Microfluidics

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Application Note

Use of Microfluidizer™ technology for production of polymer nanoparticles.

This Application Note gives an overview of the development and manufacture of polymer nano-particles using the Microfluidizer® processor. The Microfluidizer has been widely accepted as an ideal technology for generation of polymer nano-particles.[1],[2],[3] This note also describes the important factors to consider when developing a process. Polymer nano-particles hav been used for the generation of solid-lipid nanoparticles, (SLNs)[4] which can be used to enhance cellular uptake.[5]

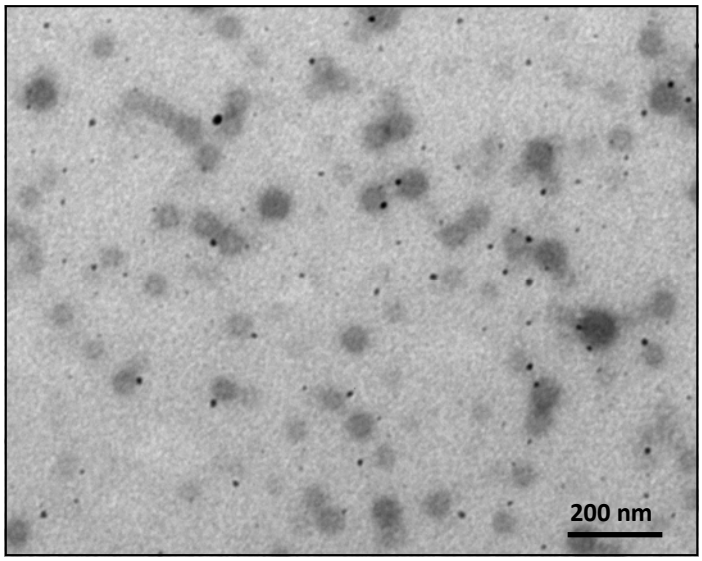

Figure 1: TEM of polymer nanoparticles that were created using Microfluidizer technology

Why Polymer Nanoparticles?

Biodegradable polymer nanoparticles have been of increasing interest over the past decade. Their benefits include:

- The ability to deliver a combination of different therapeutic ingredients.[7]
- The capability to include targeting moieties.
- The capability to protect the active ingredients from degradation forces.
- The capability to control the release of ingredients.[9]
- The option of inclusion of diagnostic capabilities.
- The ability to terminally sterilize via filtration.

Step 1: Determine Formulation:

Water phase: Water + Surfactant

The most commonly used surfactant is polyvinyl alcohol (PVA), but several researchers have had success using polymeric surfactants such as polysorbate and polyoxyethylene, or phospholipids like 1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC).

Surfactant concentrations are typically quite low. In the range of 0.1—1%wt.

Oil phase: Water immiscible solvent + polymer + other ingredients to be included (actives, contrast agents, etc.)

The most commonly used solvents are ethyl acetate and methylene chloride. When selecting a solvent, there are several factors that must be considered:

IDEX MATERIAL PROCESSING

Water Miscibility: Generally the less miscible with water, the better. When the miscibility is high (ethyl acetate will dissolve at a concentration of 8.3g/100mL), most researchers will saturate the water phase with solvent.

Boiling Point: Solvents are typically removed by solvent evaporation. Solvents with low boiling points are easier to remove, but can be more challenging to process. When processing solvents that are very volatile (Dichloromethane has a boiling point of 39ºC) it is critical to keep the sample cool during all phases of the process to avoid evaporation or flash boiling.

Toxicity: There are solvents that have excellent properties for these applications, but are carcinogenic and cause reproductive disorders like chloroform and DCM.

The most commonly used polymer is poly(lactide-*co*-glycolide) (PLGA). There are several types of PLGA that can be used to manipulate the critical characteristics of the polymer: dissolution rate, compatibility with actives, etc. The molecular weight and the ratio of lactic acid to glycolic acid can be controlled. Additionally, co-polymers of PLGA can be used to provide specific properties. Chitosan co-polymers can be used to target specific parts of the body.[11] Researchers have even bound active ingredients to the polymer. Other biodegradable polymers such as polycaprolactone (PCL) and polyester have also been used.

There are many different types of materials that can be encapsulated within the polymers.

Active Pharmaceutical Ingredients (APIs): Because of the versatility of polymer nanoparticles, APIs for many diverse indications have been developed. It is also common for researchers to use a blend of active ingredients. It is critical for these ingredients to be compatible with the polymer.

Diagnostic Ingredients: Contrast enhancers can be encapsulated in the same particles which have active ingredients.

This can be used to verify that the active ingredient load is delivered to the desired location. The use of a combination of therapeutic and diagnostic ingredients is studied in a field called *theranostics*.

Other Ingredients: There are many other ingredients that are used for various purposes. Researchers have used para-magnetic particles to enable targeting. Others have used metal oxides that can be activated to deliver targeted heat therapeutic treatments.

Step 2: Determine Process

Add oil phase to water phase.

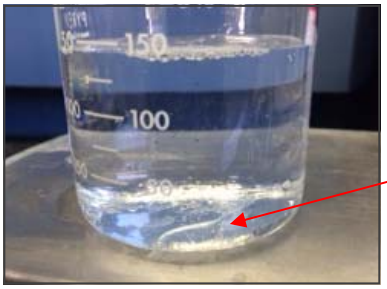

Figure 2: Pre-mix prior to rotor-stator mixing

Mix using a rotor-stator mixer to create a stable pre-mix. The pre-mix must be stable for long enough to process with the Microfluidizer.

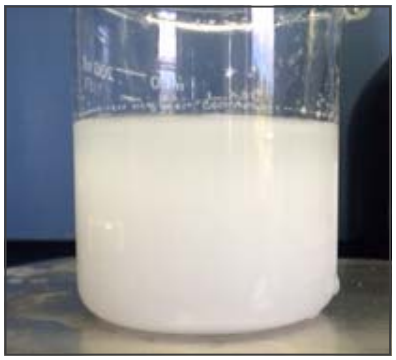

Figure 3: Pre-mix post rotor-stator mixing

Figure 4: LM10 Microfluidizer processor

Process the pre-mix using a Microfluidizer™. Critical processing parameters are the chamber type, the processing pressure, temperature and the number of passes.

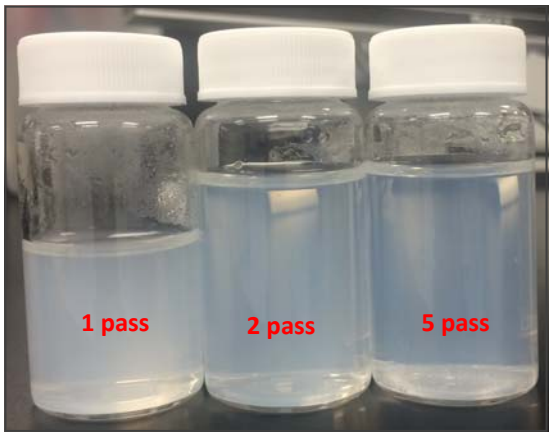

Figure 5: Aliquots of pass 1, 2, and 5 through the LM10

Step 3: Solvent Extraction

Figure 5: Evaporating solvent from the samples

There are several ways to extract solvent from the formulation once the nanoparticles have been created. One method is simply allowing the solvent to evaporate in a hood while mixing.

Other methods often involve the use of various solvent-exchange techniques, such as a separatory funnel or a rotary-evaporator.

Analysis Techniques

Polymer nanoparticles are often analyzed via particle size analysis. Dynamic light scattering, because of its inherent ability to measure very small particles, is frequently used. Optical microscopy, as well as SEM or TEM, can also be used to analyze the particles.

Results

Table 1: Malvern Zetasizer Nano-S results

Pass #	Z-Ave	PdI
1	181.4	0.249
2	158.9	0.239
5	132.9	0.24

As can be seen in the particle size distribution overlay and data, the polymer droplet size was reduced from 181 nm after 1 pass to 133 nm after 5 passes through the Microfluidizer.

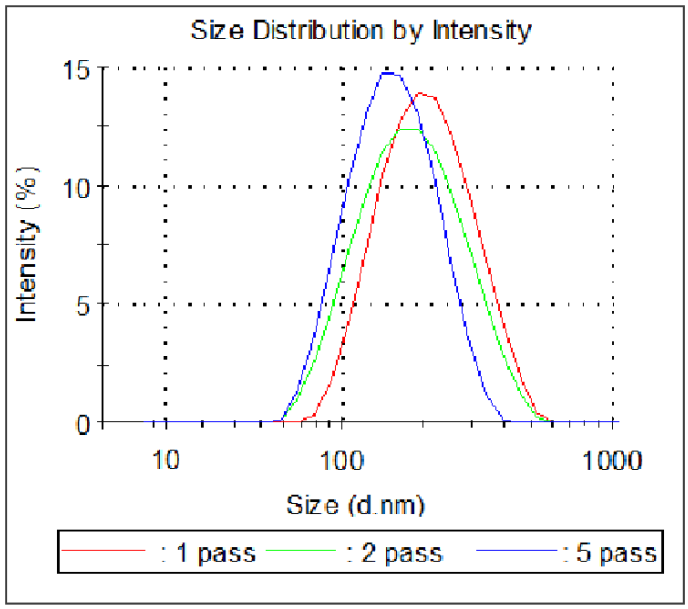

Figure 7: Particle size distribution overlay

Additional Applications of Polymer Nanoparticles

Microfluidics technology can also be used to generate pores within polymers that can be used to encapsulate hydrophilic actives.

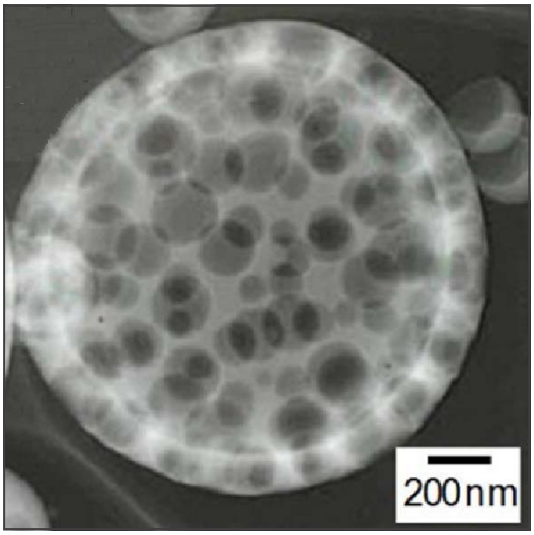

Figure 8: TEM image of porous polymer nanoparticle [13]

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