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# Microparticles produced by the hydrogel template method for sustained drug delivery

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ABSTRACT

Polymeric microparticles have been used widely for sustained drug delivery. Current methods of microparticle production can be improved by making homogeneous particles in size and shape, increasing the drug loading, and controlling the initial burst release. In the current study, the hydrogel template method was used to produce homogeneous poly(lactide-co-glycolide) (PLGA) microparticles and to examine formulation and process-related parameters. Poly(vinyl alcohol) (PVA) was used to make hydrogel templates. The parameters examined include PVA molecular weight, type of PLGA (as characterized by lactide content, inherent viscosity), polymer concentration, drug concentration and composition of solvent system. Three model compounds studied were risperidone, methylprednisolone acetate and paclitaxel. The ability of the hydrogel template method to produce microparticles with good conformity to template was dependent on molecular weight of PVA and viscosity of the PLGA solution. Drug loading and encapsulation efficiency were found to be influenced by PLGA lactide content, polymer concentration and composition of the solvent system. The drug loading and encapsulation efficiency were 28.7% and 82% for risperidone, 31.5% and 90% for methylprednisolone acetate, and 32.2% and 92% for paclitaxel, respectively. For all three drugs, release was sustained for weeks, and the *in vitro* release profile of risperidone was comparable to that of microparticles prepared using the conventional emulsion method. The hydrogel template method provides a new approach of manipulating microparticles.


## 1. Introduction

Polymeric microparticle drug delivery systems have been widely explored for controlled delivery of active pharmaceutical ingredients. Microparticles provide several advantages as drug delivery vehicles, such as protection of encapsulated drug from unfavorable environmental conditions and ability to control drug release profile for a specified period of time (Tran et al., 2011a). In particular, the potential to control drug release profile over an extended period of time is one of the most desirable attributes (Wei et al., 2012). Suitable drug candidates that may benefit greatly from such controlled drug delivery systems based on polymeric microparticles include those that have a broad therapeutic window, require a low daily dose and are used for the long-term treatment of disease.

Poly(lactide-co-glycolide) (PLGA) is probably the most extensively used polymer in microparticle drug delivery systems (Tran et al., 2011a). This copolymer of lactide and glycolide degrade by simple hydrolysis when exposed to an aqueous environment such as inside the human body. PLGA has been used in a host of drug products approved by Food and Drug Administration (FDA), such as Zoladex Depot® (goserelin), Lurpon Depot® (leuprolide), Sandostatin LAR® Depot (octreotide acetate), Nutropin Depot® (somatotropin), Trelstar® (triptorelin), Somatulin® Depot (lanreotide), Risperidal® Consta® (risperidone), Vivitrol® (naltrxone) and Bydureon® (exenatide). PLGAs are available at various molecular weights (or intrinsic viscosities) and lactide/glycolide ratios with either ester end-caps or free carboxylic acid end-caps. The properties of PLGA have been shown to influence important microparticle characteristics, such as the amount of drug loading, loading efficiency and drug release both *in vitro* and *in vivo* (Yeo and Park, 2004; Su et al., 2011; Amann et al., 2010). Previous studies have demonstrated that the rate of hydrolysis, and therefore, drug release is heavily dependent on the PLGA molecular weight and monomer composition. Consequently, it is possible to design PLGA-based microparticle drug delivery systems with tailored polymer degradation characteristics and release patterns by varying the PLGA composition.

In addition to polymer composition and properties, there are other formulation- and process-related parameters that may affect microparticle performance. Formulation-related factors include

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type of organic solvent used, concentration of polymer used, and drug–polymer interactions (Yeo and Park, 2004; Doan et al., 2011; Cho et al., 2000). Various studies have shown that these formulation-related factors affect drug encapsulation efficiency and drug distribution within polymeric matrix, which in turn influences the initial burst release. The initial burst release is one of the major challenges in developing drug-encapsulated microparticle systems. The release of a large bolus of drugs before microparticles reach a steady state release is both therapeutically undesirable and economically ineffective. Therefore, the ability to control and limit the initial burst release is highly sought-after and extensively studied. In addition, there are process-related parameters that can affect the performance of microparticles produced using these methods. Currently, spray drying and emulsion-based methods are well-established and most commonly used to prepare drug-loaded PLGA microparticles. Process-related parameters in these methods that influence drug-loaded microparticle characteristics include the ratio of dispersed phase to continuous phase and the rate of solvent removal/extraction. The factors outlined above and their effects on microparticle performance, however, have been mostly studied in the emulsion-based methods only.

Although emulsion-based and spray-drying methods are widely used, their applicability is restricted by a number of limitations. Techniques such as spray drying may be unsuitable for substances sensitive to heating and mechanical shear of atomization, which narrows the field of applicability for this technique (Maa and Prestrelski, 2000). Low product yield due to deposition of materials on the interior surface of drying chamber is yet another common concern for spray drying. For both spray drying and emulsion-based methods particle formation is random and results in microparticles with broad size distribution (Tran et al., 2011b). Microparticle size is an important factor that affects the choice of administration route (Gaumet et al., 2009; Mohamed and van der Walle, 2008; Thomas et al., 2010), drug encapsulation within the microparticle and therefore drug release profile from the delivery vehicle (Berkland et al., 2003, 2004; Siepmann et al., 2004). Another common problem with spray drying and emulsion-based methods is low drug loading, often with an average of less than 10% (Gaspar et al., 1998; Kauffman et al., 2012; Le Ray et al., 2003). Certainly there is room for improvement in microencapsulation techniques.

To address limitations associated with conventional methods of microparticle preparation, we have developed a microfabrication technique for preparation of microparticles. The approach utilizes the unique properties of physical gels that can undergo sol–gel phase transitions or water-soluble polymers that do not dissolve in organic solvents. The approach is collectively called the hydrogel template method (Acharya et al., 2010a). The hydrogel template approach allows a more precise control of microparticle size and shape, which translates into narrow size distribution and increased microparticle homogeneity. In addition, the method provides flexibility in producing microparticles of various desirable size ranges. Another improvement over existing methods is the possibility of incorporating a higher amount of drug into the polymeric matrix, since the particle formation process is no longer random, thereby allowing more control over drug encapsulation. The hydrogel template approach does not require the application of excessive heat, mechanical force or any harsh treatment conditions. It is a simple and fast process.

Early method development of the hydrogel template technology and initial study on the effect of the particle size on drug release were discussed in previous publications (Acharya et al., 2010a,b). The main objective of the present study is to evaluate the hydrogel template method for producing drug-loaded polymeric microparticles, with the goal of gaining a better understanding of this method that will ultimately aid in method optimization. Three drugs with different physicochemical properties were used as model compounds in this study. The data obtained were compared and contrasted to microparticles prepared using the conventional emulsion-based technique.

## 2. Materials and methods

### 2.1. Materials

Risperidone (RIS) and methylprednisolone acetate (MPA) were purchase from Sigma–Aldrich (St. Louis, MO), paclitaxel (PTX) was supplied by Samyang Genex Corporation (Republic of Korea). Poly(D,L-lactide-co-glycolide) (PLGA) 5050, 6535, 7525 and 8515 (corresponding to lactide:glycolide ratio of 50:50, 65:35, 75:25 and 85:15, respectively) were purchased from Lactel (Pelham, AL). Poly(vinyl alcohol) (PVA, 87–89%, 96%, 98–99% and >99% hydrolyzed) of various typical molecular weight was purchased from Sigma–Aldrich (St. Louis, MO). Benzyl alcohol (BA, analytical reagent grade), ethyl acetate (EA, analytical reagent grade) and methylene chloride (DCM, analytical grade) were purchased from VWR (Batavia, IL). All other chemicals or solvents were of reagent or analytical grade and used as received without further purification.

### 2.2. Preparation of hydrogel templates

The basic approach to producing gelatin-based templates containing an array of cylindrical posts with pre-determined diameters and heights was described before (Acharya et al., 2010a,b). A similar method was adopted to produce templates in this particular study with some modifications. A silicon wafer master template was constructed by spin-coating with SU8 2010 photoresist (Microchem, Cambridge, MA) at 3500 rpm for 30 s and baking, followed by ultraviolet exposure radiation through a mask containing an array of circular patterns 10 μm in diameter and subsequent developing and drying procedures according to manufacturer's instructions. The master template thus fabricated contained cylindrical wells 10 μm in diameter and 10 μm in height. Next, the master template was coated with Sylgard 184 elastomer (Dow Corning, Elizabethtown, KY) consisting of approximately 50 g of pre-polymer and 5 g curing agent in a flat-bottomed ceramic dish and cured at 70 °C for 2 h. The polydimethylsiloxane (PDMS) template was removed carefully from the silicon wafer master template and flushed with ethanol, followed by drying with a nitrogen stream. This intermediate PDMS template was used repeatedly in subsequent experiments to produce templates for making drug-loaded PLGA microparticles. PVA was dissolved at a concentration of 4% (w/v) in a mixture of deionized water and ethanol (40:60, v/v) with constant stirring and heating. The resulting solution was used to evenly coat the surface of PDMS intermediate template. After solvent evaporation and template solidification, the PVA template was gently peeled off the PDMS template and stored in a cool, dry place until ready to use.

### 2.3. Preparation of polymer–drug solutions

RIS, MPA and PTX were chosen as model poorly water-soluble compounds in this study. The properties of these compounds are presented in Table 1. The compounds were dissolved with the selected type of PLGA polymer in a mixture of BA and EA or DCM. The types of PLGA evaluated varied by lactide-to-glycolide ratio (L:G) and intrinsic viscosity (IV). Other parameters that varied were the concentration of PLGA in solution, drug concentration and ratio of BA to EA. A summary of the composition of drug solutions used in this study is provided in Table 2.