Ionization radiation engineered functional nanogels for biomedical applications

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Introduction

Nanoscale therapeutic systems have emerged as novel therapeutic modalities for cancer treatment and are expected to lead to major advances in cancer detection, diagnosis and treatment. At Nuklear Malaysia covalently cross-linked nanogel for PEG-DA (polyethylene glycol-diacrylate) using an inverse micelle system for irradiation with electron beam has been developed1,2. Nanogels are nanometer sized hydrogel nanoparticles (<100 nm) with three-dimensional networks of cross-linked polymer chains3. They have attracted growing interest over the last several years owing to their potential for applications in biomedical fields, such as drug delivery systems (DDS) and bioimaging.

Nanogels as pharmaceutical carriers

Nanosized polymeric networks that are held together in three dimensions through physical or chemical crosslinking

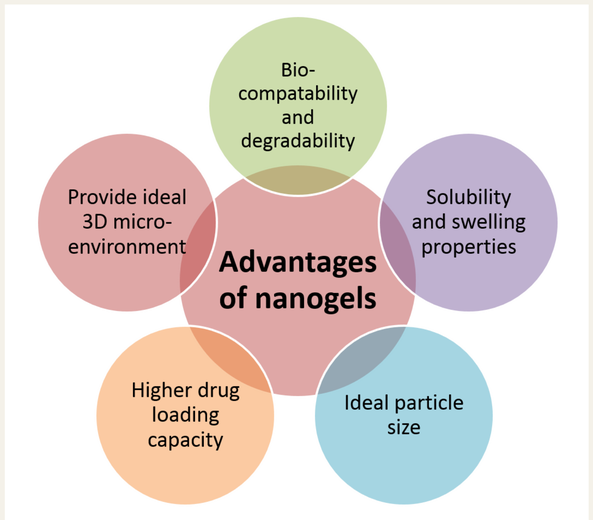


Figure 1. Common features of nanogels that are unique over other nanoparticles. Nanogels have found applications in several fields such as sensing, diagnostics, drug delivery and imaging agents

Radiation cross linking of nanogels: γ-rays and electron beam

- High energy radiation e.g. gamma rays and electron beam can be used to polymerize unsaturated substances.

	Radioisotopes	Electron accelerators
Penetration depth	High	Limited to acceleration energy
Operation	Simple	Relative complex
Radiation direction	Scattered	Well-directed
Power, energy and geometry	No control	Well-controlled
Dose rate	Low	High
Cost	Cheap	Relatively high

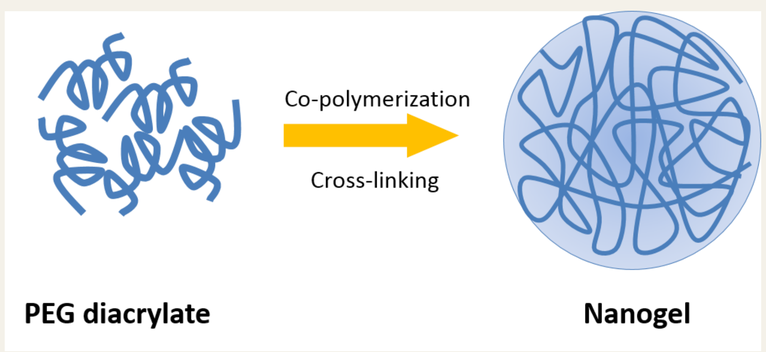


Figure 2. Nanogels are synthesized using ionization radiation-induced polymerization method. Polymerization using this method does not involve the addition of harmful chemical initiators and cross linkers.

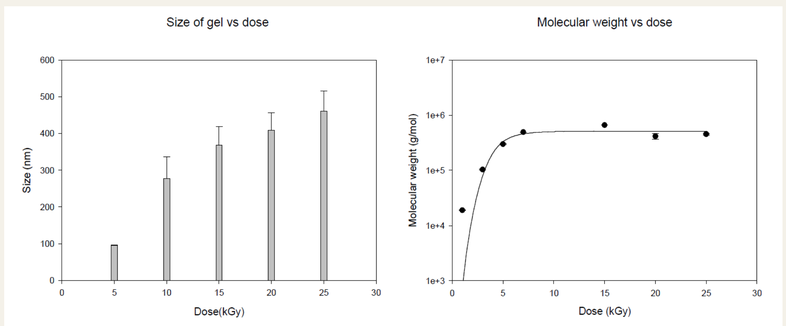


Figure 3. Tunable physical properties of nanogels using ionizing radiation-induced polymerization . A) Gels were formed at 5kGy and above. Size increased were observed at higher dose. B) Static light scattering data indicated an increase in the average molecular weight from 775 to 5.87x105 g/mol as irradiation dose increased from 0 kGy to 25 kGy.

Irradiation dose rate determines particle size

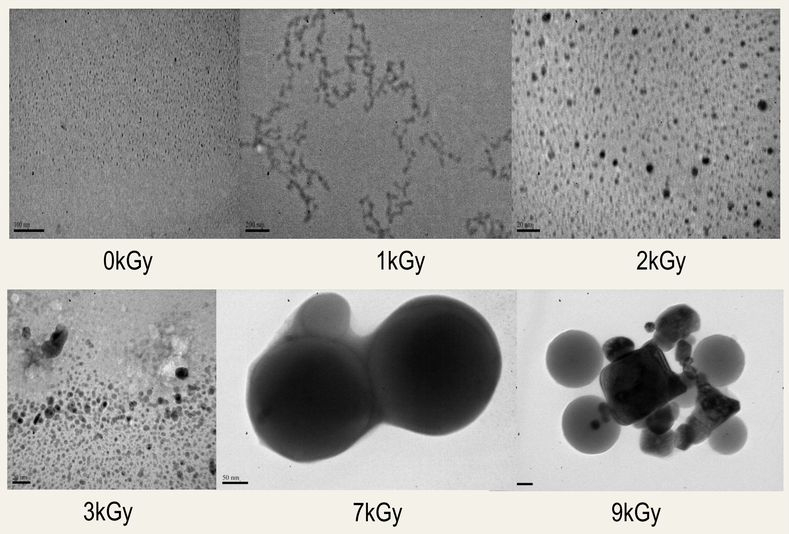


Figure 4. Formation of nanogels from micelles at lower to higher dose. The size of the nanogel increased with increasing dose. The high doses were responsible for intermolecular cross-linking leading to the increase in size.

Stimuli responsive nanogels for enhanced nanocarrier features

- Nanogels are endowed with stimuli responsiveness by incorporating acrylated polyethylene glycol, vinyl pyrolidone with NIPAAM.
- Application of external stimuli e.g. heat/temperature induces shrinking/swelling or aggregation/dispersion of polymer for tunable changes.
- Allows localization, controlled release of cargo and *in situ* response to changing pathological state.

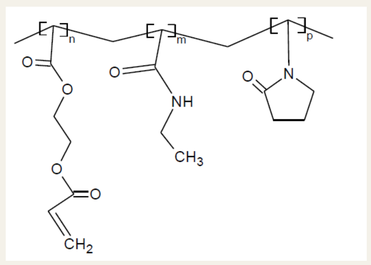


Figure 5. Proposed structure of NIPAAM/VP/PEG-A from gamma-induced copolymerization reaction. NIPAAM confers thermo-responsiveness to the construct with an LCST of ~35°C, close to the physiological temperature.

Biodegradable polyester nanoparticles for use in drug delivery systems

- Largest source of polyester-based (bio)degradable polymers are annual plants such as soybean, corn, palm, olive an coconut.
- Oil-based homo polyesters from natural resources:
  - Biodegradable and biocompatible
  - Easily available
  - Renewable resources at lower cost
  - Promising mechanical properties

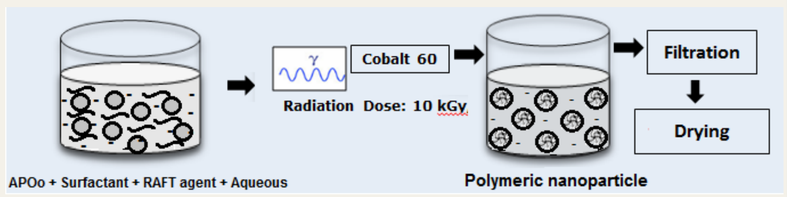


Figure 6. Synthesis of nanoparticles using an acrylated palm olein (APOo). Gamma radiation grafting polymerization technique for developing small particle size distribution of palm oil-based homo-polyester nanoparticles.

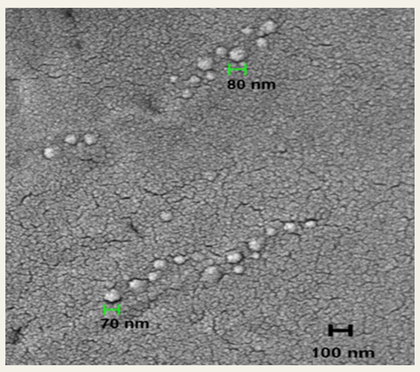


Figure 7. Tunable size distribution of APOo-co-APOo nanoparticle, irradiated using gamma radiation at 10 kGy. A) Particle size of APOo –co-APOo at 10 kGy was 85.67 nm, determined using Dynamic light scattering; B) GeminiSEM 500, 25 000X magnification, 3kV.

Incorporation of biofunctionality through copolymerization of peptide

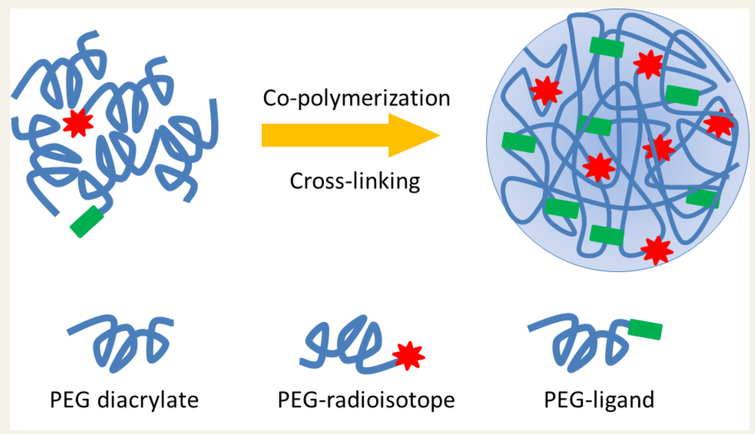
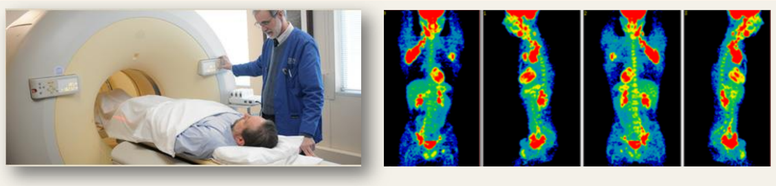


Figure 8. Biofunctional macromers can be synthesized by reacting polymer with a peptide. The tumor homing peptide RGD is appended to the polymer for specific targeting of tumor blood vessel formation (angiogenesis).

PET allows non-invasive imaging of nanogel biodistribution



- Clinical imaging technique which produces 3D images of functional processes in the body.
  - Processes visualized by injecting small amounts of radioactive tracer
- Advantages of PET:
  - Non-invasive
  - Quantitative
  - High sensitivity and specificity

Image-based PK and biodistribution using PET

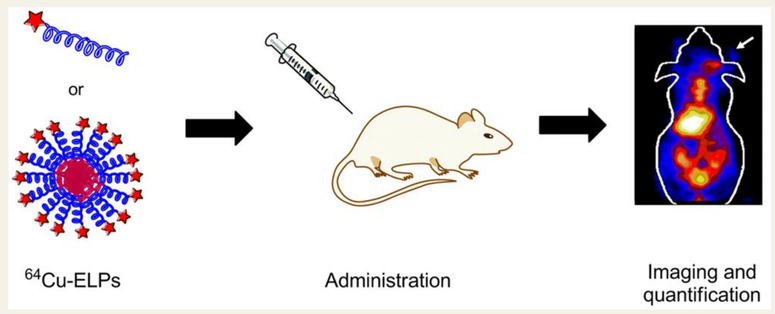


Figure 9. Non-invasive assessment of nanocarrier distribution *in vivo*. Nanogels are first radioactively labeled with a suitable radioisotope e.g. ^{68}Ga, ^{64}Cu. *In vivo* administration to mice then allow imaging and quantification to be performed.

Conclusion

- Nanogels and polyester based nanoparticles with tunable characteristics has been successfully synthesized using the ionization-radiation induced polymerization method.
- Smart nanogels that responds to external stimuli enhances the applicability of the construct as a nanocarrier.
- Nanogels can be functionalized with targeting ligands and allows investigation for anti-angiogenic activity.
- Surface modification allows for chelator conjugation and labeling with PET radioisotopes for *in vivo* biodistribution studies.

Acknowledgements

- Malaysian Nuclear Agency
- Ministry of Science, Technology and Innovation, Malaysia (MOSTI)
- National Cancer Institute, Malaysia
- International Atomic Energy Agency (IAEA)