Sonocrystallisation
Effect of ultrasound frequency & power on induction time & crystal properties

Judy Lee[1], **Lian X. Liu**[1], Dom Falconer[1], Kevin P. Girard[2a], Clarissa Forbes[2b], Alpana A. Thorat[2a], Ivan Marziano[2b]

[1]Department of Chemical and Process Engineering, University of Surrey, GU2 7XH, UK

[2a] Chemical Research and Development, Worldwide Research and Development, Pfizer, Groton, Connecticut 06340, United States

[2b] Pfizer Worldwide Research and Development, Sandwich CT13 9NJ, U.K

Contents

- Sonocrysallisation overview
- Acoustic Cavitation-Sonoluminescence
- Example of inorganic compounds
- Example of organic compounds
- Summary and Challenges

Sonocrystallisation

Ultrasound Applications: Crystal Production, Separation and Purification

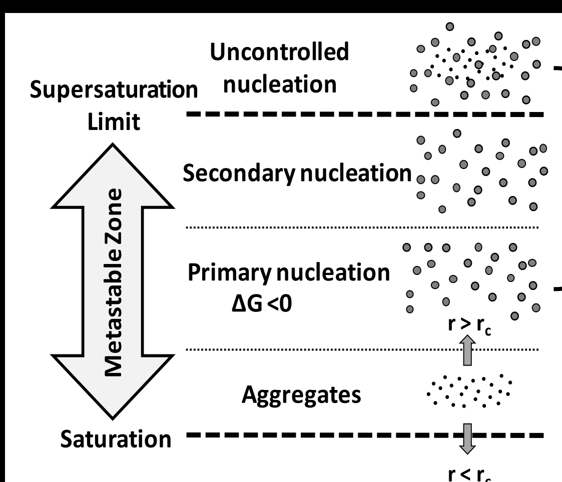
Food

Pharmaceutical

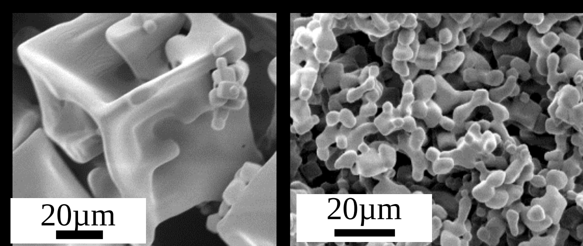
Waste

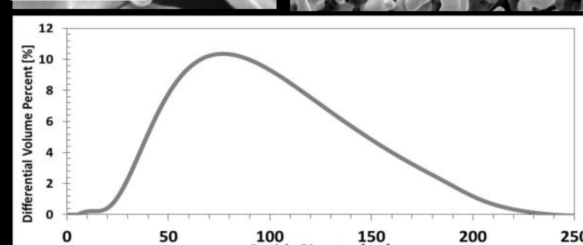
Ultrasound can help!

Crystallisation challenges



Nucleation rates & Seeding





Crystal Shape & Size

Paracetamol

Monoclinic Form I (stable)
Poor technological and biopharmaceutical properties

Orthorhombic Form II (unstable)
Better tableting properties and does not require binding agents

Polymorphism

Sonocrystallisation

Crystallisation

Primary Nucleation

Homogeneous

Heterogeneous

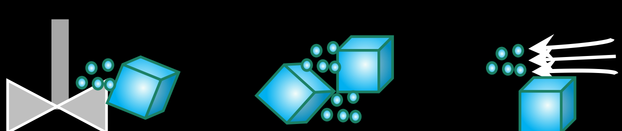
solid interface (dust, bubbles etc)

Secondary Nucleation

parent crystal

seed

Attrition, abrasion, erosion



Crystal growth & breakages

Nucleation Rate

T, ***S***, ***γ***, P

Solvent & Solute type

S generation
(T, antisolvent)

Impurities

Cooling/heating rate

Mixing rate

Spatial/Time variation

Reactor/Geometry

Ultrasound

Acoustic cavitation

Formation of cloud of bubbles in liquid, which grow, oscillate and then implode with great intensity

High Temp
T > 5000 K
High Pressure
P > 1000 bar

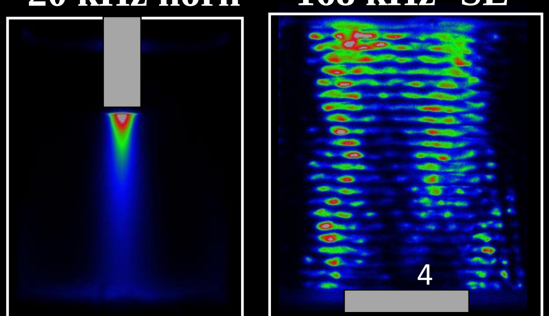
Fluid shear

Jetting & Shockwaves

Transducer type

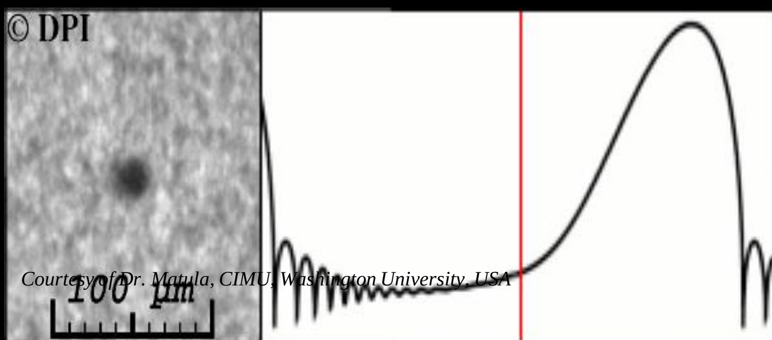
Frequency/Power

20 kHz horn **168 kHz -SL**

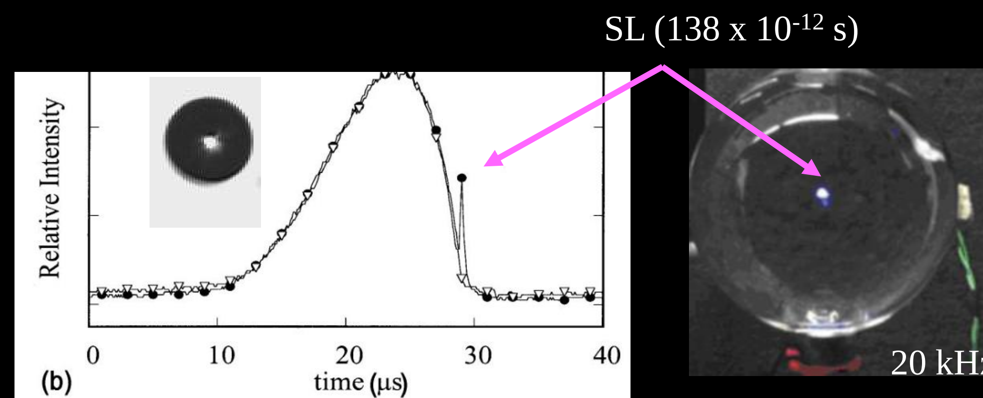


Acoustic Cavitation

Single bubble dynamics

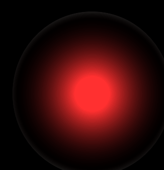


Sonoluminescence (SL)



Extreme Bubble Core Conditions

Temperatures > 5000 K

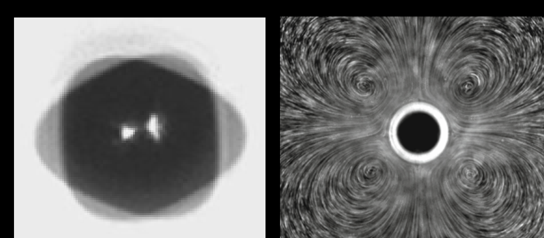


Pressures > 1000 bar

Localised fluid shear and Mixing

surface pitting

shockwaves



oscillation modes

bubble streaming

Sonocrystallisation: Possible Mechanisms

High pressure/temperature melt crystallisation

Enhancing diffusion

High Pressure

Known Effects

- ↓ **MSZW**
- ↑ **nucleation rate**
- ↓ **induction time**
- → ← **crystal size distribution**
- ↓ **Average crystal size**
- ↑ **product yield**

Heterogeneous nucleation

Homogeneous nucleation

Sonofragmentation

Evaporation (surface/core)

Surface Subcooling

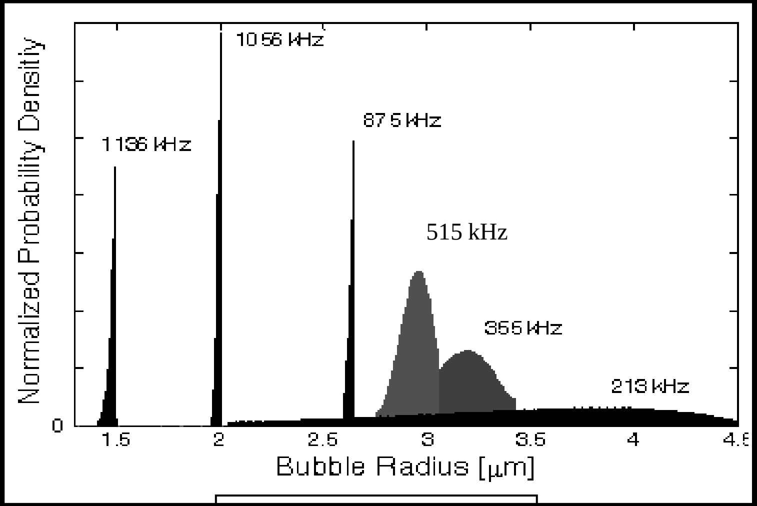
Segregation Model

Optimum Frequency

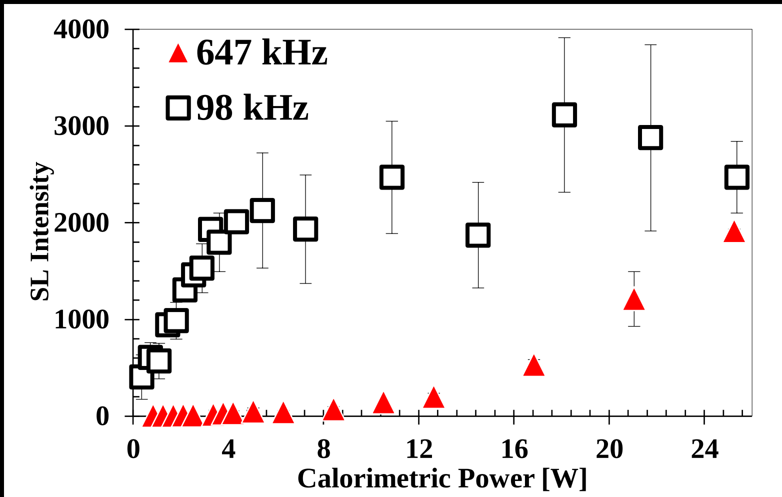
Increasing Frequency

98 kHz

168 kHz



Brotchie et al., PRL, 2009



No. Antinodes ↑

R_{max} R_{min} ↓

Collapse Intensity ↓

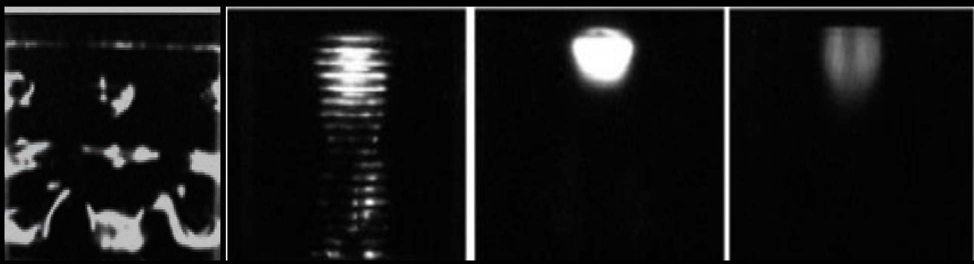
Pressure Threshold for SL ↑

↑ Increases Cavitation Bubbles

↓ Decreases Cavitation Bubbles

Acoustic Cavitation – Complex System

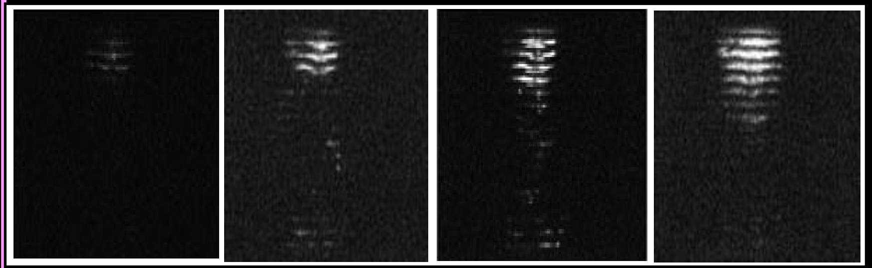
Ultrasound frequency



37 kHz | 168 kHz | 448 kHz | 726 kHz

Lee et al., *J. Ultrason. Sonochem.* 18, (**2011**), 92

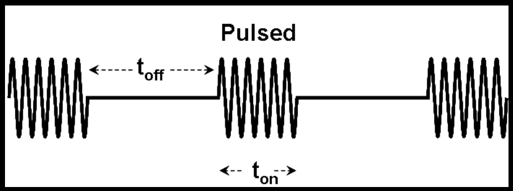
Power



8 W | 12 W | 15 W | 20W

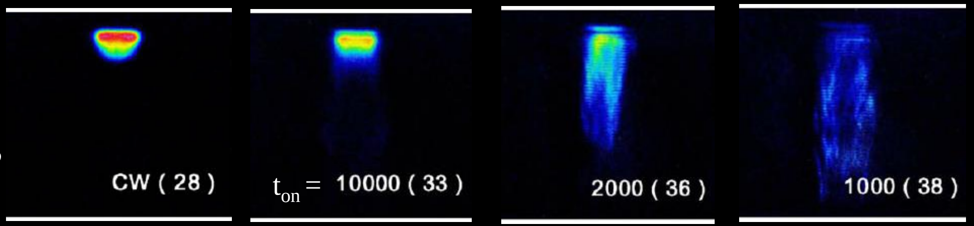
Ashokkumar et al, *ChemPhysChem* , 11, (2010) ,1680

Pulsing



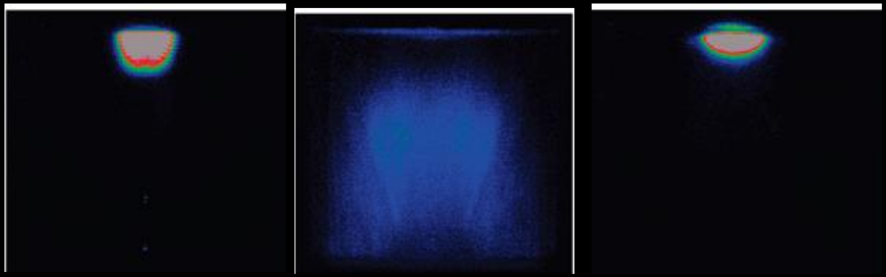
443 kHz

t_{off} =20000 cycles



Iida, Y. et al. , *Ultrason. Sonochem.* **2010, 17** ,473

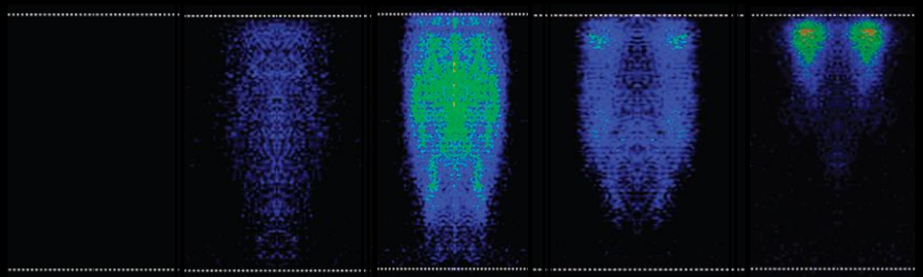
Surfactants



Water | 1mM SDS | 10 mM SDS

Lee et al., *J. Ultrason. Sonochem.* 18, (**2011**), 92

Gas Concentrations



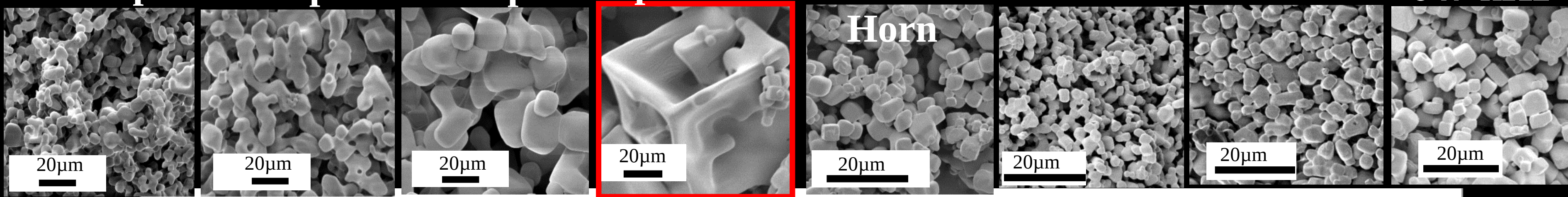
34% | 40% | 50% | 66% | 100 %

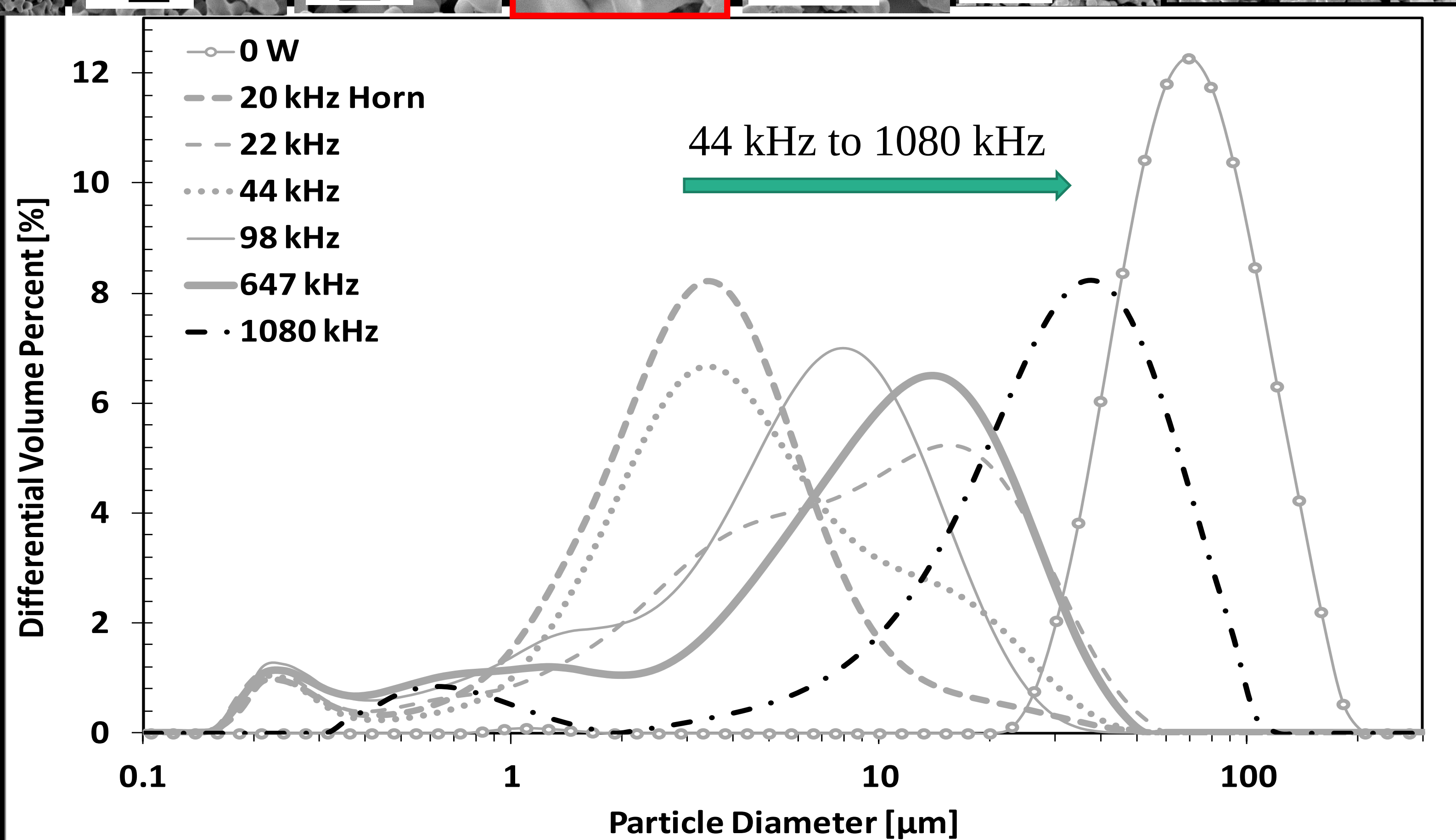
Lee et al., , *J. Phys. Chem. B.* 112, (2008), 15333

Example of Inorganic compounds (NaCl and anti-solvent)

Crystal size and size distribution (NaCl)

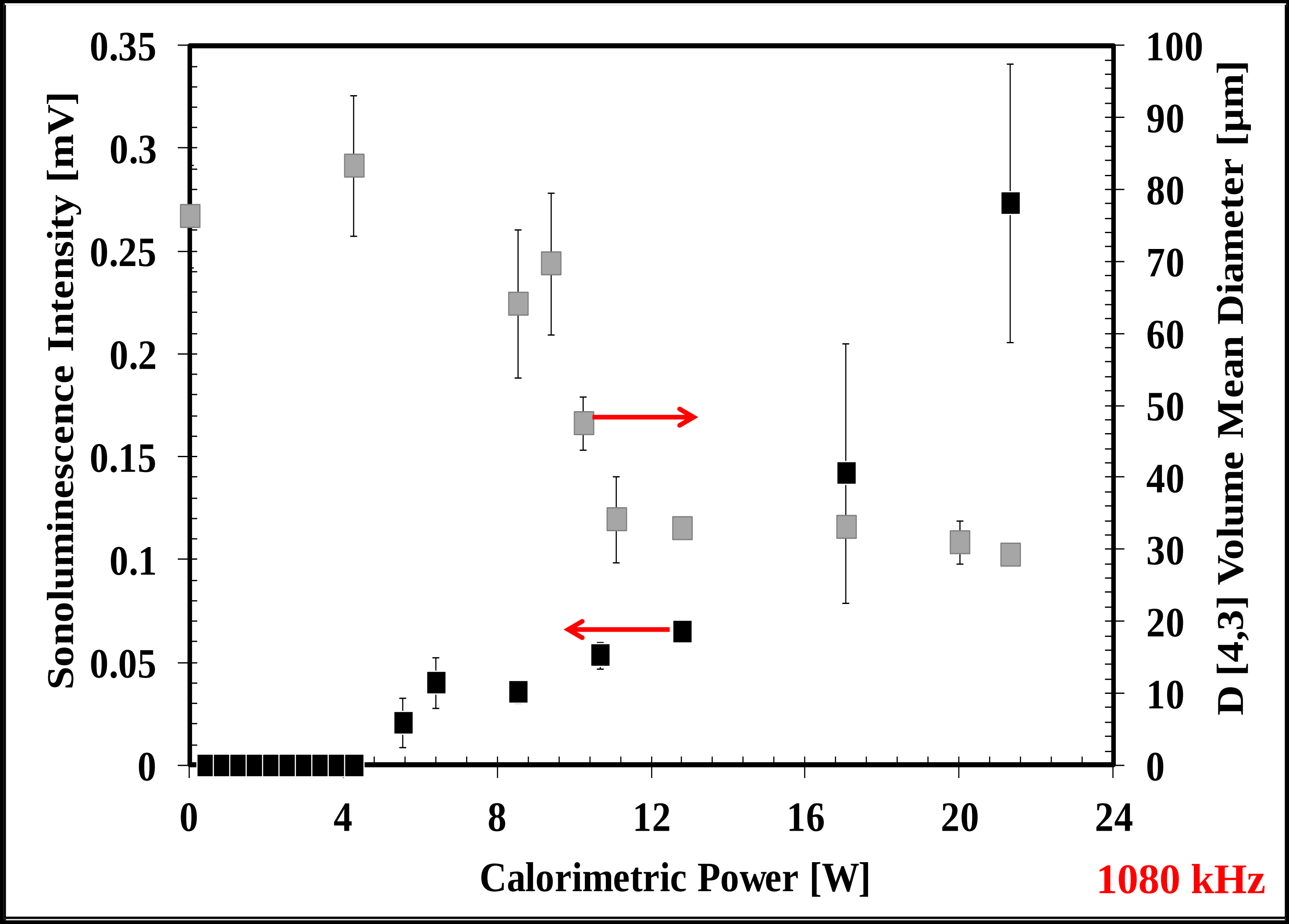
13500 rpm | 490 rpm | 200 rpm | 0 rpm/0 kHz | 20 kHz | 44 kHz | 139 kHz | 647 kHz



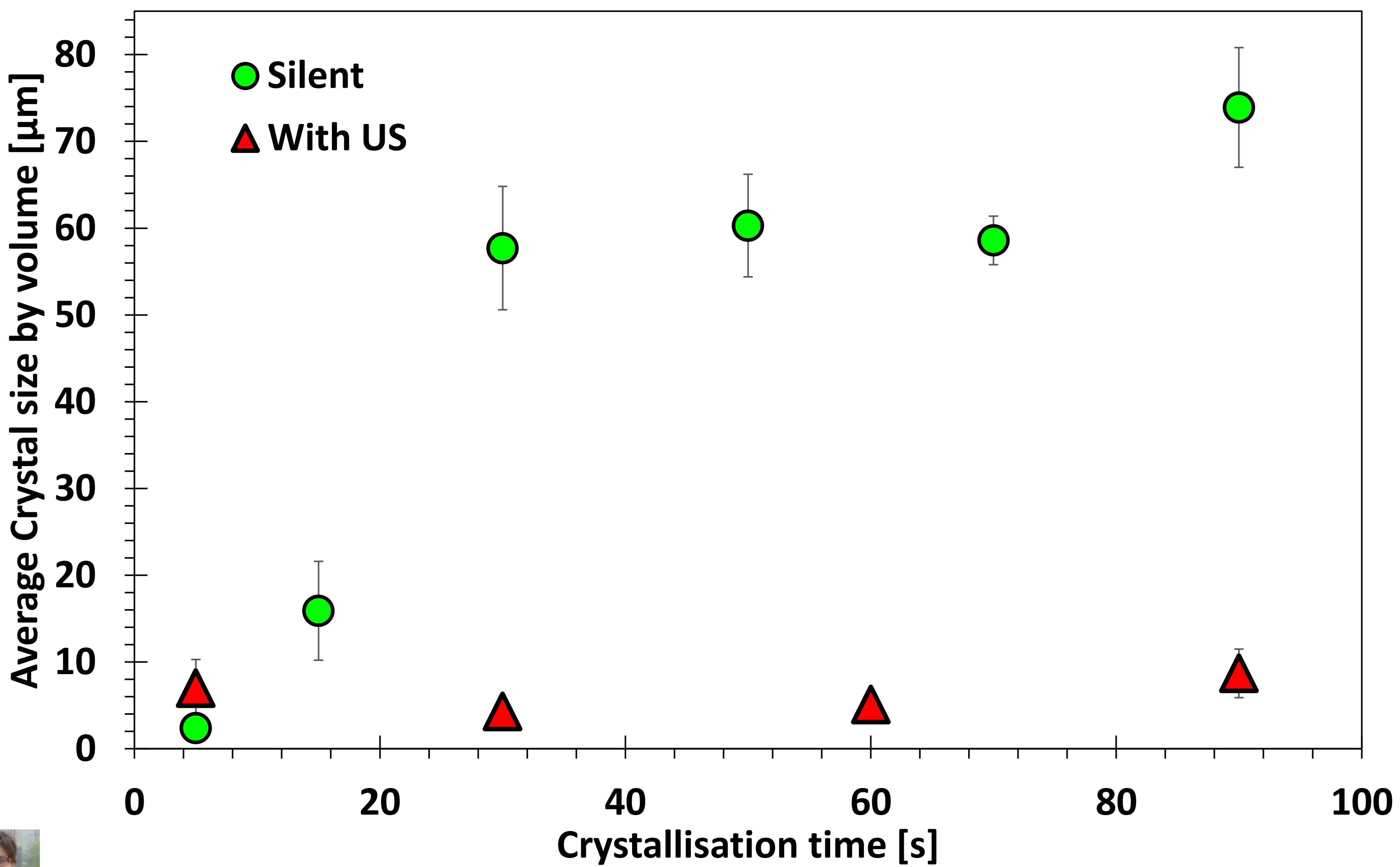


NaCl, plate US Antisolvent

SL Intensity vs NaCl Crystal size



Sonication time (NaCl)

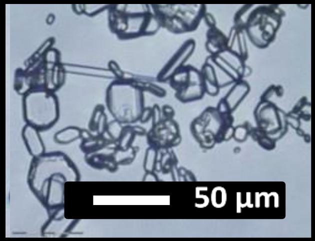


Example of Organic compounds (Paracetamol and Antisolvent)

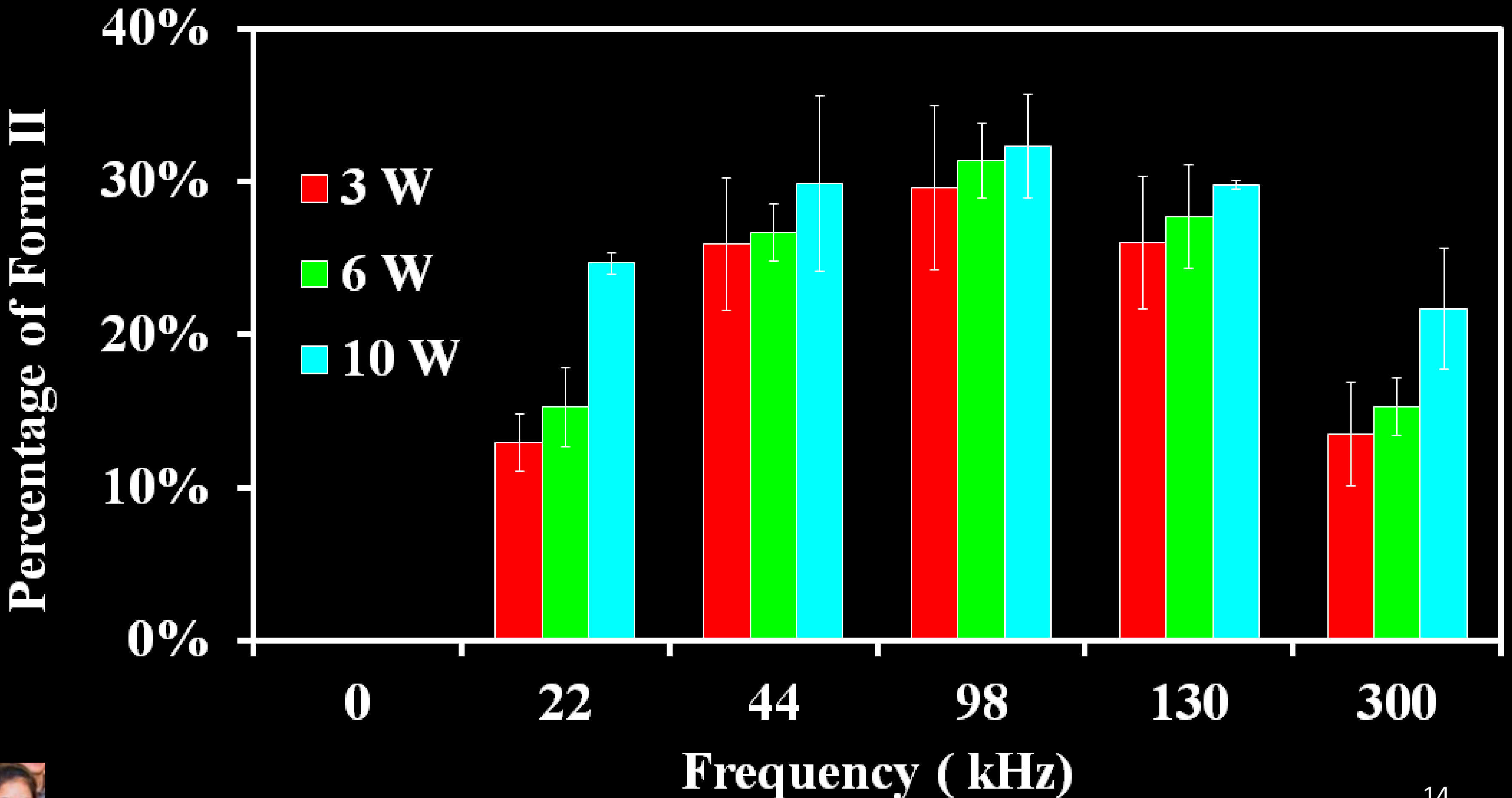
Polymorphism (Paracetamol)

Monoclinic Form I (stable)
Poor technological and biopharmaceutical properties

Orthorhombic Form II (unstable)
Better tableting properties and does not require binding agents



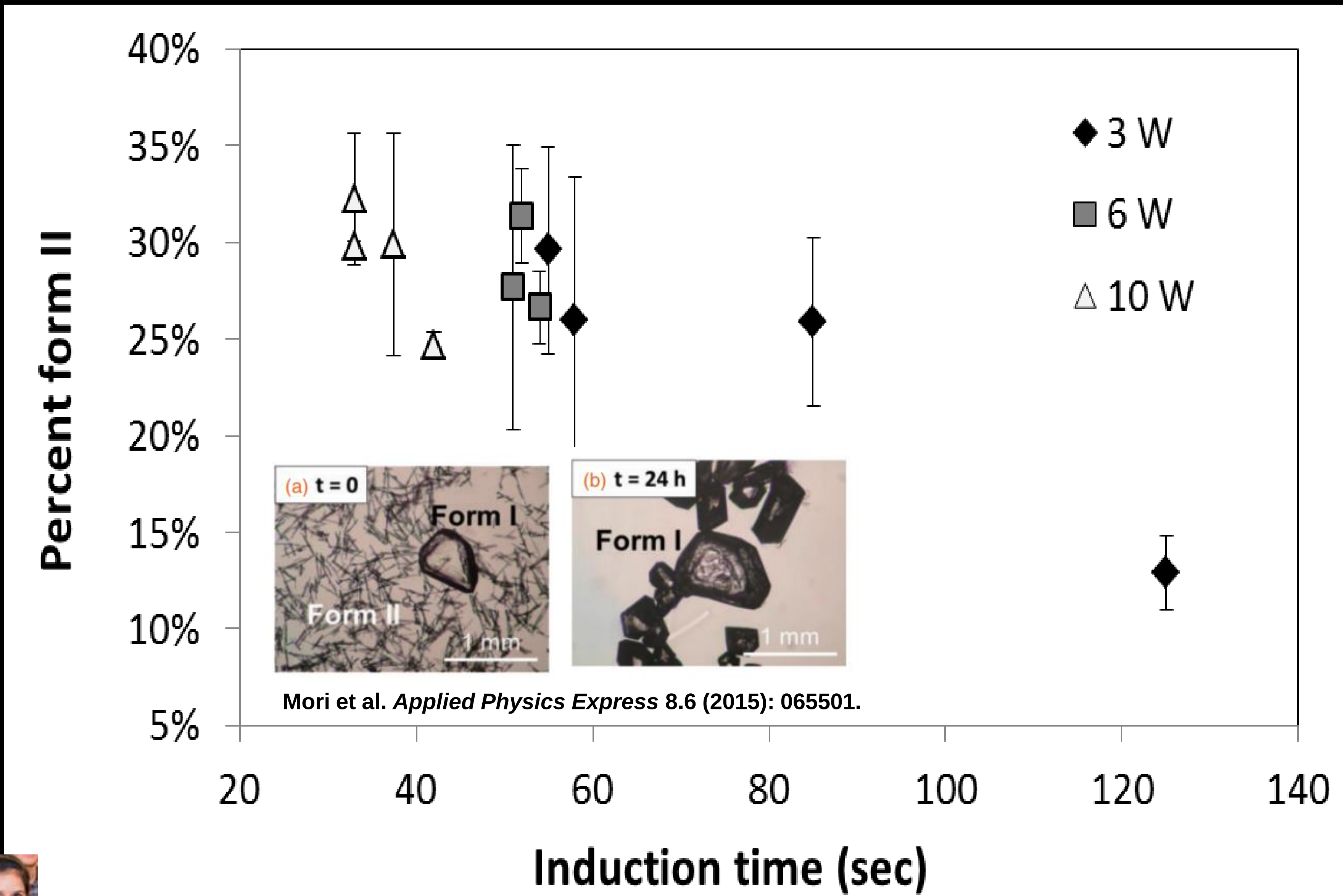
Paracetamol, Plate US, Antisolvent



S. K. Bhangu, M. Ashokkumar, and **J. Lee**, Cryst. Growth Des., 2016, 16, 1934

Polymorphism vs Induction time

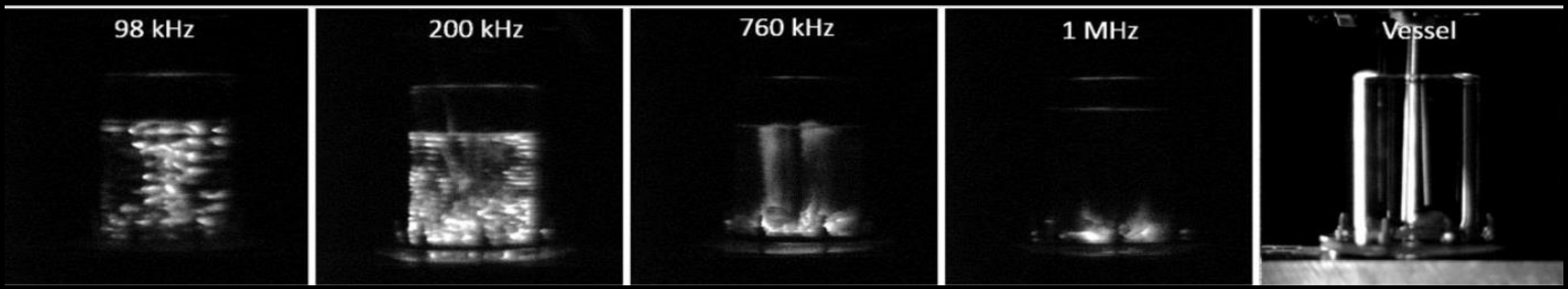
Paracetamol, Plate US, Antisolvent

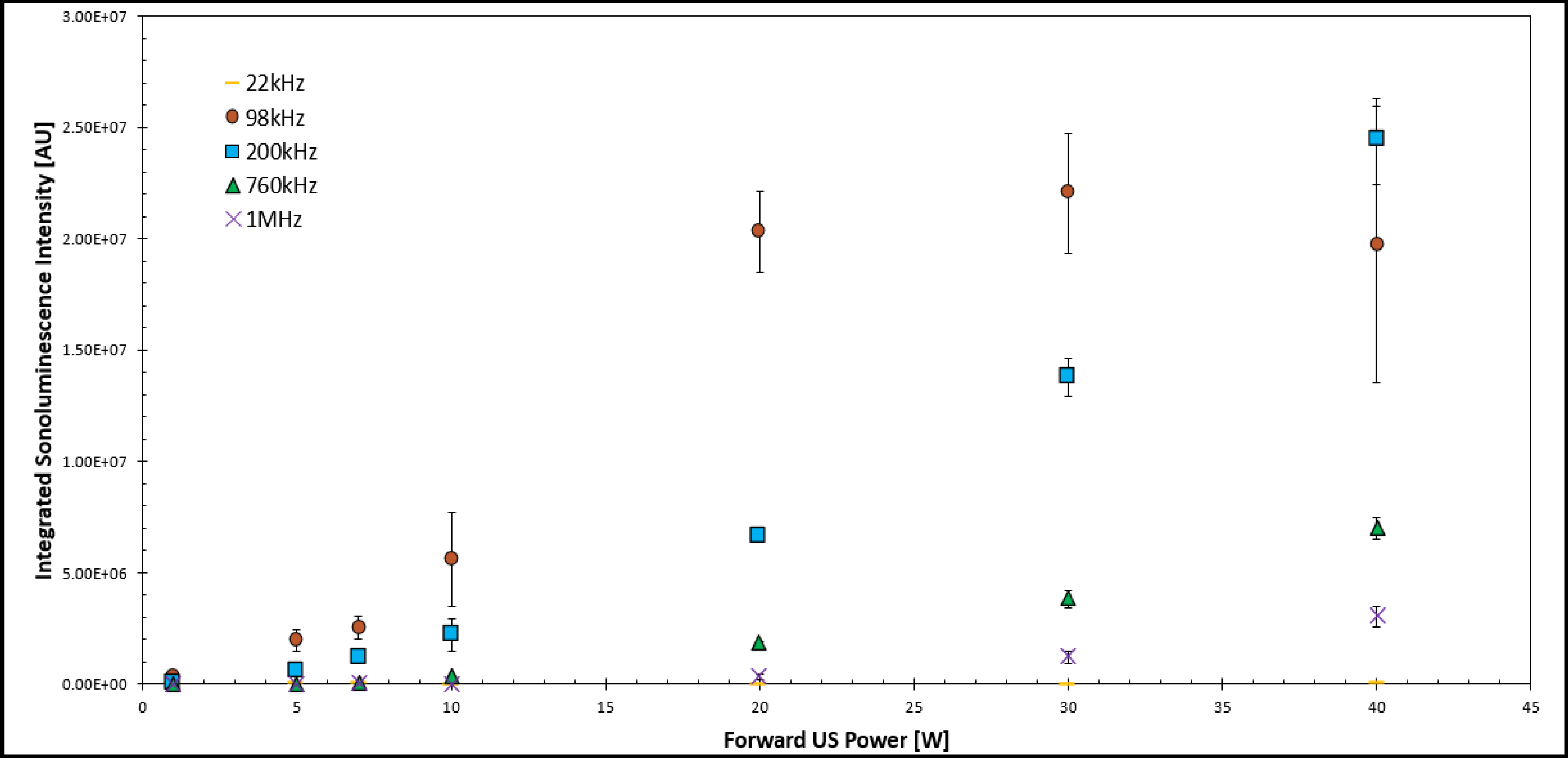


S. K. Bhangu, M. Ashokkumar, and **J. Lee**, Cryst. Growth Des., 2016, 16, 1934

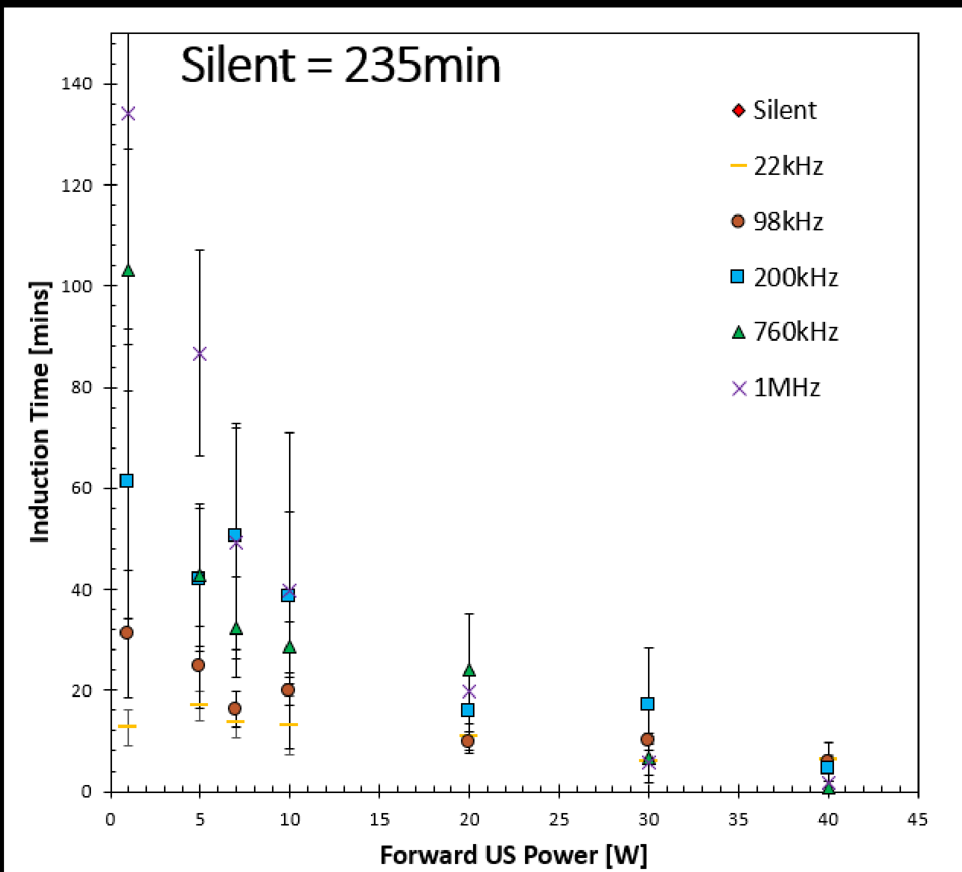
Example of Organic compounds (Compound A and Cooling crystallisation)

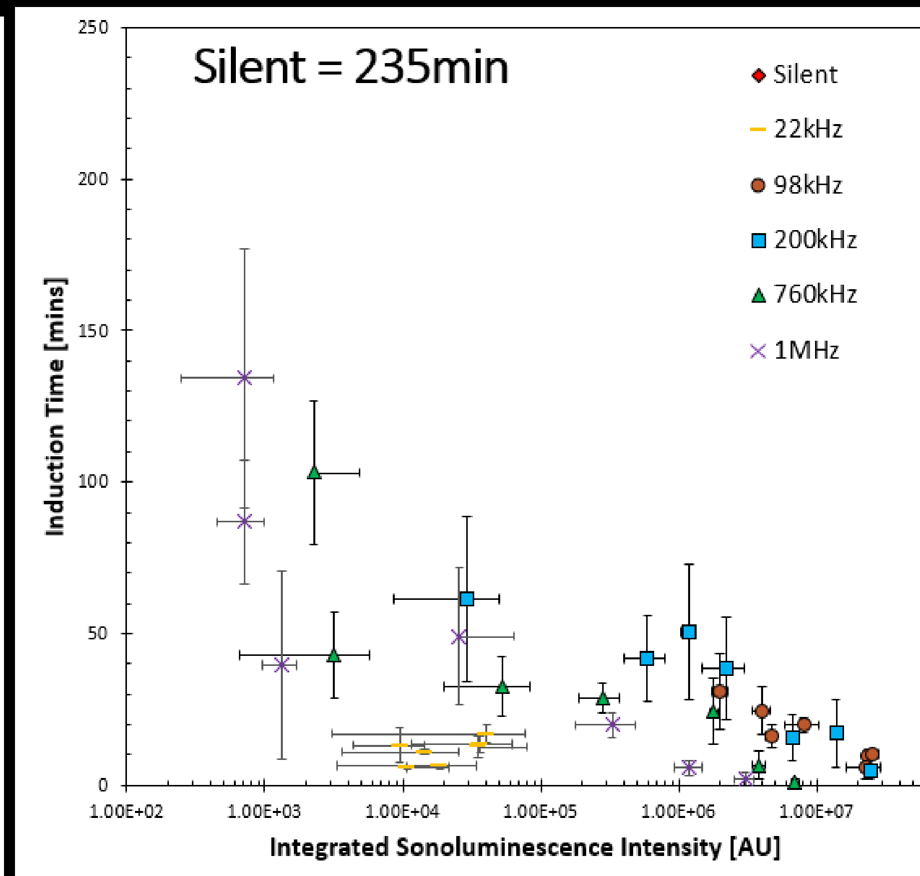
Sonoluminescence vs Power



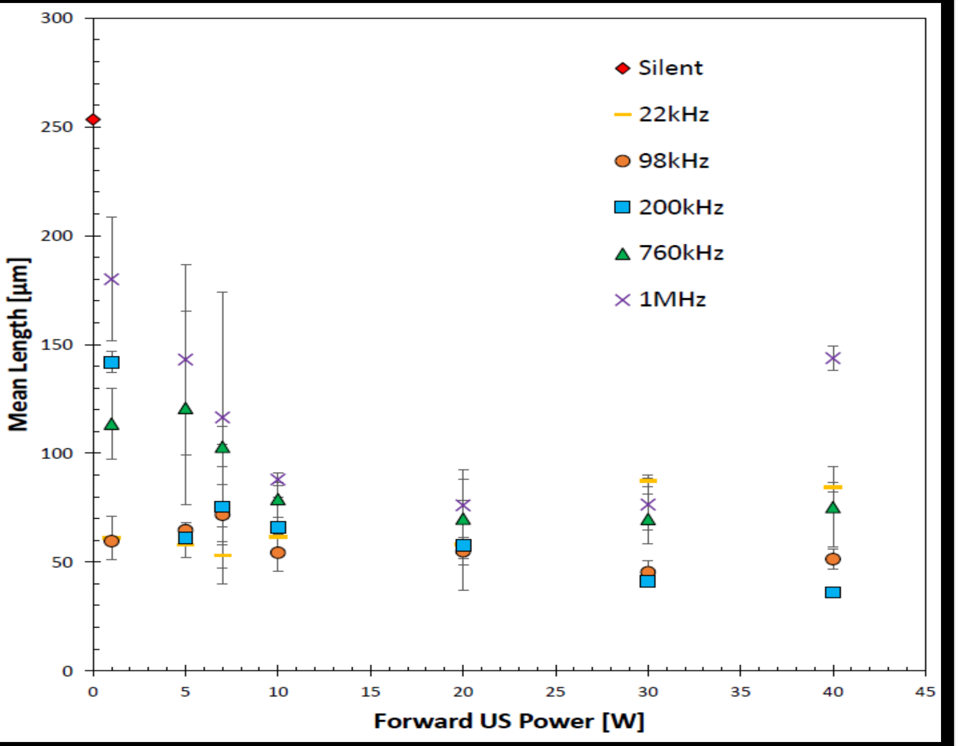


Induction Time

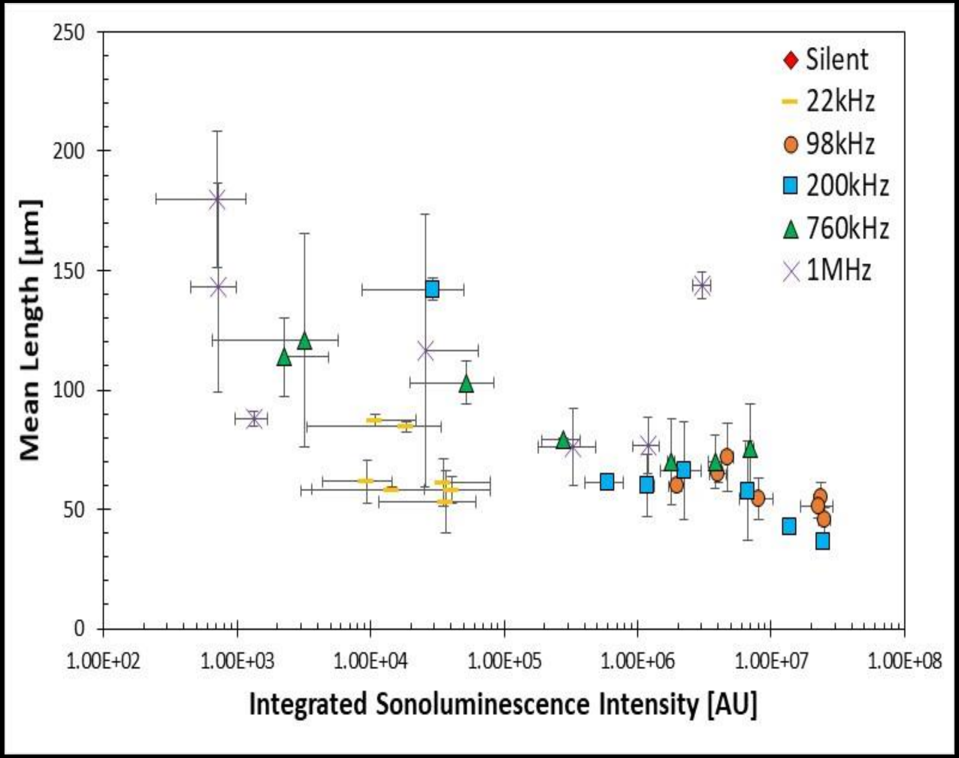




Mean Length

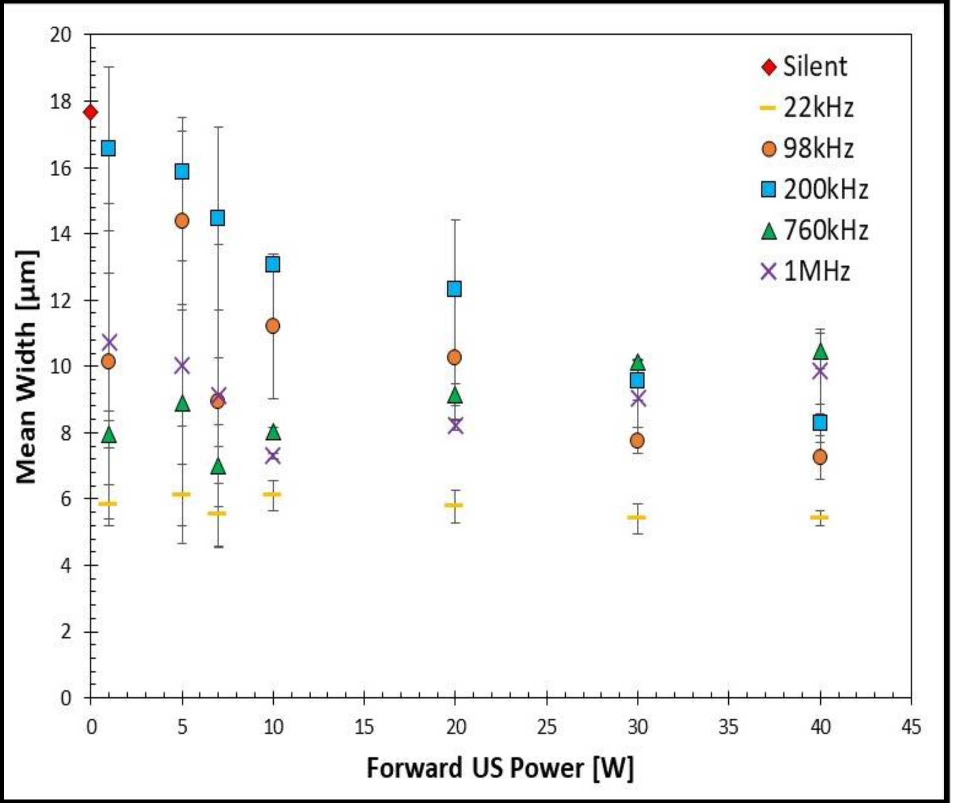


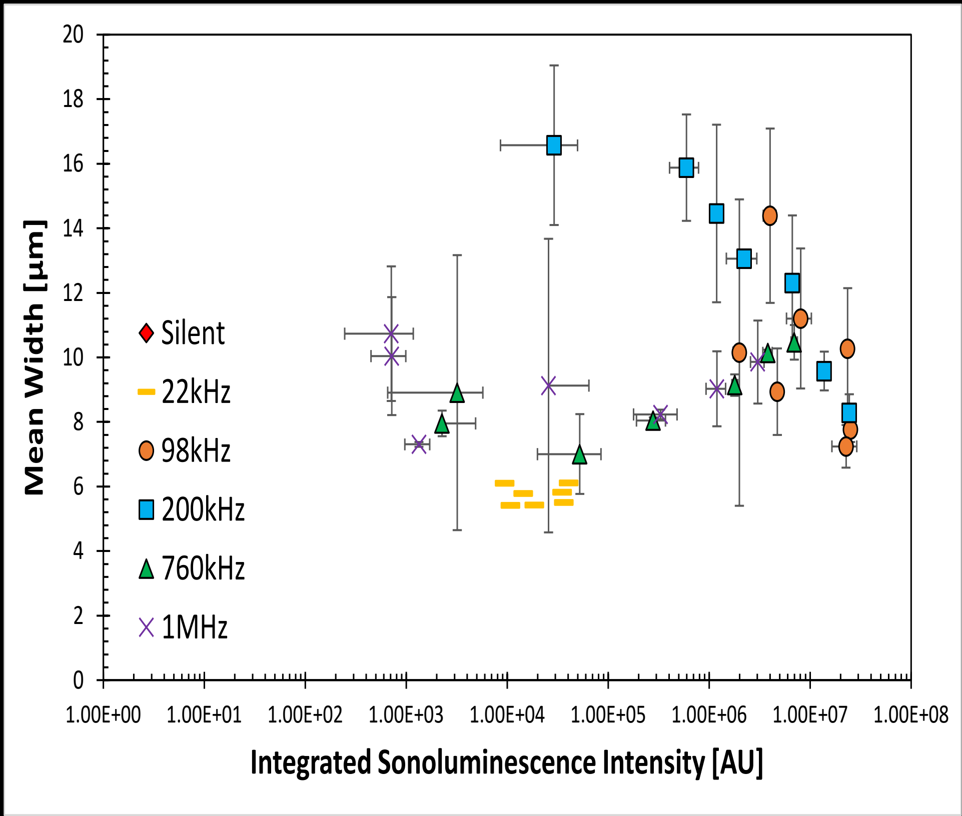
Silent
22kHz
98kHz
200kHz
760kHz
1MHz
Mean Length [µm]
Forward US Power [W]
300
250
200
150
100
50
0
0
5
10
15
20
25
30
35
40
45



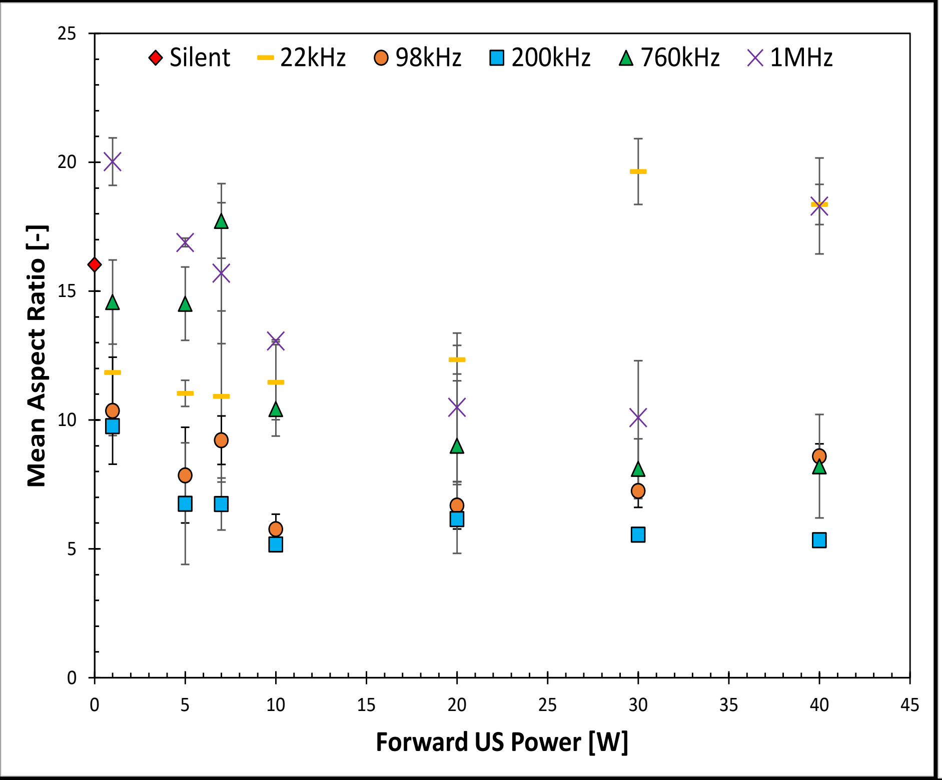
Silent
22kHz
98kHz
200kHz
760kHz
1MHz
Mean Length [µm]
Integrated Sonoluminescence Intensity [AU]
250
200
150
100
50
0
1.00E+02
1.00E+03
1.00E+04
1.00E+05
1.00E+06
1.00E+07
1.00E+08

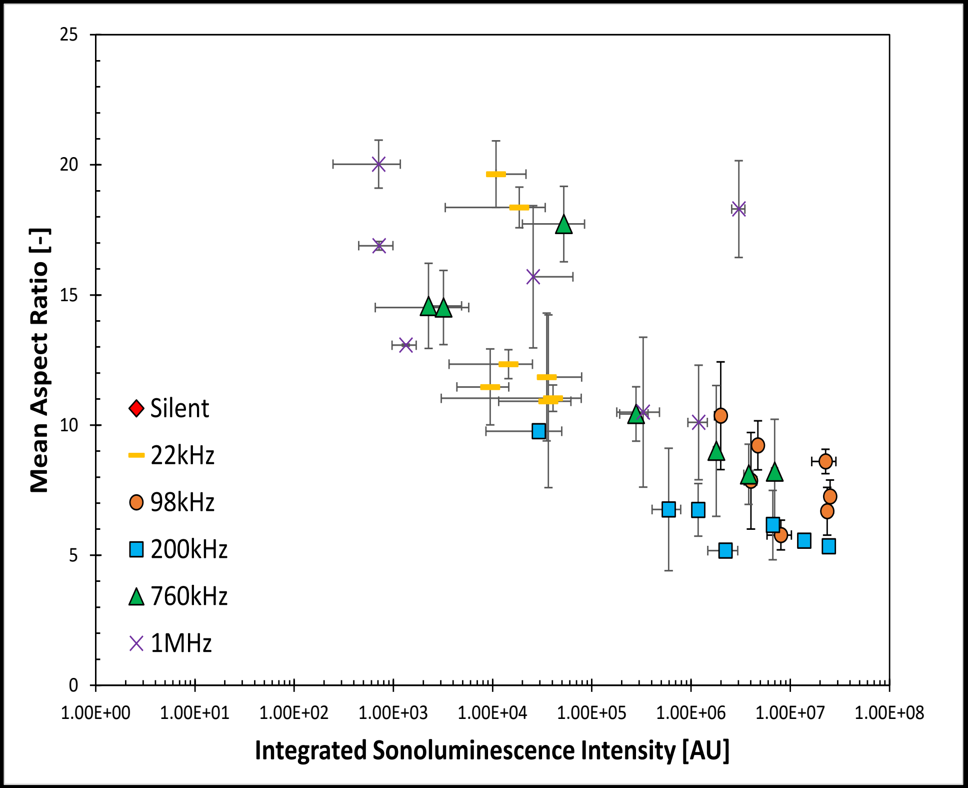
Mean Width


Mean Width [µm]
Forward US Power [W]
Silent
22kHz
98kHz
200kHz
760kHz
1MHz
0
2
4
6
8
10
12
14
16
18
20
0
5
10
15
20
25
30
35
40
45

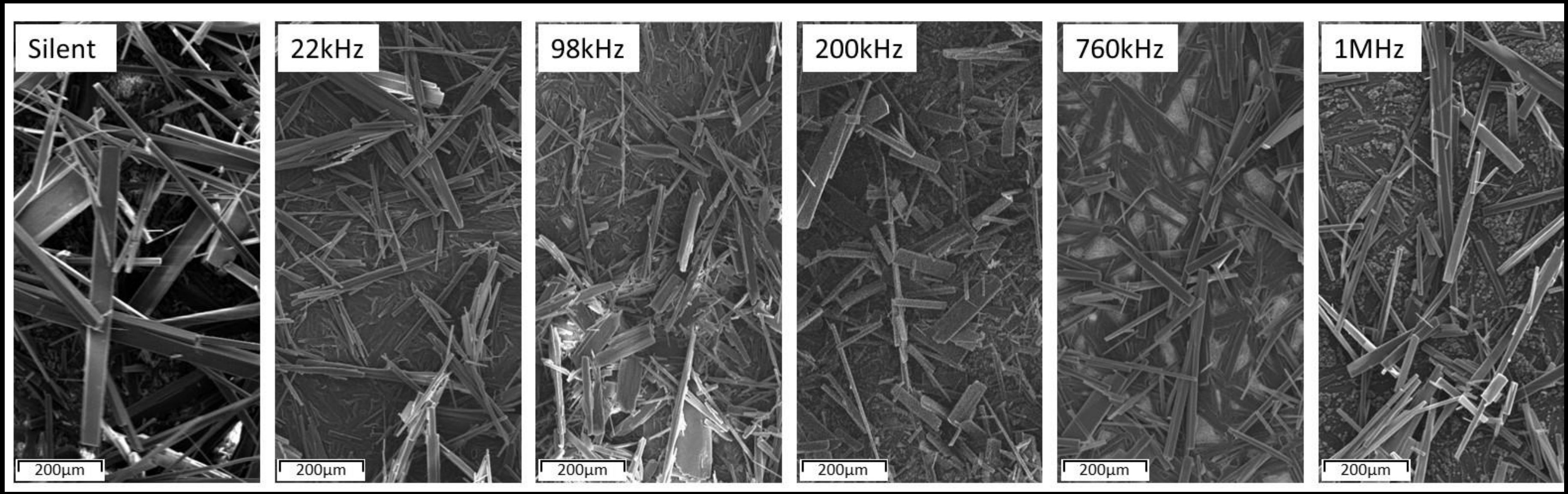

Mean Width [µm]
Integrated Sonoluminescence Intensity [AU]
Silent
22kHz
98kHz
200kHz
760kHz
1MHz
0
2
4
6
8
10
12
14
16
18
20
1.00E+00
1.00E+01
1.00E+02
1.00E+03
1.00E+04
1.00E+05
1.00E+06
1.00E+07
1.00E+08

Mean Aspect Ratio





Crystals from different frequency (20W)



Summary and Challenges

- Sonocrysatllisation - Complex Process.

- Induction time decreases with decreasing ultrasound frequency and increasing power. On crystal size -more complex

- Sonoluminescence (SL) is a better measure of cavitation activity and could provide an insight behind mechanism of sonocrystallisation. Both crystal size and induction time decrease with increasing SL

- Primary & Secondary Nucleation, fragmentation and growth are difficult to decouple, and mechanism may depend on crystallisation and sonication conditions. Therefore, understanding of ultrasound parameters on these mechanisms are important for future ultrasound applications and scale up.

Acknowledgement

PhD student

- Silvia Nalesso (Surrey)

MEng/Master students

- Roop Bhangu (Melbourne University)
- Shanshan Yang (Melbourne University)
- Mahmoud Mukhtar (Surrey)
- Benjamin Parrish (Surrey)

Collaborators

Dr. Madeleine Bussemaker

Dr. Mark Hodnett (NPL)

Prof. Muthupandian Ashokkumar (Melbourne University)

Prof. Sandra Kentish (Melbourne University)