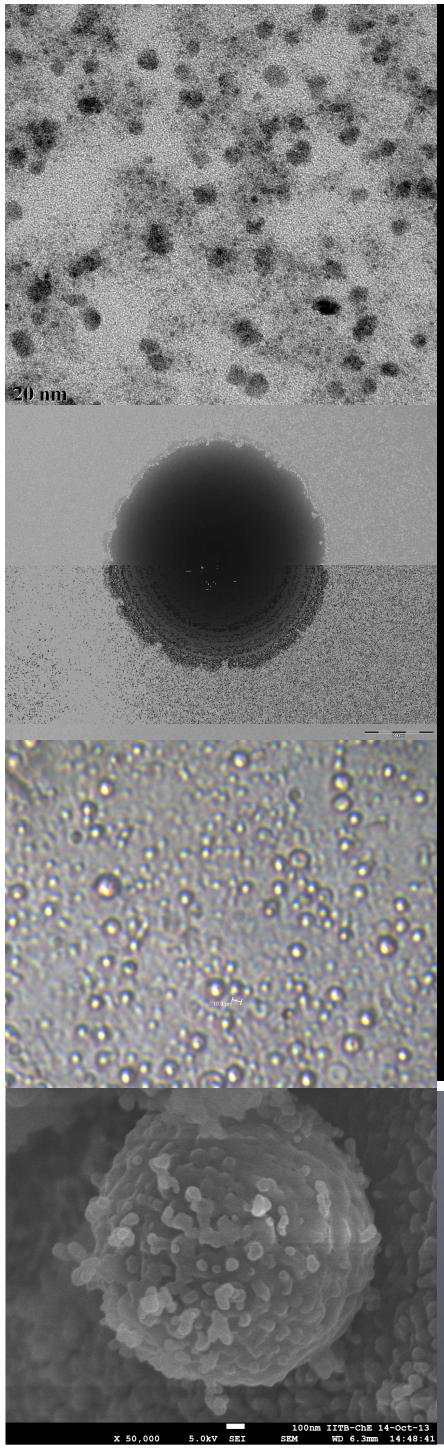
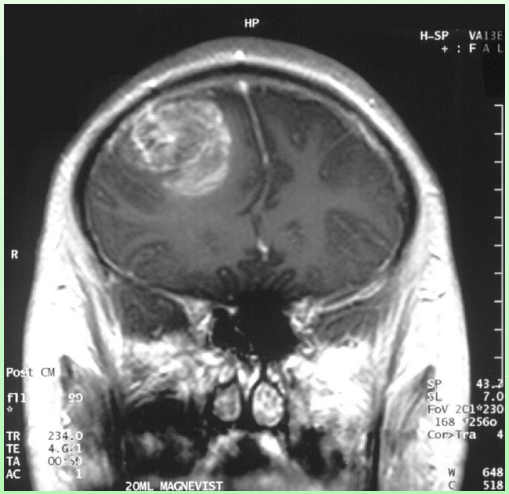


DEVELOPMENT OF NOVEL THERANOSTIC AGENTS FOR INTRA-NASAL DELIVERY OF TEMOZOLOMIDE IN GLIOBLASTOMA TREATMENT

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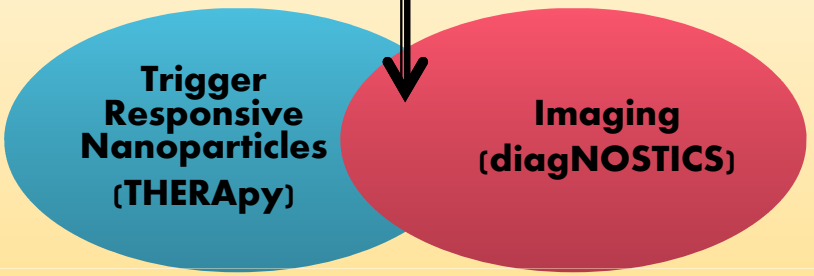
KEY COMPONENTS

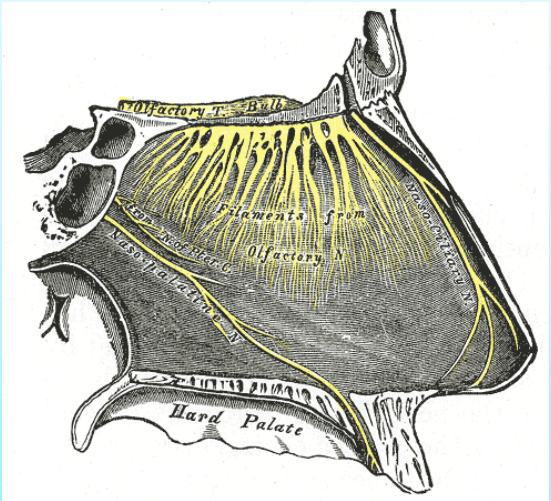


GLIOBLASTOMA

Source: http://en.wikipedia.org/wiki/Glioblastoma_multiforme

THERANOSTICS

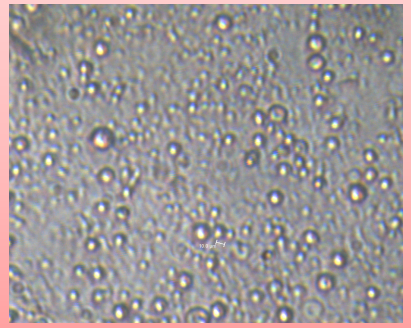




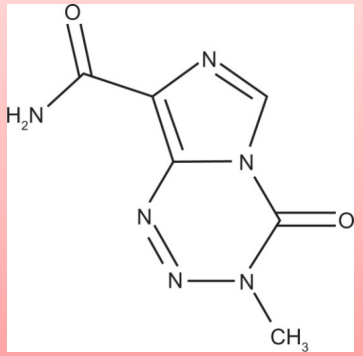
NOSE-TO-BRAIN DRUG DELIVERY

Source: Gray's anatomy : the anatomical basis of clinical practice

ULTRASOUND RESPONSIVE AGENTS



TEMOZOLOMIDE



NANOTECHNOLOGY- NANOMEDICINE



Source: http://en.wikipedia.org/wiki/Richard_Feynman

"There is Plenty of Room at the Bottom"

Richard P. Feynman to the American Physical Society in Pasadena on December 1959

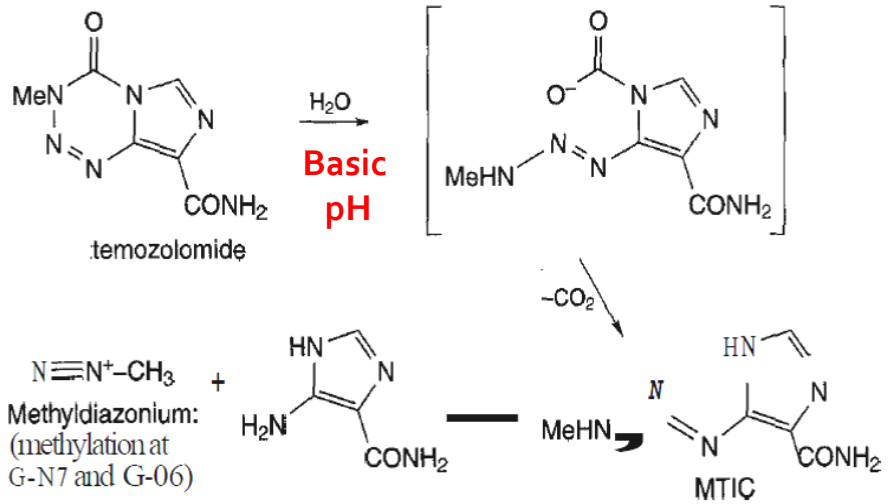
TRIGGER RESPONSIVE NANOCARRIERS

ULTRASOUND

- Inexpensive, portable, clinically trusted
- Simultaneous trigger responsive therapy and diagnostic imaging- **THERANOSTICS**
- In the CNS:
  - Opening of the BBB
  - Hyperthermia

pH

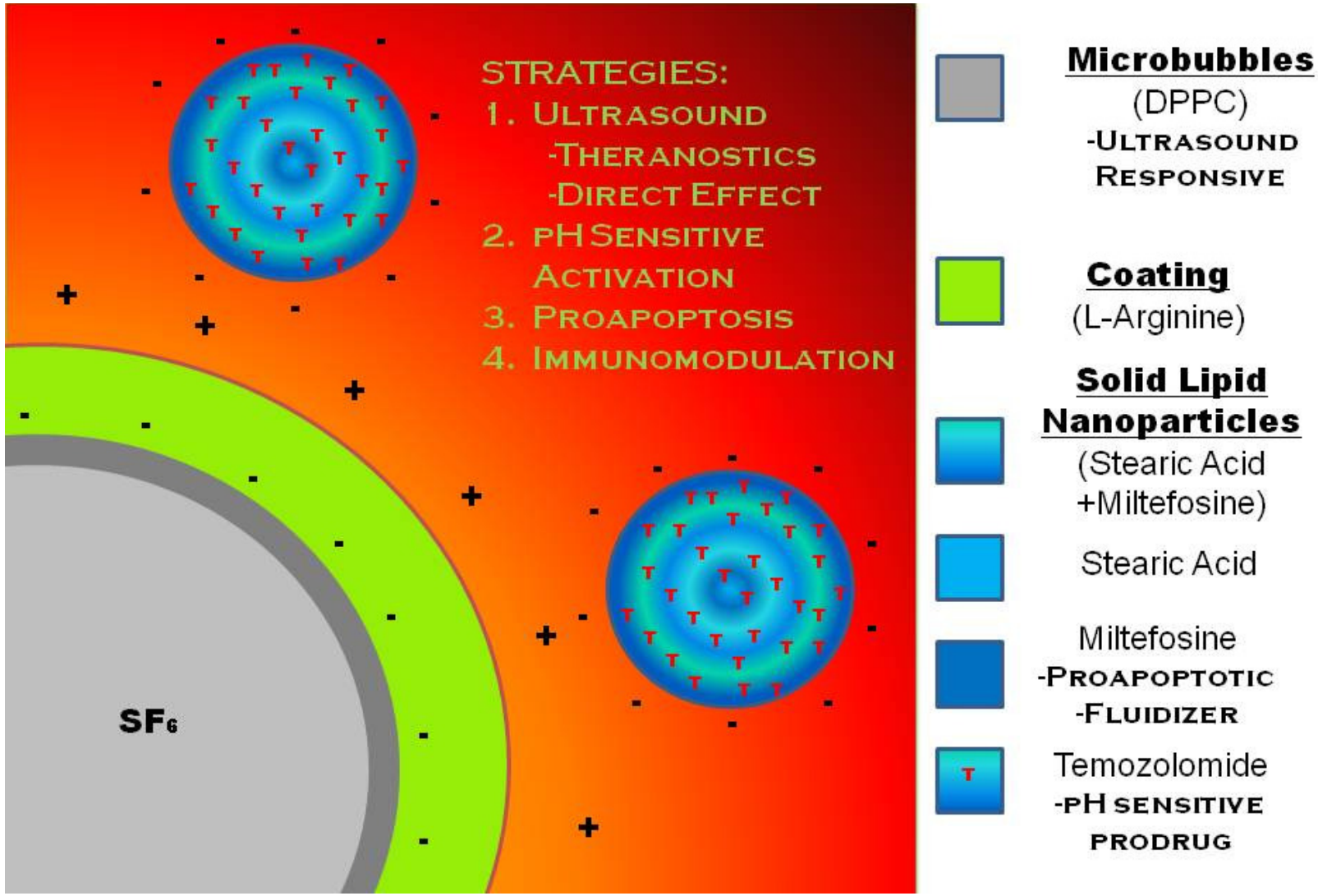
- Use of the prodrug TEMOZOLOMIDE



Source: Burger A, Abraham DJ. Burger's Medicinal Chemistry and Drug Discovery: Chemotherapeutic agents: Wiley; 2003.

- Alkaline pH of Glioblastoma

SCHEMATIC OF THE NANOCARRIER



ULTRASOUND CONTRAST AGENTS: MICROBUBBLES

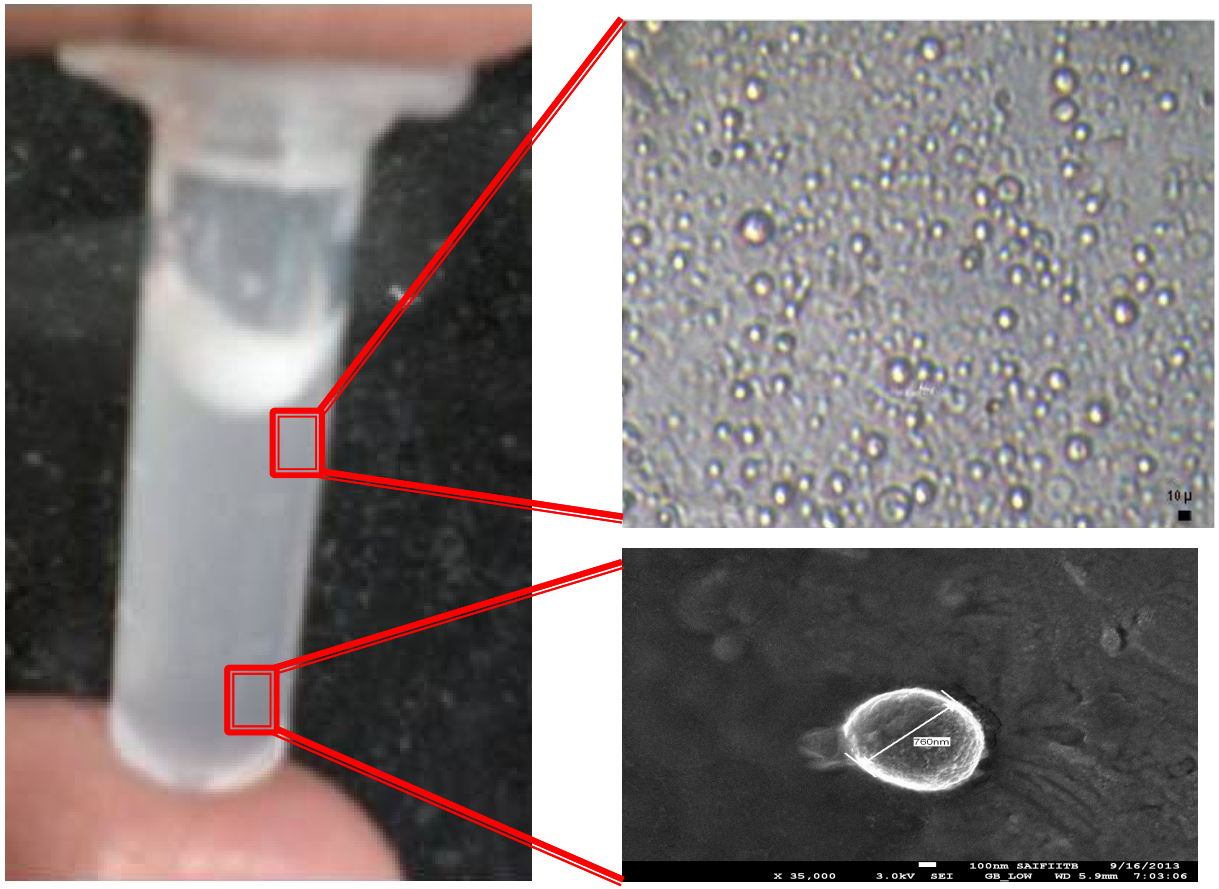
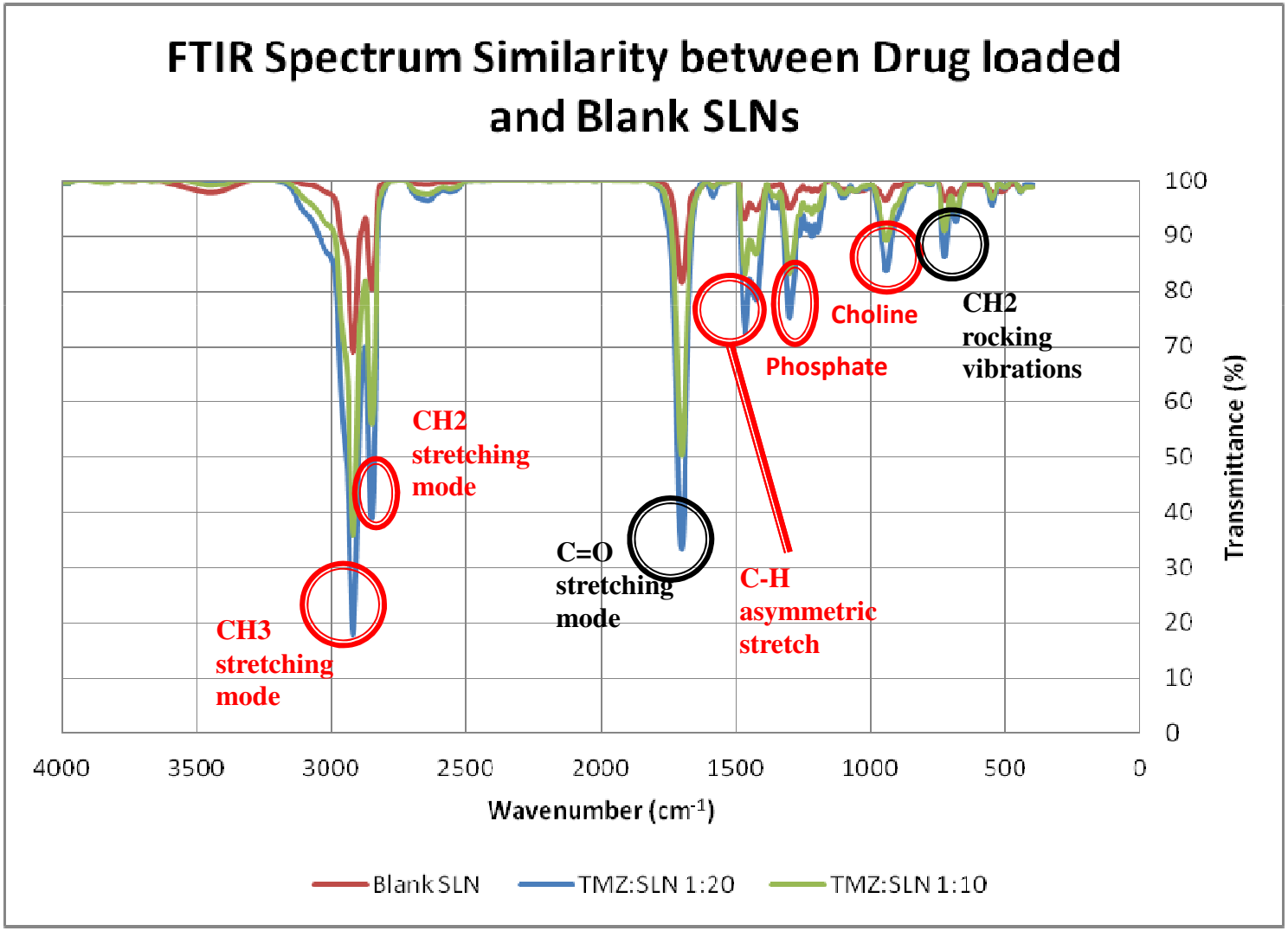
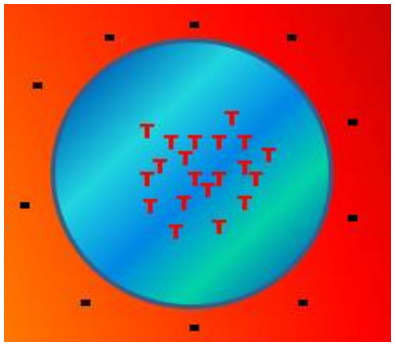


Figure: Gross appearance of the microbubble suspension showing two distinct layers. (1) Upper Layers containing the larger bubbles (Scale 10µm) (2)Lower layers containing the microbubbles (Scale 100 nm)

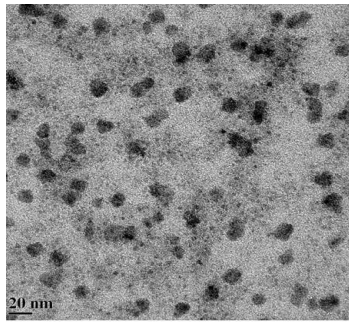
TEMOZOLOMIDE-LOADED SOLID LIPID NANOPARTICLES





Solid Lipid Nanoparticles
(Stearic Acid +Miltefosine)

Temozolomide
-pH SENSITIVE PRODRUG



FINAL STIMULUS RESPONSIVE PARTICLES

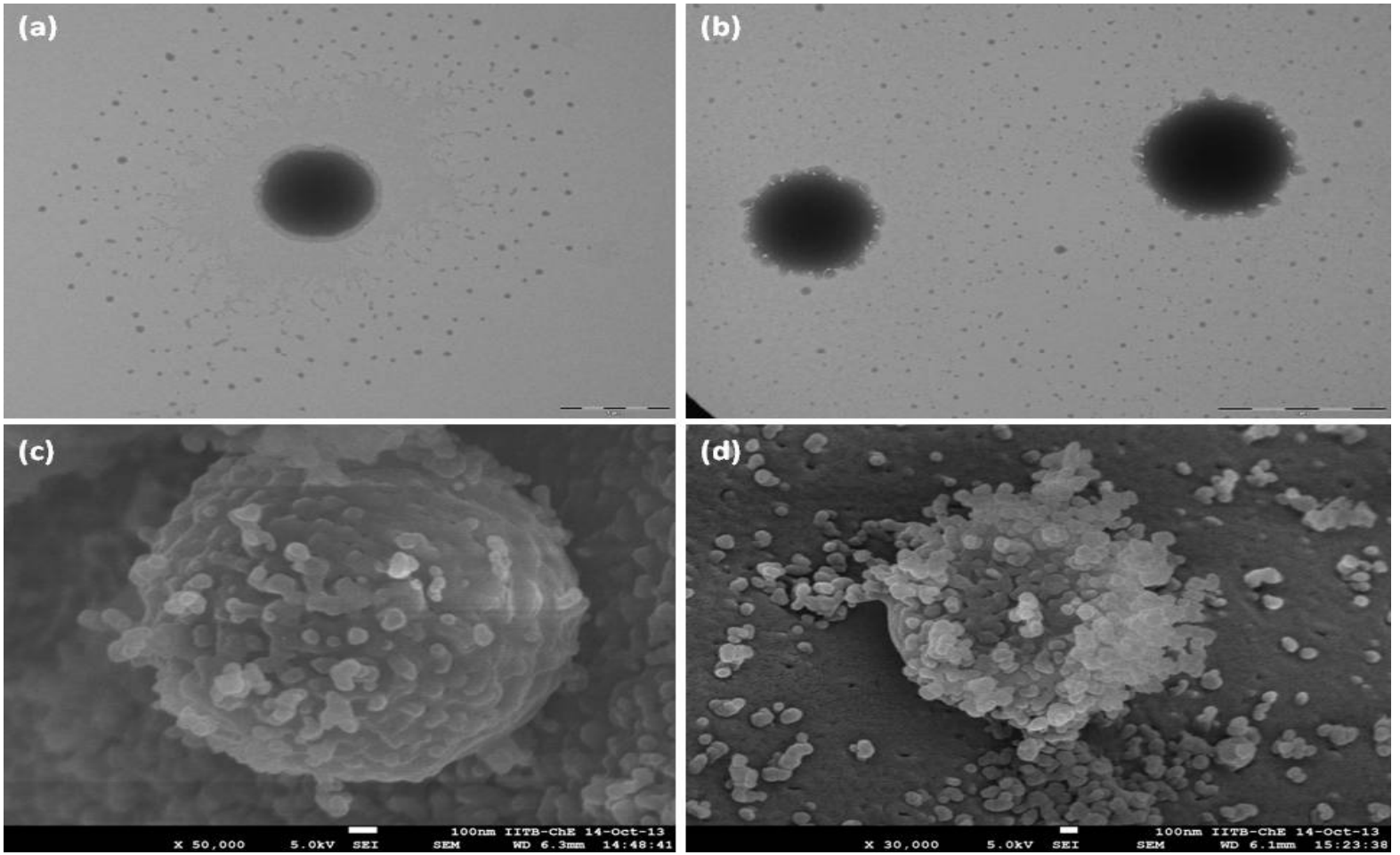


Figure: The formation of the proposed Microbubble- SLN constructs as seen in (a) and (b) Cryo TEM images and (c) and (d) Cryo FEG SEM images (Scale bars equal to 1µm in (a); 2µm in the (b); 100 nm in (c) and (d))

INTRANASAL DELIVERY: MUCOADHESIVENESS

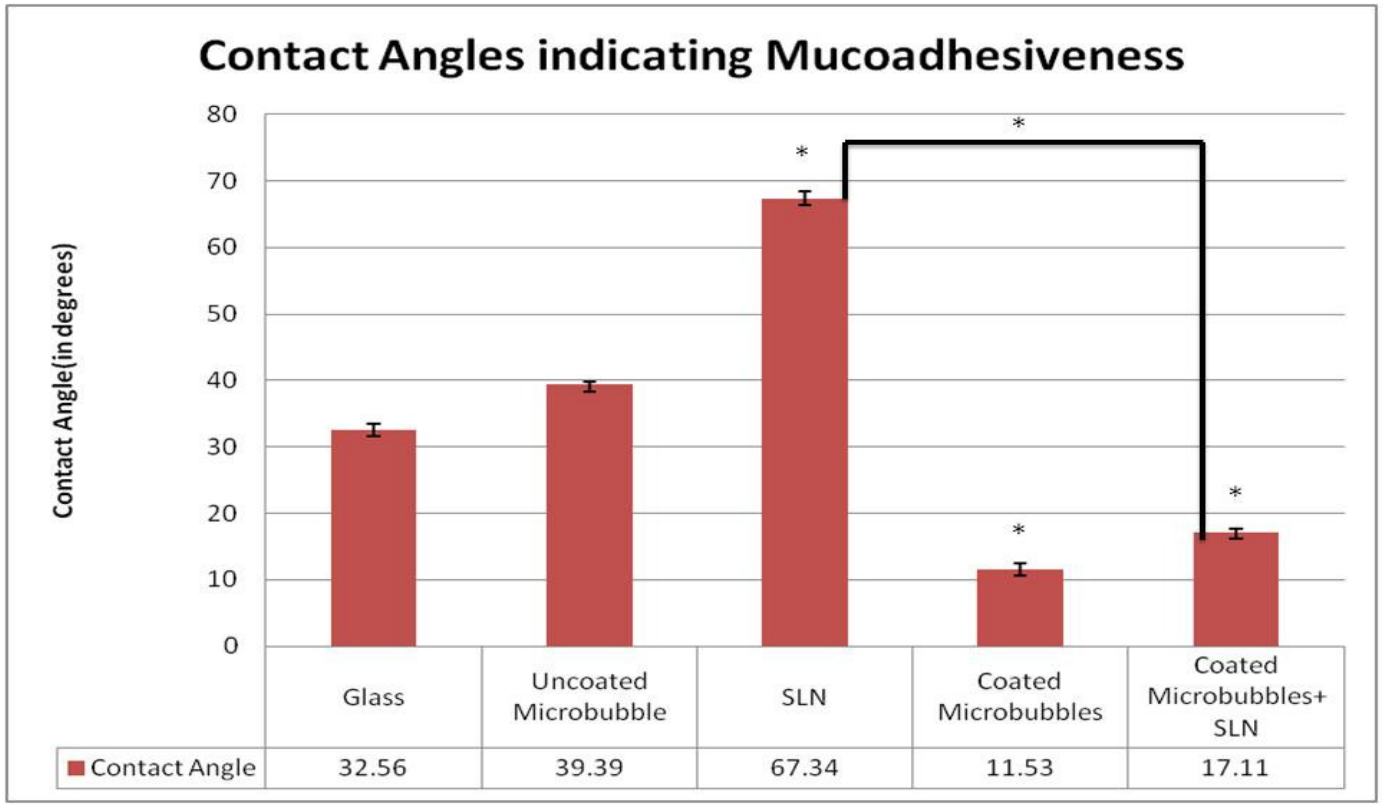


Figure: Contact angle measurements for determination of mucoadhesiveness. The values given indicate the mean contact angle and error bars indicate the standard deviation (* p value <0.0001 compared to glass). Also, significant difference shown (p value < 0.0001) between SLN and Coated microbubbles+SLN (Error Bar representing Standard Deviation)

DRUG CROSSING THE ARTIFICIAL BLOOD BRAIN BARRIER (PAMPA)

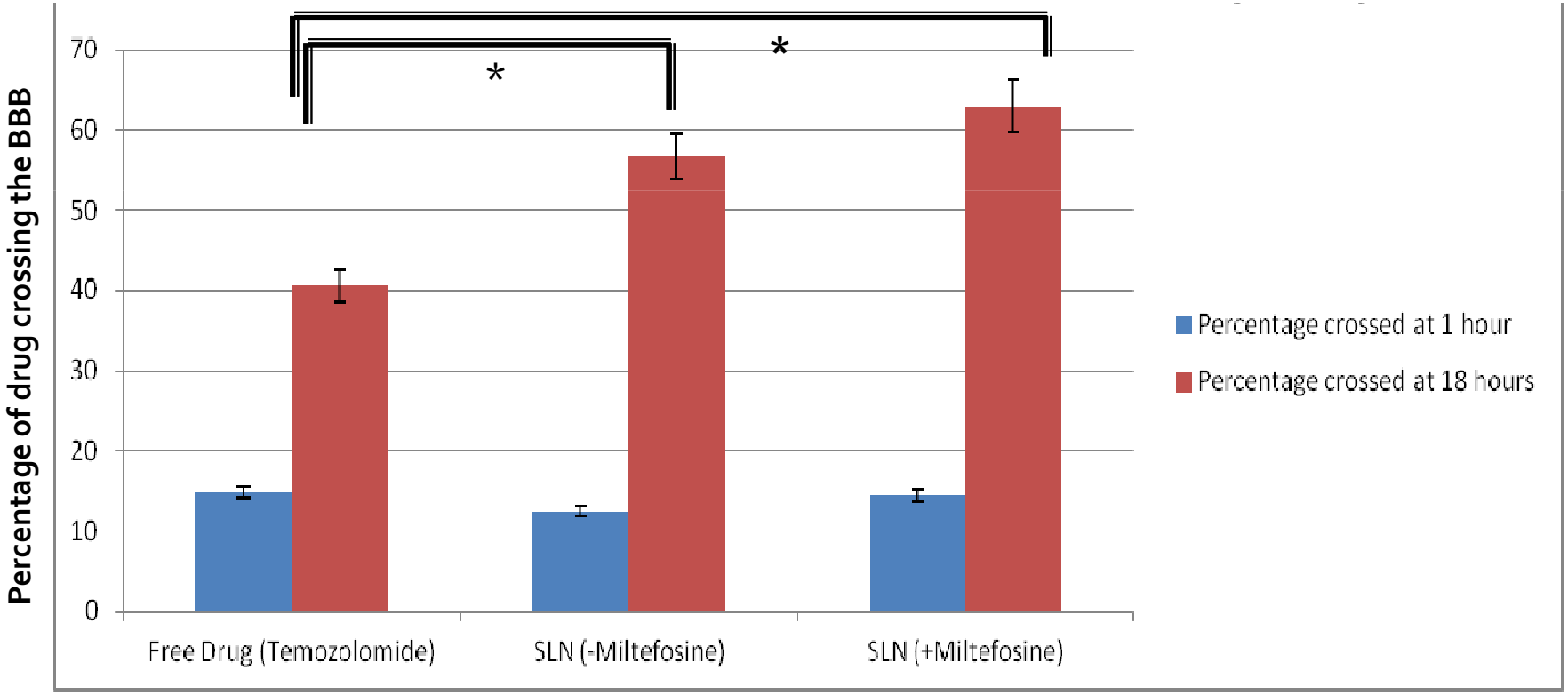


Figure: Temozolomide crossing the artificial BBB in 1 hour v/s in 18hrs for various formulations (* indicates significant difference, p-value <0.05) (error bars represent standard deviation)

THERAPY: SUSTAINED RELEASE

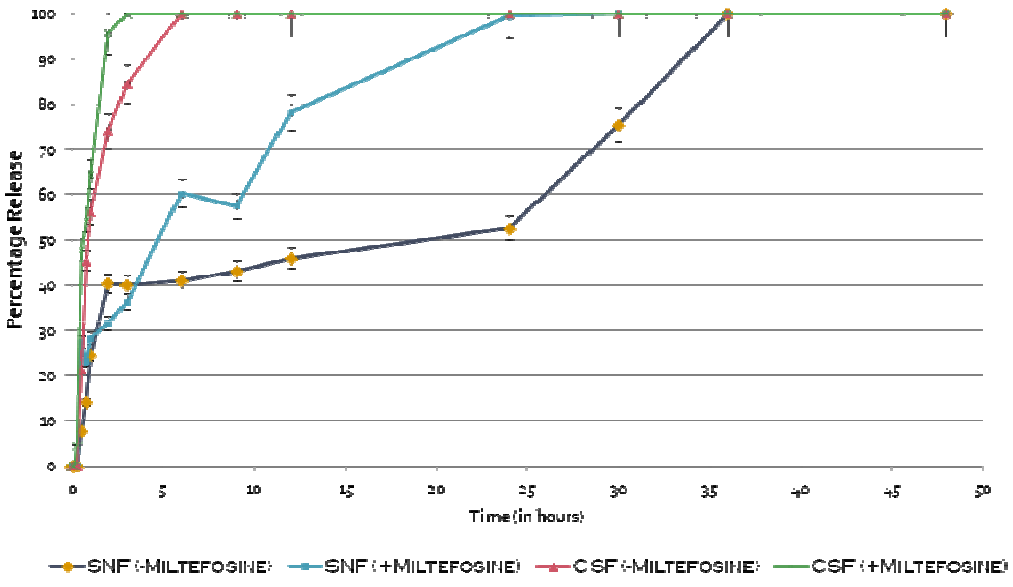


Figure: Sustained release of temozolomide from each of the solid lipid nanoparticles over time in Simulated Nasal Fluid and artificial CSF (* indicates p-value < 0.001) (error bars represent standard deviation)

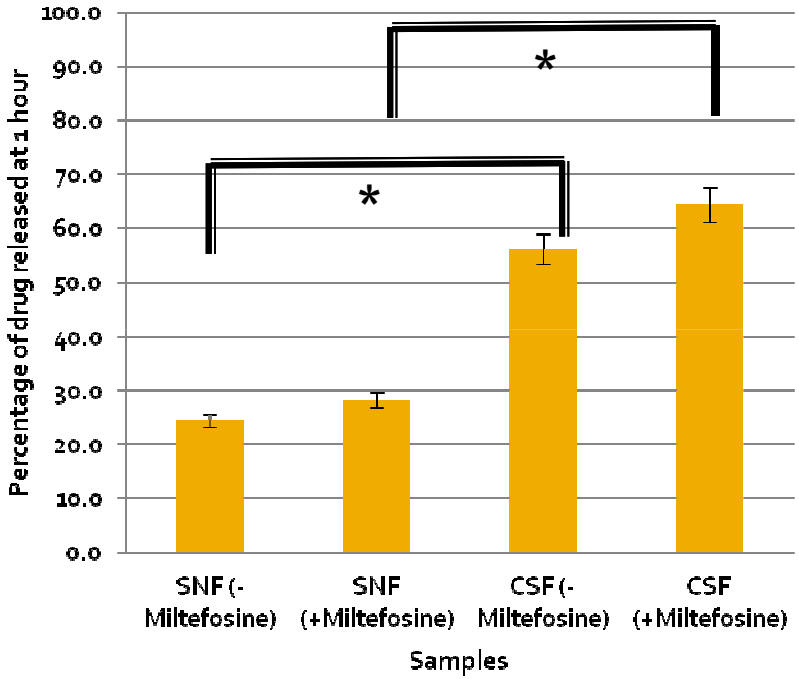


Figure: Drug release of temozolomide from each of the solid lipid nanoparticles over time in Simulated Nasal Fluid and artificial CSF at 1 hour (* indicates p-value < 0.001) (error bars represent standard deviation)

DISRUPTION OF NANOCARRIERS

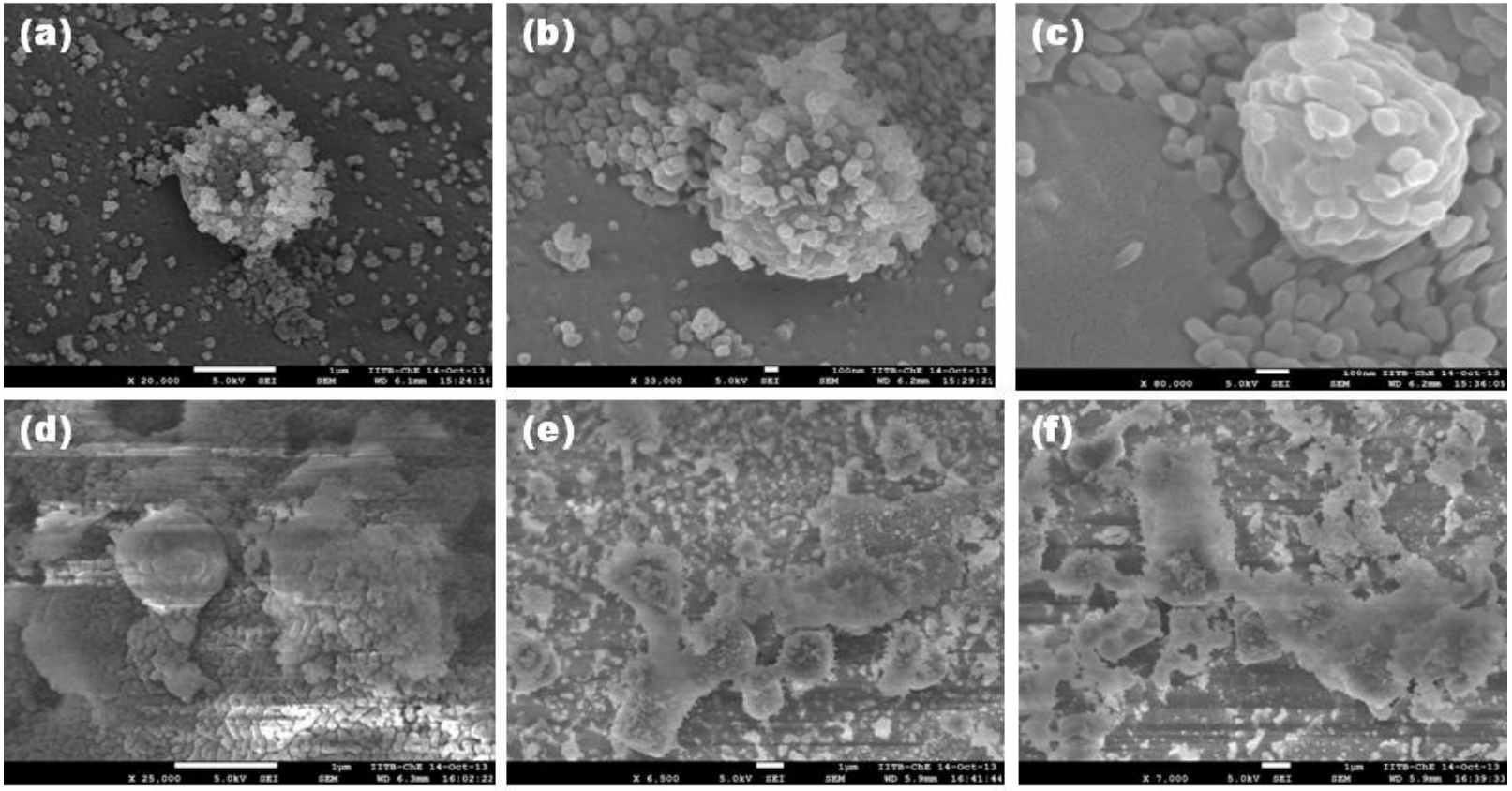


Figure : The Cryo FEG SEM images of SLN-loaded microbubbles prior to application of ultrasound (a) and after ultrasound application (b-f). Ultrasound was applied using a sonoporator probe of 1MHz frequency, 100 % duty cycle for 15 second at various intensities (in watt/cm^2) viz. (b) 0.2 W/cm^2 (c) 0.5 W/cm^2 (d) 1 W/cm^2 (e) 2 W/cm^2 (f) 3 W/cm^2

THERAPY: TRIGGERED RELEASE IN CSF

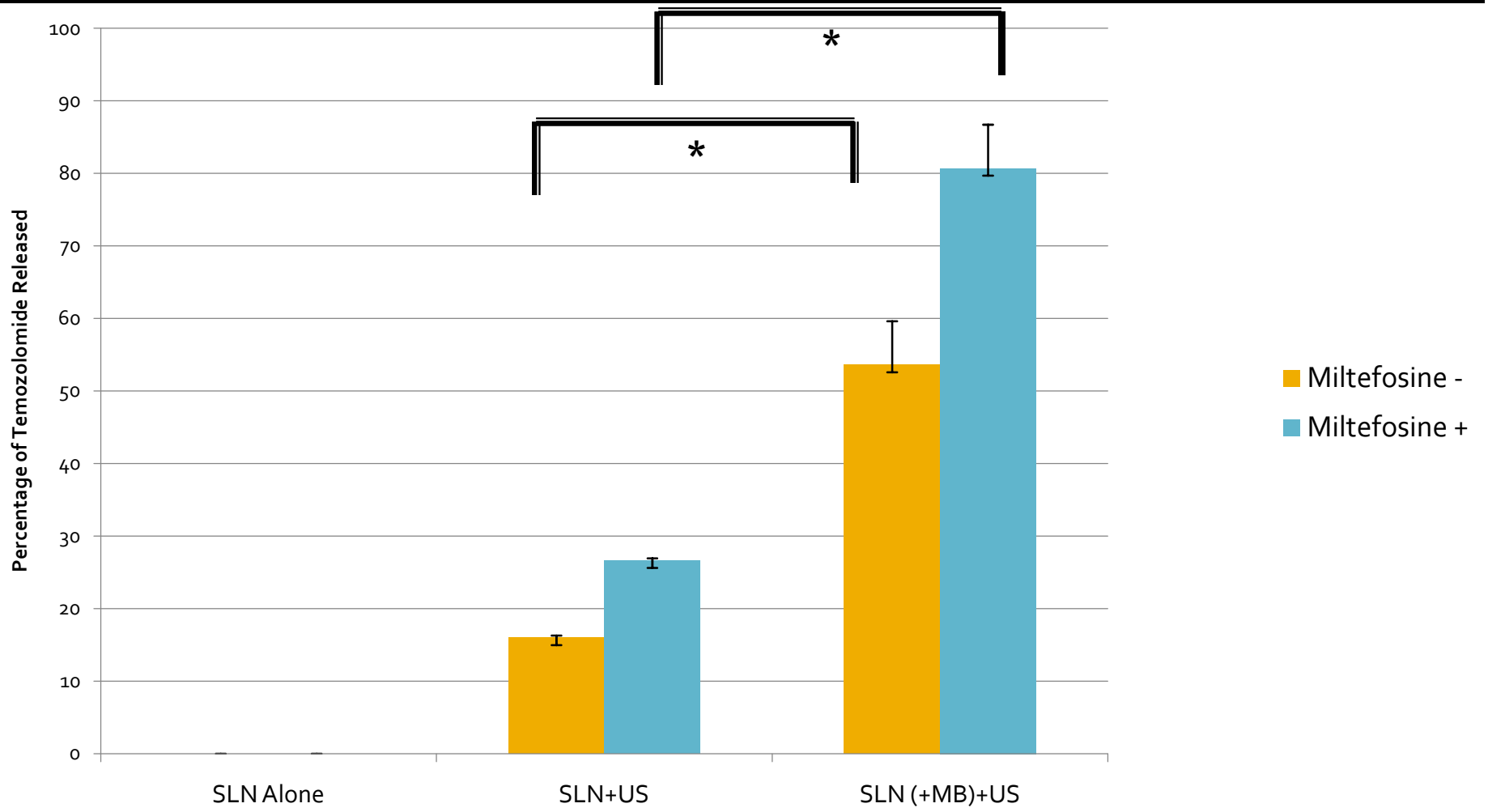
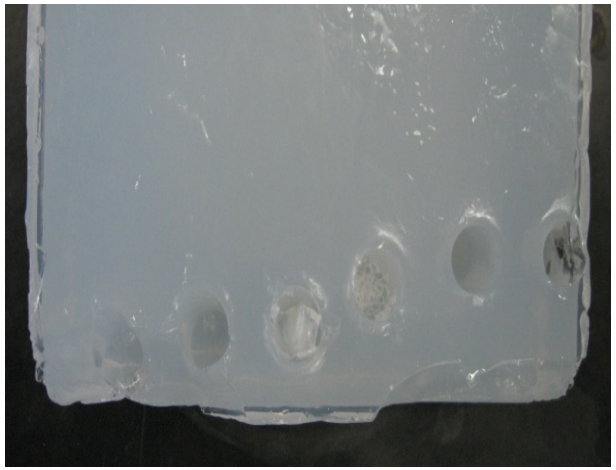
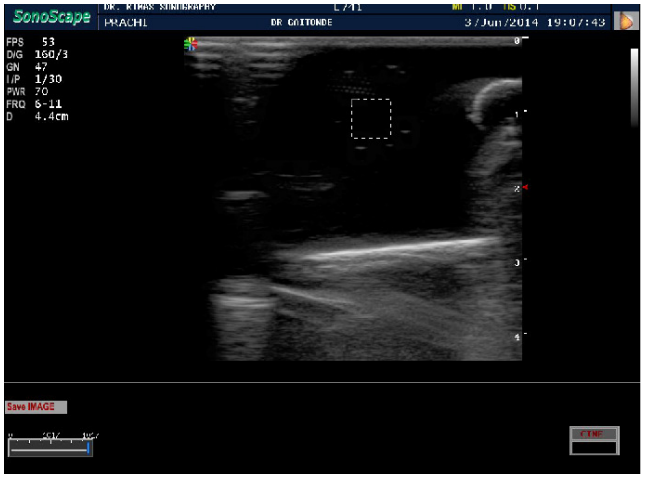


Figure : Temozolomide release from the drug delivery systems in the presence or absence of ultrasound and microbubbles for two different SLNs (* indicates significant difference, p-value <0.01) (error bars represent standard deviation)

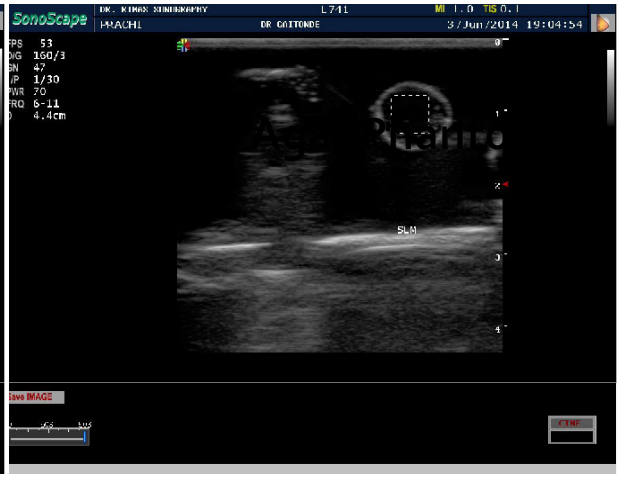
DIAGNOSTIC IMAGING: CLINICAL ULTRASOUND



Agarose Phantom



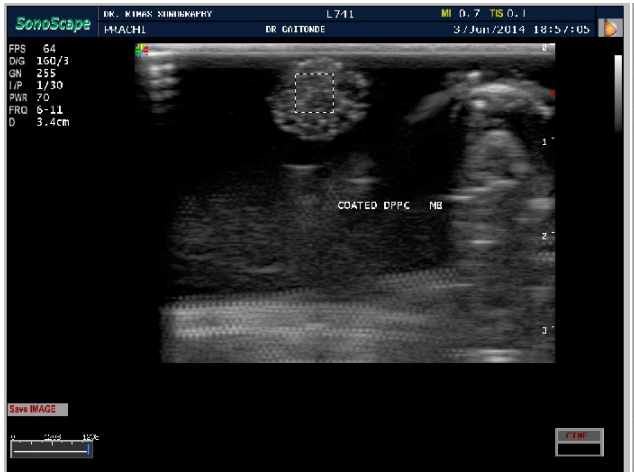
Degassed Water



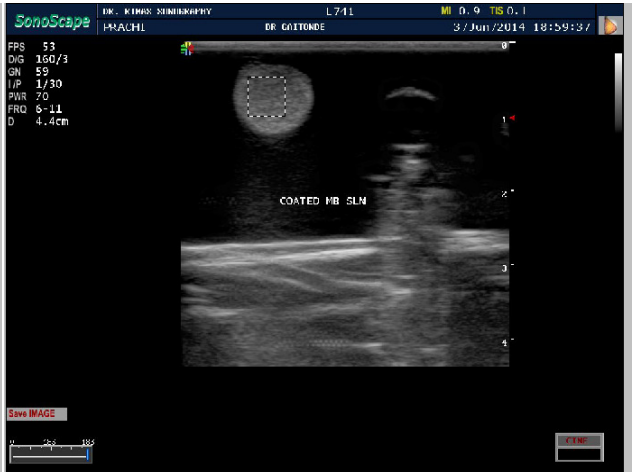
SLN



Microbubbles



Coated Microbubbles

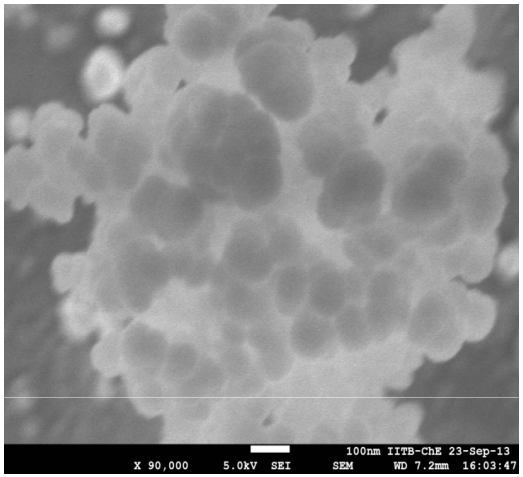


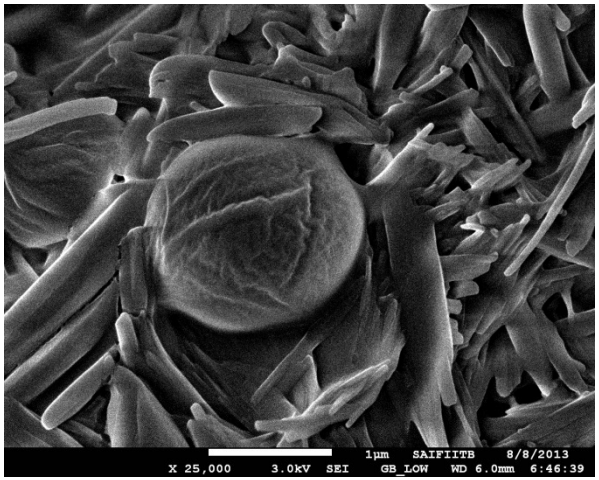
Final Particles

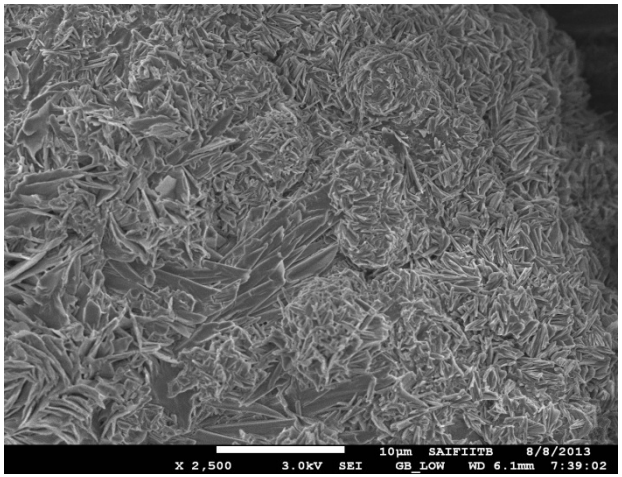
CONCLUSIONS & TRANSLATIONAL ASPECTS

- THERANOSTIC AGENT:
  -Stimulus Responsive Drug Delivery (THERApy)
  -DiagNOSTIC imaging: contrast agent
- Suitable for Intranasal Administration
- Targeted treatment- Triggered therapy
- Novel alternative for toxic and invasive treatments

THANK YOU!!!







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- Dr. Rima Mukherjee
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- Industrial Research and Consultancy Centre (IRCC)