Implantable Biomedical Devices for Localized Cancer Drug Delivery

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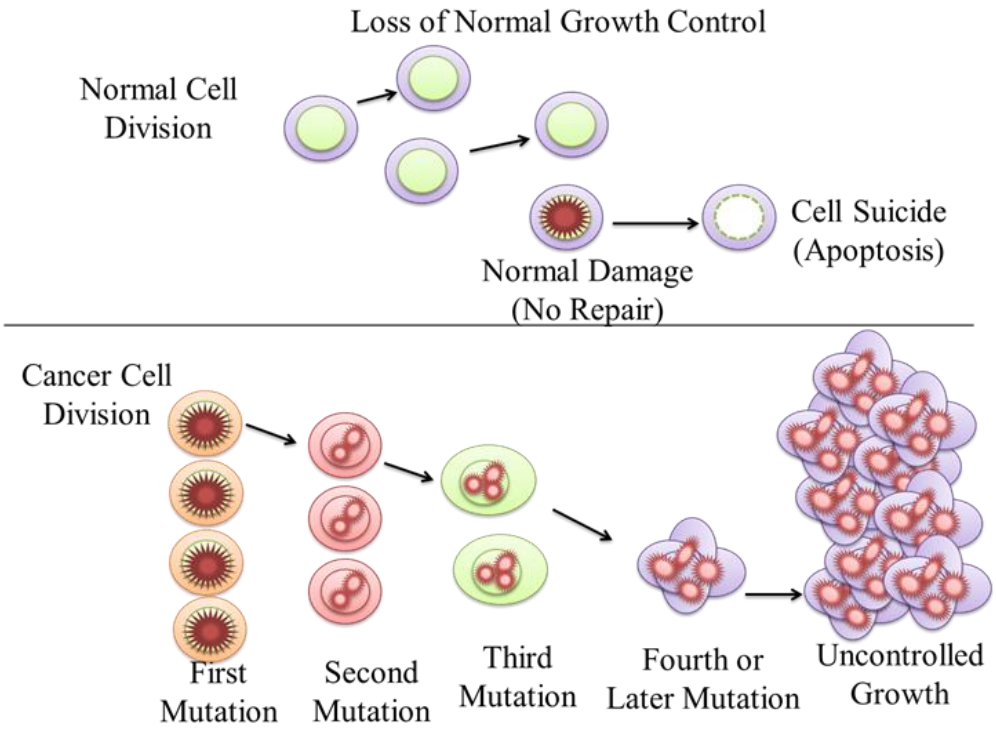
PAMI Workshop

Department of Materials Science and Engineering

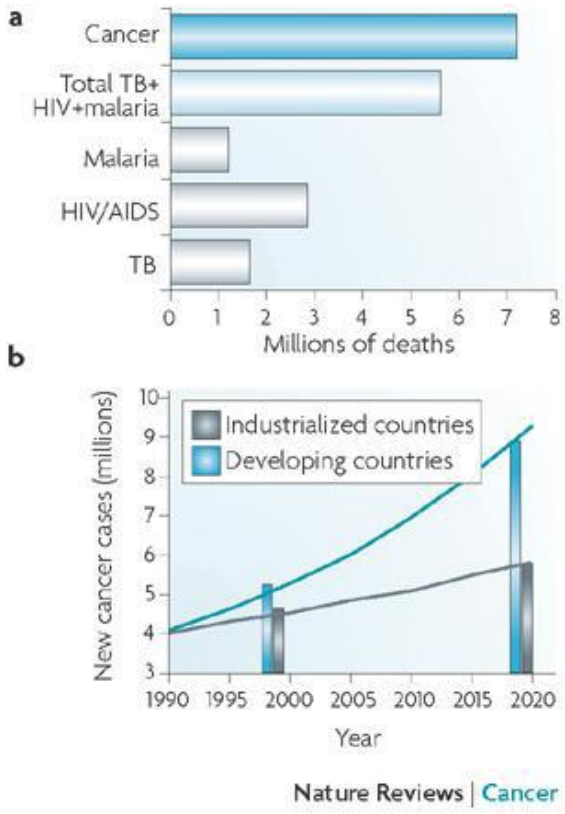
Background and Statistics

- Cancer is a group of diseases characterized by uncontrolled growth and spread of abnormal cells (Jemal et. al., 2008)
  - Caused by the malfunction of specific genes that regulate cell growth and division



- Cancer is the second leading cause of death in the world (David, 2008; Mackey et. al., 2004)
- Early detection and treatment are the keys to improved outcomes

Cancer Statistics (WHO, 2012)



2008

- WHO estimates that there were 84 million cancer deaths in 2011 (22% of all deaths)
- Projection of 26.4 million new cases with 17 million deaths by 2030
  - **cancer will become the leading cause of death**
- Breast cancer incidence is about 26% of all cancers with a mortality rate of 15%
- Similar current statistics in Africa (22% of all deaths) but rising incidence
- It is very unusual for most cancers, such as breast cancer, to present clear symptoms at their early stages
  - late detection and treatment are often conducted when the cancer reaches a metastasis stage

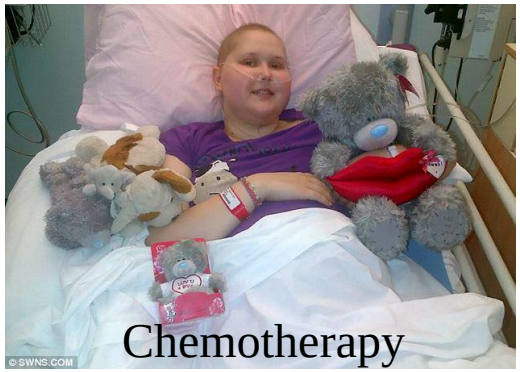
Conventional Treatments

http://www.mymedholiday.com/blog/2014

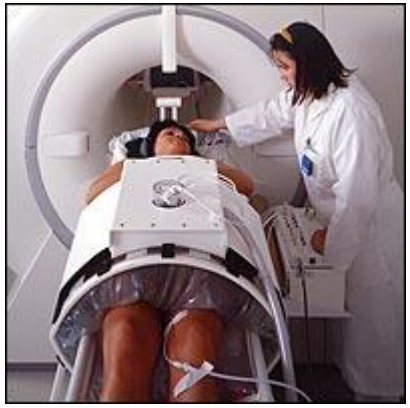
- ❑ **Chemotherapy**
- ❑ **Radiationtherapy**
- ❑ **Surgery**
- ❑ **Homone Therapy**
- ❑ **Hyperthermia**

Methods have side effects!!!!

- ❑Lacking site targeting
- ❑High concentrations of drugs
- ❑Spread of disease cells



(cheskadiva.blogspot.com)



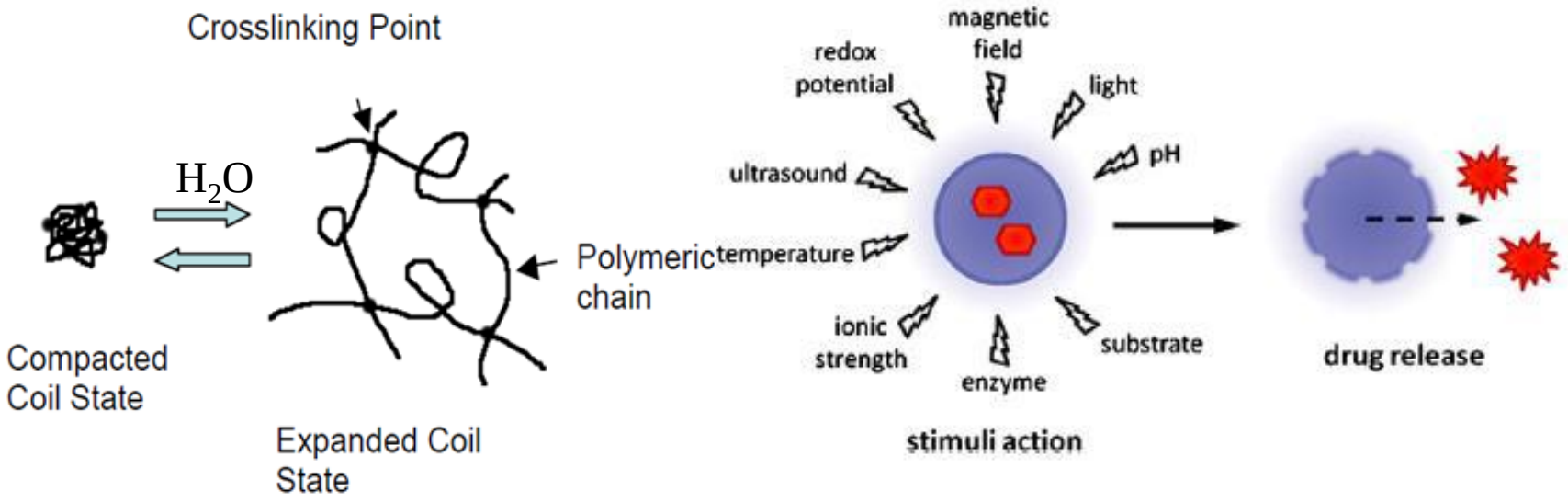
European Society for Hyperthemic Oncology (patent)

Radiation Therapy

(National Hospital, Abuja-Nigeria)

Hydrogels In Drug Delivery

- Smart hydrogels have been studied to harness their swelling behaviors and the release of fluids from the polymer matrix
  - in response to environmental stimuli such as temperature, pH, electric field and solvent composition (Afrassiabi, 1987; Schmaljohann, 2006; Farmer et al., 2008).

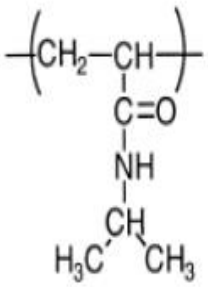


Thermosensitive P(NIPA)-based Hydrogels

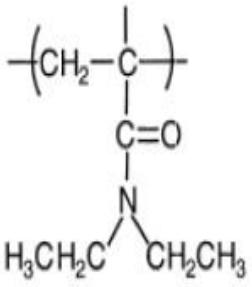
- P(NIPA) is a 3-D polymeric material with enormous water-swollen network in aqueous medium (Peppas, 1987; Hoare and Kohane, 2008)
- **Forms Cross-links** which offer the network structure and physical integrity

Temperature Sensitive Polymers

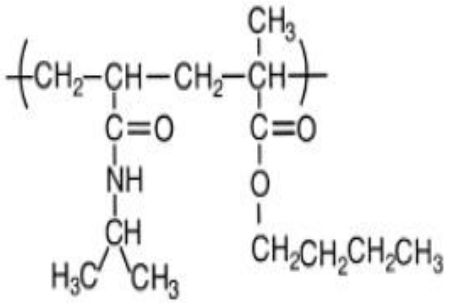
- **Objectives:**
  - Polymerization,
  - Solvent Composition
  - LCSTs and
  - Swelling Kinetics



Poly(N-isopropylacrylamide) (PNIAAm)

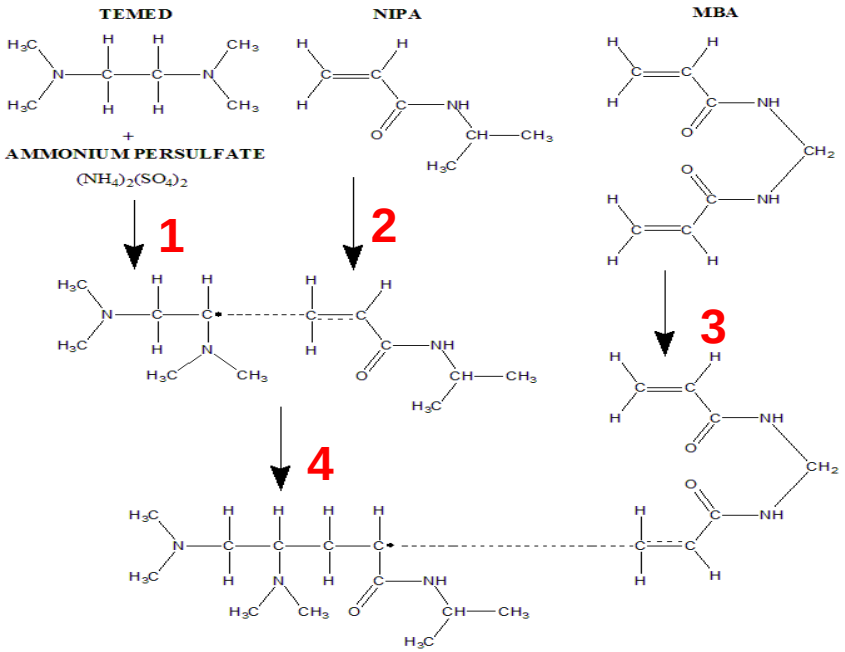


Poly(N,N-diethylacrylamide) (PDEAAm)



P(NIAAm-co-BMA)

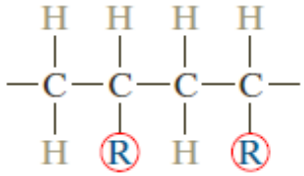
Free Radical Gel Polymerization



1. Initiation (APS as radical initiator)
2. Propagation
3. Crosslinking with MBA
4. Polymerized gels

- Acrylamide (hydrophilic monomer)
- Butyl-Methylacrylate (hydrophobic)

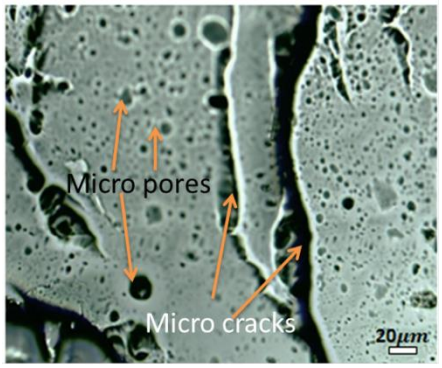
- **TEMED (catalyst) decomposes the persulfate ion to give a free radical**
- The AM monomer usually polymerizes in a head-to-tail manner into long chains which contributes to building growing chains

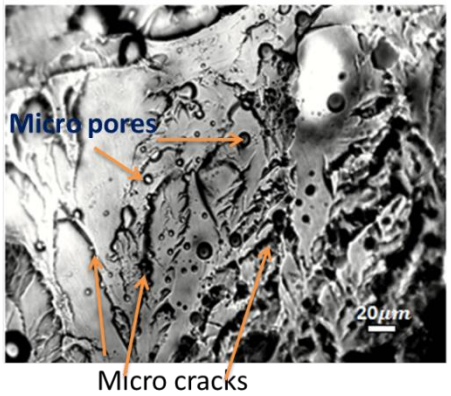


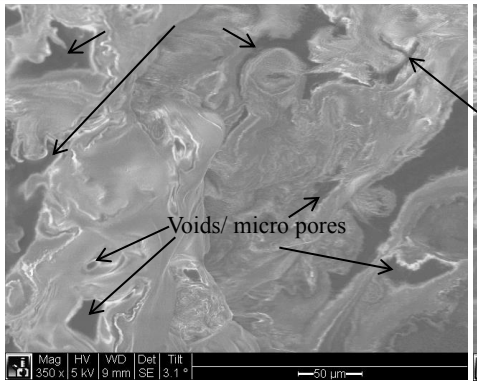
head-to-tail configuration

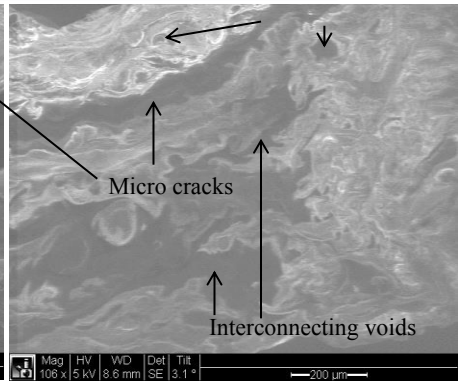
Gel Morphologies

(A) (B)



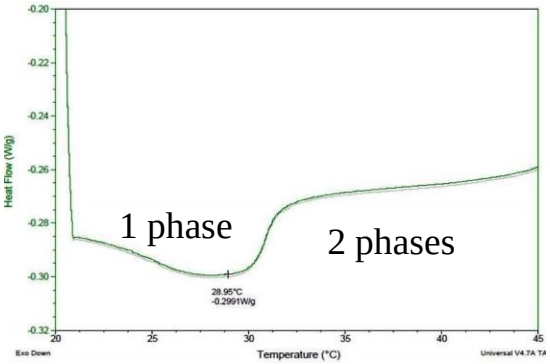




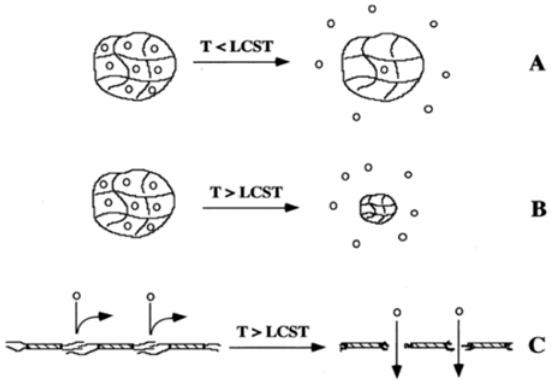


- The macro-porosity of P(NIPA)-based hydrogels depends on:
  - the phase separation that occurs during cross-linking
  - gel synthesis parameters
  - temperature and crosslinkage
  - monomer concentration

DSC of P(NIPA)-BMA



Phase Diagram for P(NIPA)-based Hydrogel in Water

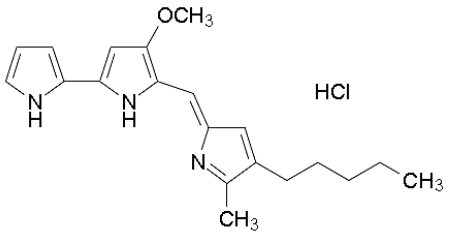


T = application temperature

LCST = Solution temperature

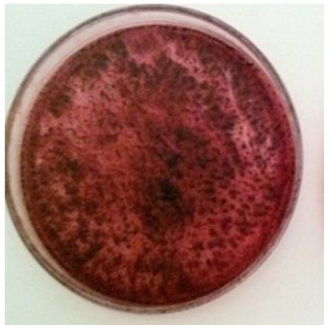
Drug molecules will be release from hydrogel if T > LCST through the loosely bonded gel structure or will not if T < LCST

Prodigiosin: Anticancer Drug



Chemical Structure

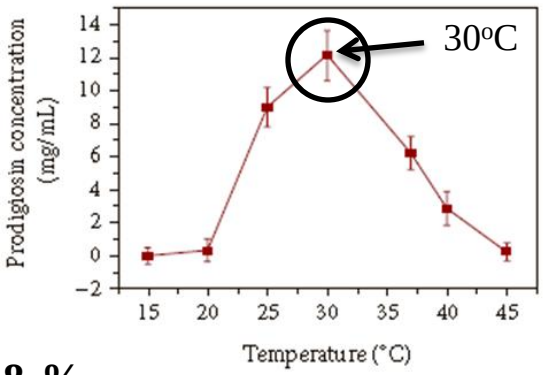
- The pigment is anticancer
- Immunosuppressant
- Antifungal (Williamson et al, 2007)

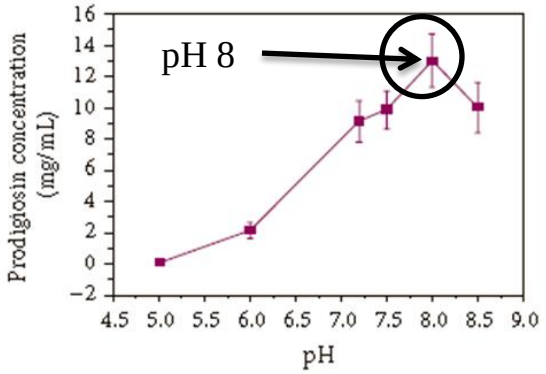


synthesized from *Serratia marcescens*

Fractions of Purified Prodigiosin (SHESTCO)

- *Serratia marcescens* is a gram negative, non-motile, bacterium

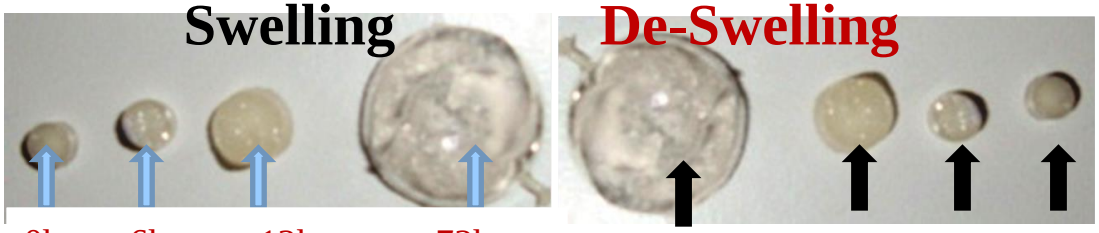




- **The purity of the sample was 92.8 % (HPLC)**
- **Used for Swelling Kinetics Studies**

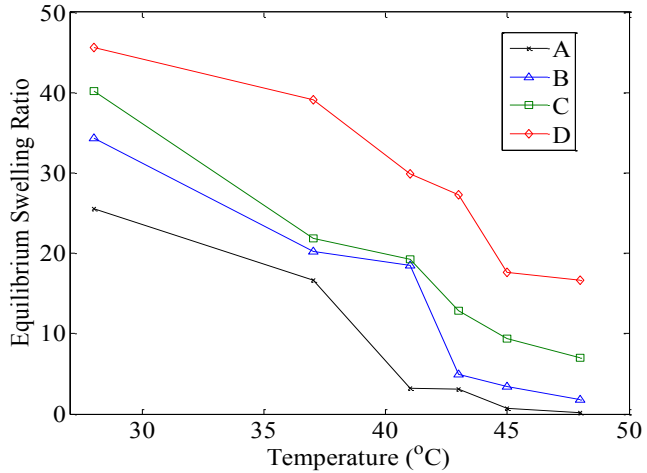
- Optimum conditions required for maximum production of prodigiosin at time 30 h

Swelling and De-swelling Kinetics

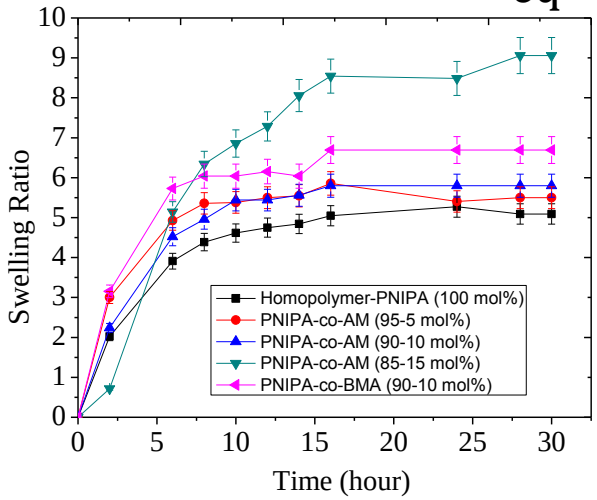


$$SR_A = \frac{M_t - M_o}{M_o} \quad (1)$$

$$V_{eq} = \frac{D^2}{D_o^2} \quad (2)$$



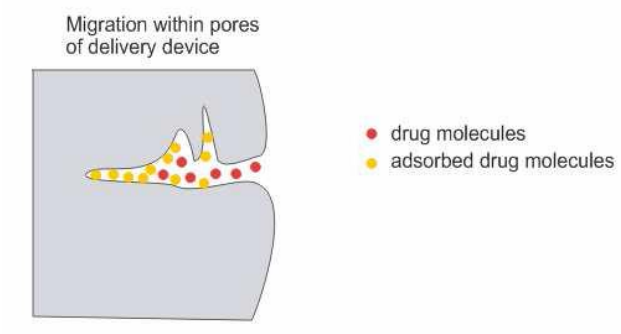
Reversed Temperature response to SR

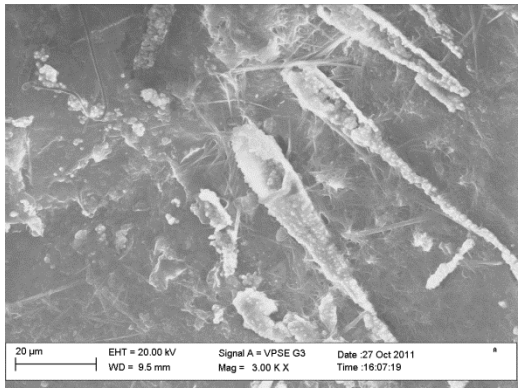


- There was significant difference on the effect of temperature on the gel swelling
- There was no significant difference on the effect of the different polymer ratios on SRa and Veq of P(NIPA)-based hydrogels

Diffusion in Polymeric Materials

- Our interest is the diffusive motion of small foreign molecules (e.g. H_2O, pharmaceutical agents)
- A polymer's permeability and absorption characteristics relate to the degree to which foreign substances diffuse into the material



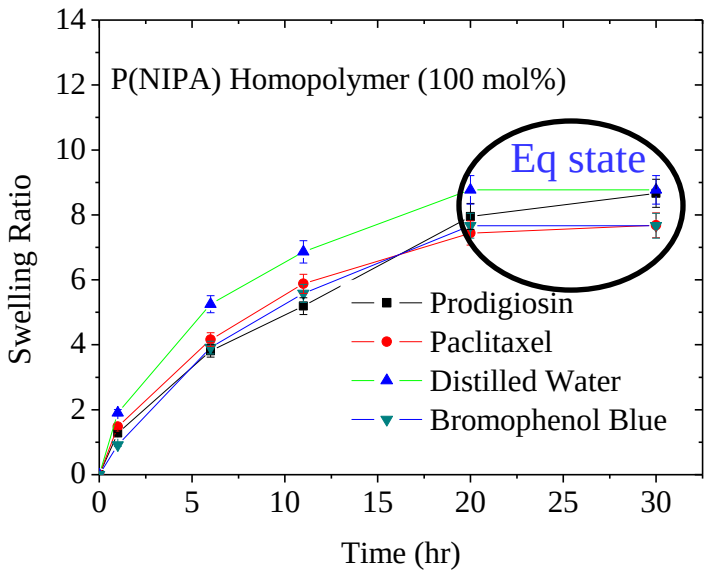


- **Fick's first law:**

$$J = P_M \frac{\Delta P}{\Delta x}$$

- Penetration of foreign substances can lead to swelling (degradation of the mechanical and physical properties)
- **Rate of diffusion**: Amorphous region, voids, foreign molecule size/chemical inertness, dissolution of the molecular species, *permeability coefficient*

Total free energy change upon swelling



$$\Delta G = \Delta G_{el} + \Delta G_{mix} + \Delta G_{ion} \qquad (3)$$

Flory and Rehner, 1943a; Flory, 1950 and Flory, 1953

- Differentiating eqn (3) wrt the number of water molecules in the system at constant temperature (T) and pressure (P)
  - **change in chemical potential (CP)**

$$\mu_1 - \mu_{1,0} = \Delta\mu_{el} + \Delta\mu_{mix} + \Delta\mu_{ion} \qquad (4)$$

μ_1 is the CP of the swelling agent within the gel and $\mu_{1,0}$ is the CP of the pure fluid

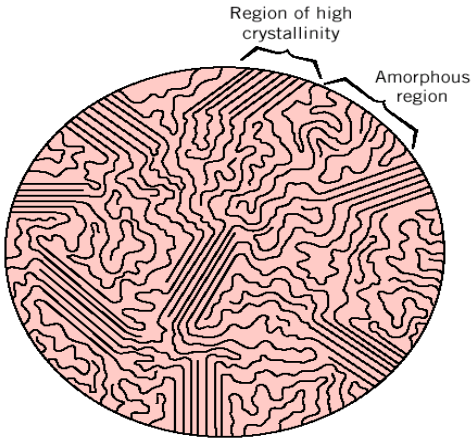
- The CP provides the thermodynamic force that drives net diffusion down a concentration gradient ($\Delta G = 2.303RT\ log\frac{\mu_1}{\mu_{1,0}}$) (J. D. Rawn,1989)
- At equilibrium state, the sum of the osmotic pressure equal to zero
- **There was no significant difference on the effect of the drugs on gel swelling ratios**

Strain on Hydrogels Due to Swelling

- The strain, ε on the gels at any time during the swelling was:

$$\varepsilon = \frac{l - l_o}{l_o} \qquad (5)$$

where l is the length at any time and l_o is the initial length



Gel Code	Prodigiosin (ε)	Distilled Water (ε)
A	0.44 ± 0.02	0.29 ±0.02
B	1.08 ±0.05	1.04 ±0.05
C	1.35 ±0.07	1.22 ±0.06
D	1.73 ±0.04	1.28 ±0.06

[NIPA]N-Isopropylacrylamide, [AM]Acrylamide, Gel codes; [A]P(NIPA) Homopolymer (100 mol% of P(NIPA)), [B]P(NIPA-co-AM) (95:5 mol%), [C]P(NIPA-co-AM) (90:10 mol%) and [D]P(NIPA-co-AM) (85:15 mol%).

- Great extensions due to elastic retroactive forces of the polymer chains
- No significant differences in ε due to PG/DW (p-value = 0.12) and polymer ratio (p-value = 0.99) after 72 hrs

Implications/Contributions from Swelling Kinetics Project #1

- The extent to which a polymer network swelled was structured by the elastic retroactive forces of the polymer chains as well as the thermodynamic compatibility of the polymer and the drug molecules
- When P(NIPA) is heated above its LCST in solution, it undergoes a reversible phase transition from a swollen hydrated state to a shrunken dehydrated state, thereby losing about 90% of its mass
- Controlled release of drugs could be managed using a heat trigger mechanism to heat up drug loaded gels to their LCSTs
- The knowledge of gel swelling kinetics provided the understanding of the network structure of the gels and their capacity to function as drug carriers
- Hydrogels offer poor mechanical properties (low strength and low modulus), especially in the swollen state
- Further work is needed to explore new ways of using P(NIPA)-based hydrogels for control drug delivery **(to avoid initial burst & structural failure**)

Project #1

Swelling Characteristics of P(NIPA)-based Hydrogels with Prodigiosin for Localized Cancer Drug Delivery

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Swelling of poly(N-isopropylacrylamide) P(NIPA)-based hydrogels with bacterial-synthesized prodigiosin for localized cancer drug delivery

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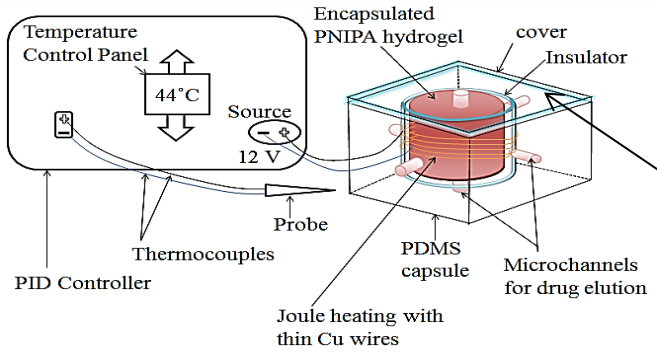
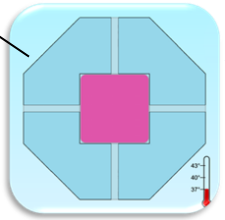
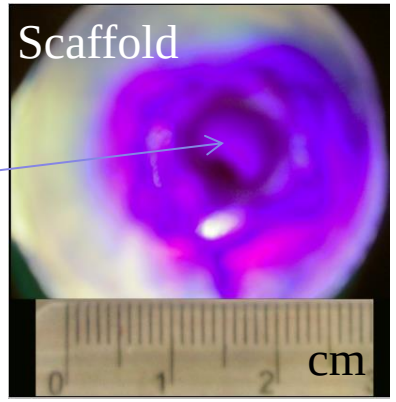
Drug Release from Device @ 37˚C

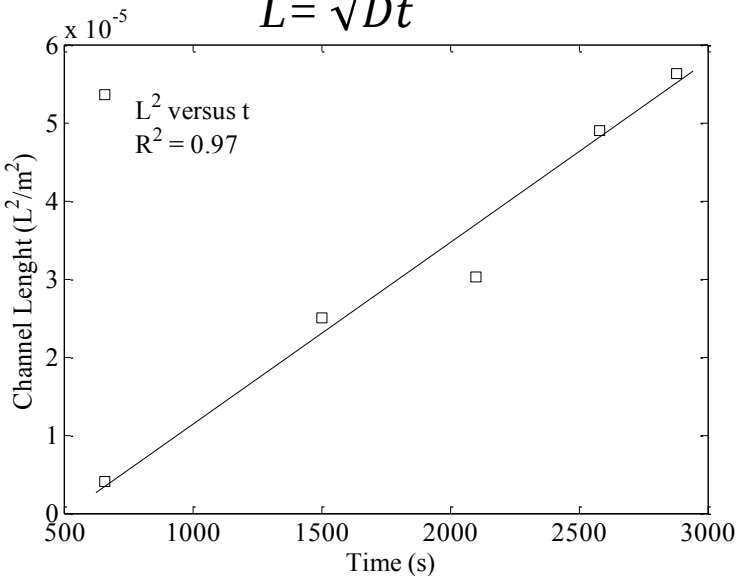


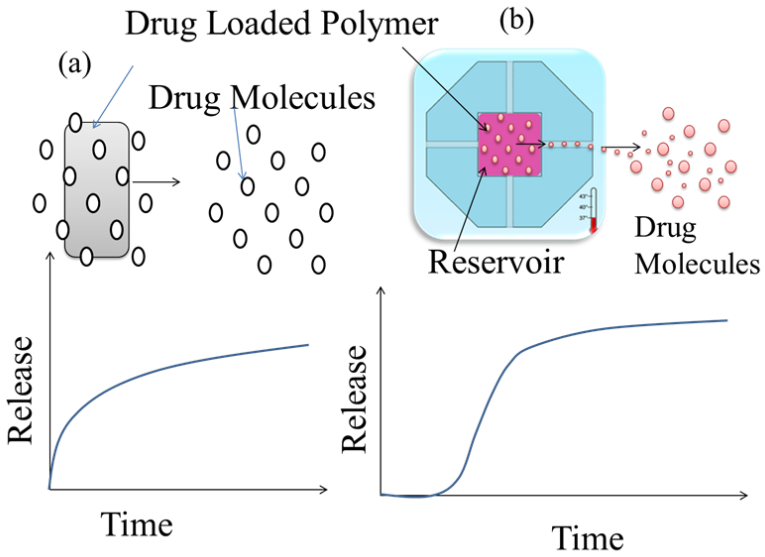




$L = \sqrt{Dt}$

$D^{eff} = 2.0 \times 10^{-8}\ m^2/s$

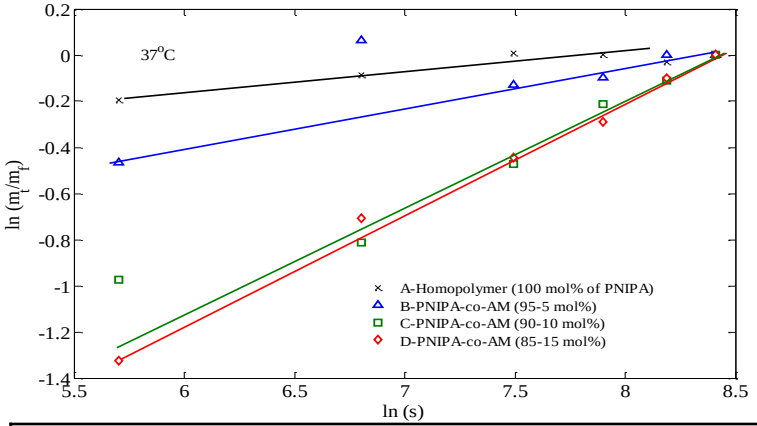




- **Drug Release-Simple diffusion and**
- **viscoelastic behavior of the swollen gels**

Determination of n, D, and Ea @ 37°C

- $\frac{m_t}{m_i} = 4\left(\frac{Dt}{\delta^2}\right)^n \quad (6a)$ (Peppas, 1985, Siepmann and Peppas, 2001; Hedeenqvist et al., 1996).
- $\ln\left(\frac{m_t}{m_i}\right) = \ln k + n \ln t \quad (6b)$
- The diffusion coefficient: $D = \frac{k\pi\delta^2}{4}$

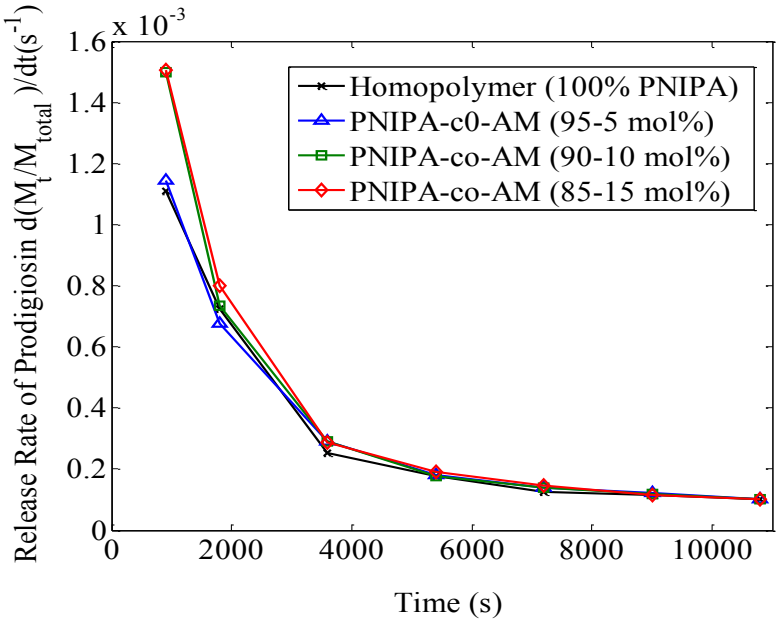


Gel Code	Release exponent (n)	Diffusion Coefficient, D (m^2/s)
A	0.5	3.6×10^{-9}
B	0.6	9.7×10^{-10}
C	0.6	9.7×10^{-10}
D	0.7	1.4×10^{-9}

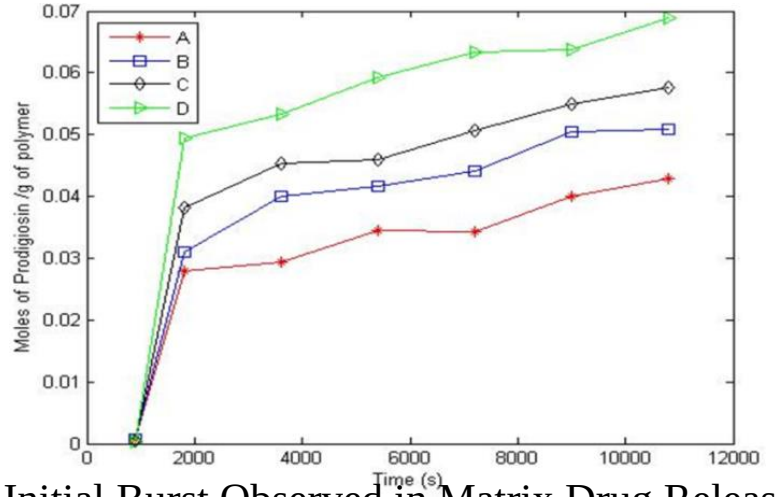
Release Exponent			**Drug Release Mechanism**
Slab	Cylinder	Sphere	
0.5	0.45	0.43	Controlled Diffusion
0.5<n<1.0	0.45<n<0.89	0.43<n<0.85	Anomalous Transport
1.0	0.89	0.85	Controlled Swelling

Drug Release Rate

$$\frac{dM_t}{dt} = 2M_{total}\left(\frac{D}{\pi\delta^2 t}\right)^{1/2} \qquad (7)$$



- Drug Release was exponentially time dependent
- Initial Burst Effect can be controlled by using microchannel device



- Initial Burst Observed in Matrix Drug Release

Activation Energy of Gels

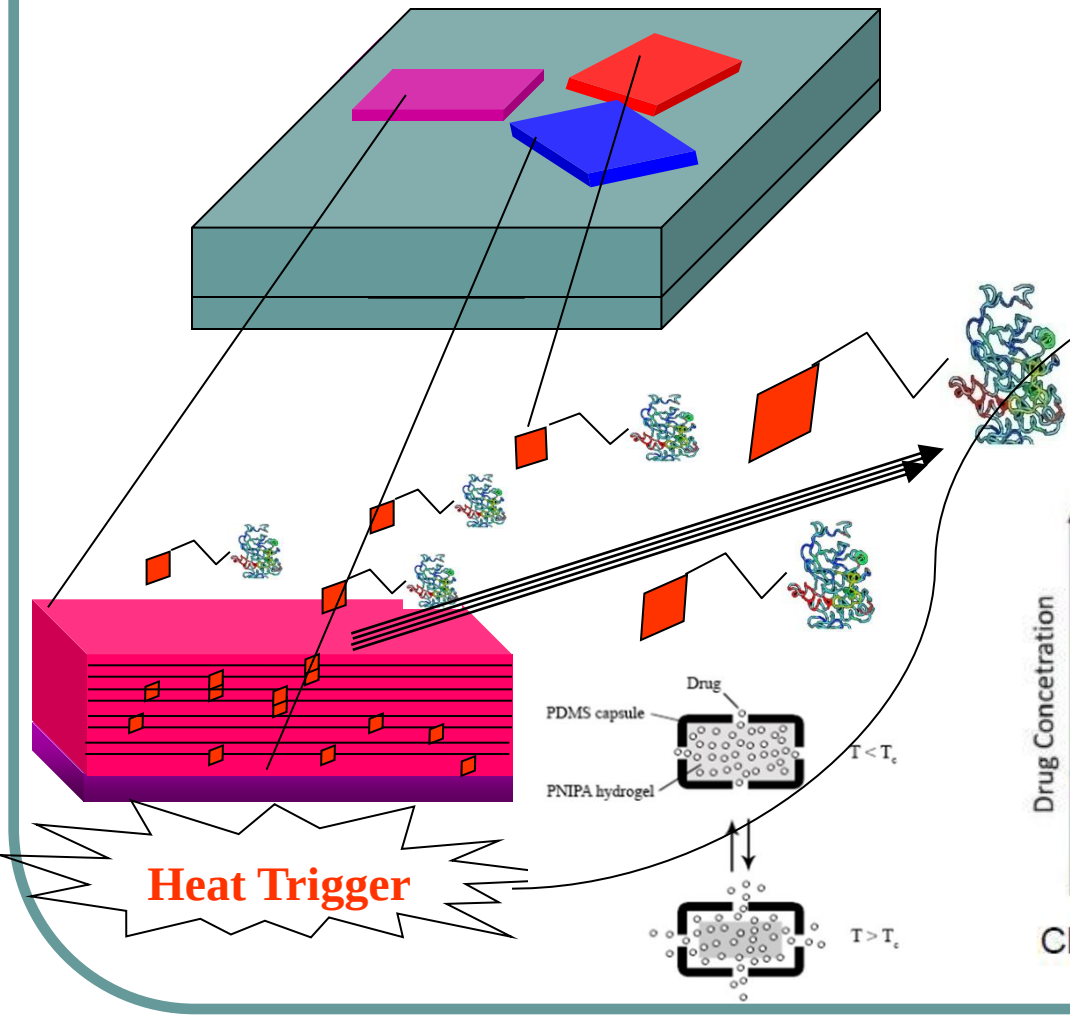
$$D = D_o exp\left(\frac{-E_a}{RT}\right) \qquad (8)$$

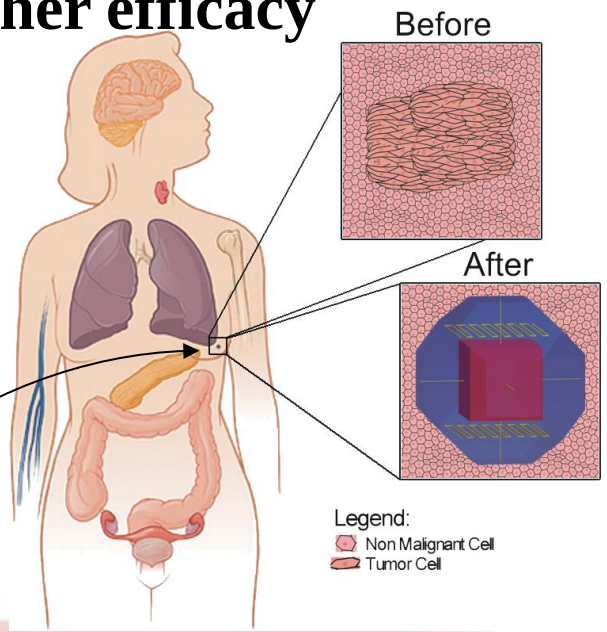
Gel Code	Activation Energy (kJ/mole)	Lower Critical Solution Temperature (˚C)
A	122 ± 6	33 ± 1.7
B	163 ± 8	36 ± 1.8
C	166 ± 8	38 ± 1.9
D	291 ± 15	42 ± 2.1
E	114 ± 6	29 ± 1.5

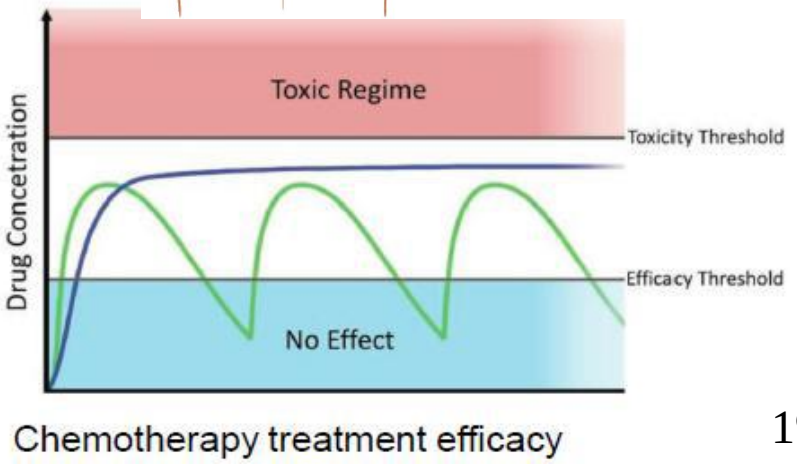
Strategy for Localized Cancer Treatment

- Important for Solid Tumors
- Disease is localized
- Reduced side effects

- Smaller dose
- Higher efficacy





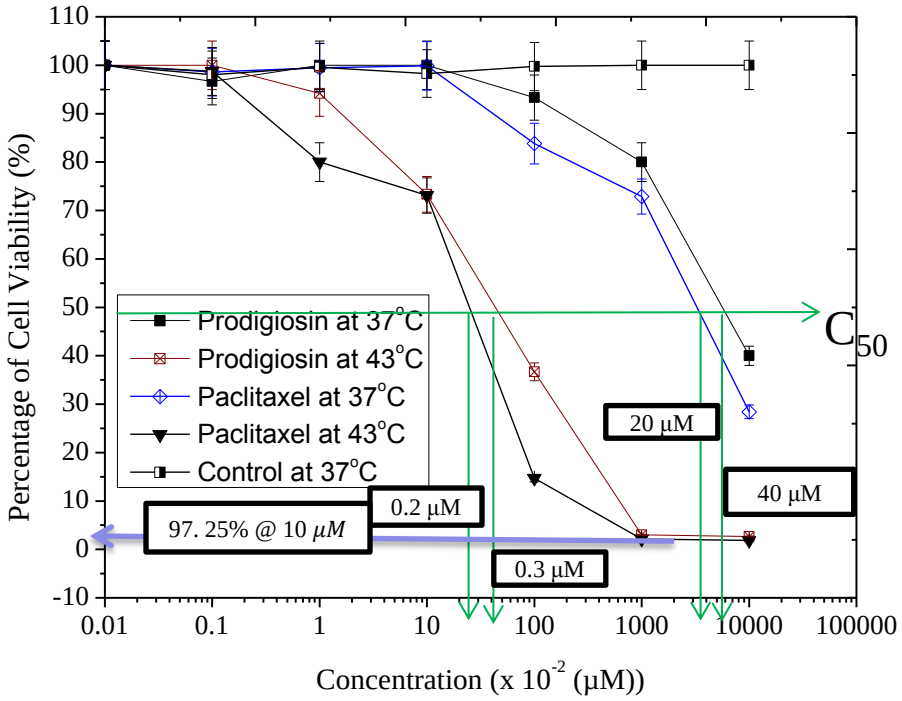


Cell Viability: Effects of Temperature and Drug Concentration for 72 h

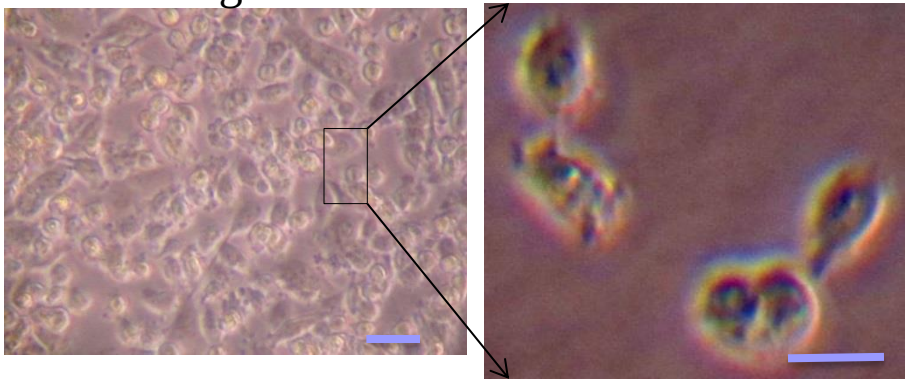
$$PE = \frac{\text{Number of colonies observed on a plate}}{\text{Number of cells plated}}$$

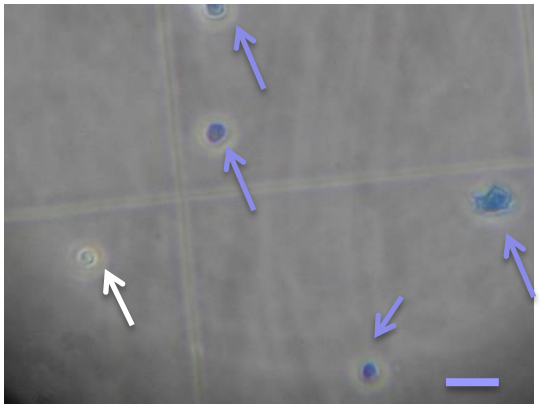
surviving fraction (SF)

$$SF = \frac{\text{Number of colonies observed on a plate}}{\text{Number of cells seededx (PE/100)}}$$

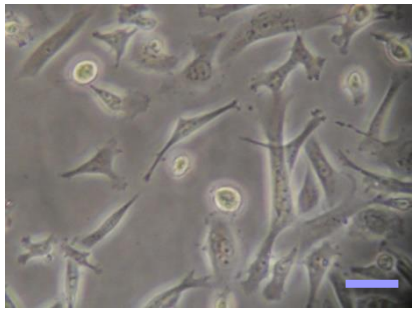


Prodigiosin





Cells on Hemocytometer



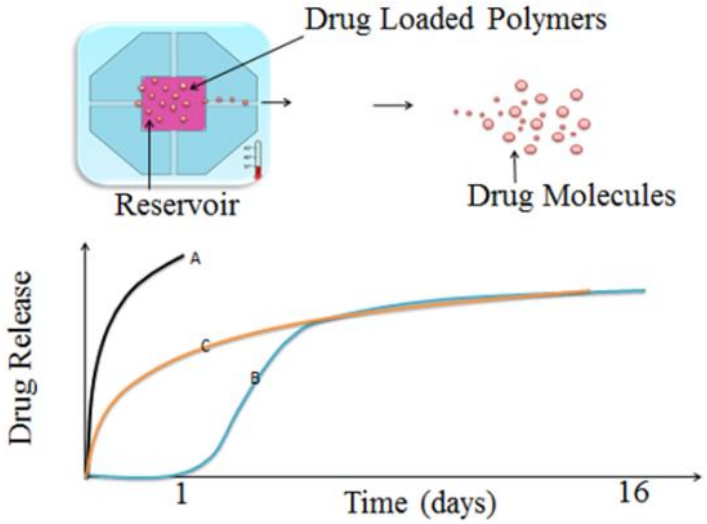
Cells on plate

40 μm

- Trypan blue is a ~960 Daltons molecule that is cell membrane impermeable and therefore only enters cells with compromised membranes. Upon entry into the cell, it binds to intracellular proteins

Project #2
Implications/Contribution from Kinetics Studies

- **These studies suggest that, the release of solutes were governed by diffusion and viscoelastic behavior of the swollen gels**
- Microchannel/Channel lengths can be used to manage the initial burst release of drugs, since the delivery of drugs from the channels is largely controlled by diffusion across the channels
- A balanced approach is, therefore, required for the design of optimal channel lengths.



Drug Release Profiles Resulting from Diffusion Controlled Release From a Diffusion through a Controlled Channel.

- Copolymers can also be selected to have compositions with LCSTs corresponding to the desired cancer treatment temperatures
- Joule heating can be incorporated
- **The need for cell work**

Project #2

Prodigiosin Release from Implantable Biomedical Devices: Kinetics of Drug Release

Materials Science and Engineering C 42 (2014) 734–745

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Prodigiosin release from an implantable biomedical device: kinetics of localized cancer drug release

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STEP - B

SHESTCO