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Towards the development of dual-responsive composites for simultaneous hyperthermia and chemotherapy

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1. Abstract

Hyperthermia is an emergent therapeutical strategy as tumour cells are more susceptible than "normal" cells to rises in temperature. One of the biggest challenges in hyperthermia is the induction of local heating in deep tumours, being magnetic nanoparticles a potential route to achieve this goal.

We are developing magnetic thermo-responsive copolymer that possesses excellent properties suitable for long-term cell culture AEtMA-Cl/DEAEA [1,2] to deliver local hyperthermia and chemotherapy in tumours. To achieve this, we are producing porous poly(AEtMA/DEAEA) nanocomposites containing Fe_3O_4-NP. Here, we will show the progress made in handling poly(AEtMA) (PAEtMA) via electrospinning and its interaction with ionic crosslinker tripolyphosphate (TPP).

2. Introduction

Thermo-responsive synthetic hydrogels based on 2-(diethylamino)ethyl acrylate have shown to support long-term human embryonic stem cell (hESC) growth over a period of 2–6 months without the loss of pluripotency (Figure 1) [1]. AEtMA-Cl/DEAEA gels permitted gentle, reagent-free cell passaging by virtue of transient modulation of the ambient temperature from 37 to 15ºC for 30 min. Given their thermo-responsiveness, this novel copolymer may also be used as a drug delivery carrier for various applications, such as cancer.

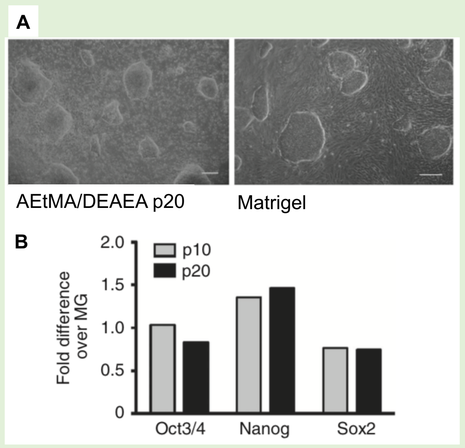


Figure 1. AEtMA/DEAEA hydrogels are suitable for long-term culture of hESC. A) Morphology of hESC after 20 passages. B) Expression of stem cell markers in comparison with Matrigel. Adapted from Zhang et al. 2012 [1].

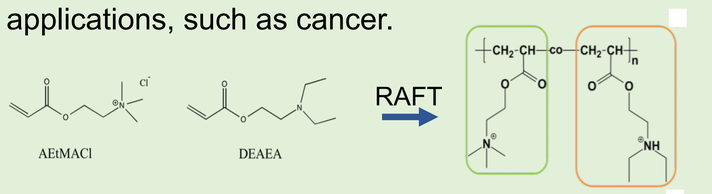


Figure 2. Illustration of chemical structure of monomers AEtMA-Cl and DEAEA, as well as AEtMA/DEAEA co-polymer [adapt. from 2].

Recently, we have produced P(AEtMA-co-DEAEA) and characterized the kinetics of polymerization via reversible addition−fragmentation chain-transfer polymerization RAFT (Fig. 2) [2].

Previously, we have produced magnetic composites by incorporating SPIONP into biocompatible polymers for simultaneous drug delivery and hyperthermia [3,4]. That is the case for chitosan-Fe_3O_4 NPs (CS-Fe_3O_4 NPs) [3]. Importantly, the incorporation of CS in Fe_3O_4 did not affect magnetic properties (Fig. 3).

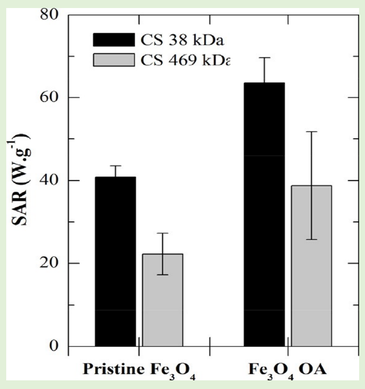


Figure 3. SAR values of CS-Fe3O4 NPs. Fe3O4 NPs were coated with CS 38 kDa or CS 469 kDa . [adapt. from 3].

3. Aim

To produce magnetic thermo-responsive synthetic hydrogels based on 2-(diethylamino)ethyl acrylate that support skin cells culture (malignant / non-malignant) to evaluate **short** and **long-term** implications of **hyperthermia** and **chemotherapy**.

4. Methodology and Results

4.1. Electrospinning of PAEtMA is facilitated by poly(ethylene glycol) (PEO)

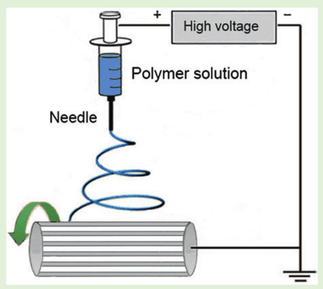


Figure 3 Schematic illustration of electrospinning apparatus used to produce poly(AEtMA) fibers.

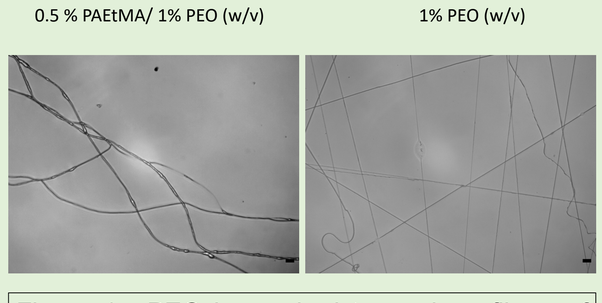
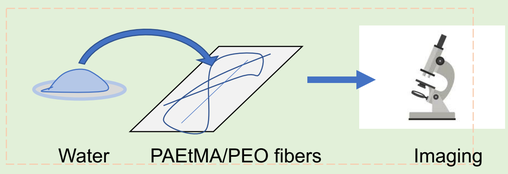


Figure 4. PEO is required to produce fibers of PAEtMA fibers by electrospinning. Representative bright field images. Scale bar 0.01mm.

4.2. PAEtMA/PEO fibers are highly soluble



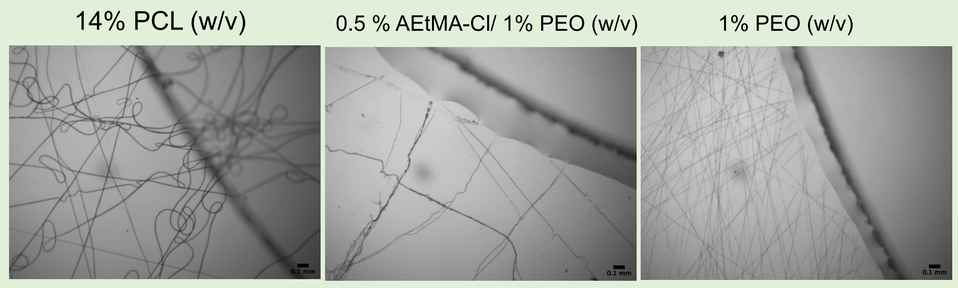
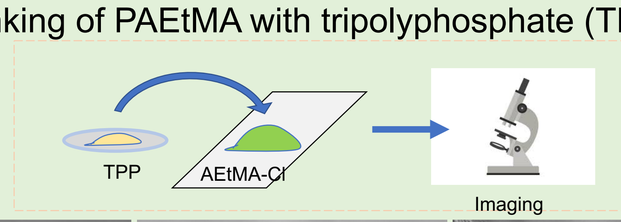


Figure 5. Solubility of PAEtMA/PEO fibers in water. Representative bright field images.

4.3. Ionic crosslinking of PAEtMA with tripolyphosphate (TPP)



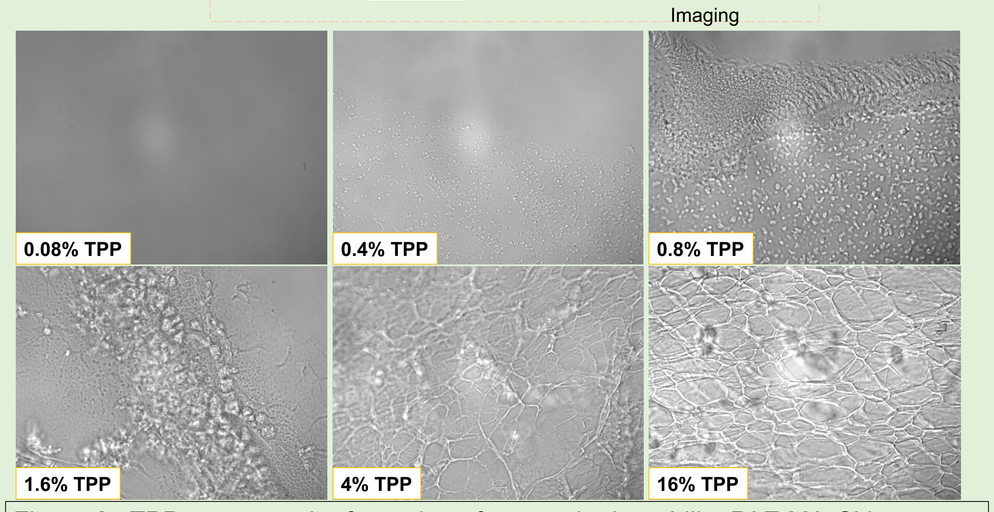


Figure 6. TPP promotes the formation of porous hydrogel-like PAEtMA-Cl in water.

4.4. Superparamagnetic iron oxide nanoparticles (SPIONP) long-term cytotoxicity

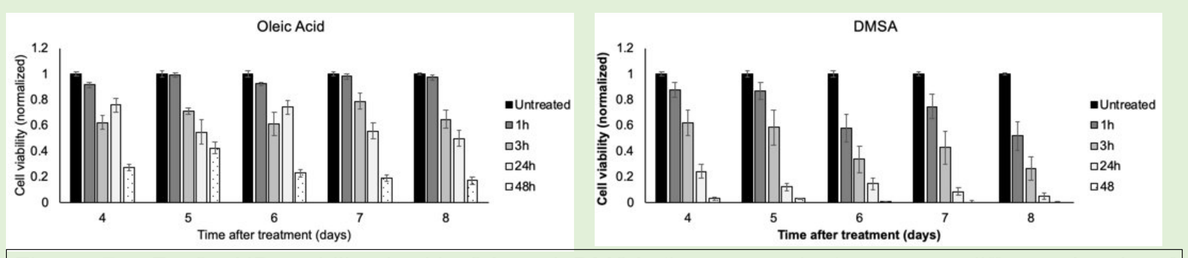


Figure 7. Fe_3O_4 NP stabilized with OA and DMSA (in suspension) promote different levels of cytotoxicity of human dermal fibroblasts.

5. Conclusion and Future Work

Fibers of PAEtMA have been successfully produced together with PEO. Preliminary data shows that ionic crosslinking may provide means to produce matrices that are insoluble in water, which is important for cell culture.

Future work includes the processing of poly(AEtMA/DEAEA) copolymer, the incorporation of Fe_3O_4 NP into the scaffolds; characterization (e.g. swelling, rheometry, SEM, TEM, TGA, DSC).

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Acknowledgements

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