pH and Temperature Responsive Novel Nanoparticles Characterised by Dynamic Light Scattering

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Objectives

- What are Lipodisqs®?
- Demonstrate the sensitivity of Lipodisq® particles to changing environmental stimuli
- pH and temperature influence on particle size control
- Precisely monitor particle size changes with Dynamic Light Scattering techniques

Lipodisq®

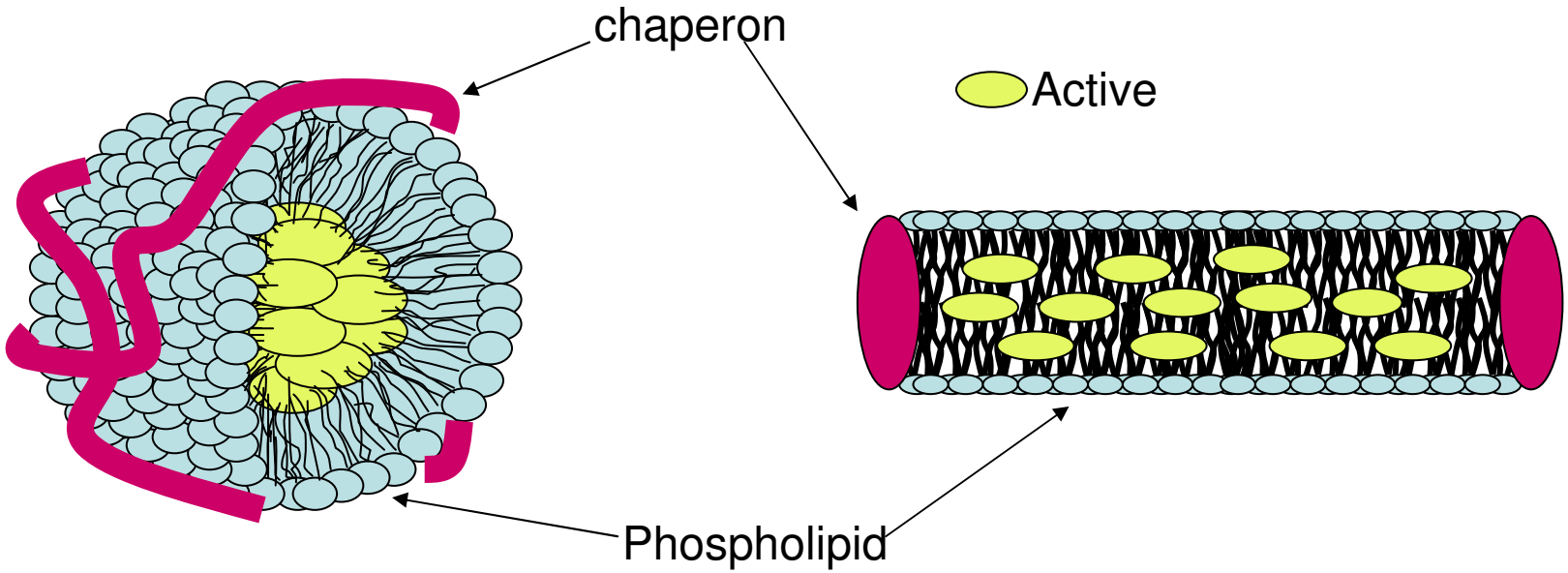
Lipodisq® particles are mimics of naturally occurring high density lipoproteins.

Lipodisq® particles are of the size range 10 to 40nm diameter.

Lipodisq® were developed by Malvern Cosmeceutics Ltd., Worcestershire, UK.

Lipodisq®

- Mimics natural lipoproteins – expected to exist in spherical or discoidal form
- Proprietary technology – primarily for use in dermal delivery of oily or lipophilic “actives”

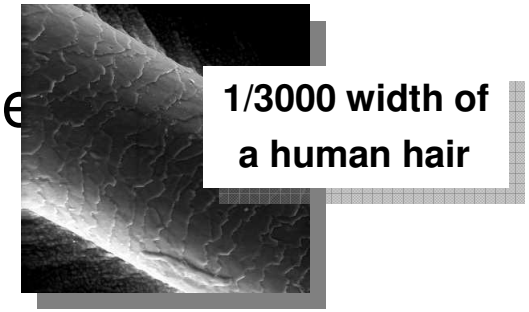


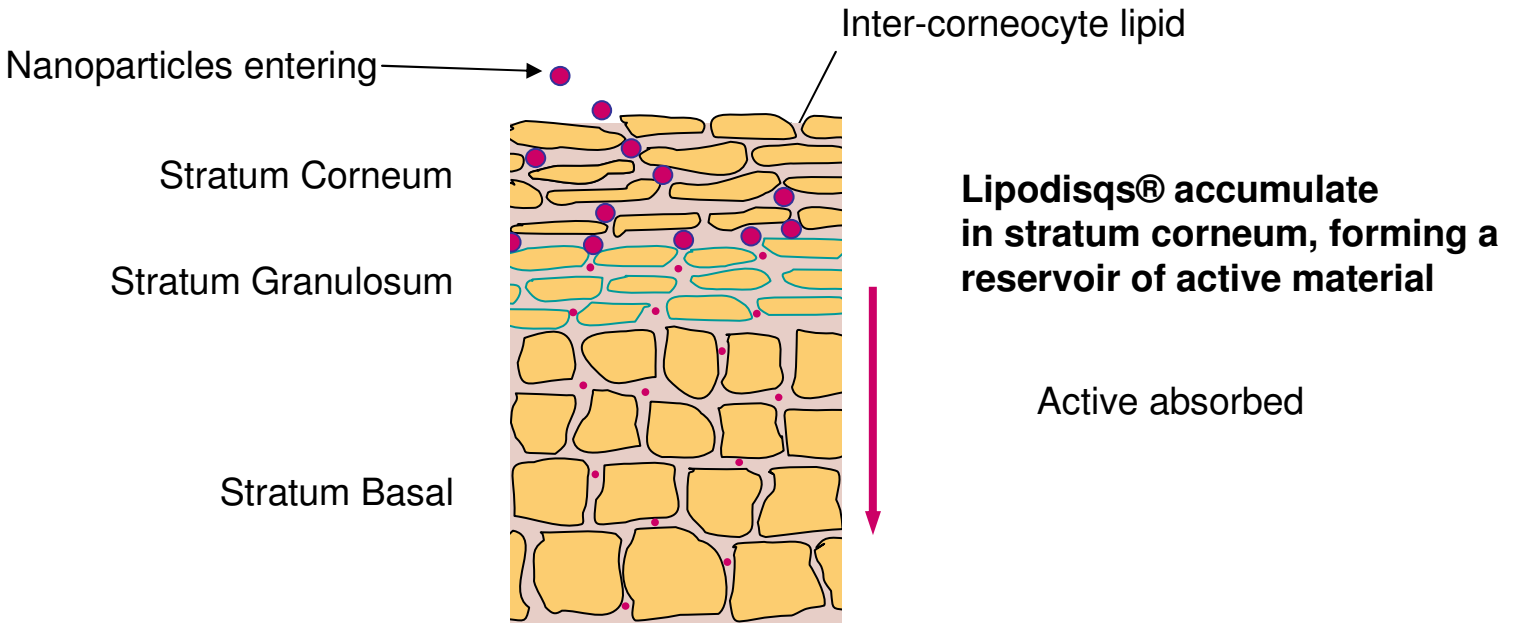
MALVERN COSMECEUTICS

Malvern

Lipodisq®

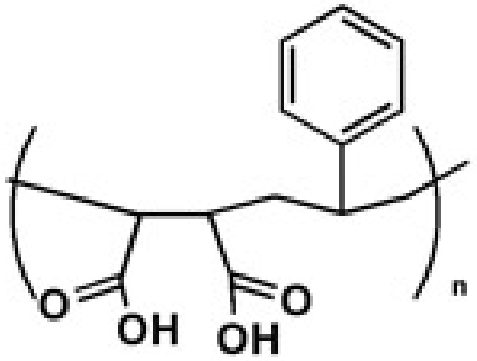
- Inter-cellular interstices <20 nm
- Particle delivery systems are typically too large for efficient penetration
- Conventional systems, e.g. Liposomes, 50 to >1000nm





pH Sensitive Lipodisq®

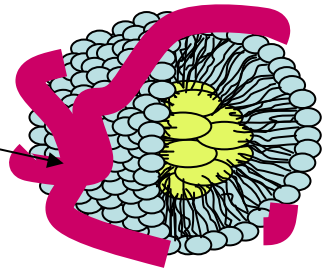
- Polymer chaperone molecules containing hydrophilic and hydrophobic moieties can spontaneously form Lipodisq® particles.
- Poly(styrene-maleic acid) [P(SMA)] is a suitable chaperone molecule.



Poly(styrene-maleic acid)

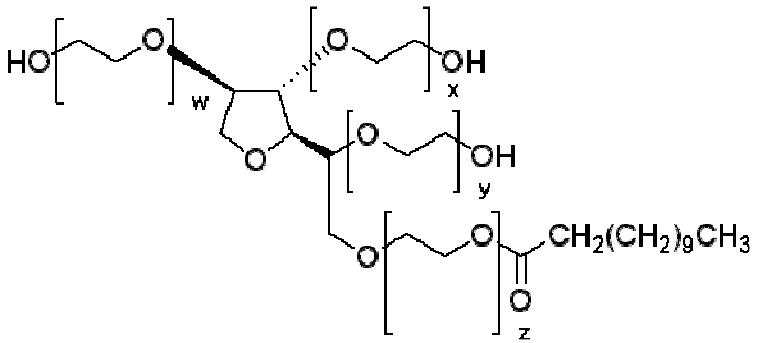
At a critical pH point the macromolecular assembly will form.

Chaperone Molecule



Temperature Sensitive Lipodisq®

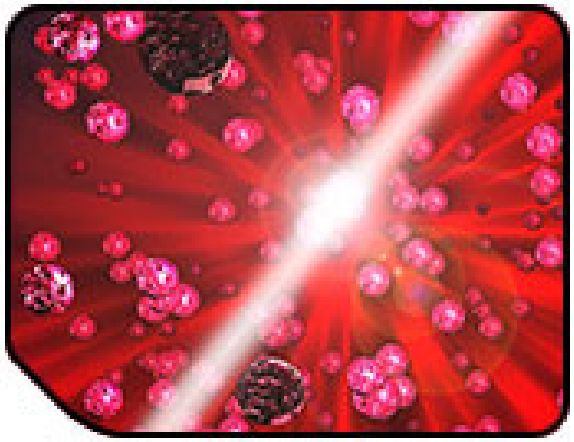
- Conventional surfactant materials can achieve the optimal structure of the P(SMA) molecule.
- Specific chain lengths and HLB required.
- Polysorbate 20 (Tween 20) is a suitable chaperone molecule.



Polysorbate 20

Dynamic Light Scattering (DLS)

- Particle size is determined from the analysis of intensity fluctuations of scattered light from a suspension of particles undergoing Brownian motion



This allows the translational diffusion coefficients of the particles to be determined and this can be converted into particle size using the Stokes-Einstein relationship

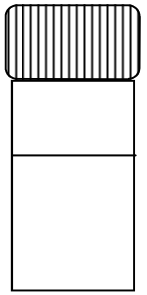
Experimental

DLS measurements were made on a Malvern Zetasizer Nano S.

Detection angle of 173° using a 4mW He-Ne laser operating at a wavelength of 633nm.

Multi Purpose Titrator (MPT2) automatically adjusted the pH using 0.1M HCl and 0.1M NaOH titrants.

Experimental
pH Sensitive



P(SMA) Lipodisq® Solution

pH automatically adjusted by MPT2

Size measurement recorded at each pH point

Experimental
Temperature Sensitive

Polysorbate 20 Lipodisq® Solution

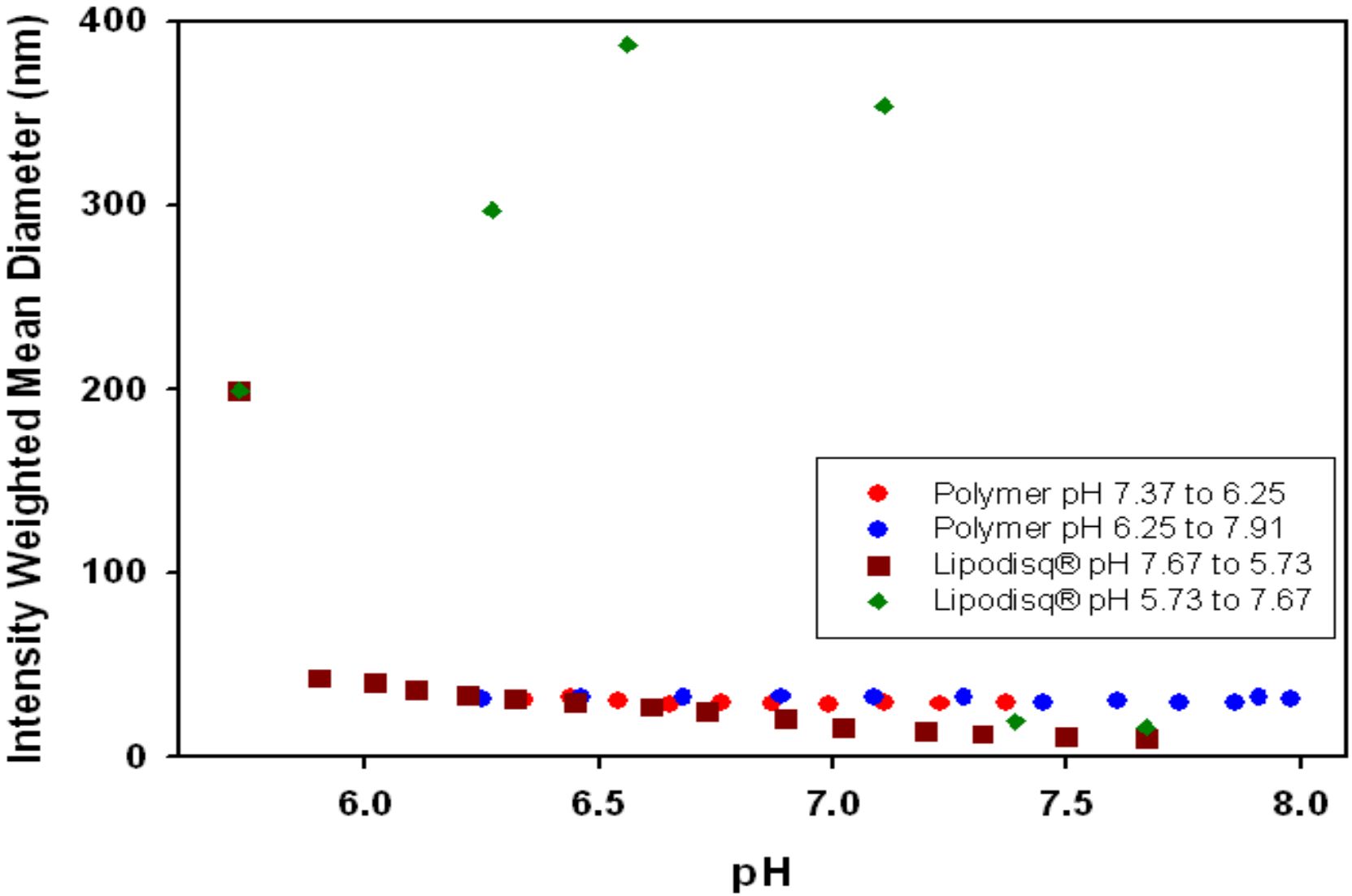
Automatic temperature trend measurements (Peltier)

20 to 90°C trend: 1° increment
1 min equilibration time

20 to 90°C trend: 10° increment
10 min equilibration time

Size measurement recorded at each degree point

Results P(SMA) Lipodisq®



Results P(SMA) Lipodisq®

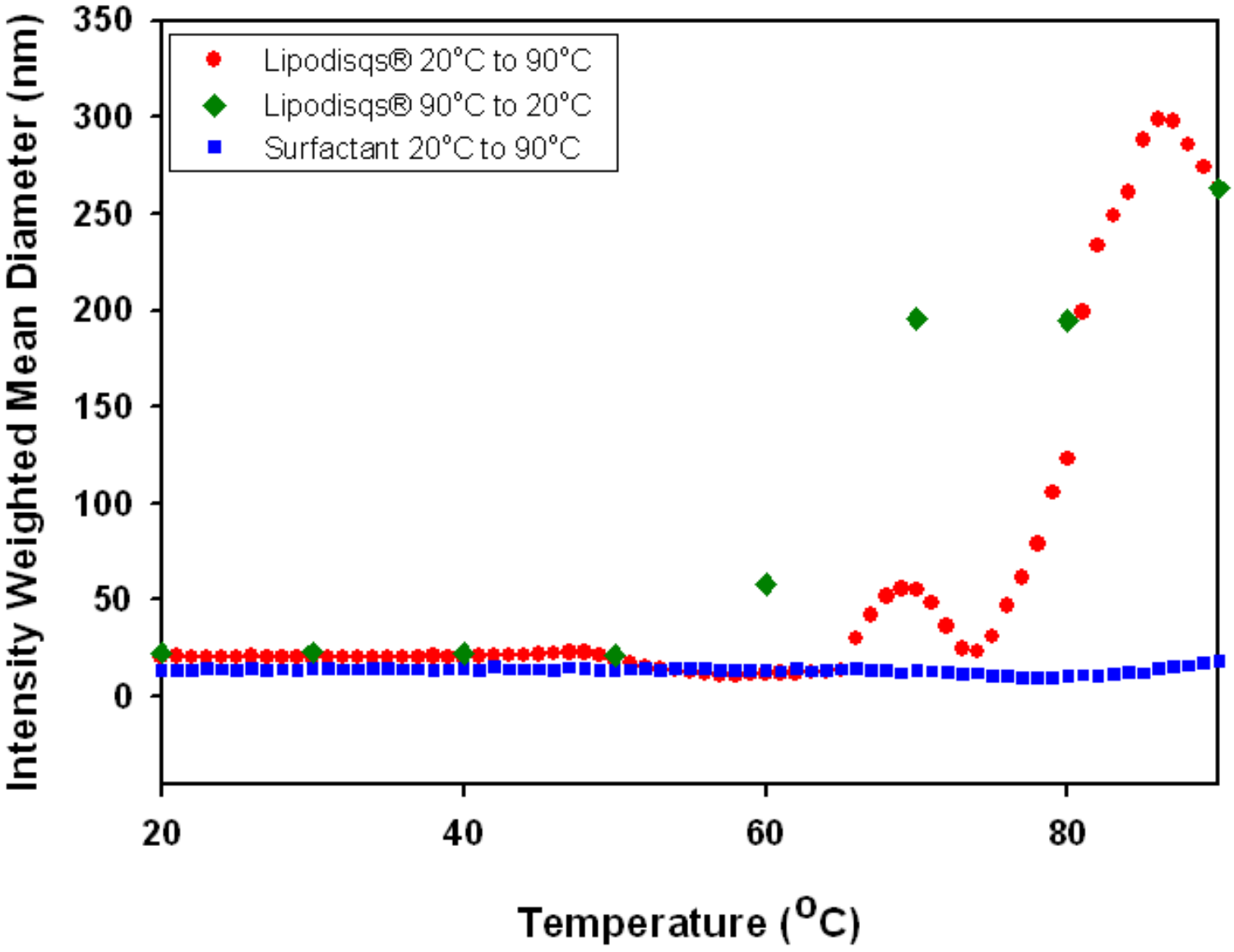
- Polymer solution remains unresponsive with a diameter of around 30nm across the pH range.
- Lipodisq® suspensions show a pH dependent change in size.
- Conformational changes in the structure of the polymer must occur upon association with phospholipid during formation of Lipodisq®
- Binding of the polymer to the phospholipid results in the adoption of a collapsed polymer structure which is highly responsive to pH changes.

Results P(SMA) Lipodisq®

- Acting as a molecular trigger to dimensional changes of the complex. Intensity weighted mean diameter of the Lipodisq® solution increases from ~12nm to more than 200nm as the pH is reduced.

- Subsequent increases in pH from 5.7 to 7.7 results in the reformation of Lipodisq® particles (reduction in particle size).

Results Polysorbate 20 Lipodisq®



Results Polysorbate 20 Lipodisq®

- A gradual increase in temperature of the polysorbate Lipodisq® results in an increase in particle size.
- Disassociation of the polysorbate Lipodisq® components leads to a disruption of the complex and release of bound phospholipid to form a dense emulsion.
- An increase in particle size is seen as temperature is increased beyond the cloud point of Polysorbate 20 (76°C).

Results Polysorbate 20 Lipodisq®

- <30nm at 50℃ to approximately 300nm at 85℃.
- Subsequent cooling results in rapid reformation of the Lipodisq® complex.
- Returning to original particle size dimensions at 50℃.

Conclusions

- P(SMA) Lipodisq® Particles demonstrate a sensitivity to pH change.

  Increasing in particle size from ~12nm to >200nm over a pH range of 7.7 to 5.7.

- Polysorbate 20 Lipodisq® particles demonstrate a sensitivity to temperature change.

  Increasing in particle size from ~20nm to ~300nm over a temperature range of 20°C to 90°C.

Conclusions

- Both Lipodisq® systems were found to spontaneously reform.
- Lipodisq® enables particle size to be precisely controlled.
- Control within the nanometer range, i.e. 0.2nm – 1nm, by adjustment of either pH or temperature.

Thank You