

Application Note

Sterile Nano-emulsions

Using Microfluidizer® technology to formulate injectable, insoluble drugs.

Nano-emulsions are becoming an increasingly important drug delivery mechanism. Since 2000 the use of solubilization technologies has increased, a trend that is expected to continue. Nano-technology in pharmaceuticals is expected to represent a \$100 billion market by 2020. Microfluidizer technology is well suited to create these materials.

Problem

Approximately 40-60 % of FDA approved drugs and NCE (New Chemical Entity) are highly water insoluble. As a result they exhibit poor bioavailability. That causes costly R&D problems and negative biological consequences.

The most common ways to increase solubilization for injectable drugs are: solvents, pH, surfactants, nano-particles, liposomes and conventional emulsions. As some drugs are significantly more soluble in the oil than water, most of the drug is contained in the oil droplets. Conventional emulsions have solubility and stability limitations that can make them difficult to manufacture.

Many of these emulsions need to be sterilized because they are injected inside the body, applied to the eyes, etc. An effective and relatively simple sterilization method is filtration through a 220 nm filter, aka terminal sterilization. If there is a large population of particles above 220nm, the filters may clog, and/or there may be loss of the active ingredient. Therefore both the particle size and size distribution are important.



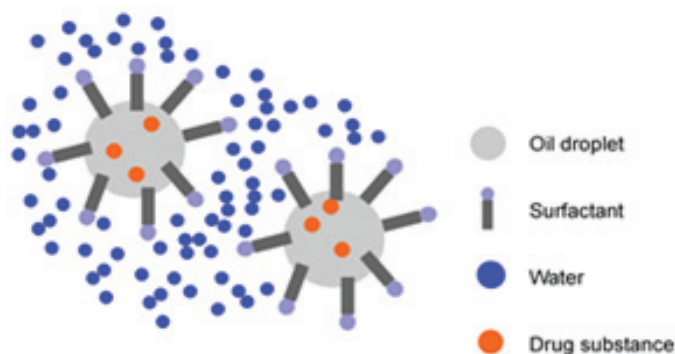
Example of regular cloudy, non-nano-emulsion

Solution

Use nano-emulsions to overcome these formulation problems.

Definition

A nano-emulsion is oil-in-water, (or water-in-oil) with a droplet size 50-100 nm.



Nano emulsions can be used for:

- Class 1,2,3 and 4 drugs
- Vein irritating drugs
- CNS (Central Nervous System) toxic drugs
- Drugs in need of new IP
- PK (*pharmacokinetic*) improvement
- Organ targeted drugs

Nano-emulsion formulation

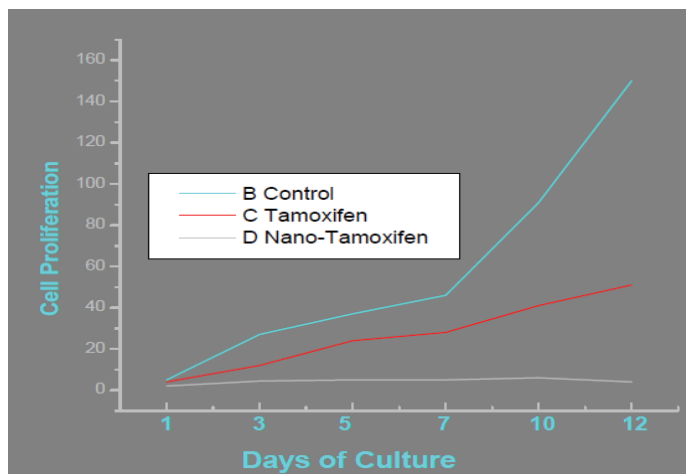
- Oil phase with the drug in injectable oil
- Phospholipids
- Emulsion stabilizers in aqueous and oil phases
- Buffer
- Water

Process

1. Premix aqueous and oil phase with a rotor stator or magnetic mixer
2. Process through Microfluidizer to form a nano-emulsion
3. Sterilize through 0.2 µm filter
4. Fill or lyophilize as needed

Advantage of using nano-emulsions

- Greatly improved drug load over regular emulsion. Reduced effective dose
- Improved stability
- Can be sterile filtered- avoids costly requirement for sterile processing
- Lyophilizable
- Can be used Intra Muscular, Sub Cutaneous or Intra Venous
- No solvent, surfactant or un-approved ingredients -reduced toxicity
- No vein irritation-less painful injection site
- Reduced action onset time
- No special aseptic facility needed
- Scale-able through MF technology



Dramatic inhibition of breast cancer cell growth (D) in the Microfluidized nano-emulsion vs. the standard Tamoxifen suspension (C)

Examples of nano-emulsion products.

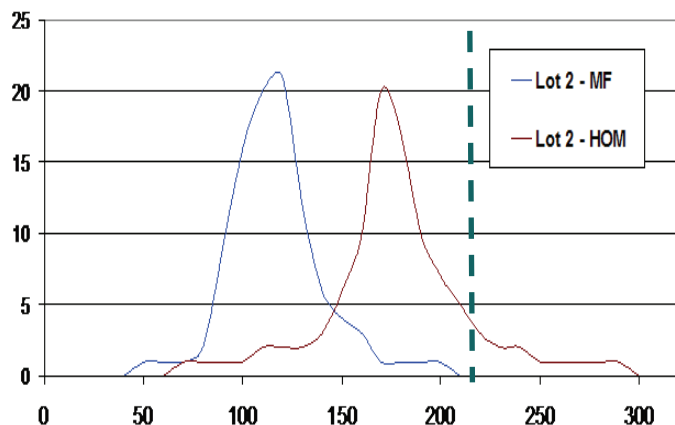
- Paclitaxel
- Propofol
- Mitomycin
- Clarithromycin
- Fat soluble vitamins
- Insoluble peptides & proteins
- More than 50 NCEs
- Progesterone
- Vinorelbine (Exelbine®)
- Docetexal (ANX-514)

Why Microfluidics

- Extremely small droplets
- Narrow PSD improves stability & filtration
- Easy to operate
- Easy to scale-up
- Reliable
- 2ml to Liters per hour
- Pilot and production machines
- GMP expertise

Mfics vs. High Pressure Homogenizer

In this study of a nano-emulsion intended for sterile filtration, the Microfluidizer significantly outperformed the HPH



Emulsions processed with the Microfluidizer contain less than 1% of particles by volume > 200nm. The HPH sample contains a significant number of particles >200nm, and could not be effectively filter sterilized.

Power consumption-Microfluidizer consumed 7.5 times less power than the high pressure homogenizer.

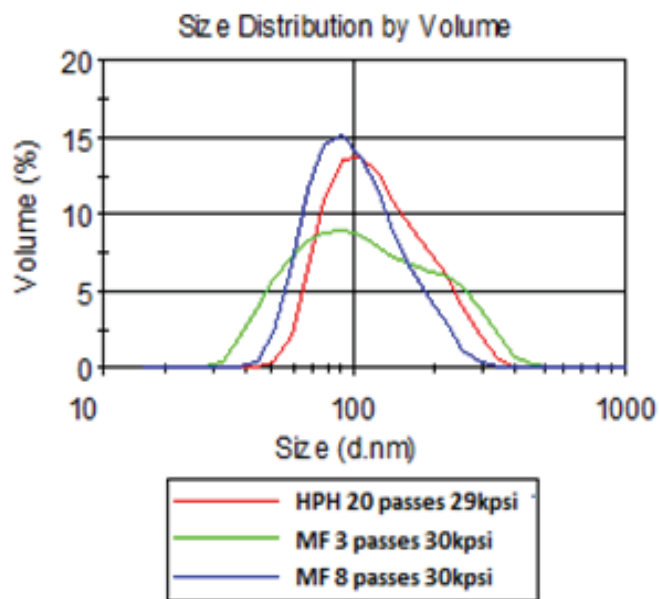
Efficiency-Microfluidizer emulsions were 18–55% smaller than the HPH when run at the same energy input.

Uniformity-Microfluidizer processor created emulsions that were 17–91% less poly-dispersed than the HPH when run at the same energy input.

Repeatability-Microfluidizer processor standard deviation was much lower (0.1–2.6) than with the high pressure homogenizer (3.8–14.8).

Case Study

In an example of a lipophilic API dissolved in oil, the Microfluidizer was able to achieve similar particle size distribution to an HPH in 3 passes vs. 20 on the HPH. A further 5 passes on the Microfluidizer decreased the particle size an additional 20%.



Clear Propofol Injection, 1% (F198)

Clear nano-emulsion formulation

Thanks to Dr. Andrew Chen, Latitude Pharmaceutical for his significant contribution to this Sales Bulletin