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PROCESS DEVELOPMENT OF A DRUG DELIVERY NANOEMULSION AND POST PROCESS STERILE FILTRATION

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ABSTRACT

Title:
Process Developments of A Drug Delivery Nanoemulsion and Post Process Sterile Filtration

Purpose:
To develop the process of producing a drug delivery nanoemulsion and subsequently determine the combined influences of particle size distributions and filter materials on the sterile filtration efficiency. Validate filters with optimized nanoemulsion through bacterial challenge test.

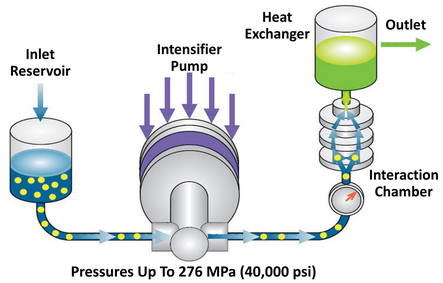
Methods:
The drug delivery system studied was an oil-in-water emulsion. The dispersed phase consists of 5 wt% squalane and 1.5 wt% surfactant. Nanoemulsions were generated using a high shear Microfluidizer® processor (Microfluidics™ Inc.). Each emulsion sample was processed at various pressures for a number of passes. The particle size distributions of the obtained emulsions were determined by a laser diffraction instrument (Horiba LA-950). All samples were then passed through 4 sterile filters, DFL, EDF, ECV and EKV (all from Pall Corporation), each contains different membrane materials. All filters were validated through bacterial challenge tests by direct inoculation of Brevundimonas diminuta (B. diminuta ATCC 19146) in the optimized nanoemulsion. The challenge tests were done at room temperature (approximately 20-25°C) with a minimum $1x10^7$ colony forming units (CFU) per effective filter area (EFA, cm^2) at three differential pressures (15, 30 and 60 psi). The entire effluent was passed through a 0.2 µm rated recovery disc, plated on Trypticase Soy Agar (TSA) and incubated at 30±2 °C for two days.

Results:
The particle size distributions of the nanoemulsion samples generated under different process conditions were obtained. The droplet diameters corresponding to the 50% (D50) and 95% (D95) of the distributions by volume varied in the ranges of 113–171 nm and 182–303 nm, respectively. It was found that smaller droplet size generally led to higher V_{90} throughput (L/m^2) and average flux (LMH). Both ECV and EKV filters gave much higher throughput than DFL and EDF filters. The highest filtration throughput of 6300 L/m^2 was achieved with the ECV filter with particle size of 227 nm (D95), and was more than 6 times higher than the next best filter, the EKV filter. The average flux did not change significantly until the droplet size dropped down to 201 nm (D95), where the maximum flux of ~2000 LMH was obtained with both ECV and EKV filters. During the bacterial challenge tests, B. diminuta was not detected in the effluent of any of the test filters.

Conclusions:
Process of producing a drug delivery nanoemulsion was developed using Microfluidizer® processor. The highest sterile filtration throughput and flux can be achieved by combining the nanoemulsion with optimum particle size distribution and selected sterile filtration membrane material. The filters were successfully validated with optimized nanoemulsion through the bacterial challenge tests.

METHODS

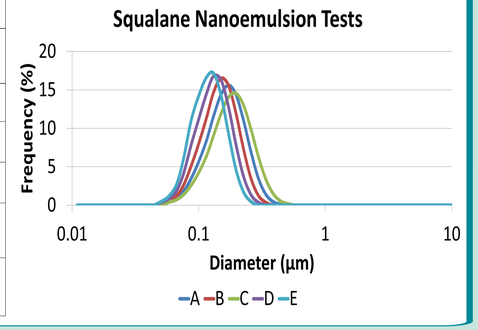
- **Model Drug delivery system: Oil-in-water emulsion**
  - ⇨ Aqueous Phase
    - 93.5% Deionized Water
    - 0.75% Surfactant
  - ⇨ Oil Phase
    - 5% Squalane oil
    - 0.75% Surfactant
- **Nanoemulsions Generation**
  - ⇨ Microfluidizer® processor (Microfluidics™ Inc.)
  - ⇨ Y-Type interaction chamber (IXC)
  - ⇨ Process conditions varied:
    - Pressure
    - Number of passes
- **Particle Size Analysis**
  - ⇨ Laser diffraction (Horiba LA-950)
- **Sterile Filtration**
  - ⇨ Nanoemulsion samples were passed through 0.2 µm filters
  - ⇨ Filters used: DFL, EDF, ECV and EKV (all from Pall Corporation)
- **Bacterial Challenge Tests**[1, 2]
  - ⇨ Bacteria used: Brevundimonas diminuta (B. diminuta ATCC 19146)
  - ⇨ Room temperature (approximately 20-25°C)
  - ⇨ A minimum of 1 x 107 colony forming units (CFU) per effective filter area (EFA, cm^2)
  - ⇨ Filter pressures at 15, 30, and 60 psi
  - ⇨ The entire effluent was passed through a 0.2µm rated recovery disc than plated on Trypticase Soy Agar (TSA) and incubated at 30±2ºC for two days



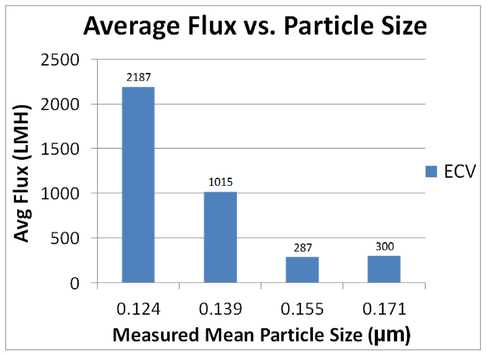
MICROFLUIDIZER RESULTS

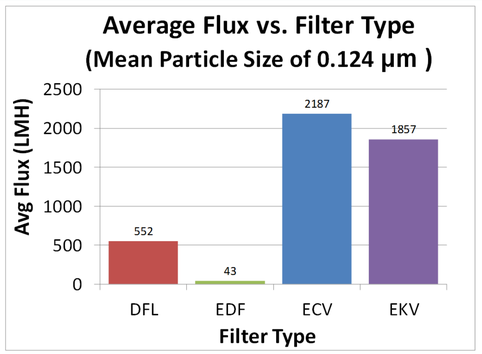
Particle Size Measurements

Test ID	Processing Conditions	d10 (nm)	d50 (nm)	d90 (nm)	d95 (nm)
A	1 pass @ 30,000 psi	94.8	155.0	236.9	263.7
B	2 passes @ 20,000 psi	88.1	138.5	206.4	227.1
C	1 pass @ 23,000 psi	101.6	171.3	269.7	303.3
D	1 pass @ 30,000 psi + 1 pass @ 30,000 psi	80.0	123.6	182.6	200.8
E	2 passes @20,000 psi + 2 passes @ 30,000 psi	75.5	112.5	164.5	181.5



FILTRATION & BACTERIAL CHALLENGE RESULTS





Bacterial Challenge Results

Filter	Test Pressure (psi)	Challenge Volume (mL)	Total Bacterial Challenge (CFU/Filter)	Challenge Level (CFU/cm^2)	Total Bacterial Recovery (CFU/Filter Effluent)
1	30	200.0	5.8×10^8	4.2×10^7	0
2	30	200.0	5.8×10^8	4.2×10^7	0
3	30	200.0	5.8 x 108	4.2×10^7	0
4	60	200.0	6.8×10^8	4.9×10^7	0
5	60	200.0	6.8×10^8	4.9×10^7	0
6	60	200.0	6.8×10^8	4.9×10^7	0

CONCLUSION

- A high shear Microfluidizer® processor was used to develop a drug delivery nanoemulsion.
- The highest sterile filtration throughput and flux can be achieved by combining:
  - a nanoemulsion with optimum particle size distribution
  - appropriate sterile filtration membrane material
- The sterile filters were validated through bacterial challenge tests using the optimized nanoemulsion inoculated with bacteria.

REFERENCES

1. ASTM, Standard Test Method for Determining Bacterial Retention of Membrane Filters Utilized for Liquid Filtration *American Society for Testing and Materials (ASTM)* **2005,** ASTM Standard F838-05.
2. PDA, PDA Technical Report No 26, Sterilizing Filtration of Liquids. *PDA J Pharm Sci Technol* **2008,** 62, (S-5), 1-60.