



**Green nanomedicine and sustainable drug-releasing systems for regenerative medicine**

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**Introduction:**

Environmental sustainability is a key challenge, driven by an increasing consumption of natural resources. Hence, more efforts are needed to the study of plant-derived materials (from agricultural waste) for medical uses. Zein is a biocompatible protein from corn. Zein nanoparticles (ZNPs) have been mostly used for the release of hydrophobic drugs, while only few recent studies have proposed ZNPs for plasmid DNA release<sup>1,2</sup>. Pectin is a biocompatible low-cost polysaccharide extracted from citrus peel waste, promising for regenerative medicine<sup>3</sup>. However, it lacks bioactivity and proper biodegradability. Herein, we designed sustainable ZNPs for microRNA (miRNA) therapy to be embedded into injectable pectin/gelatin hydrogels for controlled release.

**Methods:**

Green ZNPs loaded with miRNAs were prepared by a novel method able to minimize the use of organic solvents. Physicochemical (DLS analysis, encapsulation efficiency, release kinetics) and biological (*in vitro* biocompatibility, and cell uptake) properties of ZNPs were analyzed. Pectin was modified to introduce reactive groups and obtain crosslinkable hydrogels by blending with gelatin. Optimal pectin/gelatin compositions were selected by rheological characterizations and *in vitro* cytocompatibility tests on fibroblasts.

**Results:**

ZNPs/miRNA showed more than 90% encapsulation efficiency, which is significantly higher than the reported DNA loaded efficiency in ZNPs<sup>1,2</sup> and good biocompatibility. Optimized pectin/gelatin hydrogels showed good injectability and biocompatibility.

**Conclusions:**

In conclusion, green ZNPs were optimized for the delivery of small oligonucleotides (miRNAs, siRNAs). In the future, ZNPs will be embedded into pectin/gelatin hydrogels, obtaining new green and efficient controlled drug delivery systems for *in situ* therapies.

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