Synthesis and Characterization of pH-Responsive Polyampholyte Nanogels for Drug Delivery Applications

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Introduction

- Polyampholyte nanogels are intra-molecularly cross-linked polymeric network, which are swelled in a suitable solvent. They possess both positively and negatively charged monomers units (Figure 1)

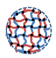

Figure 1- *Nanogel overview*

Table 1- *Nanogels properties and advantages*

Nanogel Properties	Advantages
Small size	Increases drug uptake
Large surface area	Maximizes drug loading
Stimuli responsiveness	Improves control release
Cross-linked structure	Maintains internal network
Porous structure	Permits drug loading and release
Polymeric network	Protects drug from environmental degradation

- Drug delivery system should satisfy the following goals:

1. Efficient binding of the drug to the polymeric matrix
2. Released of the drug in a controlled manner
3. Ability to release the drug through local or externally applied trigger
4. Biodegradability and biocompatibility of the drug carrier

Research Objectives

- The work presented herein demonstrates the synthesis of pH-responsive polyampholyte nanogels consisting of methacrylic acid (MAA) and 2-(diethylamino)ethyl methacrylate (DEAEMA) in the presence and absence of steric stabiliser poly(ethylene glycol) methacrylate (PEGMA) using emulsion polymerization.
- The synthesized nanogels are then characterized with light scattering, zeta potential analyzer and potentiometric and conductometric titration to study their pH behavior. The drug and nanogels interaction elucidate with isothermal titration calorimetry.

Synthesis

- Emulsion polymerization is a freely-radically-initiated chain polymerization in which the mixture of monomers are polymerized in the presence of surfactant solution to form latex.
- Emulsion polymerization consists of three steps:

1. Particle nucleation occurs by adding surfactant into the aqueous medium (Figure 2-a)
2. Particle growth by diffusion of hydrophobic monomer from droplet through aqueous phase into the particle (Figure 2-b)
3. Monomers in the droplet have been consumed and residual monomers dissolved in the aqueous phase are polymerized (Figure 2-c)

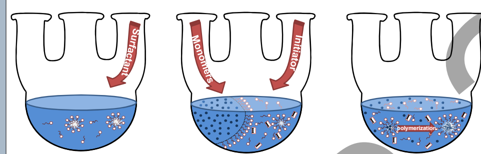

Figure 2- *Three steps of emulsion polymerization*

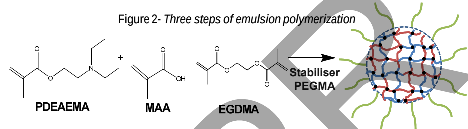

Figure 3- *Sterically stabilised cross-linked MAA-DEAEMA nanogels*

Characterization Results

- The pH and conductivity curves exhibit:
  - Three transitions points corresponding to complete neutralization and deprotonation of MAA and DEAEMA segments, respectively
  - The exact molar ratio of MAA/DEAEMA (59.73/40.27) is very close to the targeted molar ratio of MAA/DEAEMA (60/40)

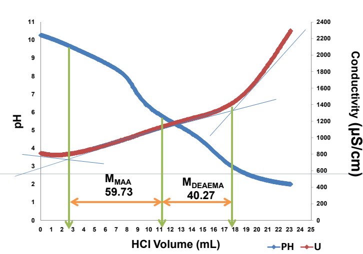

Figure 4- *Potentiometric and conductometric titration of 0.1 wt% nanogels with 0.1 M HCl*

Characterization Results (Cont'd)

- pH responsive behavior of nanogels:
  - Swelling and deswelling transition are governed by the imbalance between repulsive and attractive forces
  - Swelling occurs when intra-molecule ionic repulsion and osmotic pressure exceed attractive forces

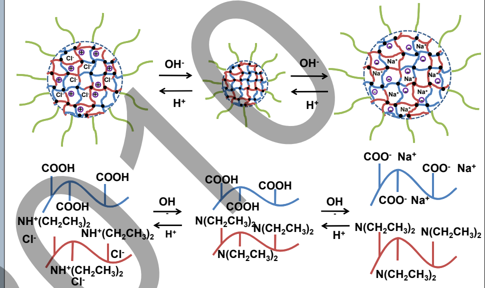

Figure 5- *pH-responsive behavior of nanogels*

- Hydrodynamic radius and electrophoretic mobility curves illustrate:
  - Nanogels swell at both high and low pH
  - Without stabiliser nanogels aggregate near IEP, due to the overall charge neutralization (Figure 6-a)
  - With stabiliser, nanogels are in compact form and due to the steric hindrance, nanogels do not aggregate (Figure 6-b)

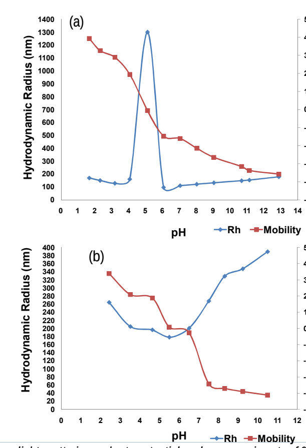

Figure 6- *Laser light scattering and zeta potential analyzer experiments of 0.1 wt% nanogels: (a) without stabiliser and (b) with stabiliser*

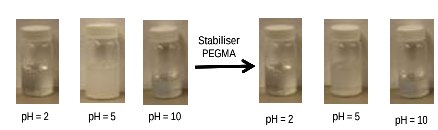

Figure 7- *Changes in solutions transmittance at different pHs*

Drug Nanogels Interaction

- ITC curves demonstrate:
  - The interaction between cationic drug, procaine hydrochloride (PrHy), and that MAA-DEAEMA nanogels are primarily hydrophobic

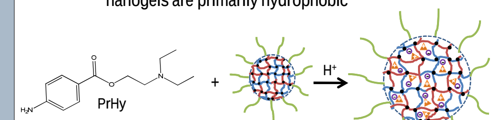

Figure 8- *Drug and MAA-DEAEMA nanogels interaction*

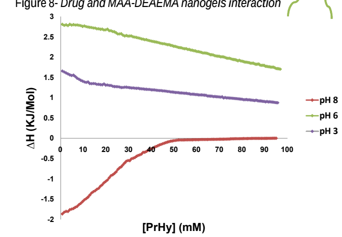

Figure 9- *Differential enthalpy curves for titrating 0.6 M PrHy into 0.1 wt% MAA-DEAEMA nanogels at varying pH*

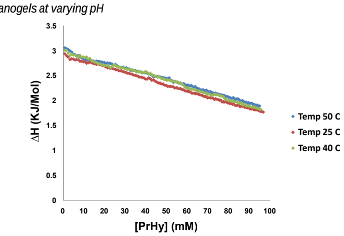

Figure 10- *Differential enthalpy curves for titrating 0.6 M PrHy into fully neutralized 0.1 wt% MAA-DEAEMA nanogels at varying temperature*

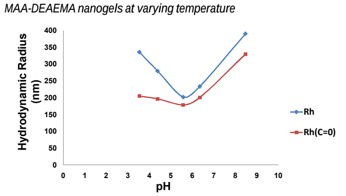

Figure 11- *Hydrodynamic radius of the MAA-DEAEMA nanogels loaded with 0.6 M PrHy*

Conclusions

- The pH-responsive nanogels exhibit hydrophilic behavior at both high and low pH value, but they are in the nonslaved state at intermediate pH.
- Grafting of the steric stabiliser on the surface of nanogels improved the colloidal stability at intermediate pH.
- Swelling character of MAA-DEAEMA nangoels reveal a promissory application as a drug vehicle
- The interaction between PrHy and MAA-DEAEMA nanogels is governed by hydrophobic forces

References

- Beng H. Tan, et al., J. of Colloidal and Interface Science, 309, 453-463 (2007)
- Todd R. Hoare, and Daniel S. Kohane, Polymer, 49, 1993-2007 (2008)

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