P-015 **NIPAM based nanogels for thermoresponsive drug delivery applications**

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INTRODUCTION AND OBJECTIVES

Controlled drug delivery is a major thrust in biomedical research due to the potent advantage of targeted release of drugs, optimal drug dose, minimized side effects and reduced cost of production. Thermoresponsive delivery is one of the modes of controlled drug delivery which has, by far, produced reliable results (Sershen 2000). This paper deals with the fabrication and characterization of thermosensitive polymer nanogels as a drug delivery vehicle for stimuli-responsive release of the payload. The thermoresponsive polymers were fabricated using N-isopropylacrylamide (NIPAM) which has a temperature response (LCST) at 32 ^{o}C (Li J et al, 2006). However, for the specific application of drug delivery the temperature responsivity needs to be slightly above the body temperature. To achieve this, maleic acid and acrylic acid was incorporated into the polymer during polymerization as addition of hydrophilic monomers into the nanogels shifts the temperature responsivity to higher temperature (Zhang Q et al, 2009). The synthesised polymer had been characterised for its thermal behaviour and morphological characters.

MATERIALS AND METHODS

Synthesis of nanogels PNIPAM nanogels were synthesized the free radical polymerization of N-isopropylacrylamide. The initiator used is ammonium persulfate and sodium bisulfite was used as a catalyst.The synthesis method for nanogels copolymerized with maleic acid (MA) and acrylic acid (AAc) is same as that for PNIPAM except that 0.004 M copolymer was added to the polymerization mixture. PEG diacrylate with a molecular weight of 700 was used as the crosslinker instead of MBA to prepare PEG-PNIPAM nanogels.

Characterization of polymeric nanogels The nanogels were characterized for its basic morphology and size using TEM. The size, polydispersity and zeta potential of the particles were analyzed using DLS and the Zeta pals analyzer. FTIR was performed to confirm the incorporation of the copolymers into the nanogels. The thermal characteristics of the nanogels were characterized using UV-VIS Spectrophotometry, DSC and DLS.

Drug loading into polymer nanogels Experiment was carried to check the drug loading efficiency of hydrophilic drug into the polymer nanogels.

Vincristine Sulfate was used as the model hydrophilic drug. For a typical experiment 2µg of polymer was dispersed in water, sonicated for 10 min and 2µg of the drug was added to it.

RESULTS AND DISCUSSION

Five different polymeric nanogels based on PNIPAM successfully synthesised. Synthesis of pegylated PNIPAM nanogels resulted in polymer suspension visibly different form other nanogels as shown in Figure 1.

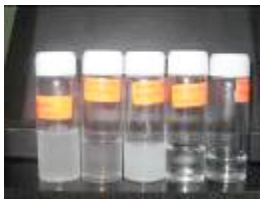

Figure 1: Nanogels at room temperature. From left to right: PNIPAM, PNIPAM-MA, PNIPAM-AAc, PEG.PNIPAM, PEG.PNIPAM-AAc

The size, polydispesity and zeta potential of the particles were analyzed using Dynamic Laser Light Scattering and the Zeta pals analyzer respectively as depicted in Table 1. Particles ranged in size from 67nm to 512nm. Maleic acid incorporation was not found to have any significant effect on the size of the PNIPAM nanogels whereas the incorporation of acrylic acid resulted in decrement of the PNIPAM nanogels by about 40%. Further, pegylation was found to considerably decrease the size of the original polymer by about 75%. The results obtained in DLS were in agreement with the results obtained through TEM (Figure 2).

Table1: DLS and Zeta Potential measurements

Polymer	Eff Dia (nm)	PD	ζ Potential (mV)
PNIPAM	477 ± 29	0.11 ± 0.07	10.12±5.8
PEG-PNIPAM	119 ± 8	0.6 ± 0.5	-2.28±5.2
PNIPAM-MA	512 ± 8	0.05 ± 0.06	1.32±7.1
PNIPAM-AAC	288 ± 33	0.005 ± 0	-14.34±7.1
PEG-PNIPAM-AAC	67 ± 9	0.25 ± 0.14	-2.21±3.5

The FTIR spectroscopy of the nanogels showed characteristic peaks at ~3500 and 1635 which corresponds to N-H stretch and N-H bend respectively of the amide group illustrating successful incorporation of PNIPAM into all nanogel preparations. The broadening of the peak at 3500 in the case of copolymerized nanogels assert the incorporation of maleic acid and acrylic acid into the polymer as

the broadening is due to the hydrogen bonded O-H stretch of the carboxylic group (Figure 3).

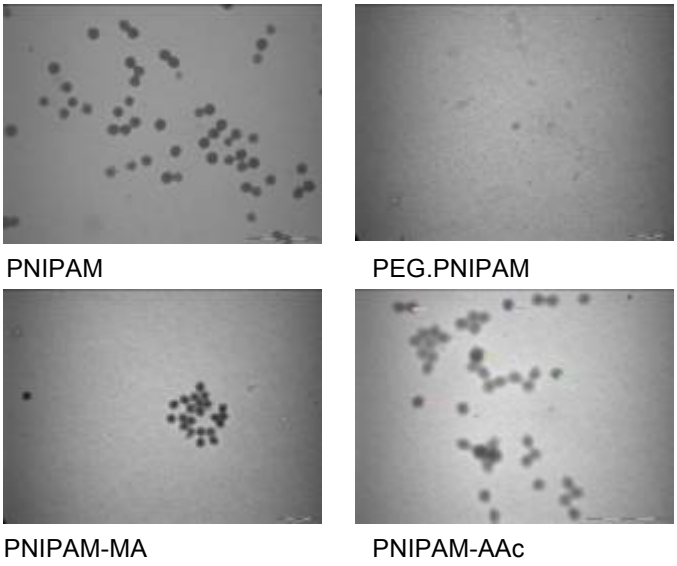

Figure 2: TEM images of polymeric nanogels

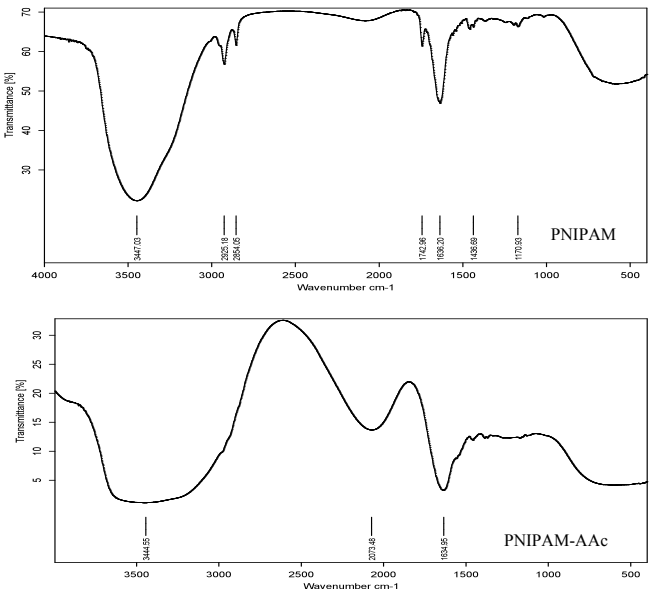

Figure 3: FTIR spectra of polymeric nanogels

The thermal response of the polymer nanogels were studied using UV-VIS spectrophotometer, differential scanning calorimetry and dynamic laser light scattering. It could be concluded from these analyses that PEG-PNIPAM is a preferable choice showing a sharp decrease in absorbance (Figure 4) within a short range of temperature (~38^{o}C to 45 ^{o}C) which is biologically significant for drug delivery applications. This decrease in absorbance is not sharp and narrow in the case of the other polymers synthesized as determined by UV-VIS. This result is confirmed through DSC experiments where the PEG.PNIPAM polymer shows thermal transition from 38 ^{o}C to 47 ^{o}C with a peak at ~42 ^{o}C. However, the DLS shows an increment in the size of the PEG-PNIPAM nanogels and the release behavior from such a system needs to be assessed further.

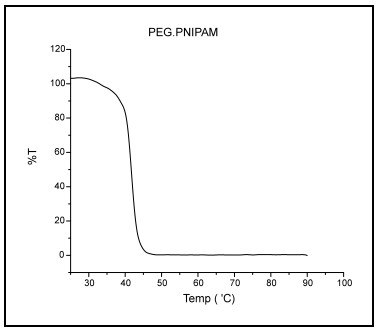

Figure 4: Cloud point measurement using UV-VIS Spectrophotometer

The drug encapsulation studies show that the maximum drug loading efficiency that could be reached with model hydrophilic drug Vincristine sulfate was 48%. The loading of hydrophilic drug into the pegylated nanogels were better than that for non-pegylated nanogels (Figure 5). The loading needs to be further studied along with drug release studies in order to gain better understanding of the drug interaction with the nanogels.

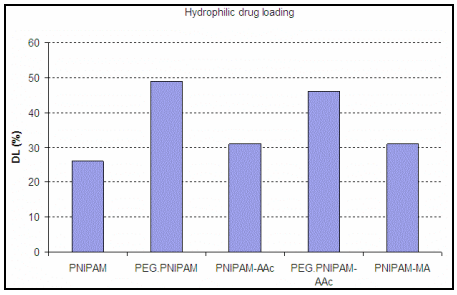

Figure 5: Loading efficiency of model drug into the Polymer nanogels

CONCLUSIONS

Synthesis and characterization of five different types of polymer nanogels based on PNIPAM is described. Use of PEG as the crosslinker instead of MBA has resulted in considerable reduction in size of the polymer nanogels. The pegylated particle has also shown a better loading of both hydrophilic compared to its counterparts. The thermal release characteristics of the drug in the particles and hence its application for photothermal mediated drug delivery need to be assessed.

REFERENCES

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