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Droplet Size Analysis of Emulsions and Nanoemulsions

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Outline

- Emulsions
- Formulation
- Particle/droplet size
- Analytical Techniques
- Standardization

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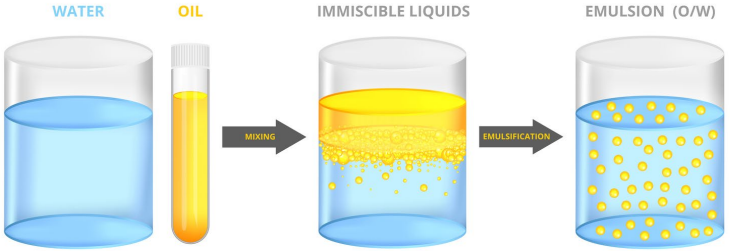
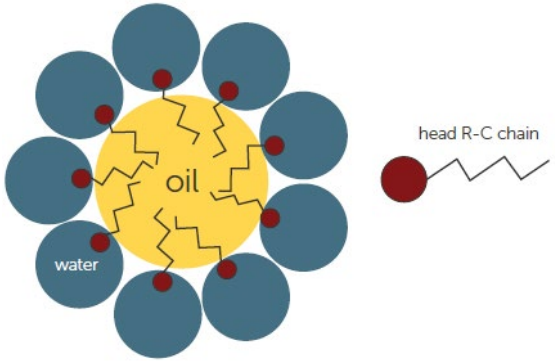
Emulsions

- Two phase system
- Oil = dispersed phase
- Water = continuous phase
- Required energy + emulsifier (surfactant)
- Formulation: surfactant(s), surface chemistry, taste
- Energy: mixers, homogenizers, ultrasonics, microfluidizers





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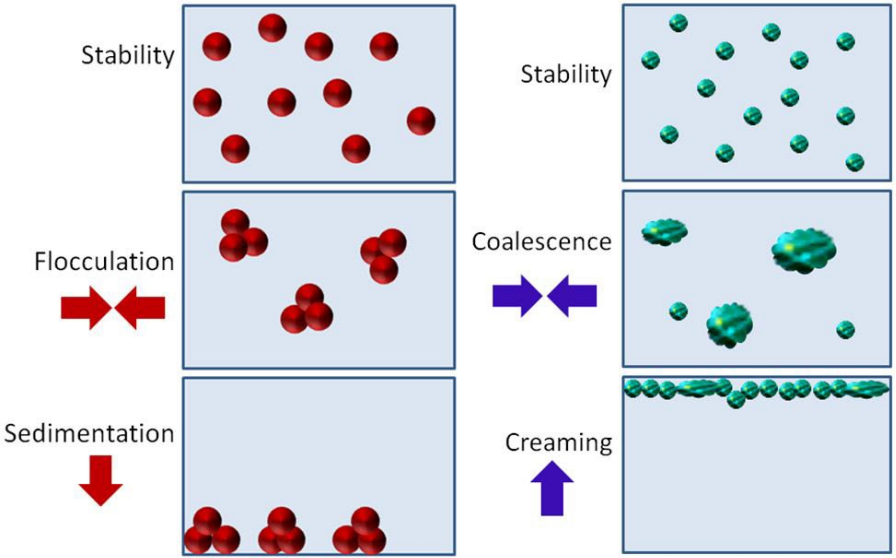
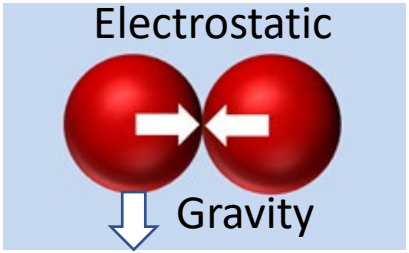
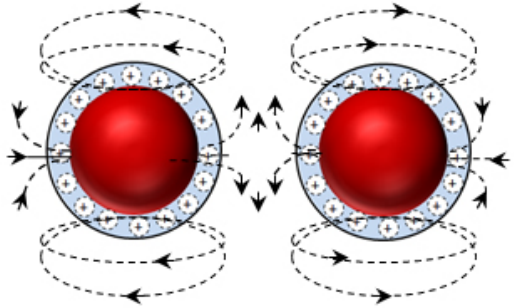
Dispersion Stability







Reduce size – minimize gravitational settling
Increase charge – minimize electrostatic attraction

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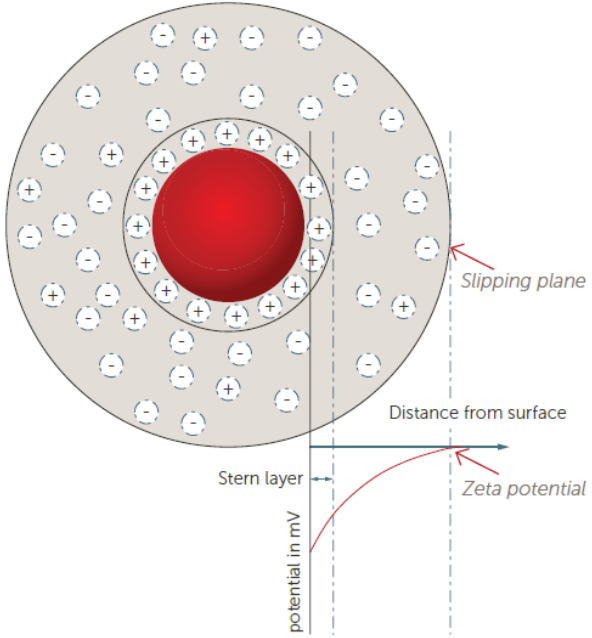
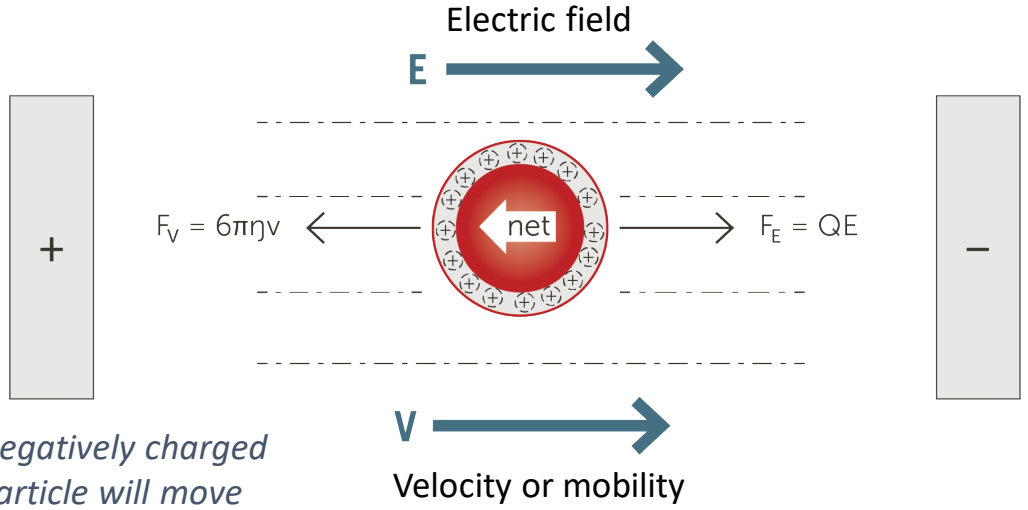
Zeta Potential (Surface Charge)

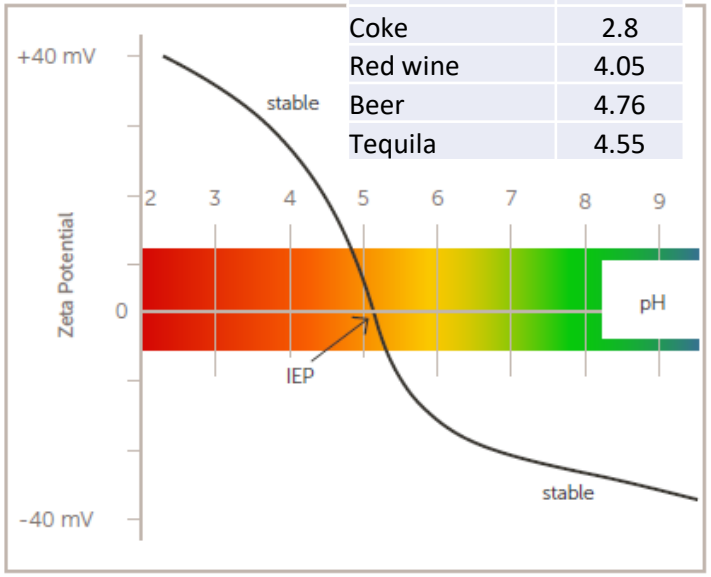




Negatively charged particle will move towards the anode

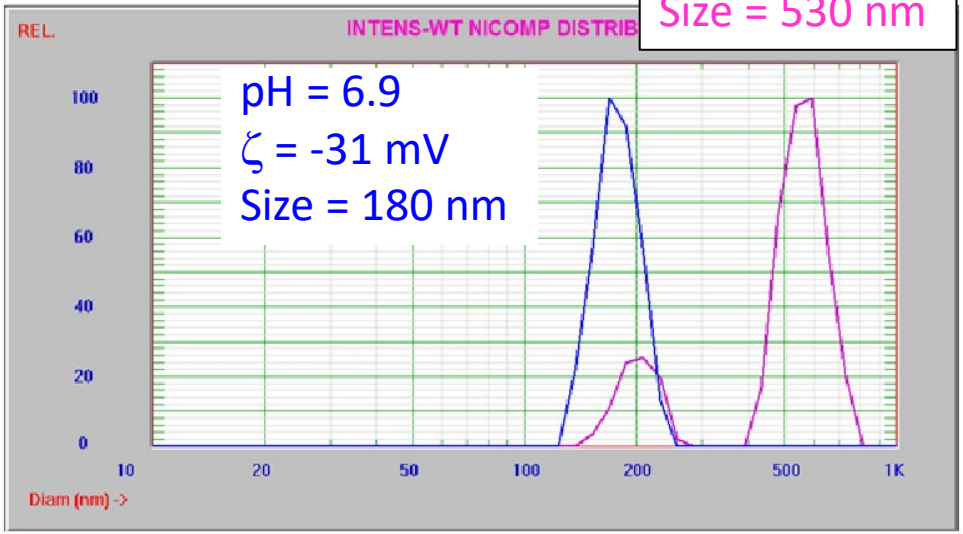
ISO Electric Point (IEP)

Beverage	pH
Sparkling water	4.89
Gatorade	3.5
Coke	2.8
Red wine	4.05
Beer	4.76
Tequila	4.55

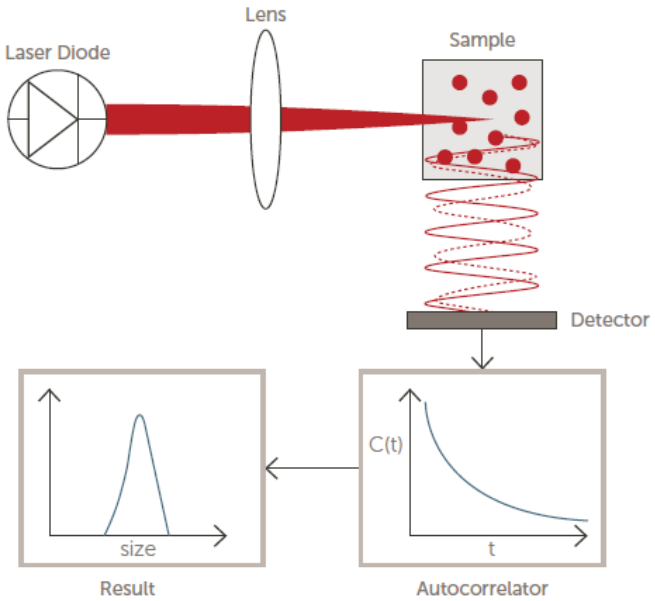


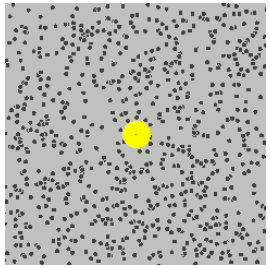
Al_2O_3, IEP = 8-9

pH = 11.2
ζ = 0.70mV
Size = 530 nm



Size & Zeta Potential by Dynamic Light Scattering (DLS)





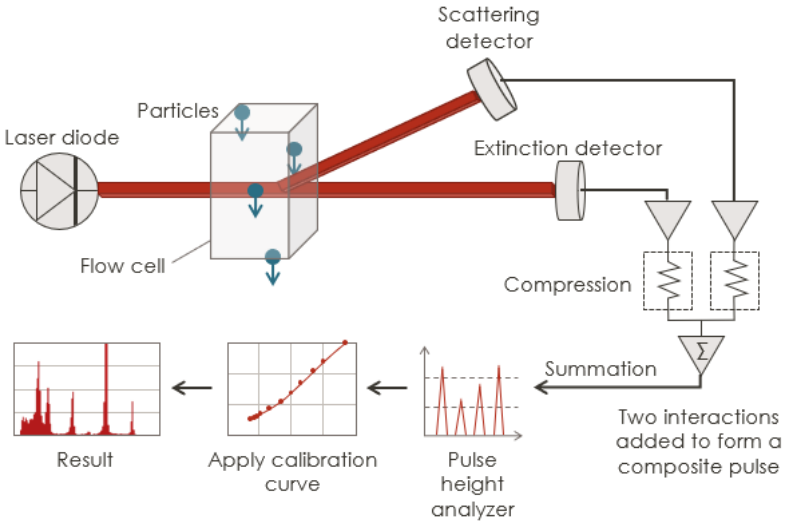
$$D = kT/6\pi\eta R$$

D = Diffusion coefficient
k = Boltzmann's constant
T = Temperature (Kelvin)
H = Viscosity of solvent
R = Radius of particle

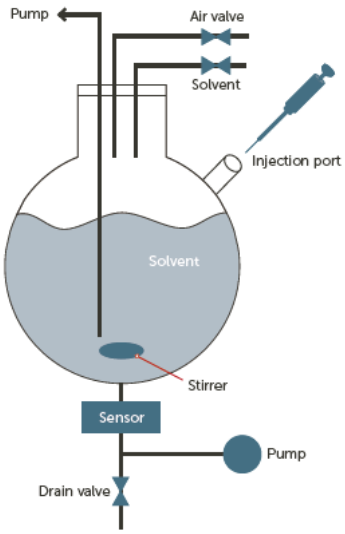
Animation source: https://en.wikipedia.org/wiki/Brownian_motion#/media/File:Brownian_motion_large.gif

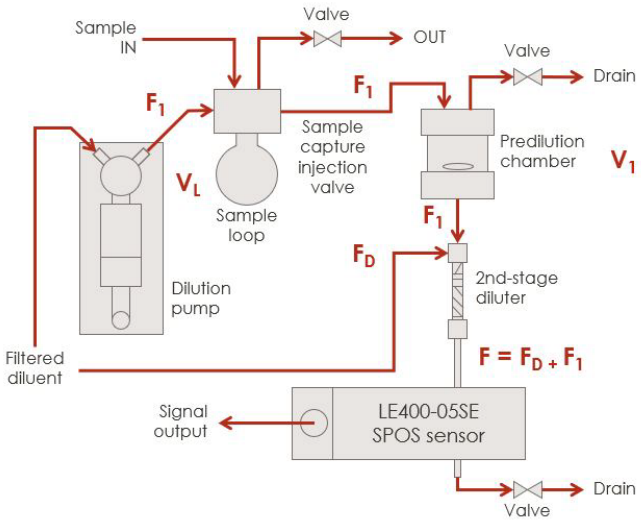
Size & Count by Particle Counter

Sensor



Dilution Fluidics





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Cannabis Processing

Preparation

Growing
Harvesting
De-stemming
Drying
Size reduction
Decarboxylating

Extraction

Solvent extraction
- CO_2
- Ethanol
- Hydrocarbons

Water extraction

Refinement

Filtration
Solvent evaporation
Crystallization
Distillation
Separation

Emulsification

Ultrasound
Homogenizer
Microfluidizer

Materials

- CBD Oil, Cheef
- Tween 80, Sigma-Aldrich P1754 HLB = 15
- Span 80, Sigma Aldrich S6760 HLB = 4.3
- StuphCorp™ Part B, no published HLB value

- Entegris Nicomp ZLS3000 DLS system for submicron size + zeta potential
- Entegris AccuSizer APS SPOS instrument for emulsion stability analysis, size + concentration
- Hielscher UP400St ultrasonicator

CBD Oil

Analyte	Results (mg/mL)
CBD	37.0096
CDC	1.3279
Δ9-THC	0.8284
CBDV	0.7144
CBG	0.6405
Δ8-THC	0.1125
Total	40.6335

37 mg/mL

1 mg/mL

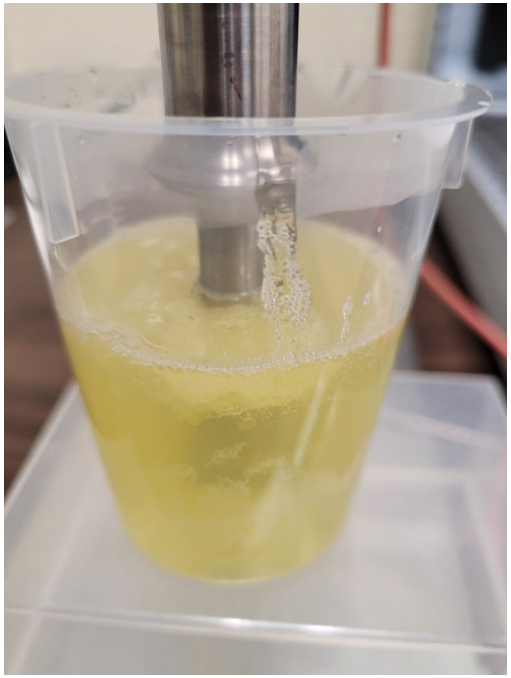
Formulations

- Formulation 1 = 4 parts Span 80 + 1 part Tween 80, combined HLB = 6.97
- Formulation 2 = 1 part Span 80 + 1 part Tween 80, combined HLB = 9.65
- Formulation 3 = Part B, no HLB number provided

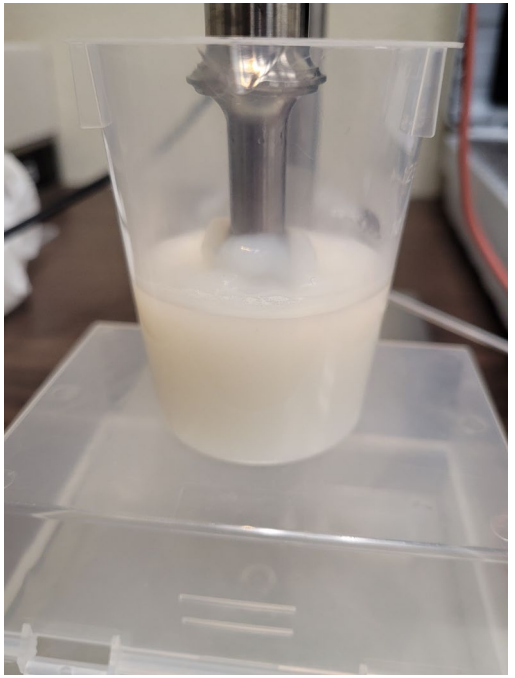
- Pour 25 grams of component B into beaker 1
- Heat beaker 1 to a temperature range of 55°C
- When step 2 is at temperature, add 3 grams of oil to beaker 1
- Fill beaker 2 with 70 grams of water, Heat cup to 55 ℃
- Place beaker 2 under the ultrasonic sonotrode.
- Position the bottom of the sonotrode just below the surface of the water.
- Start sonicating beaker 2
- Pour beaker 1 slowly and steadily into beaker 2
- Move beaker 2 in a circle motion while sonicating
- Remove samples from beaker 2 at defined time interval for analysis
- Stop process when all liquid is homogenized and clear

Sonication

Formulation 3



Formulation 1



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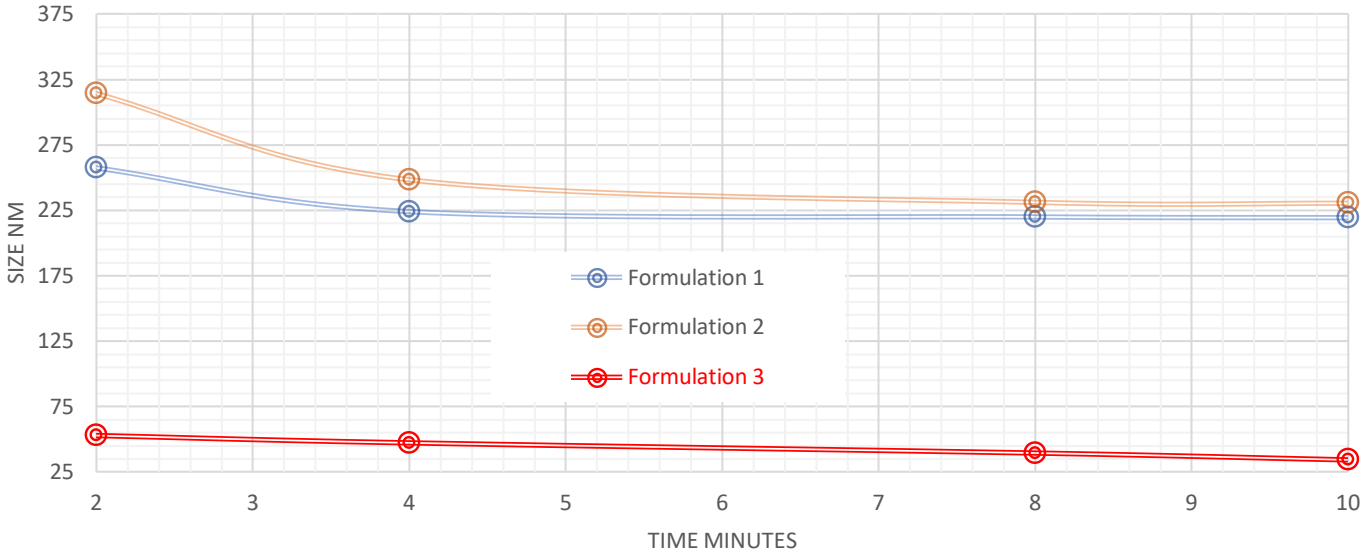
Size (nm) vs. Sonication Time

Minutes	Form 1	Form 2	Form 3
2	257.62	314.31	52.99
4	224.14	248.58	47.38
8	220	231.31	39.58
10	219.43	230.6	34.33

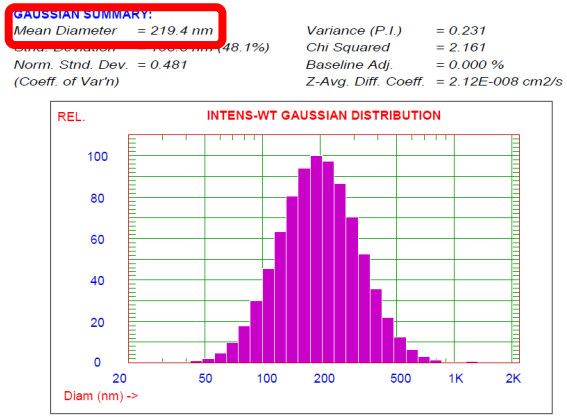
Formulation	Zeta Potential (mV)
1	-28.59
2	-34.41
3	-24.32



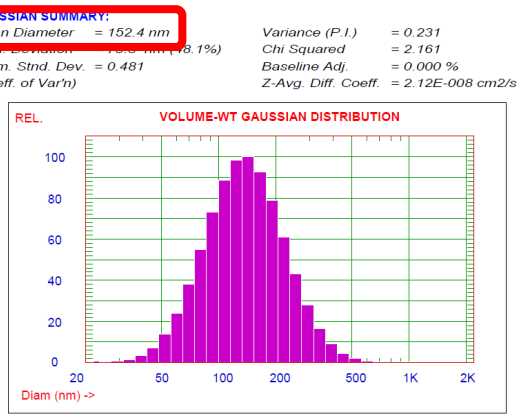
DLS; Intensity, Volume, Number

Basis	Size (nm)
Intensity	219.4
Volume	152.4
Number	58.6

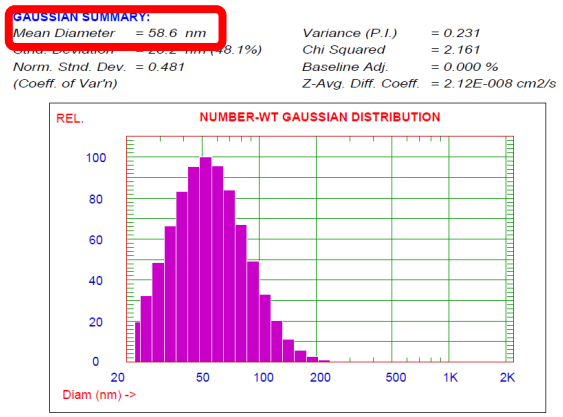
Intensity



Primary result from DLS

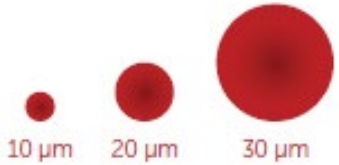


Compare to laser diffraction



Compare to SEM

Basis of Distribution



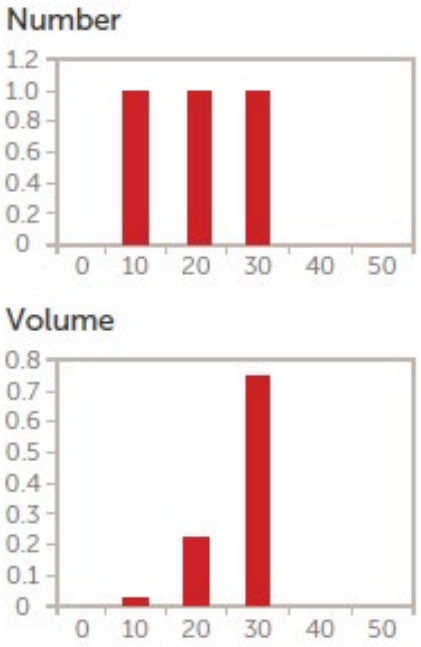
Three particles:
10, 20 & 30 µm

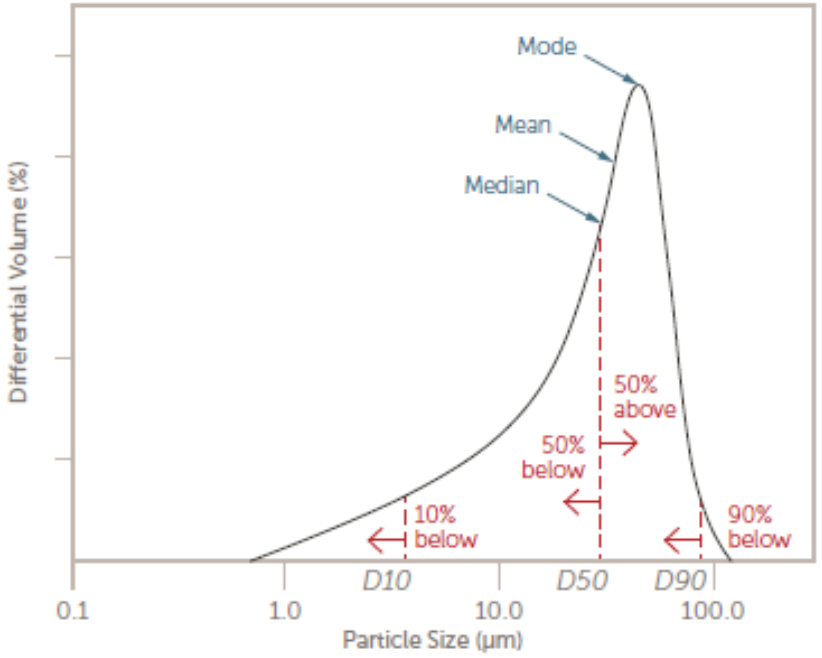
Number:
equal portions

Volume:
weighted to largest size

Number mean = 20

Volume mean = 27





Standardization; ISO, USP (PF)

- ISO 22412

  Intensity mean

  Polydispersity (PI)
- USP 430 (Discussion)

  Same

INTERNATIONAL STANDARD **ISO 22412**

Particle size analysis — Dynamic light scattering (DLS)

11 Test report

The test report shall contain at least the following information [points k) to r) are taken from ISO/IEC 17025]:

a) average particle size, $\bar{x}_{DLS}$, and its uncertainty;

b) an indication of the polydispersity of the sample (for example, the polydispersity index);

⟨430⟩ PARTICLE SIZE ANALYSIS BY DYNAMIC LIGHT SCATTERING

Average particle diameter ($\bar{\chi}_{DLS}$): Harmonic intensity-weighted averaged particle diameter expressed in nanometers.

Polydispersity index (PI): Dimensionless measure of the broadness of the particle size distribution.

PI	Type
0-0.05	monodisperse standard
0.05-0.08	nearly monodisperse
0.08-0.7	mid range polydisperse
>0.7	very polydisperse

$$\bar{x}_{DLS} = \frac{1}{a_1}\frac{kT}{3\pi\eta}\left[\frac{4\pi n \sin\left(\theta/2\right)}{\lambda_0}\right]^2$$

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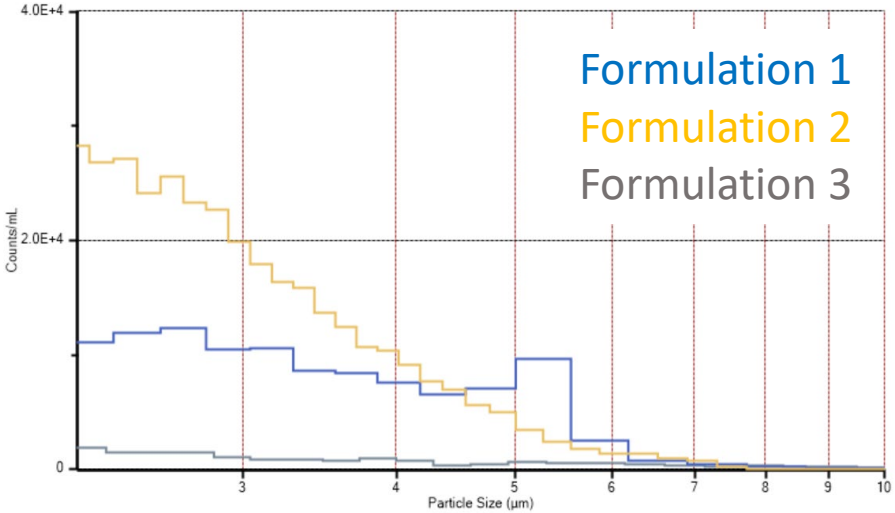
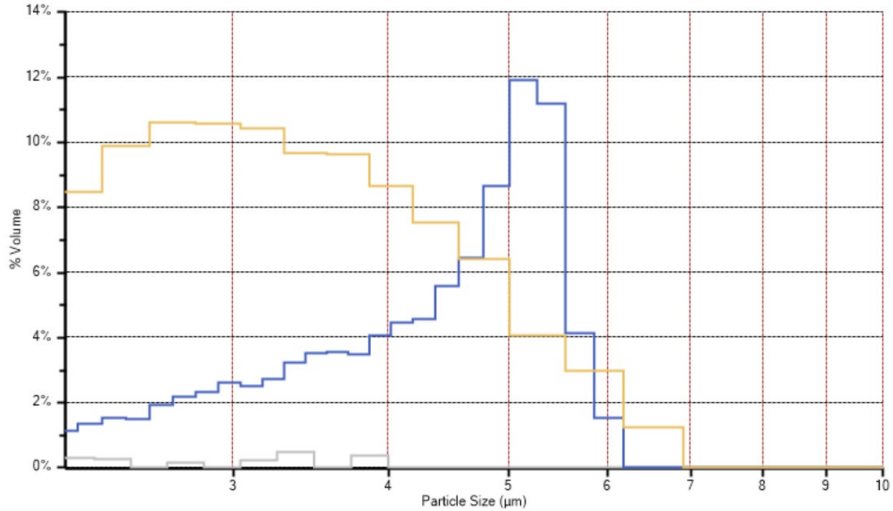
Particle Counter Results

Counts/mL (Number)



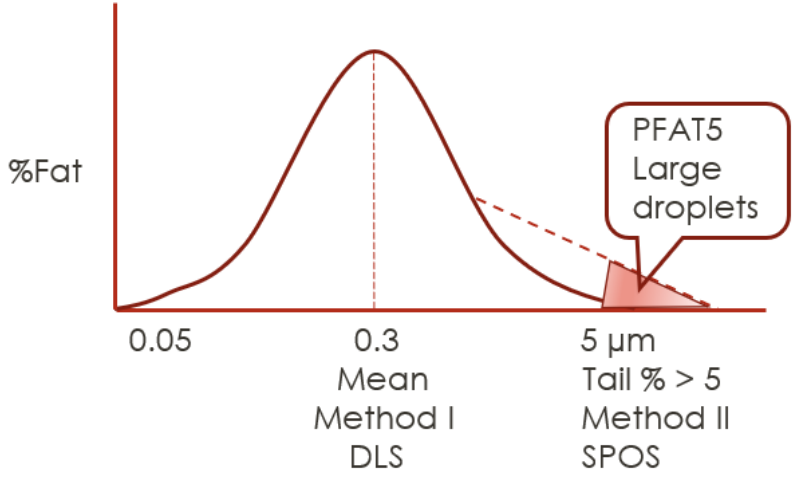
Volume%

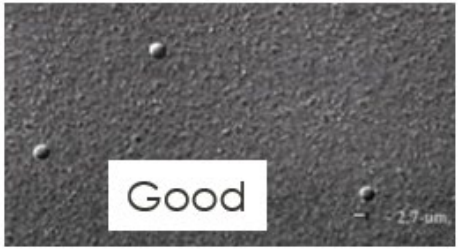


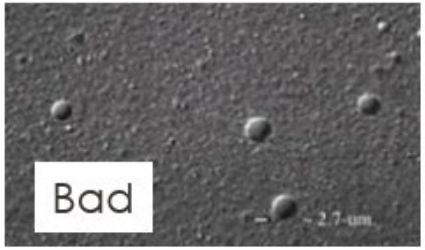
Formulation	PFAT5	Result
1	0.036	Pass
2	0.09915	Fail
3	0.0084	Pass

USP 729 PFAT5

- Method I; mean size
  - DLS or laser diffraction
  - Must be < 0.5 µm
- Method II; % > 5 µm
  - SPOS; AccuSizer APS
  - PFAT5 < 0.05%
  - Indicates stability
  - Patient safety







"Nanoparticles/ Nanoemulsions"

- Nanoparticles:
  Size (diameter) <100 nm
  - ISO/TS 27687:2008
  - ASTM E2456-06
- Emulsion; 0.1 – 100 µm
- Microemulsion*: Thermodynamically stable, D = 5-50 nm, self-assembled
- Nanoemulsion*Thermodynamically unstable, r < 100 nm
- Microemulsion < Nanoemulsion (often)
  $10^{-6} > 10^{-9}$

} Is free energy higher or lower separate state or two phase

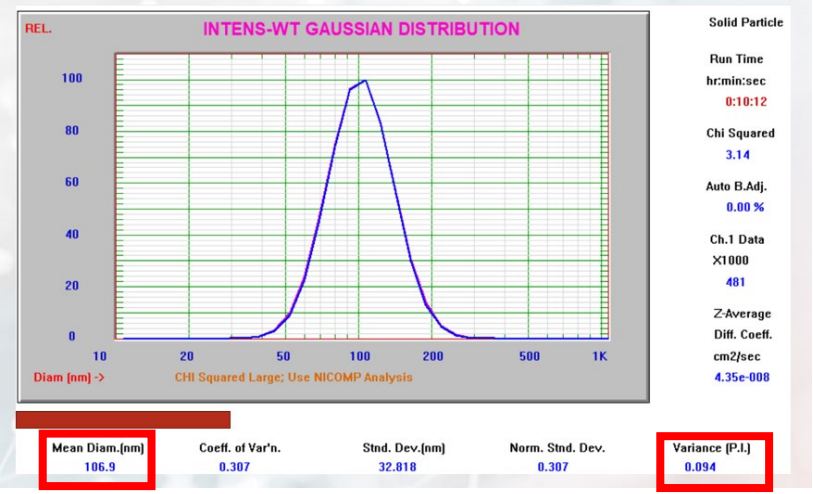
- But Nano sounds better than Micro
- Branding & Packaging

* McClements, D.J., Nanoemulsions versus microemulsions: terminology, differences, and similarities, Soft Matter, 2012, 8, 1719–1729 | 1719

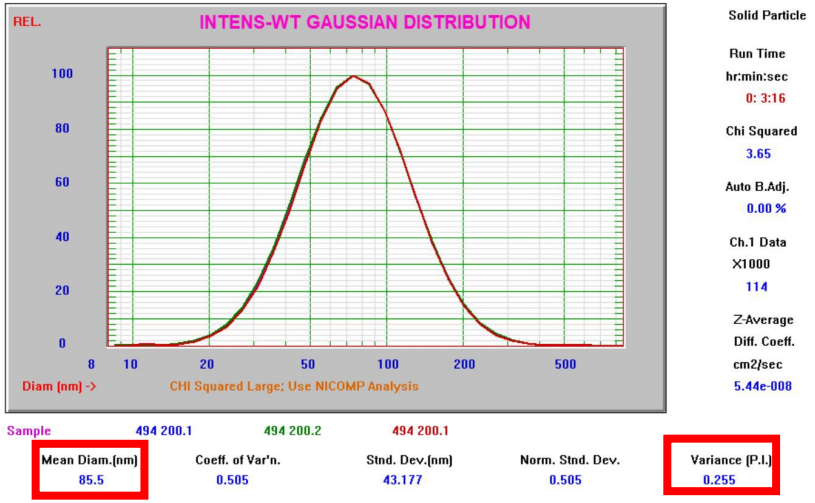
Check Width (PI)

Which is more stable?

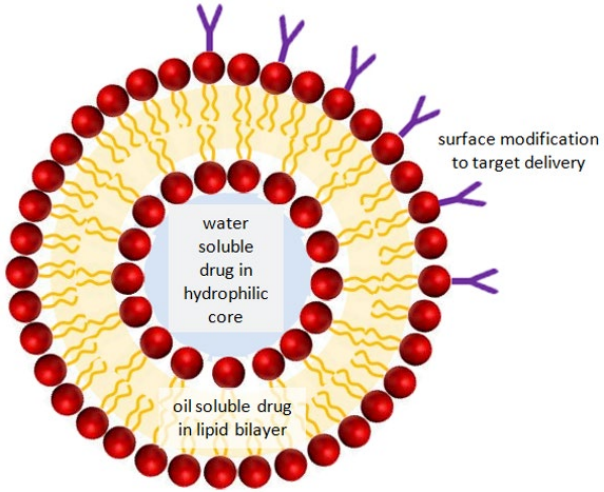
107 nm PI = 0.094, Narrow Distribution



86 nm PI = 0.255, Broad Distribution

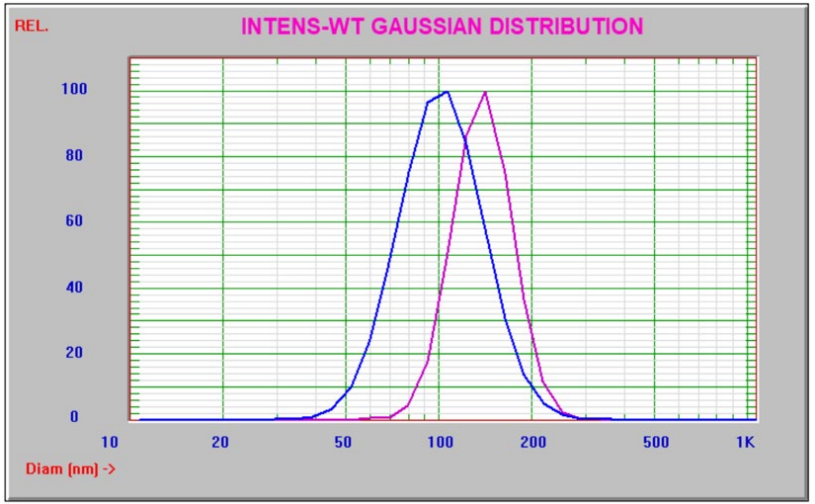


Liposomes



Liposome A; Size = 106.9 nm, PI = 0.094

Liposome B; Size = 142 nm, PI = 0.048



Conclusions/Acknowledgements

- Formulation critical
- Need to measure size, width
- Zeta potential for surface charge, pH
- Particle counter for large droplets
- Get trained

- Entegris, Inc.
- David Schaible of Pharmacann
- Michael Hnatow from Stuff Corp

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