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Review Article

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COMPLEX COACERVATION AS DELIVERY PLATFORM

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ABSTRACT

Coacervates represent an exciting new class of drug delivery vehicles, developed in the past decade as carriers of small molecule drugs and proteins. Researchers have focused a lot to explore the application of coacervates in the field of drug delivery as well as in proto cellular biology; hence the present review is timely. Chemically modified coacervates used in drug delivery research are discussed critically to evaluate the usefulness of these systems in delivering bioactive molecules.

INTRODUCTION

Delivery Platforms Building on the strengths of complex coacervation for encapsulation, several examples of ionically cross-linked colloidal polyelectrolyte (PE) coacervates-mostly conceived for biomedical applications-are reported in the literature. More recently, systems of complex coacervation have been explored for drug delivery using such naturally occurring polymers as alginate, chitosan, and heparin.[1,2] For instance, chitosan/nucleic acid polyplexes were designed for the in vitro delivery of RNA or DNA in mammalian cells.[3-5] Similarly, hybrid PEGylated nanoparticles formed via the complex coacervation mechanism have been shown to enhance the in vivo gene transfection efficiency compared with traditional carriers. On the other hand, protein encapsulation via polypeptide complex coacervation has been recently reported with the aim of delivering protein therapeutics.[6] The ability of complex coacervates to contain high concentrations of aggregation-free and fully active proteins has been exploited in the formulation and delivery of growth factors and monoclonal antibodies. Li et al.[7] showed the use of zein−chitosan complex coacervate particles in the slow release of curcumin. Zein−chitosan complex coacervation was studied by Ren et al. 8 to investigate the effect of ultrasound frequency in the encapsulation of resveratrol. Thermodynamics and wetting kinetics of zein coacervate was studied by Li et al.[9] Their study also revealed the formation of zein coacervate in a water/propylene glycol solvent and its ability to encapsulate limonene. Injectable hydrogel coacervate was used by Lee et al.[10] for the delivery of anticancer drug bortezomib. Huei et al.[11] have reported iron cross-linked carboxymethyl cellulose complex coacervate beads for the sustained release of ibuprofen drug. Chenglong et al.[12] reported a dextran-based coacervate nanodroplet as potential gene carriers for efficient cancer therapy. A water-soluble starch derivative anionic and cationic polymer that undergoes nanoparticle formation via coacervation was reported by Barthold et al.[13] The group discussed the potential use of the nanoparticles in pulmonary delivery of protein/peptides.

From a delivery standpoint, bulk and hydrogel-like coacervate-based materials are typically the most useful in circumstances that allow for bolus-style delivery (i.e., direct application or injection of the material to the site of interest). For example, coacervate-based hydrogels composed of alginate and chitosan were shown to enhance the proliferation of cells in vitro while accelerating healing efficiency and wound closure in a rat model.[14] In another series of reports, the cationic polymer poly(ethylene argininylaspartate diglyceride) (PEAD) was used in concert with the glycosaminoglycan heparin to form coacervate-based delivery vehicles that take advantage of the strong binding affinity between heparin and various growth factors to enable cargo encapsulation and protection. Applications included the use of heparin-binding epidermal growth factor-like growth factor (HB- EGF) to accelerate wound healing,[15] fibroblast growth factor-2 (FGF2) to enhance angiogenesis in both surface wounds and after myocardial infarction (Figure 28),[16,17] stromal cell-derived factor (SDF)-1a for vascular regeneration,18 bone morphogenetic protein-2 for stem cell differentiation and bone formation,19 nerve growth factor (NGF) for nerve regeneration,[20] and the anti-inflammatory cytokine interleukin-10 (IL-10).[21]

While exploring the efficiency of coacervates in drug delivery, a very interesting work was carried by Lim et al. 22 They showed that a Humboldt squid beak-derived biomimetic peptide coacervate can be used for encapsulating insulin with high efficiency along with its

controlled release. Chitosan-based coacervates for propolis encapsulation and its release and cytotoxic effect was reported by Sato et al.[23]

The lack of organic solvents in coacervation has added benefits in the context of drug delivery, beyond those related to the gentle encapsulation of biomolecules. Drug delivery platforms typically address multiple challenges, including (i) protection and/or isolation of the cargo, (ii) enabling targeted delivery and uptake into the cells or tissues of interest, and (iii) controlled release of therapeutics over time. A variety of reports have demonstrated the efficacy of coacervation as the basis of a drug delivery platform, taking advantage of the flexible and modular capabilities of charge-driven self-assembly to address each of these challenges. Reports of coacervate-based platforms for gene delivery include bulk complexes,[24-27] and micellar,[28-34] systems for the delivery of plasmid DNA, microRNA,[29] and siRNA28(small interfering RNA). Specific diseases targeted by these approaches include atherosclerosis,[29] and cancer.[34]

The issue of cargo protection is often coupled with strategies to facilitate cellular uptake. For instance, the vast majority of non-viral strategies for gene delivery rely on electrostatic complex formation between the negatively-charged DNA or RNA and a positively-charged carrier polymer, surfactant, or lipid.[35-38] Such complexation helps to protect against attack from nucleases.[30,31] The positively-charged carrier materials also help to facilitate cellular uptake by masking the negative charge of the DNA or RNA,[39] and facilitating an attractive interaction with the negatively-charged cellular membrane.[40]

CONCLUSION

While the idea of targeted delivery is typically associated with medical applications, food scientists have recently begun to adapt older concepts where complex coacervation has been used to entrap flavors and oils for the delivery of proteins, nutraceuticals, and other water-soluble actives.[41-43] Just as delivery platforms in biomedicine can be harnessed to facilitate uptake, materials design strategies are being utilized to enable more efficient absorption of nutrients, vitamins, and antioxidant molecules during digestion.[44,45] Here, the design parameters are limited in terms of biocompatibility, the availability of bulk quantities of food-grade, cost, and the need to generate a delicious product.

Notes

The authors declare no competing financial interest.

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