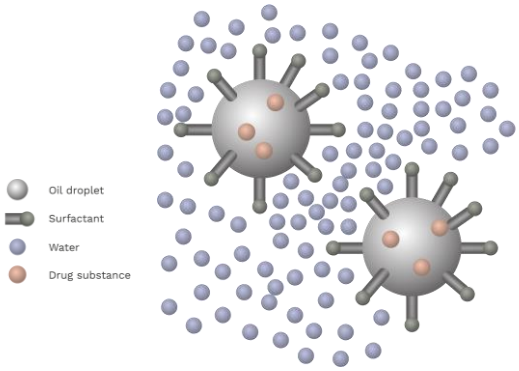
Microfluidics™

Application Note

Microfluidizer® Technology for Sterile Nanoemulsions



INTRODUCTION

This Application Note looks at using Microfluidizer® technology to formulate injectable, insoluble drugs.

Approximately 40-60 % of FDA approved drugs and NCE (New Chemical Entity) are highly water insoluble. As a result, they exhibit poor bioavailability. This causes costly R&D problems and negative biological consequences. The most common ways to increase solubilization for low solubility drugs are: solvents, pH, surfactants, nano-particles, liposomes and conventional emulsions.

Nanoemulsions are becoming an increasingly important drug or vaccine delivery mechanisms. Since 2000 the use of solubilization technologies has increased, a trend that is expected to continue. The nanoemulsion market is expected to rise to $15 billion by 2025.

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USAGE OF NANOEMULSIONS

When compared with conventional emulsions, nanoemulsions are more stable and can improve drug load in order to achieve reduced effective dose with faster onset time and less side effects.

They are also suitable for parenteral delivery by injection or applied to the eyes.

Nano emulsions are typically 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
- Vaccine adjuvants

THE DEFINITION

A nanoemulsion is similar to conventional emulsions, but with much smaller droplet sizes. Nanoemulsions can be oil-in-water (O/W), or water-in-oil (W/O) types depending on whether the oil or the water is the dispersed phase. Nanoemulsions in general have droplet sizes in the nanometer range, often less than 100 nm.

O/W nanoemulsions are ideal delivery systems for water insoluble drugs. The oil phase is usually formulated by dissolving drugs in carrier oils that are suitable for injecting. The aqueous phase typically consists of either water or buffer solutions. Surfactants or emulsifiers are key compounds in stabilizing the droplets and can be added to either phase or both.

EXAMPLES OF NANOEMULSION PRODUCTS

Propofol	Paclitaxel
Difluprednate	Vinorelbine
Cyclosporine	Progesterone
Aprepitant	Fat soluble vitamins
MF59 adjuvant	Insoluble peptides & proteins

THE PROCESS

Creating a nanoemulsion usually involves preparing two separate oil and aqueous phases first and then mixing them using a high shear mixer such as rotor-stator mixer or magnetic mixer to form a stable pre-emulsion. This coarse emulsion is then processed through a Microfluidizer processor to obtain a fine stable nanoemulsion.

THE MANUFACTURING CHALLENGES

Stability: Conventional emulsion is an inherently unstable system. Nanoemulsions are kinetically stable but their stability is affected by a phenomenon called Ostwald ripening which arises from emulsion polydispersity and the difference in solubility between small and large droplets. Therefore, to reduce the Ostwald ripening rate, manufacturing methods should not only produce nanoemulsions with small particle sizes, but also with narrow distributions.

Filterability: The route of administration requires parenteral nanoemulsions to be sterilized. An effective and relatively simple sterilization method is filtration through 220nm sterilizing-grade filters, also known as terminal sterilization. If there is a large population of particles above 220nm, it will cause reduction in filter throughput which means increased filtration cost because more filters are needed. The filters can also clog which may lead to costly product losses. Therefore both the particle size and size distribution are critically important.

Microfluidizer® Technology for Sterile Nanoemulsions

THE SOLUTION

Microfluidizer® technology creates nanoemulsions with:

- Extremely small droplet size
- Narrow particle size distribution
- Increased stability
- Filter sterilizable to avoid costly aseptic processing

Microfluidizer® processors are:

- Easy to operate
- Reliable with low maintenance cost
- Linearly scalable from 2ml to Liters per hour
- Comply with cGMP regulations

Microfluidizer® processors vs High Pressure Homogenizer

In this study of a nanoemulsion intended for sterile filtration, the Microfluidizer® processor significantly out-performed the HPH.

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

Efficiency - nanoemulsions processed through the Microfluidizer® processor were 18–55% smaller than the HPH when run at the same energy input.

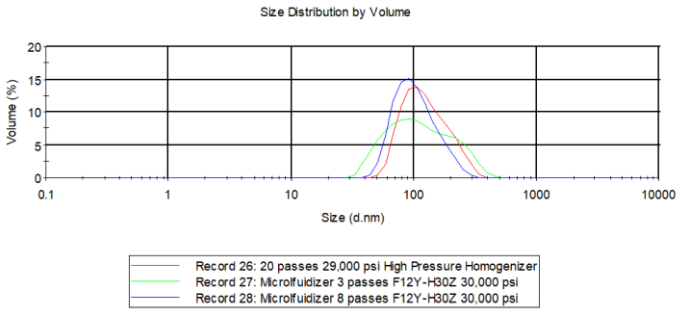
Uniformity - the Microfluidizer® processor created nanoemulsions 17–91% less poly-dispersed than the HPH when run at the same energy input.

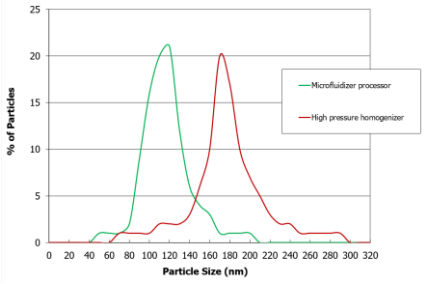
Repeatability - the particle size standard deviations of the nanoemulsions were much lower when produced by the Microfluidizer® processor (0.1–2.6) compared to the High Pressure Homogenizer (3.8–14.8).

CASE STUDY

In another example of a lipophilic API dissolved in oil, the Microfluidizer® processor was able to achieve better results in terms of particle size and size distribution than an HPH in just 3 passes compared to the 20 passes needed on the HPH.

A further 5 passes on the Microfluidizer® processor resulted in an additional 20% reduction in particle size.





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

A clear nanoemulsion formulation