Rational Design of Biodegradable Polymer Particles Using Carbon Dioxide

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ABSTRACT: Through a collaboration between the University of Delaware Chemical Engineering Department and the University of Nottingham Schools of Chemistry and Pharmacy, the viscosities of biodegradable polymers saturated with high pressure carbon dioxide were measured experimentally. At comparable levels of free volume (as estimated from the Sanchez-Lacombe equation of state), a low molecular weight amorphous copolymer of lactic and glycolic acid (PLGA) exhibited a viscosity more than an order of magnitude higher than that of higher molecular weight semicrystalline polymers poly(caprolactone) and poly(ethylene glycol). This is believed to account for the relative difficulty in processing PLGA into fine particles for drug delivery applications.

INTRODUCTION

Our IREE grant was a supplement to NSF Grant 0553659, "Rational Design of Biodegradable Polymer Particles Using Carbon Dioxide." Under the main grant we are studying drug delivery vehicles produced by a low-temperature, solvent free-process using polymers saturated with carbon dioxide. We have hypothesized that the size and shape of particles, which determine their suitability for pulmonary delivery applications, are governed by the nature of the two-phase gas-liquid flow during the depressurization process. This flow, in turn, is influenced by the viscosity of the polymer droplets which eventually solidify into particles. Although polymer viscosity reduction from the presence of absorbed CO_2 is well-known, few reliable experimental measurements have been made, especially on the biodegradable polymers used in drug delivery. Furthermore, published experimental data disagree on the suitability of the Williams-Landel-Ferry (WLF) equation, in concert with an equation of state, for describing the dependence of viscosity on pressure and temperature of CO_2-containing polymers. Our IREE research objectives were to measure the viscosity of polymer/CO_2 mixtures useful for drug delivery applications, and to determine whether a free volume equation such as WLF could describe the observations, and hence be used for process design.

This IREE collaboration was between Prof. Steve Howdle of the University of Nottingham (UK) School of Chemistry and Prof. Annette Shine of the University of Delaware (US) Department of Chemical Engineering. Both research groups study the production of drug delivery particles using supercritical CO_2. However, the UK group, through its School of Pharmacy, had available a dedicated instrument for measuring viscosity of polymers saturated with CO_2. Unfortunately, sub-optimal equipment design limited their ability to acquire quantitative data. The US research group developed a calibration technique which allowed the UK equipment to be used quantitatively. Hence, this collaboration was beneficial to both institutions. Mr. Rob Bleecher, a University of Delaware Chemical Engineering undergraduate, worked under IREE in the Nottingham laboratory from 20 June to 20 December, 2008. He was selected because he had helped develop the instrument calibration technique for a senior project at Delaware, and because he was weighing career options of graduate school vs. entrepreneurship. Prof. Howdle is also Chief Executive Officer of Critical Pharmaceuticals Ltd, a startup company with 7 employees, specializing in drug delivery applications. Hence, the IREE visit enabled Mr. Bleecher to compare first-hand graduate school research vs. corporate startup research.

RESEARCH ACTIVITIES AND ACCOMPLISHMENTS OF THE INTERNATIONAL COOPERATION

While at Nottingham, Mr. Bleecher implemented the calibration technique and determined the viscosity of poly(ethylene glycol) (PEG), poly(caprolactone) (PCL) and lactide/glycolide copolymers (PLGA). Each of these polymers has been studied by both the UK and US groups in particle formation processes. Swelling and free volume behavior was modeled using the Sanchez-Lacombe equation of state, which both research groups have previously employed. During this time, Mr. Bleecher worked directly with other graduate students and postdoctoral fellows in the Howdle laboratory. Before leaving, he trained UK researchers in the experimental and analysis techniques he developed for their equipment.

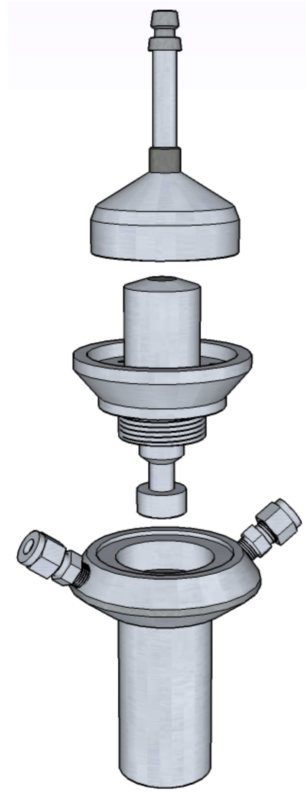

Figure 1. High pressure cell

Figure 1 shows a schematic diagram of the Nottingham high pressure rheological measurement cell. Because of parasitic torque in the magnetic coupling (topmost element in Fig. 1), and the squat cylindrical shape of the rotating bob (center element), the instrument had to be calibrated with a series of Newtonian fluids of different volumes. Because this geometry was non-standard, all data analysis was done separate from the computer control system associated with the rheometer.

Measured CO_2-saturated polymer viscosities are shown in Figure 2 below. On the x-axis is plotted the ratio of occupied to unoccupied volume, as predicted by the Sanchez-Lacombe equation for each polymer mixture. The semi-empirical Doolittle equation,

$$\eta_0 = A\exp\left[B\left(\frac{Vocc}{Vfree}\right)\right] \qquad (1)$$

of which the universal constant WLF equation is a special case with B=1.002, is plotted for comparison purposes. The data appear to be linearized by the, Doolittle equation but the slope of the Doolittle plots, especially for PCL, vary from that of the universal WLF constants.

Of the polymers studied here, the semicrystalline PCL and PEG are both relatively easy to process into drug delivery particles. However, they have extremely long (PCL) and extremely short (PEG) release times, so the amorphous copolymers of PLGA are considered better candidates for such applications. Unfortunately, PLGA is difficult to process into particles, tending instead to generate foams. Figure 2 provides insight into the cause. Despite the extremely low molecular weight of the PLGA (1500 Da), this polymer has a much higher viscosity (by 1 to 2 orders of magnitude) than does PCL or PEG. This is probably due to a combination of the amorphous nature of PLGA, and a high monomeric friction coefficient. Unfortunately, this may make PLGA unsuitable for processing into pulmonary drug delivery particles, since lowering its viscosity by a reduction in molecular weight would reduce release times to unsatisfactory levels.

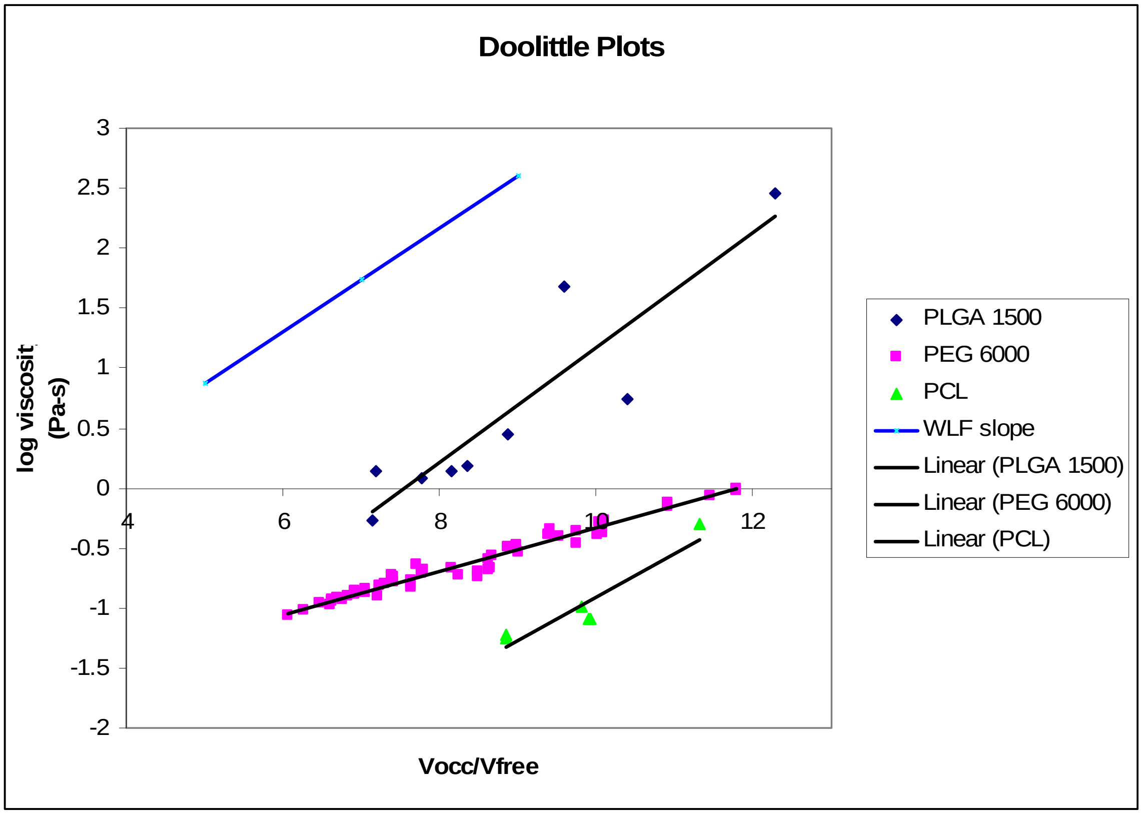

Figure 2. Viscosity of biodegradable polymers saturated with carbon dioxide

BROADER IMPACTS OF THE INTERNATIONAL COOPERATION

The time period covered by this IREE grant included the week of the 2008 US presidential election. Rob Bleecher, who voted by absentee ballot, fielded questions and engaged in many discussions with his European coworkers, who were extremely interested in this election. He felt that this was a valuable opportunity to explain the US political process, and to educate our allies that policy decisions by the presidential administration do not always reflect popular opinion.

As part of a teambuilding exercise in Nottingham, the entire research group participated in a go-kart race. Rob Bleecher, who was paired as a driver with Steve Howdle, came in second place. However, perhaps as an indication of cultural differences, the European and US participants disagreed on whether or not Rob's aggressive driving and last-lap crash precluded a possible first place finish.

Partly as a result of his IREE experience, Mr. Bleecher elected to pursue a career in the nascent biofuels industry in the US, and is currently employed as a process engineer for Coskata, Inc. in Warrenville, IL. Amusingly, he observed that much of the time of the UK professor was spent in fundraising to support his large research group, leaving little time for direct research involvement. The two research groups are preparing a joint manuscript for submission to an international journal (Rheologica Acta) on the rheology results.

DISCUSSION AND SUMMARY

Through this collaboration, we have uncovered the cause of inherent difficulties in processing PLGA copolymers into drug delivery particles using a low temperature, solvent-free method which utilizes high pressure carbon dioxide. Specifically, even low molecular weight PLGA, when saturated with carbon dioxide, has an extremely high viscosity, in comparison to other easy-to-process polymers. Unfortunately, a further reduction in molecular weight, which would reduce viscosity, is not possible. Instead, we will examine the efficacy of injecting additional gas during the atomization/depressurization process, in order to facilitate droplet formation before solidification.

Much of the advice we received from our pre-trip conference was extremely useful, especially the recommendation to provide the traveler with an official document explaining his status in the country (for immigration control). One difficulty we encountered was an extreme delay (nearly 3 months) in ordering chemical supplies. This glitsch occurred because we were ordering (and paying for) chemicals in one country, while shipping to another country, during a heightened terrorist alert. We were originally advised to submit the order through the UK affiliate's web site, but this turned out to be incorrect. For future IREE "Best Practices," I would either suggest ordering all supplies before leaving the US, or else develop a mechanism to transfer funds directly to the host group, so that ordering and delivery addresses will be the same.

ACKNOWLEDGEMENTS

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BRIEF BIOGRAPHIES OF RESEARCHERS

Annette D. Shine received bachelor degrees from Washington University in St. Louis in 1976. She received her M.S. degree in Macromolecular Science from Case Western Reserve University in 1979 and a Ph.D. degree in Chemical Engineering from MIT in 1983. Following three years at Eastman Kodak, she had held academic positions at the Colorado School of Mines and the University of Delaware, where she is currently an Associate Professor of Chemical Engineering. She is a registered professional engineer, and serves on the governing council of the Delaware Association of Professional Engineers, the state licensing board.

Robert D. Bleecher received the BChE in Chemical Engineering from the Ujniversity of Delaware in 2008. He is currently employed as a process engineer at Coskata, Inc. in Warrenville, IL.