Hydrotrope-Controlled pKa Shifts and Supramolecular Reorganization in Glycyrrhizic Acid Hydrogels for Advanced Solubilization

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Achieving sustainable solubilization and encapsulation of hydrophobic molecules is still a key obstacle in contemporary formulation science. Although ammonium glycyrrhizinate (AGA)-based hydrogels offer promising biodegradability and biocompatibility, their natural capacity to solubilize poorly water-soluble compounds is limited. In this work, short-chain alcohols are systematically investigated as hydrotropes and co-solvents to tailor the acid-base equilibria, supramolecular organization, and nanocarrier performance of AGA/water/alcohol hydrogels.
Hydrotrope-specific effects on apparent pKa values, ionization states, and network structures were analysed in detail. Ethanol, characterised by its relatively low dielectric constant and pronounced amphiphilicity, induces an increase in apparent pKa values, while simultaneously promoting enhanced dissociation of glycyrrhizic acid. This seemingly counterintuitive behavior is attributed to hydrotrope intercalation within fibrillar aggregates, leading to increased spacing between carboxylate groups and modified electrostatic interactions. At moderate ethanol contents, these competing effects favour the formation of extended, entangled fibrillar networks, whereas at higher concentrations, fibril destabilization results in fragmentation into micelle-like aggregates. Isopropanol exhibits an even stronger impact, consistent with its lower permittivity and higher hydrotropic efficiency. In contrast, glycerol induces only minor pKa shifts and primarily stabilises AGA ions via extensive intra- and interfibrillar hydrogen bonding, yielding a moderately developed but increasingly robust network with rising glycerol content.
The resulting structural variations directly influence solubilization capacity and nanocarrier efficiency. These properties were evaluated using solutes of different hydrophobicity. In particular, the poorly water-soluble natural sweetener rebaudioside A exhibits up to a 25-fold increase in solubility in the presence of AGA hydrogels, along with thermoreversible gelation behaviour that surpasses conventional surfactant-based systems. Scattering and recovery experiments support a dual-aggregate scenario, involving both partial co-assembly within AGA fibrillar networks and the formation of solute-rich, spheroidal domains, analogous to systems containing ethanol.
Overall, AGA/short-chain alcohol hydrogels emerge as highly tuneable and sustainable solubilization systems and nanocarriers. Their properties can be precisely adjusted through hydrotrope selection and concentration, offering significant potential for applications in food, cosmetic, and pharmaceutical formulations.

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glycyrrhizic acid, molecular gel