

# Variables in the Synthesis of Quality Biodegradable Magnetic Microspheres

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## Background and Purpose

Biodegradable micro/nanospheres are used to encapsulate drugs for targeted delivery or for selective detoxification of the blood. Synthesis of quality spheres is crucial. That is, the sphere properties must be homogeneous and predictable. We discuss the plethora of synthesis variables and known effects on micro/nanosphere synthesis.

## Solvent Evaporation

Most commonly cited technique for synthesis

1. Polymer dissolved in volatile organic
2. Oil phase vigorously mixed with water phase containing surfactant
3. Volatile organic evaporates from solution, leaving hardened sphere in suspension
4. Purification by multiple washing with deionized water or buffer
5. Separation by centrifugation, magnetic separation, or dialysis

## Variables

Polymers	Poly(D-lactide), poly(L-lactide), poly(D,L lactide), poly(lactide-co-glycolic acid), polymers and copolymers linked to polyethylene glycol, poly(caprolactone)
Surfactants	Poly(vinyl alcohol), poloxamer, polyethylene glycol, TPGS, sodium dodecyl sulfate
Volatile organics	Dichloromethane, chloroform, acetone, ethyl acetate
Mixing speed	1,000-20,000 rpm, 15-95 W insonation
Mixing modality	High-speed dispergation, ultrasonic insonation, paddle mixing, magnetic stir bar
Polymer/organic solvent ratio	1-10%
Oil/water ratio	1-10%
Mixing time	Several sec to min depending on modality to form initial emulsion, several hr to harden
Polymer MW	2-300 kDa
Surfactant MW	PVA 10-150 kDa
Surfactant concentration	PVA 0.1-10%
Magnetic phase	Magnetite Fe <sub>3</sub> O <sub>4</sub> , maghemite γ-Fe <sub>2</sub> O <sub>3</sub> , passivated Fe, passivated Co
Temperature	Unknown, may reduce coalescence

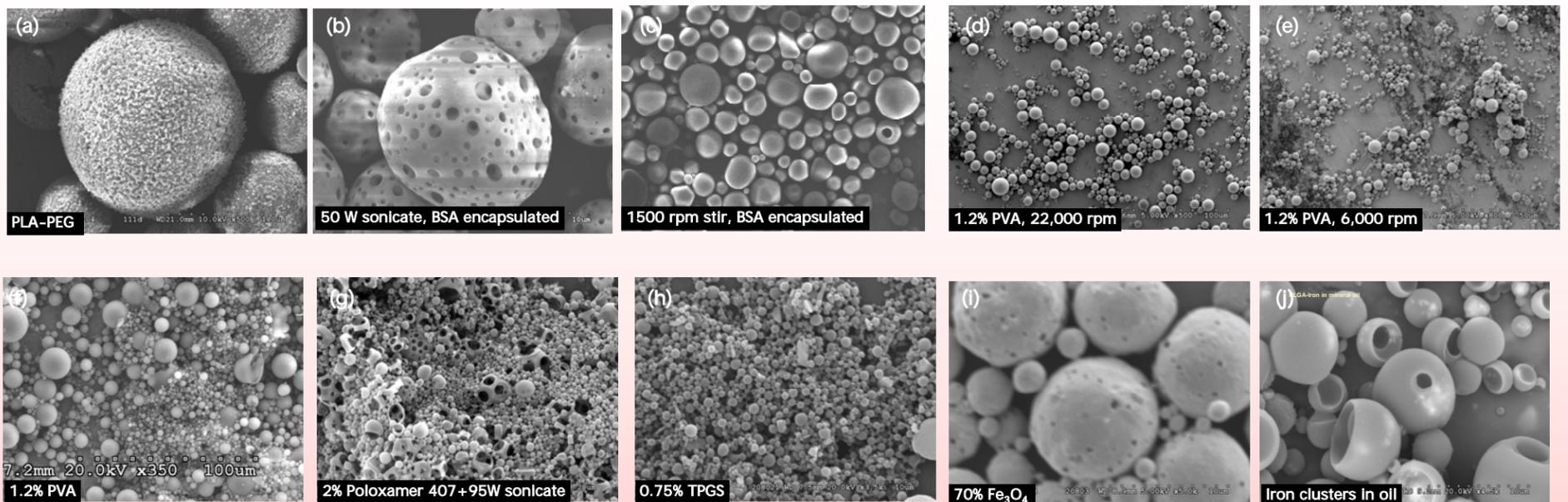
## Ideal Properties of Injectable Magnetic Microspheres

- **Long-circulating:** Dense surface PEGylation is the best known approach to preventing opsonization and phagocytosis (**a below**).
- **Smooth or intact surface:** Some synthesis parameters such as high magnetic fraction and high surfactant concentration can lead to holes in surface or exposure of non-PEGylated components, leading to opsonization (**b and c below**).
- **Small and uniform size:** All things being equal, smaller spheres avoid RES recognition longer, i.e., 100-200 nm. Uniform size facilitates QA/QC.
- **Magnetic:** Magnetic targeting or filtration requires sufficient moment. High encapsulation of magnetic nanophases is desirable.
- **Procedurally efficient:** High yield and reproducible results necessary for federal approval.

*Nowhere in the literature are all these properties combined!*

## Polymer properties

- Poly(L-lactide): semi-crystalline with  $T_g=60-67^\circ\text{C}$ ,  $T_{\text{melt}}=170-180^\circ\text{C}$ .
- Poly(DL-lactide): amorphous with  $T_g=50-60^\circ\text{C}$ .
- Poly(lactide-co-glycolide):  $T_g=54^\circ\text{C}$ , 25-70% glycolic acid is amorphous. Hydrophilicity increases as glycolide ratio increases. Results in less viscous solvent than PLA.
- Poly( $\epsilon$ -caprolactone): crystalline with  $T_g=-60^\circ\text{C}$ ,  $T_{\text{melt}}=61^\circ\text{C}$ . High permeability to low MW species. Hydrolyzes slower than PLA or PLGA.



## Effects of Process Variables

- **Stir speed:** Higher speed produces smaller spheres; no change above 6000 rpm. +Ultrasonic insonation produces smaller spheres (**d and e above**).
- **Surfactant:** Some surfactants electrostatically protect emulsions better. Low surfactant leads to agglomerated spheres; too high makes cleaning difficult (**f, g, and h above**).
- **Magnetite content:** Phase separation occurs at high loading. PLA-coated magnetite should improve (work by Professor Judy Riffle at VPI). Magnetite increases size (**i and j above**).
- **Oils:** May be necessary to fill spheres and provide volume for drug encapsulation. Higher surface tension and viscosity lead to larger spheres.
- **PLA/chloroform ratio:** Lower PLA/chloroform ratio leads to larger particles.
- **PEGylation:** Makes smaller particles. PEG neutralizes surface charge of polymers. PEG chain length related to  $T_{1/2}$  for circulation; 30 min for PEG 6000 and 20 h for PEG 170,000 (Yamaoka et al., J. Pharm. Pharmacol. 4, 479, 1995).

## Summary

- Seek to design procedure for magnetic biodegradable nanospheres suitable for (a) selective toxin binding *in vivo* and (b) targeted drug delivery to internal organ targets.
- Completed a parametric study on PLA and PLGA synthesis. PLA-PEG synthesis study ongoing.
- Magnetic requirement may force need to encapsulate oil in spheres to increase magnetic phase loading.
- Surface smoothness necessary to maintain PEGylation and avoid opsonization.
- Solvent evaporation retains too many variables and hinders QA/QC.
- Clearly, a novel technique is needed to eliminate influence of process parameters on properties such as size.