis detector that was set at 210 nm for BP detection. Chromatographic separations were achieved using a Perkin-Elmer Pecoshere HS-3 C18 reversed-phase column, 3µm particle size, 33x4.6 mm, at 25°C. The injection volume was 10µL, and a mixture of 60% water (0.1% TFA), 30% acetonitrile (0.1%TFA), 10% methanol (v/v) with a flow rate of 0.7 mL/min was used as eluent. The total run time was 5 min. and the retention time of BP was 2.3 min. Validity of the method was established through a study of specificity, linearity and accuracy according to the ICH guidelines [41]. Standard calibration curves were prepared at concentrations ranging from 0.97µg/mL to 0.25 mg/ml and exhibit linear behavior over this range of concentration. The detection limit was 0.23µg.The specificity was determined by comparing the results from the placebo supernatant, containing only the copolymers

incubated for the given time period with the standard solutions of the BP and no interference was observed.

2.5 Glass transition temperature, water uptake and hydrolytic degradation studies

The glass transition temperature (T_g) was determined by differential scanning calorimetry (2910 Modulated DSC, TA Instruments) on 10-15 mg samples. Specimens were sealed in aluminum pans and subjected to a heat-cool-reheat temperature program from -50 to 150°C at a heating rate of 10°C/min. Glass transition temperature was determined as the temperature at the inflection point in the second heating scan of the DSC temperature program.

For water uptake and degradation measurements, small disks of copolymer and composite films (3mm diameter x 500μm thick) were immersed in PBS at 37°C and at appropriate time points were removed from the media, wiped dry and weighed until they reached constant mass. The water uptake, averaged for 3 replicates, was calculated as $(m_f-m_i)*100/m_i$, where m_i and m_f were the mass of the sample before and after immersion, respectively. In order to monitor the hydrolytic degradation of the copolymers, the sample disks were incubated in PBS at 37°C and removed from the media at 3 and 5 days. After freeze-drying, the mass and the molecular weight variations were used to follow the degradation; these properties were summarized in **Table 1**.

3. Results and Discussion

3.1 Drug release from xerogels

In accord with our previous results for the specific sol-gel synthesis conditions also used here [26], a broad range of time-dependent release rates for bupivacaine (BP) and mepivacine (MP) can be obtained with these cast and ground silica xerogels (**Figures 2a**). The release kinetics can be approximated by two-stage processes in which the cumulative release in the initial, fast release stage and the subsequent, slow release stage are each linearly dependent on $t^{1/2}$ (**Figure 2b**). Each stage can be well approximated by the Higuchi square-root- of-time model (Equ. (1)), which is based strictly on diffusion controlled behavior [26]

(1) $Q = [(D\varepsilon/\tau)(2AC- \varepsilon C^2)t]^{1/2} = k_H\, t^{1/2}$

where Q is the amount of drug release in time, t, D is the diffusion coefficient of the drug, τ is the tortuosity factor, A is the total amount of drug in the matrix, C is the solubility of the drug in the permeating fluid, and ε is the porosity of the matrix. Drugs are released as water penetrates the nanoporous xerogel, allowing diffusion along the solvent-filled capillary channels. The initial rate of release and the total release after 5 days are directly proportional to Rs, the water:TEOS ratio used to synthesize the xerogels and to control their porosities which increase as Rs increases [22, 42]. . This direct dependence of drug release rates on Rs is demonstrated by the bupivacaine results at 24 hr, where 32%, 41% and 55% of the BP are released by the Rs6, Rs10 and Rs15 xerogels, respectively (**Figure 2b**). The Higuchi rate coefficients, k_H, calculated from equation (1) for the 0-24 hr and 24-48hr stages, all increase with increasing Rs, as summarized in **Table 2**. At comparable drug loading levels, the early, fast stage release of mepivacaine is significantly greater than that of bupivacaine from xerogels of identical composition. This can be ascribed, per Equ. (1), to both the much greater aqueous solubility of MP (7.0

mg/mL) than BP (2.4 mg/mL).and the faster diffusion of the smaller MP molecule (283Da molecular weight) than the larger BP molecule (325 Da molecular weight).

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Hydrolytic degradation of the xerogels has previously been shown [26] to follow first-order kinetics independent of any specific bound drug:

(2) $\ln[(C_e-C)/C_e] = kSt$

where C is the concentration of silica in solution, C_e is the equilibrium solubility of the silica, S is the particle surface area, k is the rate constant and t is the time. For the silica xerogel microparticles, the degradation rate is a rather slow process, with negligible dissolution over the first 8 hr and a rate constant, k, of approximately 0.02/hr [26]. Given the rapid early release of BP and MP from the xerogels, it is clear that the first stage drug release reflects primarily dissolution and diffusion processes. The mathematical models for diffusion-controlled release kinetics and for degradation both provide good fits to the slower, second stage of release and so do not enable a definitive resolution of the mechanism [26].

3.2. Drug release from copolymers

Drug release rates from polymeric matrices are dependent upon several interrelated physical factors, including the water influx, drug dissolution, drug solubility in the polymer matrix, and erosion of the polymer matrix [43]. Bupivacaine release rates from the tyrosine-PEG derived poly(ether carbonate)s are found to be time-dependent and can be characterized by an initial, burst release stage in the first 4 hr followed by a prolonged, slow release stage thereafter (**Figure 3**). Applying the Higuchi model,

equation (1), to each of the two stages, values for the coefficient k_H are obtained with correlation coefficients all exceeding 0.95 (**Table 3**). The initial burst release of BP from the copolymers is much faster than from the xerogels and the total amount released from the copolymers increases with increasing PEG content; e.g., after seven days there is less than 10% cumulative release of BP from the DTO-5%PEG copolymer but almost 100% release from the DTO-20%PEG copolymer. This is due to the increased hydrophilicity of the copolymers as the PEG content is increased, causing increased water influx that drives drug dissolution [43]. At equilibrium, the DTO-10% PEG copolymer takes up 17% water while the DTO-20% PEG copolymer takes up 65% water (**Table 1**). Further increasing the copolymer hydrophilicity by decreasing the length of the pendent ester group in the tyrosine-derived monomers from octyl (DTO) to ethyl (DTE) causes the water uptake to increase from 65% for the DTO-containing copolymer to 73% for the DTE-containing copolymer.

The greater water uptake by the DTE-containing copolymers at a given PEG content increases the drug release rate relative to the DTO-containing copolymers, as may be seen by comparing the cumulative release over the first 24 hr for the DTO-20%PEG-40BP to that of the DTE-20%PEG-40BP (**Figure 3**). The BP release rates from the copolymers in the early, burst release stage ($t < 4hr$) are dependent upon the drug loading, with the rate increasing with increasing loading in a manner consistent with diffusion controlled processes (**Figure 4**).

An even more pronounced burst release rate is observed for mepivacaine (MP) than bupivacaine from either the xerogels or the copolymers (**Figure 5**). Using equation (1) to fit the initial burst release stage data (**Figures 3 and 5)**, the Higuchi rate

coefficients for release from the DTO-10%PEG copolymer are k_H (BP) = 22.9 and k_H (MP) = 36.4 at approximately the same 40 mg/g BP vs. 50 mg/g MP drug loading concentrations. The faster dissolution and diffusion of MP is expected, given the greater aqueous solubility of MP (7.0 mg/mL) than BP (2.4 mg/mL). That MP release is retarded less by the copolymer matrix than is BP release can be anticipated from the lower octanol:water partition coefficient of MP (log P= 2.2) than BP (log P= 3.6). Stronger binding of BP than MP to the copolymer matrix is further demonstrated by calculations of the Flory-Huggins interaction parameters, χ_{sp}, for BP and MP with each of the copolymer components:

(3) $\chi_{sp} = (\delta_s - \delta_P)^2 V_s / RT$

where the Hildebrand solubility parameters are δ_s for the drugs and δ_P for the polymer components (i.e., DTO, DTE, PEG), V_s is the molar volume of the solute and T the temperature (^oK) [44-46]. The closer χ_{sp} is to zero, the more compatible and soluble a given drug is within the polymeric component. From the calculated χ_{sp} values summarized in **Table 4**, it is clear that at any given PEG content the copolymer matrices with either DTE or DTO have higher affinity for BP than MP, and hence at any given composition of these copolymers the release rate is expected to be relatively faster for MP.

The hydrolytic degradation rates for the copolymers are slow, with no observed mass loss over 5 days. The copolymer molecular weights do decrease over that time period following first-order kinetics (**Figure 6**). The molecular weight degradation rate increases as the PEG content is increased from 5% up to 20%. These results are indicative of a bulk erosion process controlled by the rate of water influx rather than a

surface erosion process that would be dependent on the hydrolysis rates of the copolymer's carbonate bonds. These results are consistent with previous hydrolytic degradation studies of DTE-containing copolymers, where the molecular weight decreases for DTE (0% PEG), DTE-5%PEG and DTE-30% PEG are approximately 5%, 10% and 20%, respectively, after 7 days in PBS at 37^{o}C [35]. It is therefore concluded that the early burst release of the drugs from the copolymers is primarily driven by drug dissolution and diffusion forces rather than by matrix erosion.

3.3 Drug release from copolymer-xerogel composites.

When the xerogels and copolymers are combined to form composites, the drug release kinetics are very different from those observed with the separate components. In the composite studies presented here, the drug is initially loaded only in the xerogels. The initial fast release from the xerogel is modulated by the presence of the composite's copolymer matrix, such that a single stage, $t^{1/2}$-dependent release can be observed, as shown for a composite of 50:50 (wt:wt) DTO-20%PEG copolymer and Rs10-75BP xerogel **(Figure 7**). The $t^{1/2}$ dependence is deceptively simple as the composite system is concurrently undergoing hydrolytic degradation, drug dissolution and drug diffusion first through the nanopores of the xerogel and then through the copolymer matrix, which is itself being plasticized and swollen by the influx of water. The copolymer matrix acts first as a barrier to limit the influx of water, thereby slowing the dissolution of the drug in the xerogel. The more hydrophobic the copolymers, the more slowly they absorb water [35]. Hence, at a given porosity (Rs) of embedded xerogels, the composites prepared with the more hydrophobic DTO monomers release the drug more slowly than

composites made with the more hydrophilic DTE monomers at a fixed PEG level and, as the PEG content of the copolymers is increased to make the composites more hydrophilic, the drug is released more rapidly (**Figure 7 and 8**). The release rates from the composites are also strongly dependent on the porosity of the xerogels. At fixed copolymer composition, the composites made with the more porous R_s10 xerogels release BP faster and more completely than those made with the less porous R_s6 xerogel **(Figure 9).**

Composites containing xerogels loaded with mepivacaine (MP) release the drug with kinetics again resulting from the integration of the release properties of the xerogels and copolymers alone (**Figure 10**). The MP release rate from a given composites is greater than the BP release rate, as may be seen from the substantial initial burst release rate of MP from DTO-10%PEG-50%Rs15-200MP as compared to the slow, nearly zero-order release rate of BP from the same type of composite composition, DTO-10PEG-50%Rs15-200BP (**Figure 11**). This difference is ascribed to the lower aqueous solubility and the higher copolymer matrix binding affinity (higher log P and lower χ_{sp} values) of BP compared to MP.

Within the composites there is no strong interfacial interaction expected between the xerogel microparticles and the copolymers to influence the drug release rates. This is supported by the data for the glass transition temperatures measured for the composites as a function of xerogel content (**Table 1**). No significant differences are observed in the Tg's for composites of the DTO-10%PEG with between 25% and 75% xerogel by weight and only a small, statistically insignificant difference of 2^oC is observed between the Tg's of these composites and that of the copolymer alone. This is not surprising given that

there are no strong covalent or electrostatic interactions between the copolymer's monomers and the silicon oxide of the xerogels. In contrast, there is a very substantial change of -22 ^{o}C in the Tg of the composites when the PEG content of the copolymer is increased from DTO-10%PEG to DTO-20%PEG, which is due to the inherently very low Tg of PEG. Increasing the PEG content of the copolymers increases their chain mobility and promotes both greater rates of water influx and drug diffusion-driven efflux from the composites at any given level of xerogel content and xerogel drug loading. The Tg's are 4^{o}C or less, reflecting that the composites will be in a rubbery elastic state at room or body temperature.

4. Discussion

It has been demonstrated here that the properties of composites of silica xerogels and tyrosine-derived-PEG- poly(ether carbonate) copolymers can be tuned to achieve controlled release of drugs approaching time-independent, zero-order kinetics (**Figures 7, 8 and 9**). This represents an important advance in the development of fully biodegradable, tissue compatible active wound dressing material capable of delivering a broad range of therapeutic agents. The release kinetics of the drugs from these composites are dependent upon a number of factors including the water influx rate, drug dissolution, drug loading in the xerogels, and drug binding in the copolymer matrix, as has been observed for other polymeric and composite delivery systems [33, 44-48]. With the novel composites presented here the porosity and drug loading of the xerogels and the hydrophobic: hydrophilic balance of the copolymer matrix can be independently adjusted to control the release rates of the drugs. The copolymer matrix acts as a barrier with

controllable drug binding affinity to regulate water influx into and drug diffusion out of the composites. There is no strong chemical interaction between the xerogels and the copolymers in these composites that might otherwise have limited the xerogel content of the composites. Studies of the mechanical properties of the composites have been initiated (data not shown here) and tensile strength and flexibility properties commensurate with the needs for wound dressings have been measured. Evaluation of the *in vivo* drug release properties and the efficacy of drug delivery in an animal pain model are also in progress.

4. Conclusion

Active composite wound dressing were prepared by dispersing drug-loaded xerogel microparticles into a continuous polymeric phase consisting of tyrosine-poly(ethylene glycol)(PEG)-derived poly(ether carbonate) copolymers. Sustained, controlled release of bupivacaine and mepivacaine, two water-soluble local anesthetics from these composites was demonstrated *in vitro.* Compositional parameters of the composites, including the hydrophilic:hydrophobic balance of the tyrosine-derived monomers and the poly(ethylene glycol) in the copolymers and the porosity, weight ratio and drug content of the xerogels, can be adjusted individually to obtain zero-order drug release kinetic. The copolymer - xerogel composites can provide a unique solution for the sustained delivery of therapeutic agents from tissue compatible wound dressings.

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FIGURE CAPTIONS

Figure 1. Tyrosine-PEG-derived poly(ether carbonate) structure. Adjustable parameters are: x and y, the mole fractions of the tyrosine-derived monomers and PEG; n, the pendent alkyl chain length; and the PEG mol wt (fixed at 1000 in these studies).

Figure 2 a and b. Effect of xerogel Rs (H_2O:TEOS ratio) on the kinetics of bupivacaine and mepivacaine release . Open triangles: R_s6-100(BP); Open squares: R_s10-100(BP); Open circles: R_s15-100(BP); Dark triangle : Rs6-100(MP); Dark squares: Rs15-100(MP); Darl circles: Rs15-200(MP). (a) abscissa linear with time; (b) abscissa linear with the square root of time

Figure 3. Effects of copolymer hydrophilicity on the kinetics of bupivacaine release from tyrosine-PEG-derived poly(ether carbonate)s. Open diamonds: DTE-20%PEG-40(BP); Open circles: DTO-20%PEG-40(BP); Open squares: DTO-10%PEG-40(BP); Open triangles: DTO-5%PEG-40(BP).

Figure 4. Effects of copolymer drug loading on the kinetics of bupivacaine release. Open squares: DTO-20%PEG-250(BP); Open triangles: DTO-20%PEG-150(BP);Open circles: DTO-20%PEG-75(BP).

Figure 5. Comparison of the mepivacaine release from copolymers and xerogels. Open circles: Rs6-100(MP); Open triangles: Rs6-150(MP), Open squares: Rs15-200(MP); Dark circles: DTO-10%PEG-100(MP); Dark triangles: DTO-10%PEG-75(MP); Dark squares: DTO-10%PEG-50(MP).

Figure 6. Hydrolytic degradation of copolymers in PBS at 25^{o}C. Triangles: DTO-5%PEG, Circles: DTO-20%PEG; Squares: DTO-10%PEG.

Figure 7. Comparison of bupivacaine release from a composite and its component xerogel and copolymer. Triangles: copolymer, DTO-20% PEG-37(BP) (3.5% BP in the copolymer); Circles: xerogel, R_s10-75(BP) (7% BP in xerogel); Squares: composite, DTO-20%PEG-50%R_s10-75(BP) (3.5% in overall material).

Figure 8. Effect of copolymer PEG content and monomer hydrophilicity on bupivacaine release rate from composites. Open circles: DTE-20%PEG-50%R_s15-200(BP); Dark circles: DTO-20%PEG-50%R_s15-200(BP). Triangles: DTO-10%PEG-50%R_s15-200(BP).

Figure 9. Effect of tyrosine monomer hydrophilicity and xerogel porosity on bupivacaine release from composites. Dark squares: DTE-20%PEG-50%R_s10-50(BP); Open diamonds: DTO-20%PEG-50%R_s10-50(BP); Open squares: DTE-20%PEG-50%R_s6-50(BP); Dark diamonds:DTO-20%PEG-50%R_s6-50(BP)

Figure 10. Comparison of mepivacaine release from a composite and its component xerogel and copolymer; Open triangles: copolymer, DTO-10%PEG-50(MP); Dark circles: xerogel, R_s6-100(MP); Open rectangles: composite, DTO-10%PEG-50%R_s6-100(MP)

Figure 11. Effect of drug hydrophilicity, drug loading, and xerogel R_s on release kinetics from composites; Open diamonds: DTO-10%PEG-50%R_s15-200(MP); Dark triangles: DTO-10%PEG-50%R_s6-150(MP); Open rectangles: DTO-10%PEG-50%R_s6-100(MP); Dark circles: : DTO-10%PEG-50%R_s15-200(BP)

Table 1. Molecular weights, polydispersity index, glass transition temperature (dry state), and equilibrium water uptake for copolymers and composites.

Copolymers	M_n (kDa)	M_w (kDa)	M_w/M_n	Tg (°C)	Water uptake (%)
DTO-10%PEG	81	160	1.97	2	17
DTO-20%PEG	64	104	1.63	-19	65
DTE-20%PEG	75	159	2.13	1	73
Composites					
DTO-10%PEG-25%Rs10-100	81	160	1.97	2	15
DTO-10%PEG-50%Rs10-100	81	160	1.97	4	13
DTO-10%PEG-75%Rs10-100	81	160	1.97	4	11
DTO-20%PEG-50%Rs10-100	64	104	1.63	-18	27

Table 2. Higuchi release rate coefficients, k_H, for bupivacaine and mepivacaine from xerogels as a function of Rs (water:TEOS)

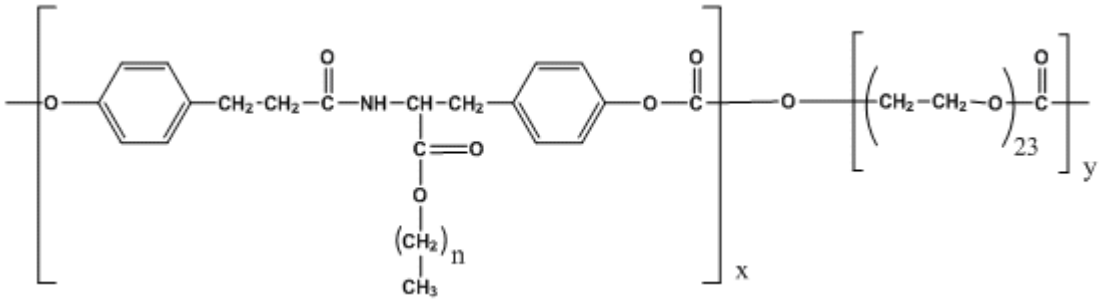
Sample name	k_H ($x10^{-2}$, $h^{-1/2}$)	
	0-24 hr	24-48 hr
Bupivacaine		
Rs6-60	3.57	3.87
Rs6-100	5.42	3.55
Rs6-200	8.02	4.26
Rs10-100	8.42	4.34
Rs15-100	11	5.93
Mepivacine		
R6-100	6.57	0.91
R6-150	15.11	1.35
R15-200	24.11	0.5

Table 3. Higuchi release rate coefficients, k_H, for bupivacaine and mepivacaine from copolymers

Sample name	k_H ($x10^{-2}$, $h^{-1/2}$)	
	0-24 hr	**24-48 hr**
Bupivacaine		
DTO-5%PEG-40mg/g	0.92	0.58
DTO-10%PEG-40mg/g	22.91	1.80
DTO-20%PEG-40mg/g	54.13	1.37
DTE-20%PEG-40mg/g	57.57	0.55
Mepivacine		
DTO-10%PEG-50mg/g	36.44	0.38
DTO-10%PEG-75mg/g	48.81	0.53
DTO-10%PEG-100mg/g	67.36	0.30

Table 4. Solubility Parameters and Flory-Huggins Interaction Parameters for Bupivacaine and Mepivacaine with the Copolymer Components

	δ_s	δ_P	χsp (BP)	χ_{sp} (MP)
BP	**21.6**			
MP	**22.0**			
DTO		**25.5**	**1.87**	**1.34**
DTE		**27.5**	**4.23**	**3.29**
PEG		**21.4**	**0.00**	**0.04**



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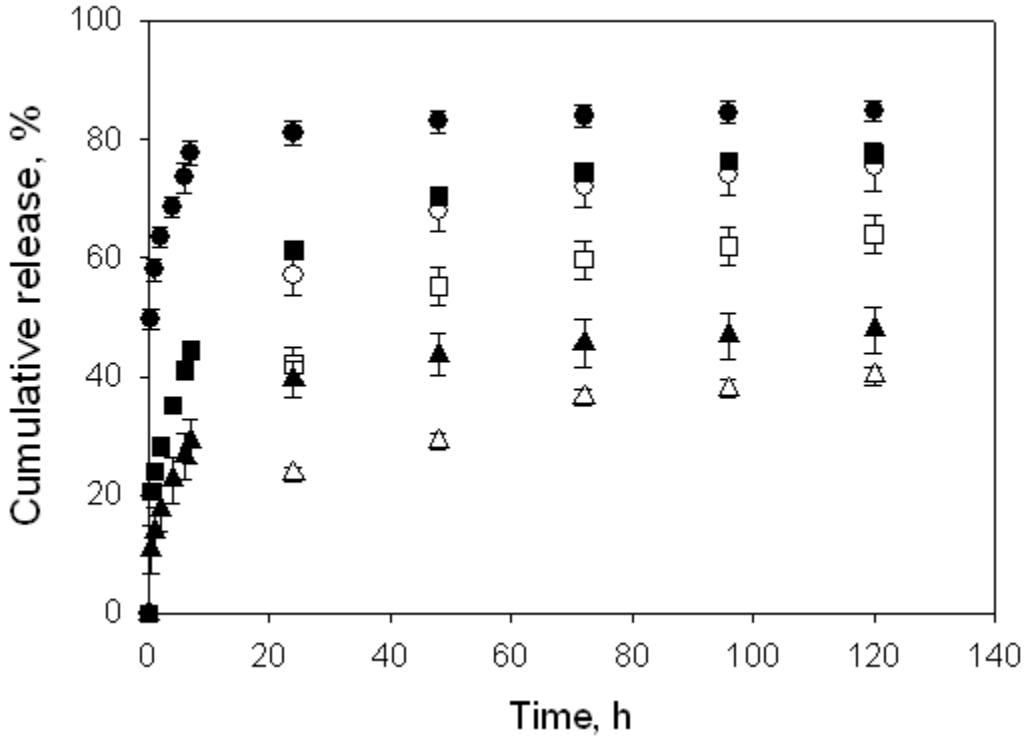

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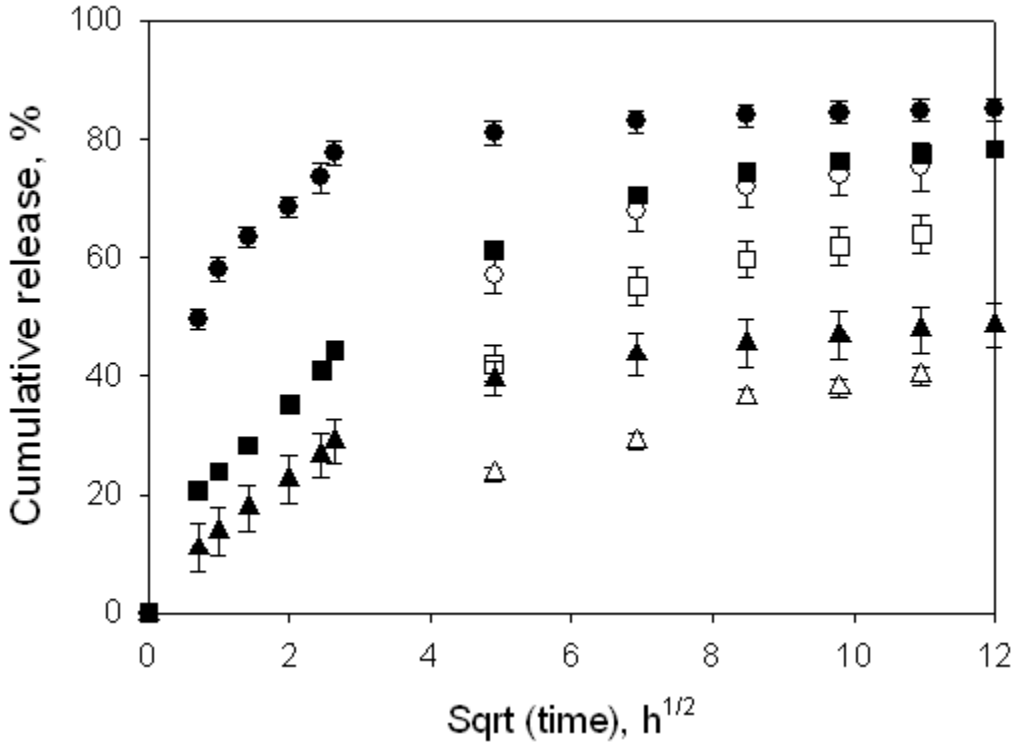

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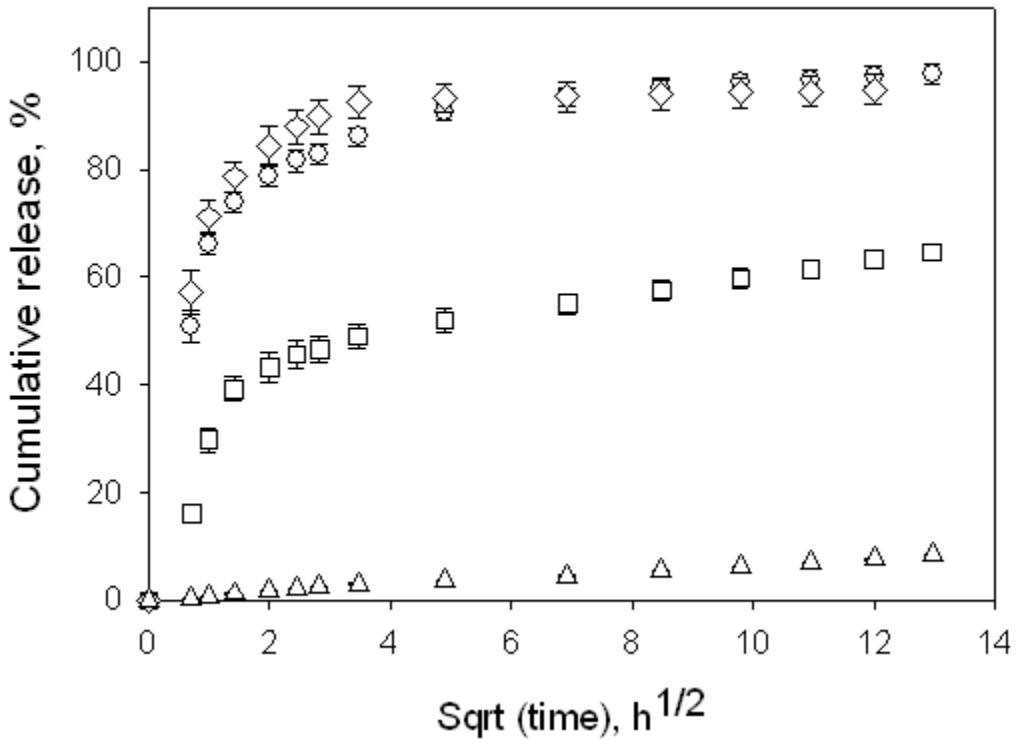

Cumulative release, %
100
80
60
40
20
0
0
2
4
6
8
10
12
14
Sqrt (time), h 1/2

Figure 3

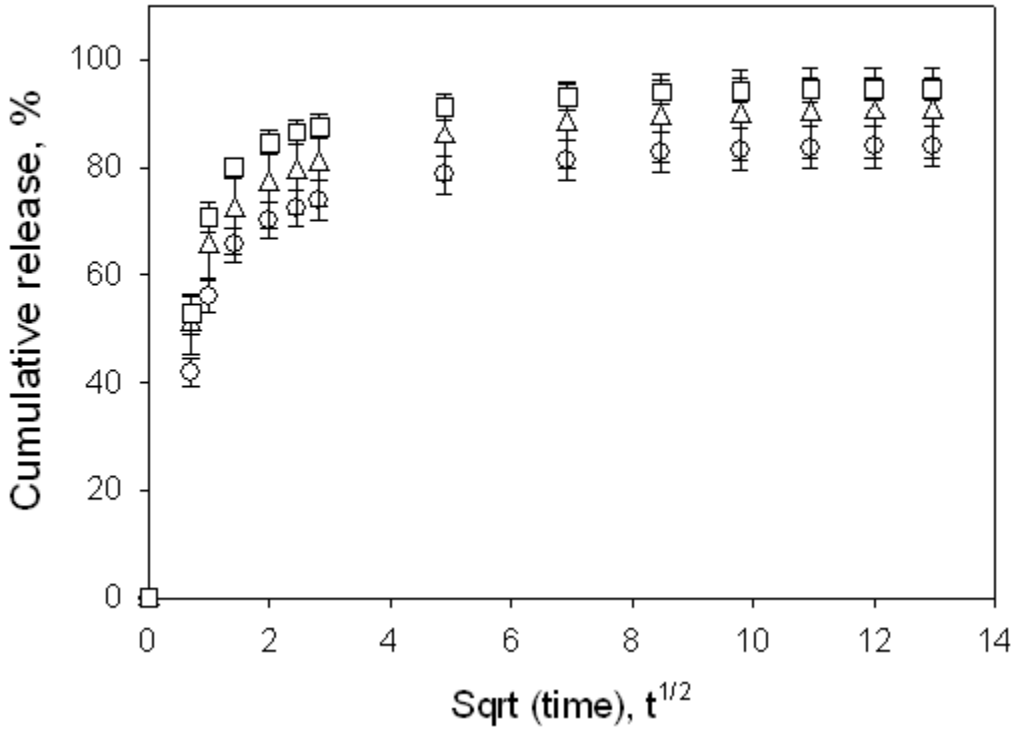
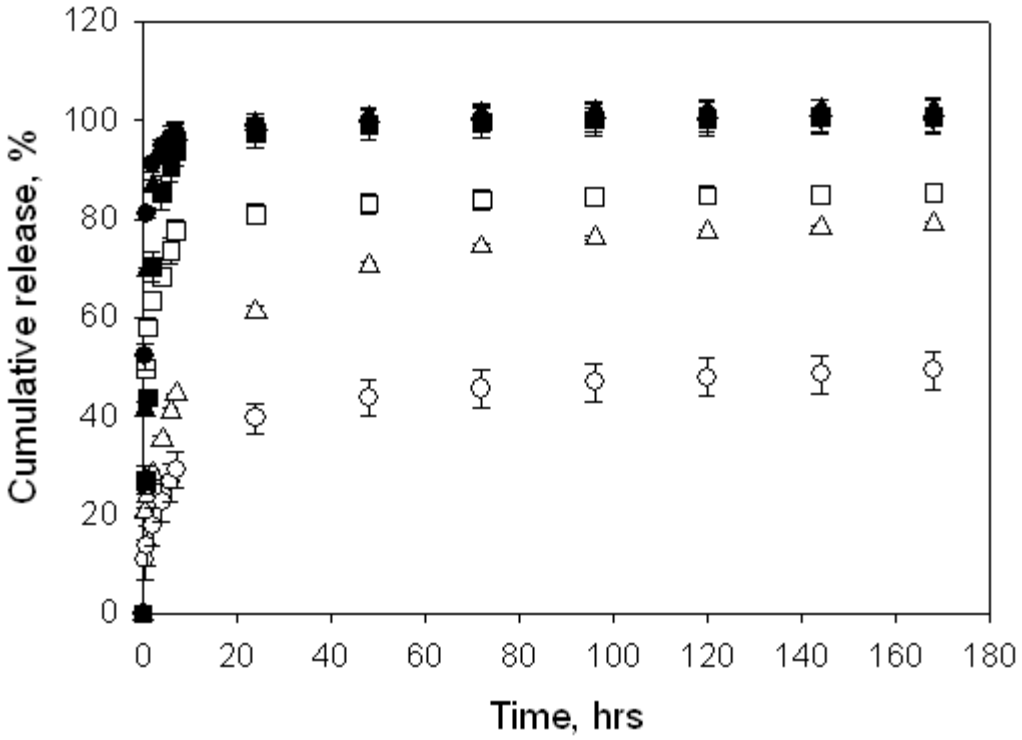

Cumulative release, %
100
80
60
40
20
0
0
2
4
6
8
10
12
14
Sqrt (time), t1/2

Figure 4.



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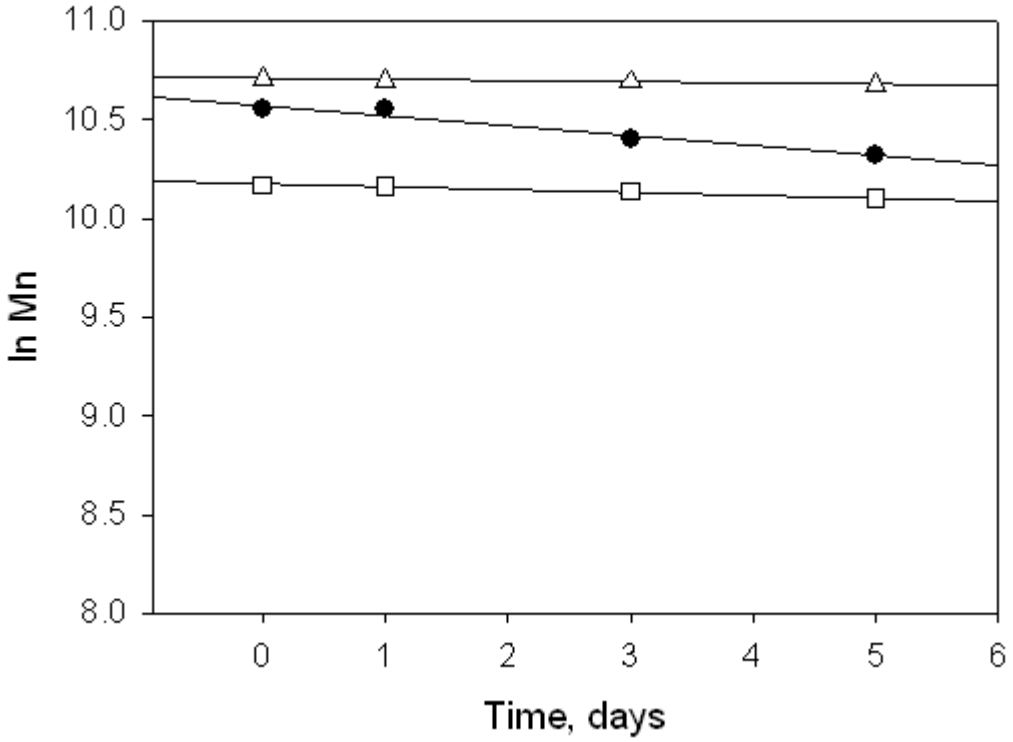

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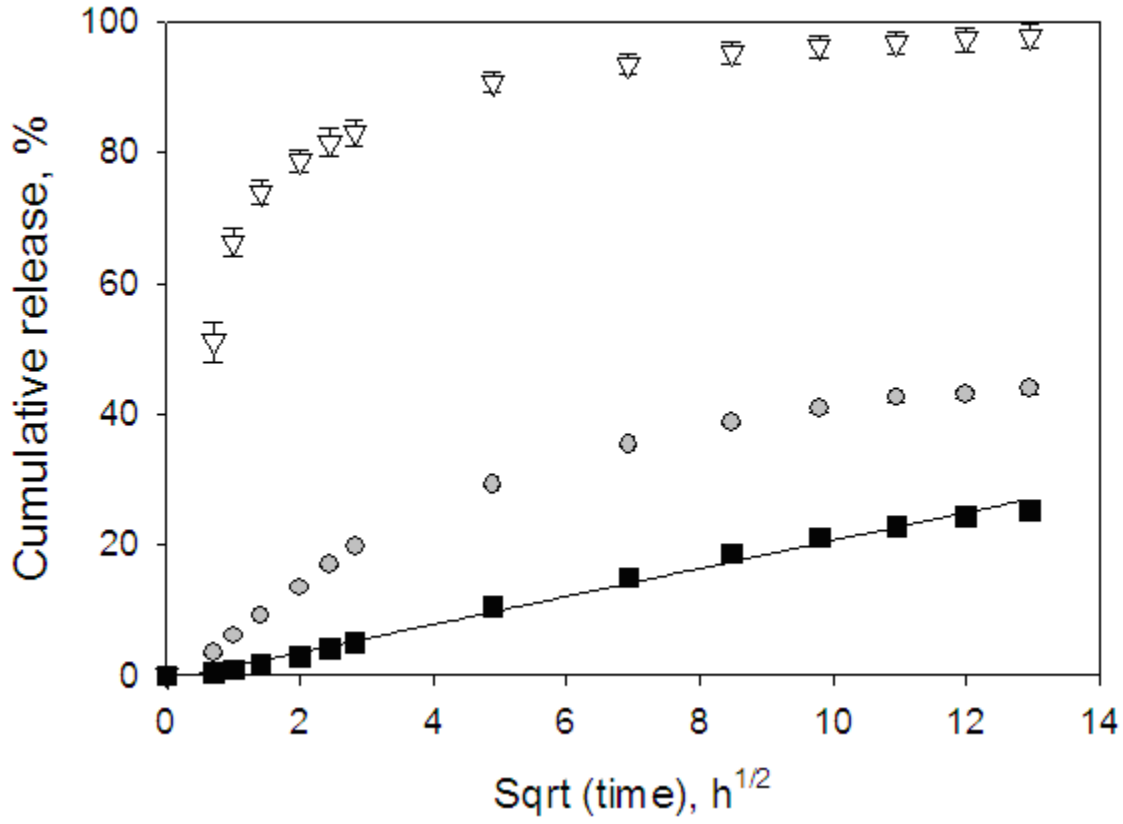
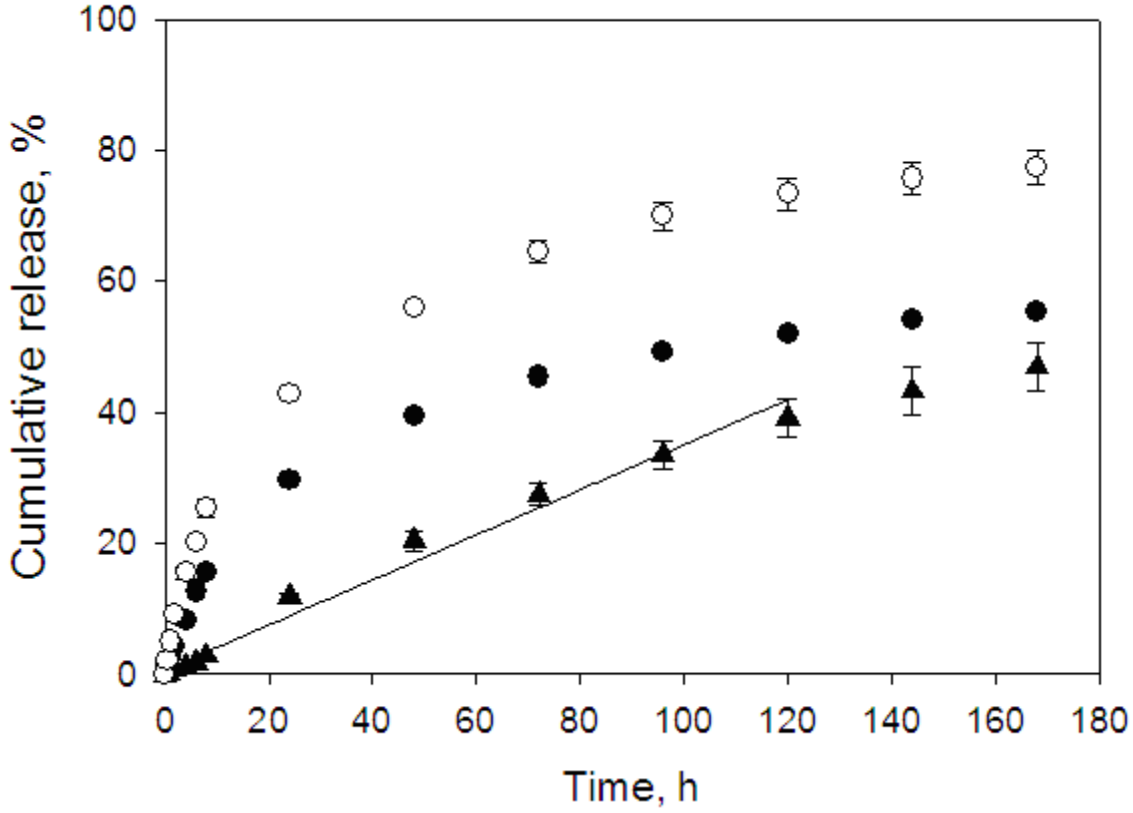

Cumulative release, %
100
80
60
40
20
0
0
2
4
6
8
10
12
14
Sqrt (time), h1/2

Figure 7.



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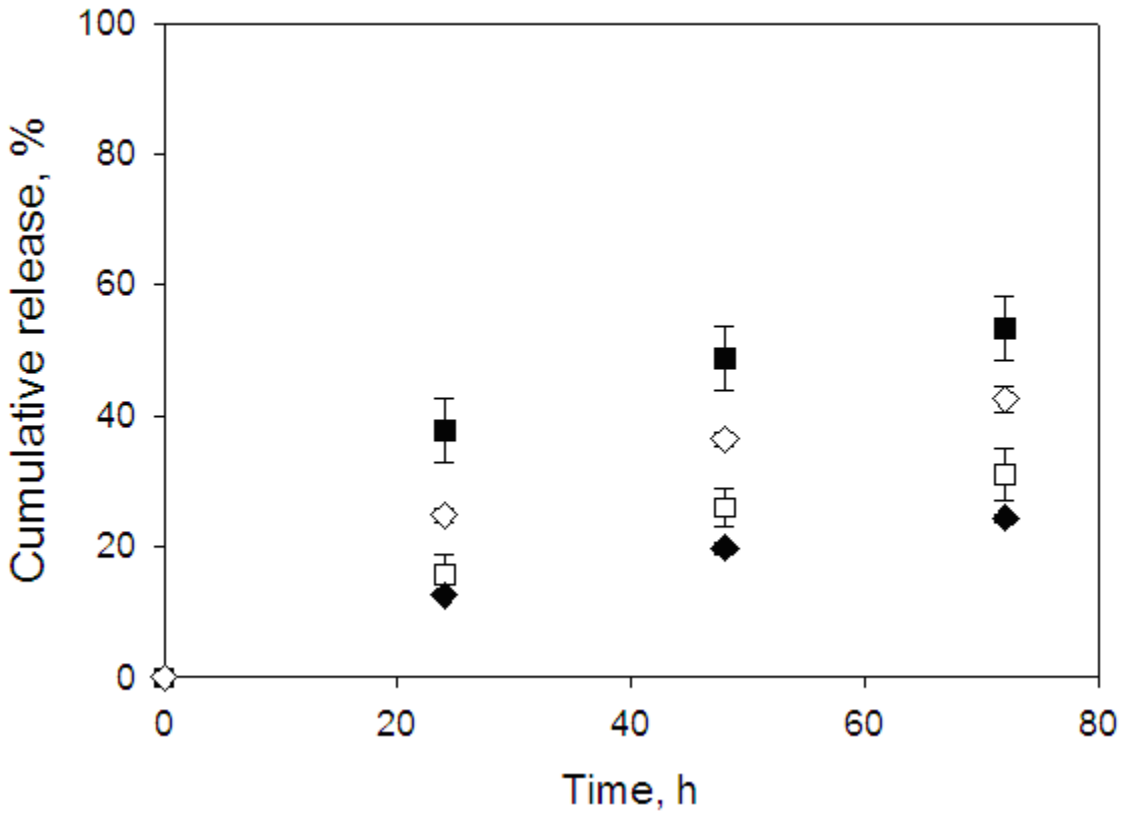

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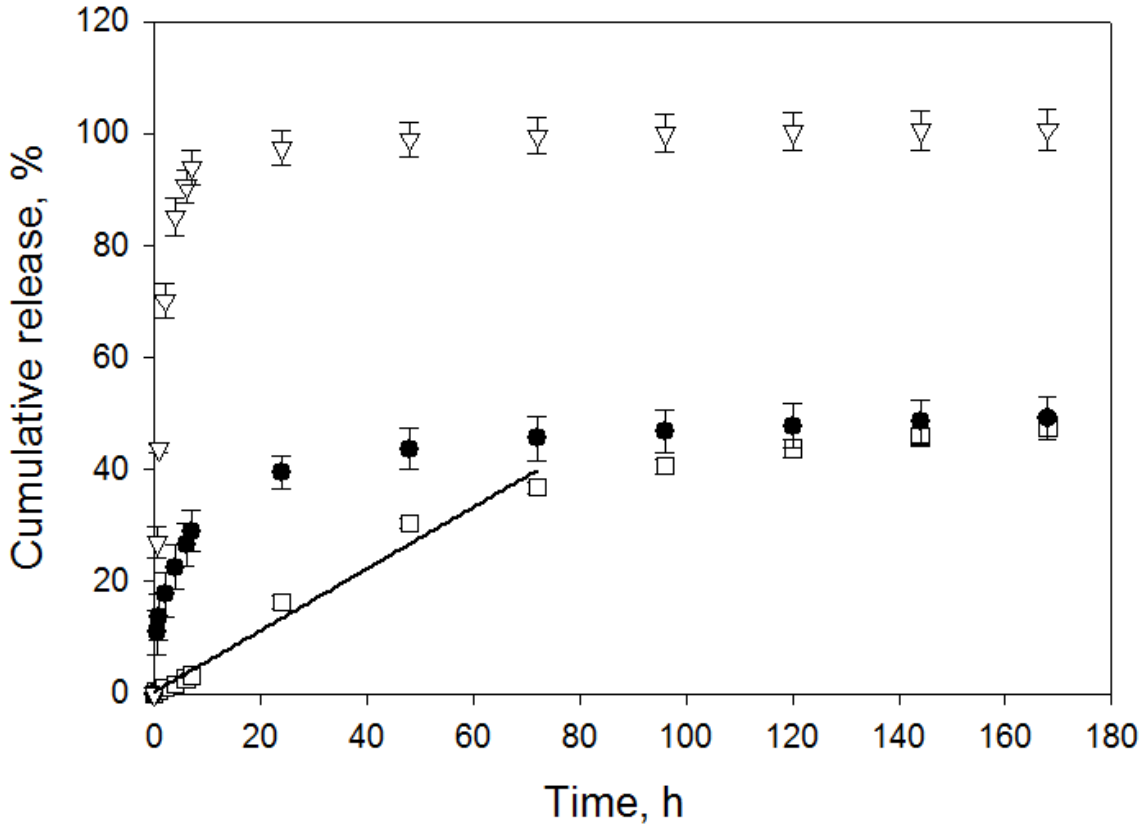

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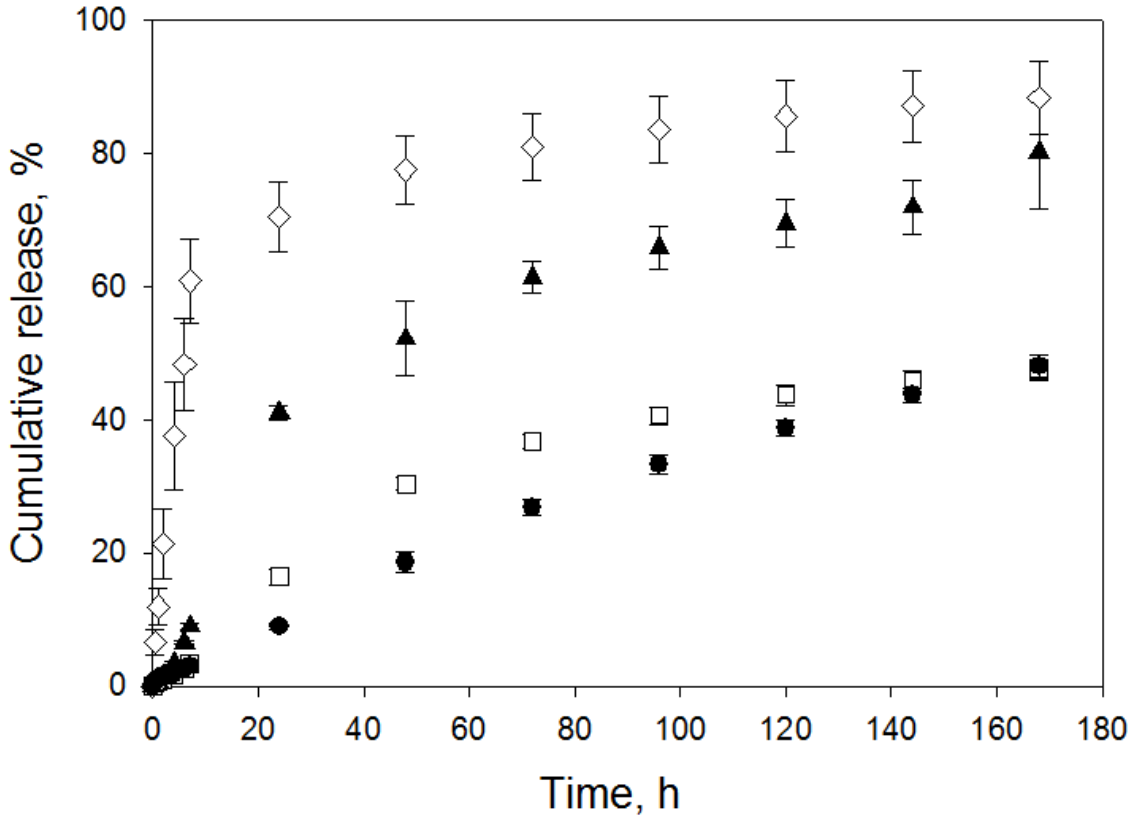

Figure 11.