NANOGEL- BASED DRUG DELIVERY: TAILORING BMP-2 RELEASE FOR BONE REGENERATION

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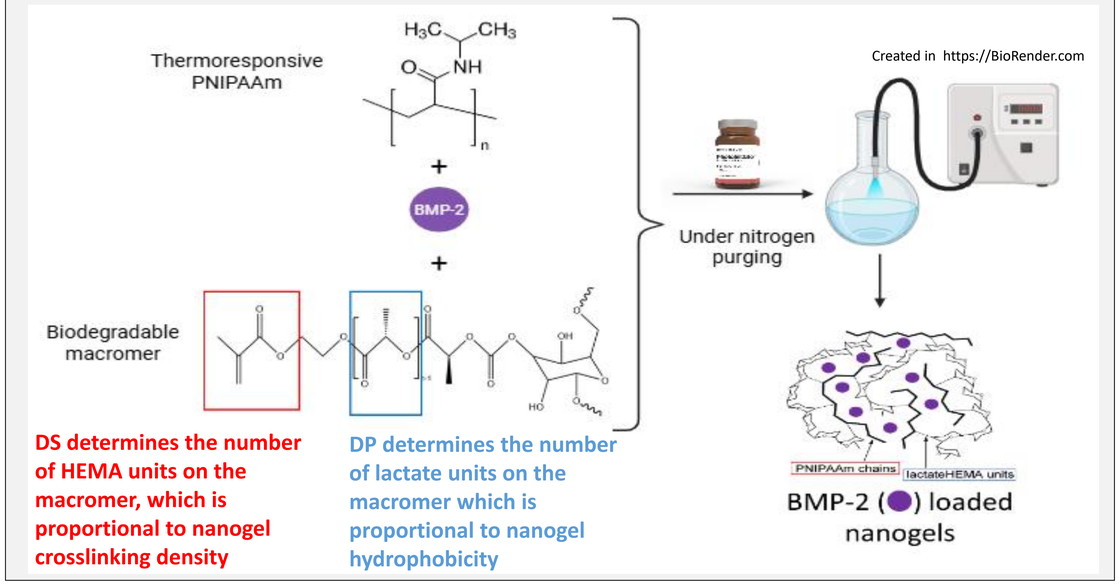
Introduction

Critical sized bone defects (CSBDs) do not heal spontaneously, requiring medical intervention. Bone morphogenetic protein-2 (BMP-2), a growth factor inducing osteogenic differentiation, plays an important role for CSBD regeneration. However, continuous release of intact BMP-2 at the CSBD site is needed due to its short half-life, potential toxicity and side effects at high dose. The objective of this study is to develop a novel non-toxic biodegradable nanogel system that can load BMP-2 in aqueous solution to maintain its integrity and sustain release of intact BMP-2, and tailor the released kinetics of BMP-2 by changing the nanogel composition. The long-term goal is to use the BMP-2-loaded nanogels for CSBD regeneration.

Materials and Methods

Nanogels composed of thermoresponsive poly(N-isopropylacrylamide) (PNIPAAm), and hydrolytically degradable dextran-poly(lactate (PLA)-2-hydroxyethyl-methacrylate) were synthesized in aqueous solution by UV emulsion polymerization technique. Macromers containing PLA with different degrees of substitution and degree of polymerization (DP/DS), 6/2.49, 8/3.73 and 8/4.7, were used during synthesis. BMP-2 was loaded into the nanogels during the synthesis at 1 µg/mg nanogel. The nanogel size and zeta potential measured and analyzed via Zetasizer. BMP-2 release from the nanogels was studied using Float-A-Lyzer G2 100 kD devices in PBS (pH 7.4) for 18 days and quantified by ELISA (n = 4). The cytotoxicity of the nanogels to dental pulp stem cells (DPSCs) was assessed using an MTT assay.

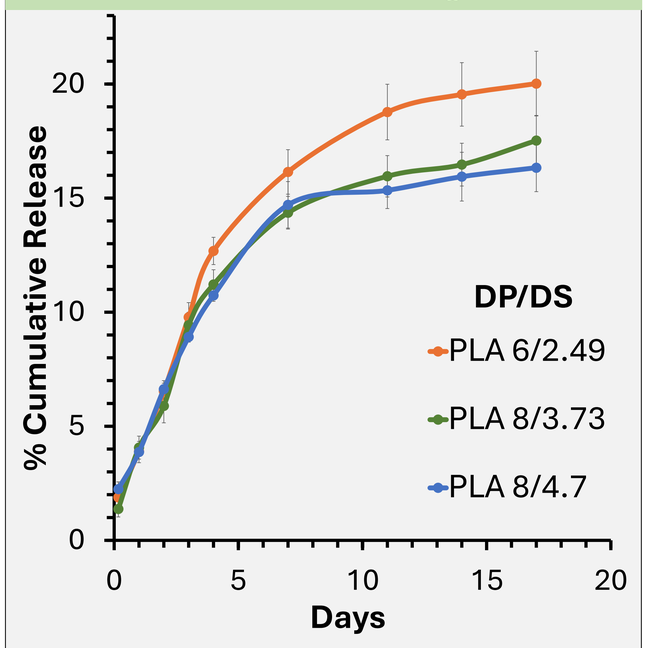
Growth Factor Loaded Nanogel Synthesis



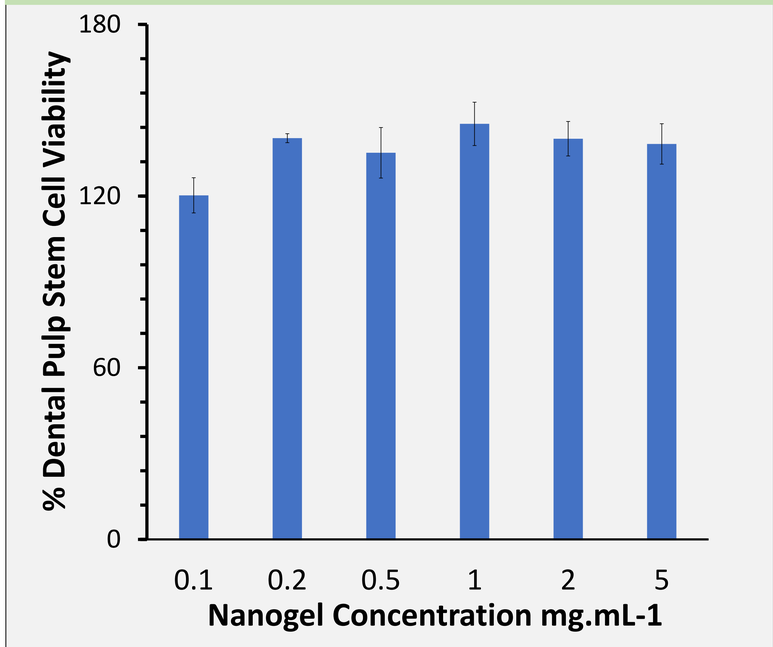
Hydrodynamic Size, Zeta Potential and BMP-2 Encapsulation Efficiency of Nanogels

DP/DS	Hydrodynamic Size (nm, 37°C)	PDI	Zeta Potential (37°C)	Yield (%)	Encapsulation Efficiency (%, n = 4)
6/2.49	80.96 ± 3.16	0.51	-21.57 ± 1.17	93%	91.17 ± 3.20 %
8/3.73	112.60 ± 2.82	0.32	-14.27 ± 0.31	89%	89 ± 2.45 %
8/4.7	196.24 ± 2.03	0.40	-26.70 ± 0.42	85%	92.65 ± 6.84 %

Altering Macromer DP/DS Tailors BMP-2 Release From Nanogels



Nanogels are Non-Cytotoxic to DPSCs



Conclusions

- BMP-2 loaded nanogels are successfully synthesized with around 90% yields and encapsulation efficiencies.
- BMP-2 loaded nanogels are between 81 to 196 nm in size with zeta potentials ranging from -14 to -27 mV.
- Nanogels are capable of slow releasing BMP-2 for 17 days which can be further slowed down by increasing macromer DP and/or DS.
- Nanogel vehicles are non-cytotoxic to dental pulp stem cells at concentrations up to 5mg/mL.
- The novel nanogels are a safe drug delivery vehicle capable of controlling the local BMP-2 dosage along a CSBD.

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