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UCL

Polyelectrolyte complex Nanoparticles for cancer therapy

Abstract: In this project, we report synthesis of well-defined charged polymers with narrow molecular weight distribution using Reversible Addition Fragmentation chain Transfer (RAFT) polymerisation. Block-copolymers were obtained by sequential RAFT polymerisation. Optimal control in RAFT polymerisation was confirmed by the linear increase of molecular weight and the low PDI of the polymers (<1.2) as determined by ^{1}H NMR analysis and GPC, respectively. Spherical sub-100 nm nanoparticles were formed by self-assembly of oppositely charged polyelectrolytes, poly(methacrylic acid) (PMAA) and poly(2-(dimethylamino) ethyl methacrylate) (PDMAEMA) with poly(ethylene glycol) methyl ether methacrylate (PEGMA) acting as the stabilising agent.

Keywords: RAFT polymerisation; Polymers; PEC nanoparticles

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Introduction

Polymers

Various polymers with stealth behaviour have been developed and used in drug delivery systems (e.g. Poly(ethylene glycol)). Synthesis of polymers with well-defined architectures can be carried out using different polymerisation methods. Reversible Addition-Fragmentation chain transfer polymerisation allows polymerisation of a wider range of functional monomers capable of undergoing radical polymerisation using different solvents.

Polyelectrolyte complex (PEC) nanoparticle

Polyelectrolyte complex (PEC) nanoparticles are usually made by mixing two solutions of oppositely charged polyelectrolytes. PEC nanoparticles usually have small sizes and a narrow size distribution due to the electrostatic interaction between the opposite charges forming a charged-neutralised core. The surface of the particles is composed of the polyelectrolyte in excess; carrying a positive or a negative charge.

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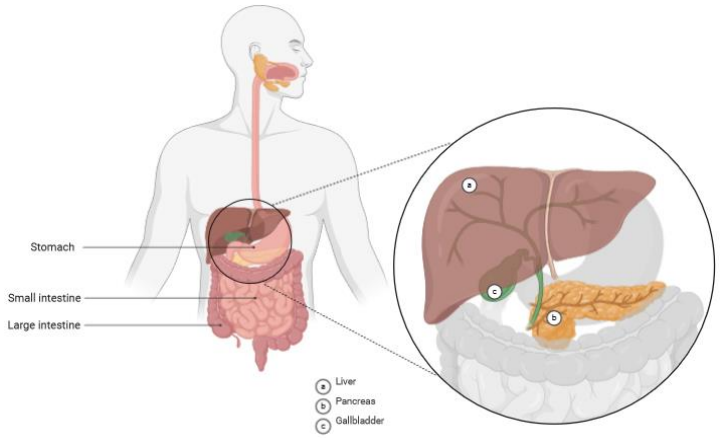
Introduction

Application

Cancer therapies are limited by their short half-life, high toxicity, and low bioavailability. In order to overcome these challenges, PEC nanoparticles can be employed to load anticancer drugs and efficiently deliver the drug to the target site and therefore reduce the side effects.

The use of stimuli-responsive nanoparticles will permit high concentrations of chemotherapy to reach the tumour which can reveal sensitivity of the tumour cells to conventional cytotoxic agents and result in improved survival.

Cancer tissues (e.g. pancreatic cancer) have slightly lower pH than normal tissues. The resulted acidic microenvironment is therefore an attractive target for cancer diagnosis and treatment.



Aim

The aim is to prepare pH-responsive polyelectrolyte complex nanoparticles composed of hydrophilic stabilising polymers and two oppositely charged polymers.

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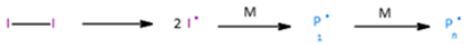
Polymer synthesis via RAFT polymerisation

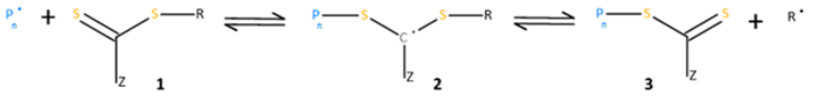
Key advantages

- Simple process
- Allows polymerisation of a wider range of functional monomers
- Provides good control over formation of polymers with predetermined molecular weight and narrow molecular weight

Initiation and Propagation:

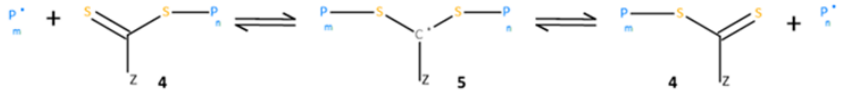


Pre-equilibrium:



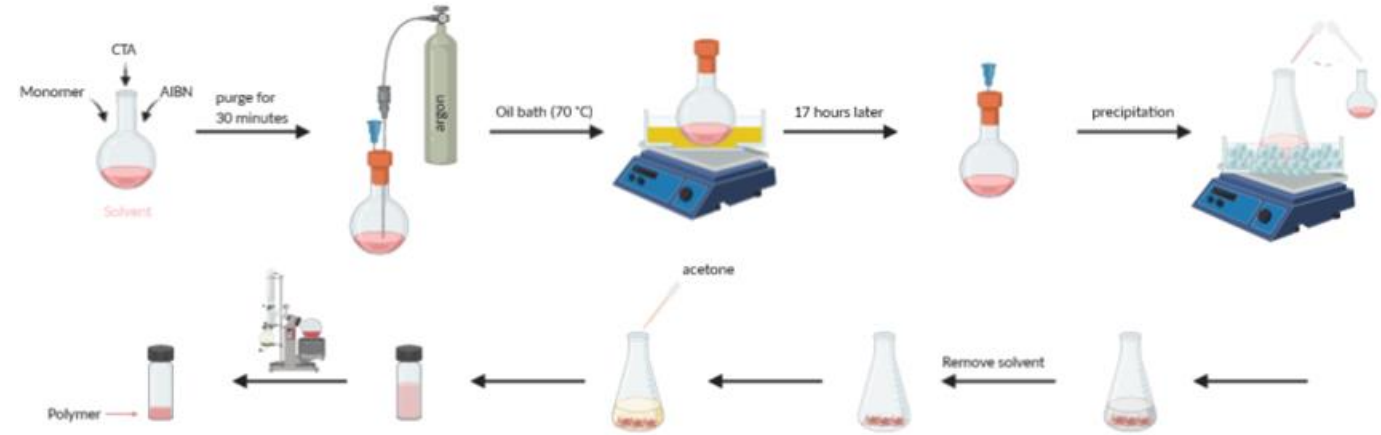
Re-initiation:

Main equilibrium:



Termination:

Process of polymer synthesis



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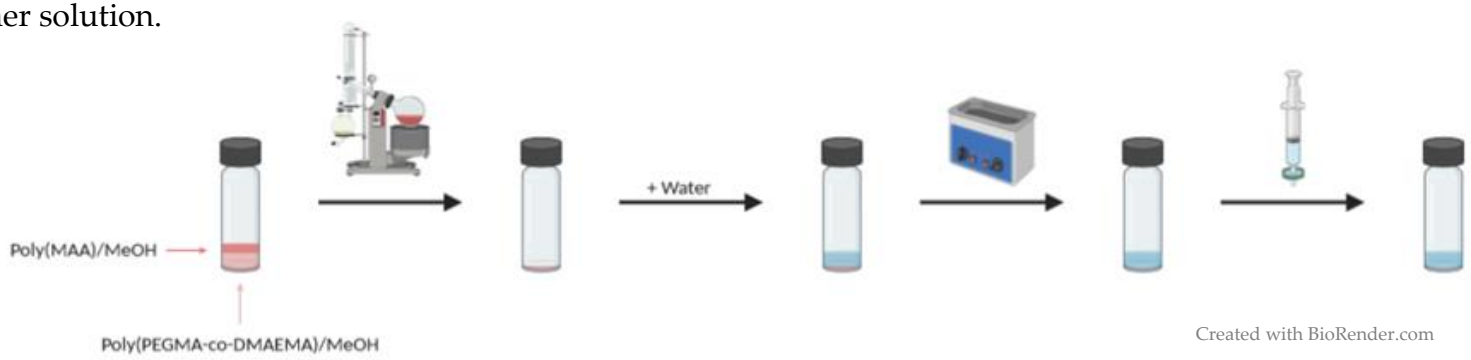
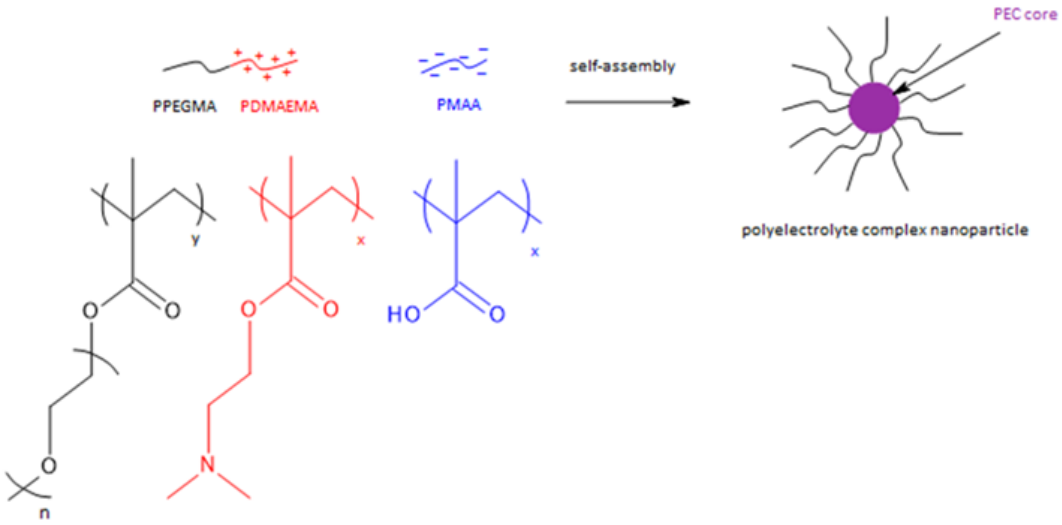
Formation of PEC Nanoparticles

The self-assembly of the PEGMA-b-DMAEMA copolymer and MAA polymer into polyelectrolyte complex nanoparticles was induced by addition of water to the thin film formed at the bottom of a vial after evaporating the methanol from the polymer solution.





The hydrophilic PEG chain segments are expected to form the shell and act as the stabiliser in solution, while the core consists of polyelectrolyte chain segments.

PEGMA: Poly(ethylene glycol) methyl ether methacrylate; DMAEMA: 2-(dimethylamino) ethyl methacrylate; MAA: Methacrylic acid

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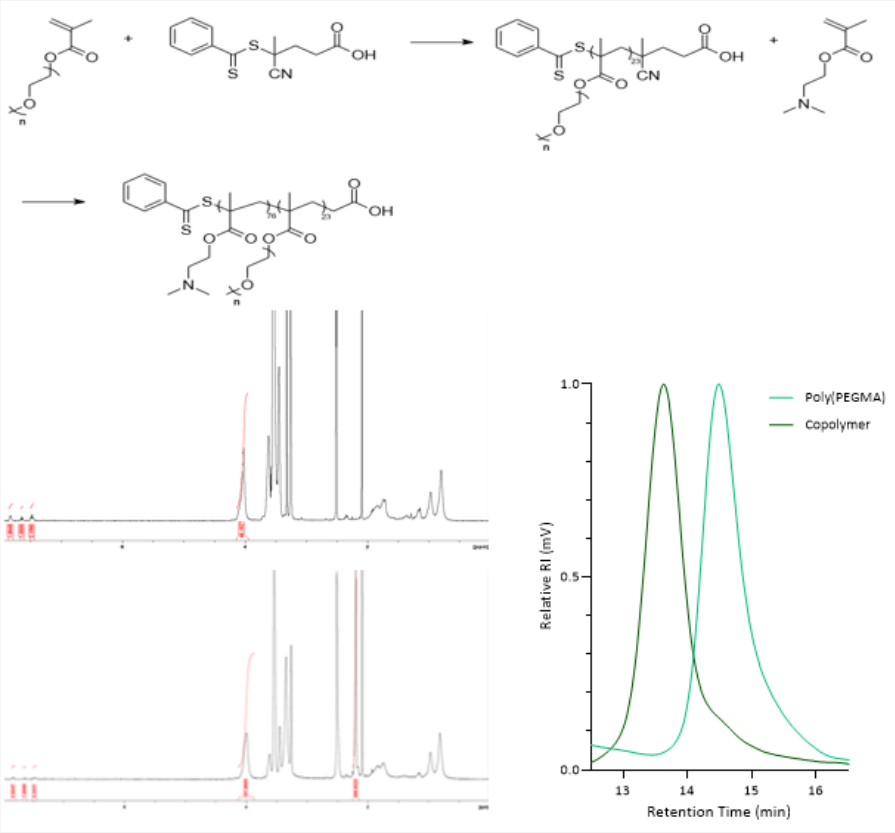
Results and Discussion

Polymer synthesis via RAFT polymerisation

Synthesis of poly(PEGMA-co-DMAEMA)



- Poly(PEGMA) with degree of polymerisation of 23 was synthesised.
- The poly(PEGMA) was then used as a macro-CTA for the RAFT polymerisation of DMAEMA to form hydrophilic pH-responsive block copolymers with a total of 100 repeated units per chain.
- Copolymerisation of poly(PEGMA) was associated with a shift to shorter elution time on GPC.
- The synthesised polymer and copolymer had narrow molecular weight distributions.

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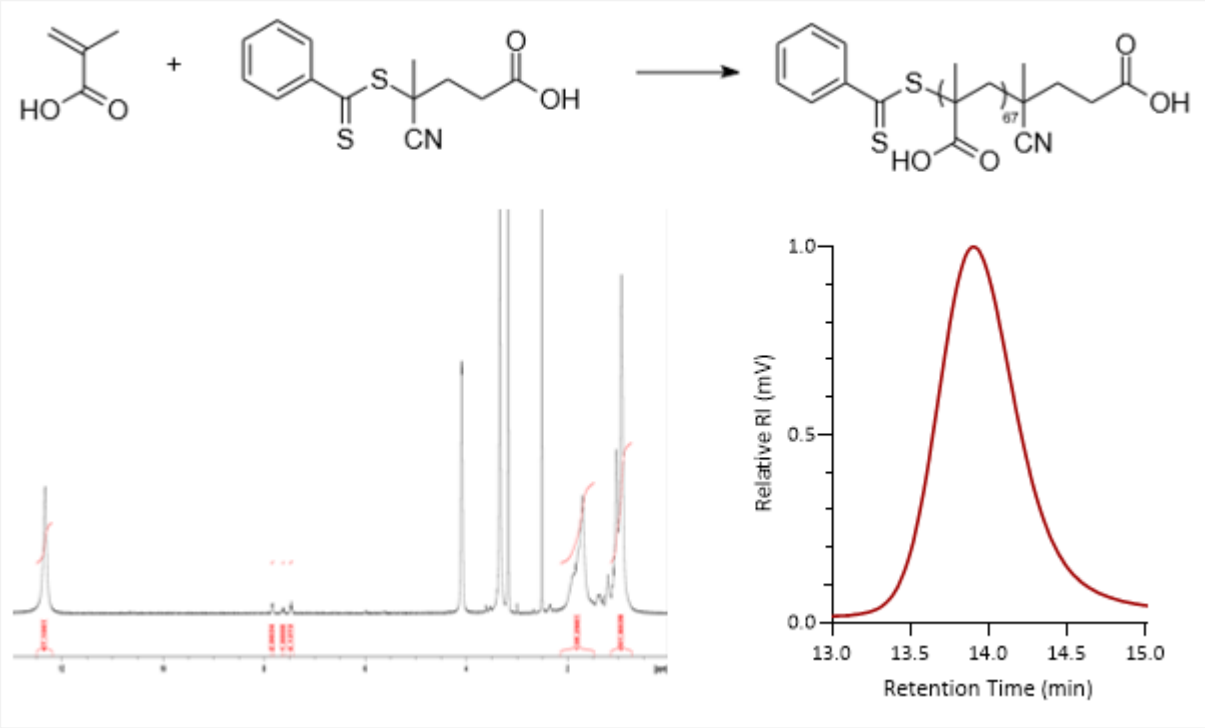
Results and Discussion

Polymer synthesis via RAFT polymerisation

Synthesis of poly(MAA)

- Poly(MAA) with the same chain length as the DMAEMA block in the copolymer was synthesized
- The synthesised polymer and copolymer had narrow molecular weight distributions (1.05-1.19)



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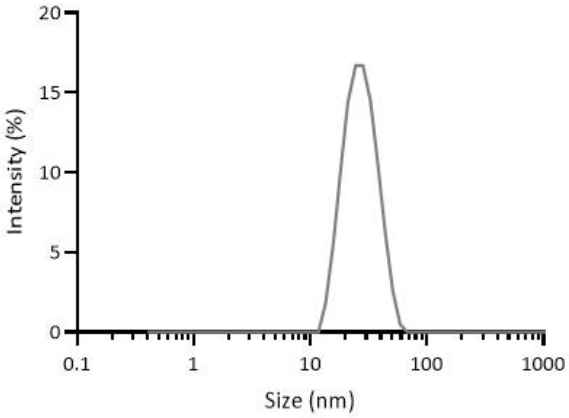
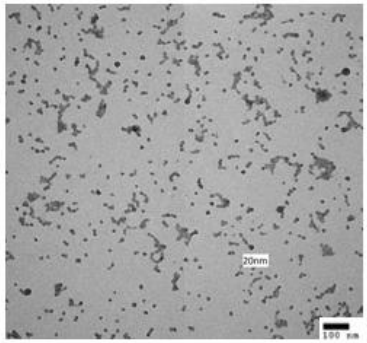
Results and Discussion - Characterisation of PEC Nanoparticles



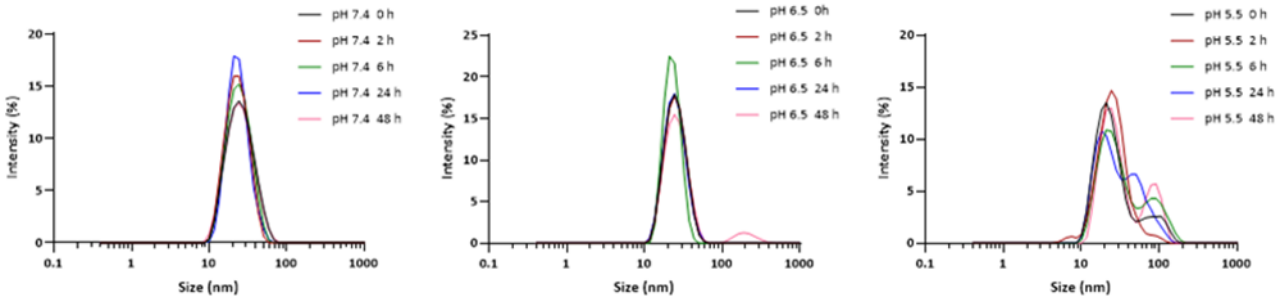


Particle size and morphology

- Self assemble at physiological pH
- Small average size (D_h = 25 ± 3 nm)
- Narrow size distribution (PDI = 0.08)
- Stable at room temperature over 28 days

Change in hydrodynamic diameter of PEC nanoparticles in PBS solutions at different pH

- The size of nanoparticles remained unchanged for 48 hours in PBS at pH 7.4.
- At pH 6.5, their size remained unchanged after 24 hours, but showed an increase in size and distribution at the 48 h time point.
- The nanoparticles became unstable in PBS at pH 5.5.



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Conclusion

- Polymers and copolymers with pre-determined degrees of polymerisation were synthesised using RAFT polymerisation.
- Optimal control in RAFT polymerisation was achieved by choosing an appropriate RAFT agent for the monomers and was confirmed by the linear increase of molecular weight and the low PDI of the polymers obtained by ^{1}H NMR analysis and GPC, respectively.
- PEC nanoparticles with a narrow size distribution were formed upon mixing aqueous solutions of poly(PEGMA-co-DMAEMA) and poly(MAA).
- The spherical nanoparticles were stable in PBS at pH 7.4 but their size and distribution increased in mildly acidic conditions.

The nanoparticle formulation is currently being evaluated in vitro as a tumour-targeted drug delivery system.

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