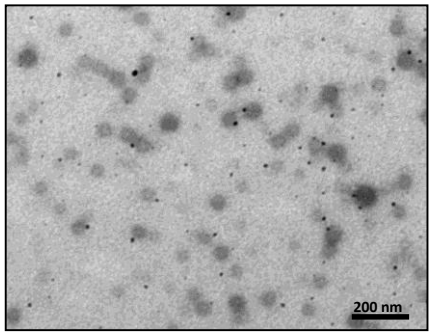
Microfluidics™

Application Note

Microfluidizer® Technology for production of polymer nanoparticles



TEM of polymer nanoparticles created with Microfluidizer® Technology

INTRODUCTION

This paper gives an overview of the development and manufacture of polymer nanoparticles.

The Microfluidizer® processor has been widely accepted as an ideal technology for creating polymer nanoparticles[1-5].

This note also describes the important factors to consider when developing a process.

Polymer nanoparticles have gained considerable interests over the past decade within pharmaceutical industry due to their potential in delivering various types of drug molecules, thus improving therapeutic efficacy and diagnosis sensitivity.

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WHY POLYMER NANOPARTICLES

Biocompatible and biodegradable polymer nanoparticles represent one of the most innovative delivery systems with a number of benefits :

- FDA approved materials available such as:
  - poly (lactide acid) (PLA)
  - poly (ε-caprolactone) (PCL)
  - poly (lactic-co-glycolic acid) (PLGA).
- The ability to deliver a combination of different therapeutic ingredients.
- The capability to include targeting moieties.
- Protecting the active ingredients from degradation forces.
- Controlling the release of ingredients.
- The inclusion of diagnostic capabilities.
- The ability to sterilize via filtration.

PREPARATION OF POLYMER NANOPARTICLES

There are a number of different ways to prepare polymer nanoparticles. The preparation methods are often overlooked compared to the behaviors of those particles.

Conventionally, polymer nanoparticles are produced via the nanoprecipitation method based on the so-called Ouzo effect.

However, this approach does have a major drawback in that only a narrow region of the polymer/solvent/antisolvent composition or the so-called Ouzo region works and can produce nanoparticles. Outside the region, microparticles are usually generated which lead to a broad distribution for the final product.

Furthermore, mixing the polymer dispersed phase in the antisolvent/aqueous phase takes place at a bulk scale which makes controlling the process very difficult and therefore hard to scale up.

Another approach available is the emulsion-template technique, under which oil-in-water (O/W) emulsion solvent evaporation/extraction is usually the preferred method.

This method involves dissolving polymers in solvent to form the oil phase which is then emulsified in an emulsifier-containing aqueous phase. After generation of nanoemulsions, the solvent is removed by evaporation or extraction to allow solidification of polymer nanoparticles.

Microfluidizer technology has the unique ability to generate small and uniform nanoemulsions, thereby making it the ideal processing technology for this application.

The following sections of this bulletin explain some key formulation considerations when developing O/W emulsion evaporation processes as well as a step-by-step guide for creating polymer nanoparticles using the Microfluidizer processors.

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KEY FORMULATION CONSIDERATIONS

Aqueous phase:

The surfactant is usually introduced into the aqueous phase, typically at relatively low concentrations of 0.1-2%wt.

The most commonly used surfactant is polyvinyl alcohol (PVA), other surfactants such as polysorbate, polyoxyethylene or phospholipid 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) have successfully been deployed.

Oil phase:

As mentioned before, the oil phase is formed by dissolving polymeric and other hydrophobic ingredients (e.g., actives, contrast agents) in water immiscible solvent. The most commonly used solvents are ethyl acetate and dichloromethane (DCM or methylene chloride).

When selecting a solvent, there are several factors that must be considered:

- Water Miscibility - as a general rule, the less miscible with water, the better. But when the miscibility is high (ethyl acetate will dissolve at a concentration of 8.3g/100mL), the aqueous phase should be saturated 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 39°C) 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 can cause reproductive disorders. Chloroform is a typical solvent in this category.

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 copolymers can be used to target specific parts of the body. Other biodegradable polymers such as PLA, PCL and polyester have also been used.

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STEP-BY-STEP GUIDE TO PROCESSING WITH MICROFLUIDIZER PROCESSORS

1) Prepare separate oil and aqueous phases

2) Form a coarse emulsion

Add the oil phase slowly into the aqueous phase (Figure 1)

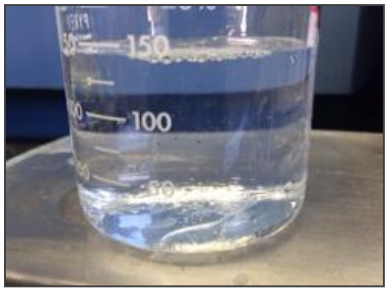

Figure 1 Oil phase – pre-mix

Mix using a rotor-stator mixer to create a stable pre-emulsion (Figure 2).

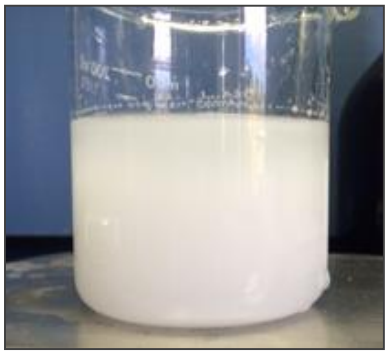

Figure 2 The pre-mix after the rotor-stator mixing step

The coarse emulsion must be stable for long enough to process with the Microfluidizer processor.

3) Process the pre-mix using a Microfluidizer processor

As an example we have shown an LM10 Microfluidizer process in Figure 3. Critical processing parameters that can be adjusted are the type of Interaction Chamber™, processing pressure, temperature and the number of passes.

Figure 3 LM10 Microfluidizer processor

The achieved O/W nanoemulsions typically look like the samples shown in Figure 4. This shows the relationship between decreasing particle size with increasing number of passes. At the top end of passes the nanoemulsion visibly becomes more translucent.

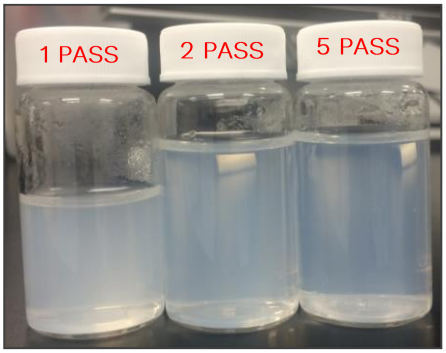

Figure 4 Aliquots of pass 1, 2, and 5 through the LM10

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4) Solvent removal

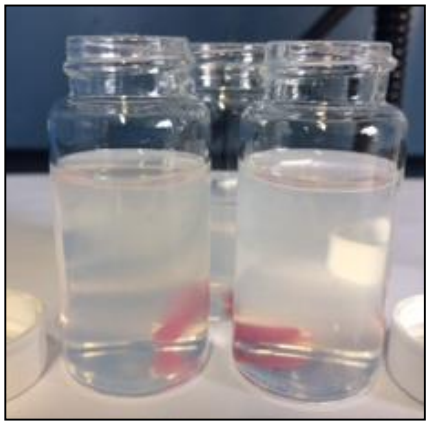

Figure 5 Evaporating solvent from the samples

There are several ways to remove solvent from the formulation once the nanoemulsions have been created. One method is simply allowing the solvent to evaporate in a hood while mixing or use a rotary evaporator. Figure 5 showed a couple of samples after solvent has been evaporated.

Other methods often involve the use of various solvent-exchange techniques, these include a separatory funnel, dialysis, defiltration or ultrafiltration.

RESULTS

As can be seen in the particle size data (Table 1) and distribution curves (Figure 6), the polymer nanoparticles obtained from the Microfluidizer processor were all smaller then 200nm.

Particle size around 130 nm was achieved after 5 passes. The narrow particle size distribution, as demonstrated by the Polydisperse Index (PdI) values and the distribution curves, indicate these polymer nanoparticles are likely to pass through sterile filters easily.

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

Table 1 Malvern Zetasizer Nano-S results

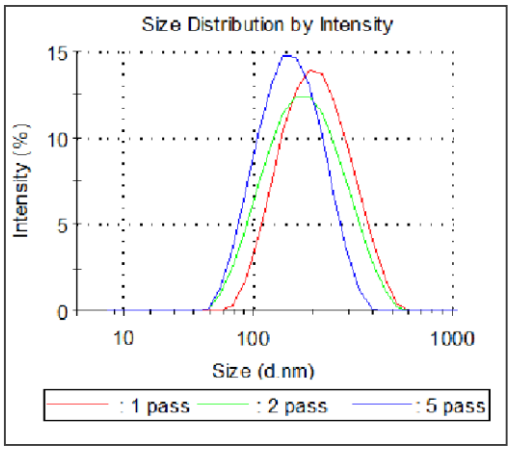

Figure 6 Particle size distribution overlay

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ADDITIONAL APPLICATIONS IN CREATING POROUS POLYMER MICROSPHERES

Polymer nanoparticles are good delivery platforms for hydrophobic actives.

For encapsulating hydrophilic actives, porous polymer particles can be prepared via double emulsion, usually water-in-oil-in-water (W1/O/W2) double emulsions, evaporation method[6,7]. The final particles are usually in the micrometer range and are also known as multicompartmental polymer particles or nanoparticle-in-microsphere polymer (NiMP) particles.

Microfluidizer technology can also be used to generate these types of particles, especially for creating the first water-in-oil (W/O) emulsion. Figure 7 shows an example of such a particle produced with the Microfluidizer processor [7].

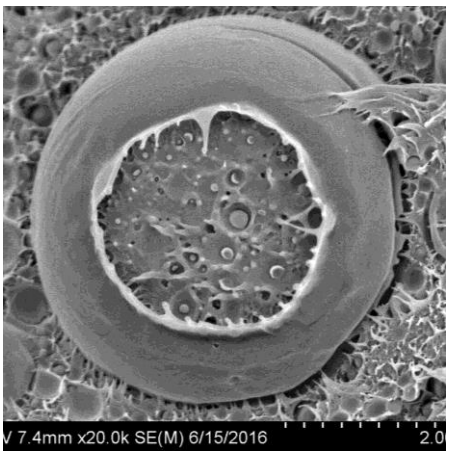

Figure 7 TEM image of porous polymer nanoparticle

REFERENCES

1. S.N. Sani, et al., J. Microencapsul., 2009; 26(6): 556-561.

2. J. Sankaranarayanan, et al., ACS Nano, 2010; 4(10): 5930-5936.

3. S. Alqahtani, et al., J. Colloid, 2015; 445: 243-251.

4. M.S. Alkanawati, et al., Macromol. Mater. Eng., 2018; 303: 1700505.

5. H. Zhou and H. Qian, Drug Des. Devel. Ther., 2018; 12:2601-2609.

6. D.R. Robello, et al., J. Appl. Polym. Sci., 2015; 132(23): 42021.

7. K. Jandrasitz, et al., poster presentation at 2016 AAPS Annual Meeting, Denver, CO.