



2008

Poly(D,L-lactide-co-glycolide) microcomposite containing magnetic iron core nanoparticles as a drug carrier

Sweta Naik

Virginia Commonwealth University

Everett E. Carpenter

Virginia Commonwealth University, ecarpenter2@vcu.edu

Follow this and additional works at: http://scholarscompass.vcu.edu/chem_pubs

 Part of the [Chemistry Commons](#)

Naik, S., and Carpenter, E. E. Poly(D,L-lactide-co-glycolide) microcomposite containing magnetic iron core nanoparticles as a drug carrier. *Journal of Applied Physics*, 103, 07A313 (2008). Copyright © 2008 American Institute of Physics.

Downloaded from

http://scholarscompass.vcu.edu/chem_pubs/22

This Article is brought to you for free and open access by the Dept. of Chemistry at VCU Scholars Compass. It has been accepted for inclusion in Chemistry Publications by an authorized administrator of VCU Scholars Compass. For more information, please contact libcompass@vcu.edu.

Poly(D,L-lactide-co-glycolide) microcomposite containing magnetic iron core nanoparticles as a drug carrier

Sweta Naik and Everett E. Carpenter^{a)}

Virginia Commonwealth University, Department of Chemistry, Richmond, Virginia 23284, USA

(Presented on 6 November 2007; received 2 October 2007; accepted 6 November 2007; published online 11 March 2008)

Today many potent anticancer drugs like cisplatin are available which carry a number of side effects. A promising way of reducing the side effects is to target the drug to tissue sites by coating it with biocompatible materials like Poly (dl-lactide-co-glycolide) (PLGA) polymer where controlled drug release is achieved during the biodegradation of the polymer. Also the efficacy of anticancer drugs like cisplatin increases at elevated temperatures, so if local heating can be achieved where the drug is targeted. Local heating can be achieved by introducing iron core nanoparticles in the composites along with the drug, which can be heated by the 2.4 GHz microwaves. Local heating of the nanocomposites also helps to swell the polymer shell and enhance the drug release. The magnetic nanocomposites were synthesized using iron nanoparticles, PLGA and a fluorescent dye, tris-(2,2'-bipyridyl) dichlororuthenium (II) using an oil-in-emulsion technique. The emulsion contains PLGA, dye, and iron nanoparticles dissolved in the oil phase and polyvinyl alcohol (PVA) as a stabilizer. As the sample is homogenized, and dried, uniform 100 nm composites are formed where the dye and iron nanoparticles are encapsulated in a PLGA shell. Control of the thickness and loading efficiency of the nanocomposite can be controlled by varying the ratio of PLGA, iron, and dye. The amount of loading was determined using TGA confirming from 20–50% (w/w) loading. As the dye is released from the composite the fluorescence intensity decreases due to self-quenching. This self-quenching allows for the determination of the release kinetics as a function of temperature using fluorescence spectroscopy. Initial results suggest that there is a release of 5–10% of the dye from the composite at 25 °C and complete release after the nanocomposite reaches 90 °C. Using local microwave heating the complete release of the dye can be accomplished with three two second pulses of 2.4 GHz microwaves. This allows for the complete drug delivery platform which allows for the controlled release using microwave frequency. © 2008 American Institute of Physics. [DOI: 10.1063/1.2836795]

INTRODUCTION

Pharmaceutical research today is more concentrated on drug delivery systems rather than new drug discovery. An ideal drug delivery system would be one that can target the drug or release of the drug in a specific region, thereby reducing the drug's toxicity and enhancing the drug efficacy. An effective way of achieving these goals is by creating a composite containing the drug with biocompatible polymers and magnetic nanoparticles.^{1,2} Polyesters such as poly(D,L-lactide-co-glycolide) (PLGA), poly(D,L-lactide) (PLA), and poly(glycolide) (PGA) are approved by the FDA due to their biocompatibility, biodegradability, and lower toxicity. The encapsulation of the drug of interest in the desired biocompatible polymer can be achieved by oil-in-water emulsion techniques yielding microsized composites.³ In these cases, through irradiation of a region with microwave radiation, the magnetic nanoparticles cause the polymer to swell, thus, releasing the drug in the given region. This has the additional advantage of increasing the efficacy of some anticancer

drugs increasing at elevated temperatures.^{4–6} Although the 2.45 GHz microwave radiation also heats water, the nanoparticles absorb far more of the radiation heating faster creating a localized heating effect around the composite.

II. EXPERIMENTAL AND CHARACTERIZATION

The PLGA coated magnetic microcomposites were prepared using magnetic iron core nanoparticles, PLGA, and fluorescent dye-tris-(2,2'-bipyridyl) dichlororuthenium (II) [Ru(bpy)₃Cl₂·6H₂O] as the drug mimic by oil-in-water emulsion technique.^{7,8} Tris-(2,2'-bipyridyl) dichlororuthenium (II) was used as the drug mimic because it is a metal complex based fluorescent dye that can be quenched by iron oxide. Poly(D,L-lactide-co-glycolide 50:50i.v (PLGA) was obtained from Polysciences, Inc. Poly(vinyl alcohol) 88% hydrolyzed with an average molecular weight of 88 000 and anhydrous dichloromethane (DCM) were purchased from Arcos organics. Tris-(2,2'-bipyridyl) dichlororuthenium (II) [Ru(bpy)₃Cl₂·6H₂O] was purchased from Sigma Aldrich. All chemicals were used as received without further purification.

The iron-iron oxide core-shell nanoparticles were synthesized via reverse micelles under nitrogen using Schlenk line techniques as found in the literature.^{9,10} A schematic

^{a)}Author to whom correspondence should be addressed. Tel.: (804) 828-7508. FAX: (804) 828-8599. Electronic mail: ecarpenter2@vcu.edu. Present address: 1001 W. Main Street, P.O. Box 842006, Richmond, VA 22148.

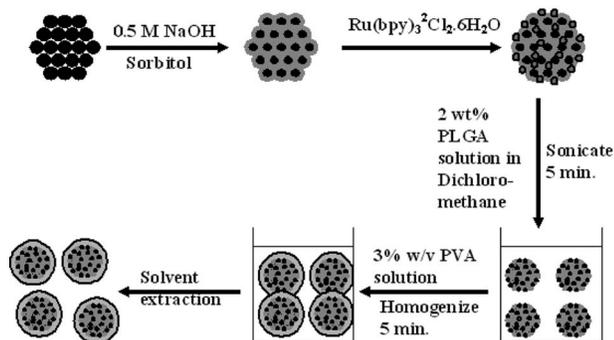


FIG. 1. Schematic representation of PLGA encapsulation of iron nanoparticles and fluorescent dye.

representation of the encapsulation process is shown in Fig. 1. As shown in the figure, the as synthesized iron-iron oxide core-shell nanoparticles were dispersed in 0.5M NaOH and then treated with equivalent grams of sorbitol and sonicated for 4 h. Sorbitol was used to provide a negatively charged particle surface to which the ruthenium dye could easily adhere. The sorbitol treated nanoparticles were then magnetically separated and 50 mg of ruthenium dye $[\text{Ru}(\text{bpy})_3\text{Cl}_2 \cdot 6\text{H}_2\text{O}]$ in 2 ml of water was added. This was further sonicated for 4 h and freeze dried to obtain the nanoparticle-dye mixture. Then, 2 wt % of PLGA in DCM polymer solution was prepared and 50 mg of the nanoparticle-dye mixture was then added and sonicated for 5 min. This organic mixture (oil phase) was then mixed with 50 ml of aqueous phase containing 3.8% w/v poly(vinyl alcohol) solution and homogenized with Ultra Turrax IKA T-18 basic homogenizer at 22 000 rpm for 5 min. Then, 100 ml distilled water was added to the oil-in-water emulsion, which dilutes the organic solvent concentration in water and leads to the hardening of the microcomposites. The solution was stirred overnight to evaporate the organic solvent and then freeze dried. The loading efficiency and the thickness of the PLGA coating can be controlled by varying the ratios of PLGA, iron nanoparticles, and the fluorescent dye.

The size distribution and the morphology of the prepared microcomposites were determined using a scanning electron microscope (SEM) with a Zeiss EVO 50 (Carl Zeiss, Inc.) The core-shell morphology and size of the nanoparticles were determined by transmission electron microscope (TEM) with a Joel JEM-1230 (Joel Ltd.) The loading efficiency of the iron nanoparticles and the dye, and the release rate of the dye were determined by fluorescence spectroscopy and thermogravimetric analysis (TGA).

DISCUSSION

SEM was performed to determine the size distribution and the morphology of the prepared microcomposites. Figure 2 shows the SEM image of the magnetic PLGA microcomposites which are roughly around 200 nm–1.5 μm in size and show fairly spherical structure. The inset shows the TEM image of the iron nanoparticles which illustrates the core-shell structure of the particles with an average particle size of 15 nm. The size distribution of the microcomposites is attributed to the oil-in-water droplet formation and the solvent

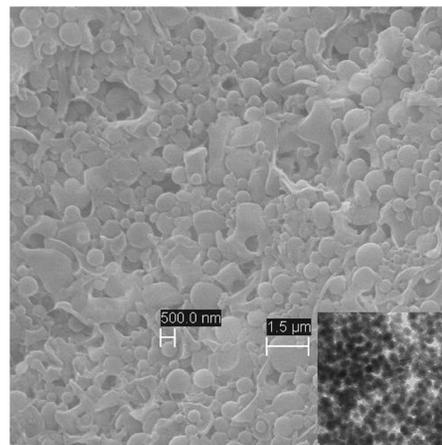


FIG. 2. (Color online) SEM image of the magnetic PLGA microcomposites. The inset shows the TEM image of the iron core-shell nanoparticles.

evaporation from the polymer solvent interface. There are other factors such as the duration of sonication and homogenization, the speed of homogenizer, etc., which affect the size of the microcomposites formed.⁸ In general, longer sonication/homogenization times and higher speed of the homogenizer which produces high shear induced by the homogenizer blade, thus, leading to smaller particle size. Too much loading of the ruthenium dye leads to a loss of morphological control and the composites turn into irregular shapes. It can be speculated that the ruthenium dye could precipitate in due to lack of water during the nanoparticle-dye mixture preparation. The particle size of the precipitated dye could be bigger than the oil-in-water bubbles formed, thus, disturbing the droplet formation. The other speculation would be that as the dye content is increased, more dye is likely to disperse in the aqueous phase, thus, disturbing the droplet formation.

The loading efficiency of the prepared magnetic PLGA microcomposites was determined using TGA and fluorescence spectroscopy. A 5 mg of the microcomposite was dissolved in dichloromethane. The iron nanoparticles and the ruthenium dye fall out in the organic solution. Known volume of water was added to the organic solution to extract the dye in the water. Fluorescence measurements were performed on the water layer to determine the dye content in 5 mg of the composites. Fluorescence intensity of known concentration of ruthenium dye was measured and a linear curve fit was performed which yields around 0.25% w/w fluorescent dye loading in the microcomposites. Attempts were made to improve the loading efficiency of the dye but it leads to the loss of the spherical morphology of the composites, as discussed earlier. TGA results also confirmed the percentage dye loading and shows approximately 40% w/w iron nanoparticles loading in the composite. TGA results combined with theoretical calculations based on the volume-density resulted into approximately 4000 iron nanoparticles embedded into roughly 500 nm composite. However, this leads to the loss of morphology control, as discussed previously.

Fluorescence spectroscopy was performed to study the release kinetics of the dye. As the dye is released from the

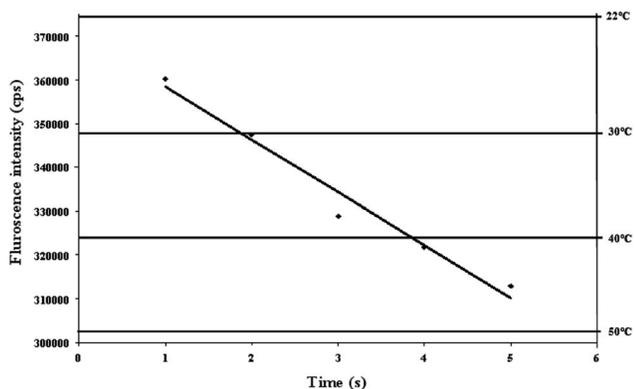


FIG. 3. Plot of fluorescence intensity vs time. The horizontal lines show the fluorescent intensity at room temperature (22 °C), 30, 40, and 50 °C temperature as measured by fluorescence spectrometer.

composite, the fluorescence intensity decreases due to the quenching of the ruthenium dye by the iron nanoparticles which allows for the determination of the release kinetics as a function of temperature. The composites were dispersed in water and heated with 2.45 GHz microwave by irradiating with a pulse of 1 s duration each utilizing a laboratory microwave unit. To achieve uniform heating of the composite sample and water as the reference, the turntable within the microwave unit was removed and the composite sample and water were heated from one to five times with a pulse of 1 s duration each. The iron nanoparticles encapsulated within the composite absorb the microwaves and heat up providing local heating. This also swells up the polymer coating and leads to the release of the dye. The bulk water temperature of the composite sample as well as the reference reached up to 32 °C after irradiating the sample five times with a pulse of 1 s duration each. Fluorescent measurements were carried out after irradiating the sample for one to five times with 1 s pulse each, as well as heating the sample to 30, 40, and 50 °C. The sample was just heated five times as further heating leads to increase in the temperature drastically. Figure 3 shows the plot of the fluorescence intensity with time of irradiation of the sample by the microwaves. The horizontal lines on the plot correspond to the fluorescence intensity of

the sample when heated externally up to 30, 40, and 50 °C. It can be seen that the rate of release of the dye at 2 s is equal to that of 30 °C and the 4 s irradiation release equals to 40 °C. Thus, we were able to achieve higher dye release by locally heating the sample with 2 GHz microwave pulse compared to externally heating the composite sample. Heating the composites five times with 1 s pulse each did not elevate the temperature above 32 °C but the composite experienced a temperature rise roughly at about 50 °C with higher release of the dye.

CONCLUSION

The magnetic PLGA microcomposites prepared showed enhanced dye release when irradiated with 2.45 GHz microwaves. The composite when heated by the pulsed microwaves experienced a temperature rise of 32 °C while showing a drug release at roughly about 50 °C. The magnetic PLGA microcomposites thus show the potential of being the ideal drug delivery system for cancer treatment.

ACKNOWLEDGMENTS

“Research support was provided by PM-USA INEST research gift, Office of Naval Research, and Thomas and Kate Jeffress Memorial Foundation.”

- ¹K. Derakhshandeh, M. Erfan, and S. Dadashzadeh, *Eur. J. Pharm. Biopharm.* **66**, 34 (2007).
- ²L. Garcia-Contreras, K. Abu-Izza, and D. R. Lu, *Pharm. Dev. Technol.* **2**, 53 (1997).
- ³P. B. Odonnell and J. W. McGinity, *Adv. Drug Delivery Rev.* **28**, 25 (1997).
- ⁴B. S. S. Rao and P. U. Devi, *Indian J. Med. Res.* **103**, 315 (1996).
- ⁵S. Srivastava, S. Srivastava, V. D. Gupta, and V. P. Gupta, *J. Macromol. Sci., Phys.* **B43**, 791 (2004).
- ⁶K. W. Wolf, M. Mentzel, and A. S. Mendoza, *Annals of Anatomy-Anatomischer Anzeiger* **178**, 425 (1996).
- ⁷J. R. Jeong, S. J. Lee, J. D. Kim, and S. C. Shin, *IEEE Trans. Magn.* **40**, 3015 (2004).
- ⁸S. J. Lee, J. R. Jeong, S. C. Shin, J. C. Kim, Y. H. Chang, K. H. Lee, and J. D. Kim, *Colloids Surf., A* **255**, 19 (2005).
- ⁹E. E. Carpenter, S. Calvin, R. M. Stroud, and V. G. Harris, *Chem. Mater.* **15**, 3245 (2003).
- ¹⁰M. D. Shultz, S. Calvin, P. P. Fatouros, S. A. Morrison, and E. E. Carpenter, *J. Magn. Magn. Mater.* **311**, 464 (2007).