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Rational design of tetrahydrogeraniol-based hydrophobically modified poly(acrylic acid) as emulsifier of terpene-in-water transparent nanoemulsions

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ABSTRACT

Amphiphilic copolymers based on renewable resources were involved as emulsifiers to prepare transparent terpene-in-water nanoemulsions. The amphiphilic copolymers are composed of hydrophobically modified poly(acrylic acid) (HMPAA) grafted with different fractions of hydrophobic bio-based tetrahydrogeraniol (THG) side chains. The well-defined PAA were synthesized by reversible addition fragmentation transfer (RAFT) polymerization in order to tune the number-average molar mass of the initial PAA. The self-assembly in aqueous solution of the HMPAA copolymers was investigated through the measurement of their critical aggregation concentration by viscometry, tensiometry, dynamic light scattering and the determination of their aggregation number by static light scattering. Series of oil-in-water nanoemulsions using dihydromyrcenol (DHM) terpene as dispersed phase and PAA-THG as emulsifier were prepared with different PAA-THG/DHM weight ratios and DHM/water weight ratios. The level of transparency of the emulsions was monitored though the transmittance value measured at 600 nm and the measurements of the hydrodynamic diameter of droplets by dynamic light scattering. This study highlights that the structure of the PAA*x*-THG*y* is a key parameter to prepare terpene-in-water nanoemulsions with the required high level of transparency. The optimised structure of the emulsifier consists in a moderate degree of polymerization of PAA backbone ($\overline{DP}_{n,\mathrm{PAA}} \leq 180$) along with an intermediate average degree of substitution in hydrophobic THG side chains ($13 \leq \overline{DS} \leq 32$).

1. Introduction

Microemulsions were defined as a system of water, oil and surfactant (also named stabilizer or emulsifier) which is a single optically isotropic and thermodynamically stable system with dispersed domain size varying approximately from 10 to 100 nm, usually 10–50 nm [1,2]. In a microemulsion, the domains of the dispersed phase in the phase diagram are either globular (water-in-oil (W/O) or oil-in-water (O/W) droplets) or interconnected to provide a bicontinuous structure. A microemulsion mostly involves a

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quaternary system composed of water, oil, surfactant and a hydrophobe miscible in water like *n*-butanol [3] or acetone [4] for instance. In the present work, we will focus our attention on O/W emulsion with droplet structure prepared by applying ultrasonication shear in the absence of additional hydrophobic solvent apart from the oil. The term nanoemulsion is also used for O/W emulsions with droplet size in the order of 100 nm [5–8]. By contrast to the thermodynamically stable microemulsion independent of the preparation process (simple mixing), nanoemulsion is associated to kinetically stable emulsions formulated with a lower amount of surfactant to produce process dependent droplets prepared for instance by external shear [5]. In summary, microemulsion and nanoemulsions have similarities in the final size of droplets but nanoemulsion are kinetically stable emulsions with small droplet sizes (range 20–100 nm) regardless the method of preparation [6–8]. Therefore, the term nanoemulsion will be preferred in the present work.

The range of nanoemulsion applications includes drug delivery systems, food industry, and cosmetic industry [8–10]. Contrary to macroemulsions (often called shortly as an 'emulsion' with droplet size of hundreds of micrometers), no inherent creaming, sedimentation, flocculation, or coalescence is observed for nanoemulsions [11]. Another difference concerns their appearance as emulsions are cloudy while nanoemulsions are transparent or translucent. This property is especially relevant for the cosmetic industry to develop alcohol-free transparent formulation of fragrances. In specific applications of cosmetics, different challenges should be simultaneously addressed: preparation of transparent alcohol-free fragrance formulations, use of efficient emulsifier with minimum toxicity and meeting the increasing demand for reducing the dependence on fossil resources by increasing the use of renewable resources. In cosmetics, nanoemulsions are preferred to microemulsion to minimize the toxicological risk of skin irritation induced by a high level of surfactant.

The present work aims to address these challenges by synthesizing amphiphilic copolymers from renewable resources as macromolecular emulsifiers of terpene-based transparent nanoemulsions. Such macromolecular emulsifiers improve the emulsion stability with respect to the conventional molecular surfactants due to much slower desorption kinetics at the interface of the droplet [12]. Moreover, macromolecular emulsifiers of molar mass above 5–10 kDa reduce skin toxicity by limiting diffusion across skin barrier. According to Osipow et al. [13], a transparent nanoemulsion is favored by matching the stabilizer and the oil phase chemical structure. In addition, the transparent nanoemulsions are characterized by droplet sizes in the range of 20–100 nm and by high storage stability against Ostwald ripening. As terpenes are a major component of fragrance formulations, the covalent attachment of hydrophobic terpenes onto a hydrophilic polymer backbone to prepare amphiphilic copolymers is a strategy to match the structure of the dispersed phase while simultaneously integrating renewable resources in the copolymer emulsifier. Amphiphilic copolymers provide attractive surface and interfacial properties resulting from the incompatibility between the chemically different sequences linked together in the same macromolecule [14,15]. The platform terpene molecules (α- and β-pinene) are produced from pine woods via distillation of either turpentine or paper oil, a by-product of the paper-making industry. The range of synthesized terpenes, which are branched or cyclic C10 and C15 molecules, represent an alternative to oil seeds and palm oil. It is worth to mention that acrylic acid monomer used to synthesize poly(acrylic acid) (PAA) can be produced from renewable resources, *ie* from 3 hydroxypropionic acid produced from glucose [16,17]. PAA is among the most common pH-responsive polymer with a pKa of 4.5 [18,19]. The level of protonation of the carboxylic groups switches the net hydrophilic–hydrophobic character of the polymer. At pH values above 4.5, the PAA is neutralized to form the water soluble anionic poly(sodium acrylate) (PANa). On the contrary, at pH $<$ 4.5 precipitation occurs in aqueous solutions due to protonation of the carboxylate groups, which renders the polymer only sparsely soluble in water [20]. Hydrophobically modified poly(acrylic acid) (HMPAA) have proved to be an interesting class of amphiphilic copolymers with a wide range of properties. HMPAA are extensively used as stabilizers and rheology modifiers in paints, cosmetics, pharmaceuticals, foods, enhanced oil recovery, water treatment and controlled release of bioactive materials [21–23]. The hydrophobic interactions, and thus the solution properties, can be controlled by either the type or the grafting density of hydrophobic groups [24,25]. or by addition of salts and surfactants [26,27]. HMPAA have demonstrated stabilizing properties for the preparation of gold nanoparticles [28] or for direct oil-in-water emulsions [14,29–32]. Lockhead et al. [32] highlighted that hydrophobically-modified PAA were more efficient stabilizers than non-modified PAA for cyclohexane/water and mineral oil/water emulsions in a semi-dilute regime. Perrin et al. [14,30] studied the emulsifying properties of a series of HMPAA for n-dodecane/water macroemulsions and concluded to a stronger anchoring of polymers to oil droplets and hence a better stabilization for a substitution degree ($\overline{DS}$) higher than 10 mol% or a longer alkyl chains. PAA samples of molar mass ranging between 5 and 5000 kg mol^{-1} were hydrophobically modified with aliphatic aromatic or fluorocarbon groups by peptidic coupling or by copolymerization [14,24,30–33]. Up to now, mostly fossil-based resources were involved in the hydrophobic modification of PAA while there is a global need in reducing the dependence on petrochemical resources [34–36]. In the variety of biomass feedstock, terpenes have known a growing interest in recent studies of polymer chemistry [37–41].

The originality of the present work is to prepare amphiphilic copolymers based on tetrahydrogeraniol (THG) terpene and well-defined poly(acrylic acid) in order to stabilize solvent-free transparent nanoemulsion of dihydromyrcenol (DHM) in water. In addition to mimicking the structure of the stabilizer side groups with the one of the dispersed oil phase, the use of tetrahydrogeraniol increases the biomass content. At this point it is worth mentioning that the preparation of terpene-in-water nanoemulsions, using exclusively D-limonene as oil phase, was studied until now only in the presence of commercially available stabilizers, generally based on ethylene oxide units [42–44], and mixed surfactants of low molecular weights [45]. The major drawback of these surfactants is related not only to their polydispersity in composition and in molar mass but also to their possible irritating effect on skin which makes them undesirable in cosmetic formulations. Moreover, it was stated by Schellekens et al. [46] that the oligo(ethylene oxide) sequences of these products may be immunogenic and that the anti-OEO antibodies induce blood clearance and reduce efficacy of the products.

In order to thoroughly investigate the relationship between the macromolecular features of the HMPAA stabilizers, their solution