



Gel formation of puerarin and mechanistic study during its cooling process

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ARTICLE INFO

Keywords:

Puerarin
Hydrogel
Kinetics
Crystallization
Rheology

ABSTRACT

Recently, low molecular weight gelators are getting increasing interests in pharmaceutical field. In the current study, puerarin (PUE), a natural and bioactive flavonoid from the plant *Pueraria lobata*, was found to be able to gelate water to form hydrogel during cooling down process of its hot solution. In order to explore its gelation mechanism, the crystallization process, characterization, interaction force, morphology, rheological properties of PUE hydrogel were investigated by polarized light microscopy (PLM), X-ray diffraction (XRD), thermogravimetric analysis (TGA), Karl Fischer (KF), Raman spectrum, ¹H-NMR, environmental scanning electron microscope (ESEM) and rheometer. The results indicated that at a high supersaturation condition, the gelation process of PUE was initiated by nucleation, and then fibers emanated rapidly from the nucleation center. The types of fiber growth changed from “fiber-like” growth to “less-linear” growth as the increase of supersaturation, leading to a denser structure with higher fractal dimension and stronger mechanical properties. Notably, the C=O... π interaction facilitated the gelation assembly process, and the crystallographic mismatch branching played a vital role in constructing the network of PUE hydrogel.

1. Introduction

Recently, molecular gels derived from low molecular weight gelators (LMWGs), fundamentally different from polymer gels, has been a rapidly expanding area of research, especially because of their application in drug delivery such as controlled release (Bhuniya et al., 2006; Nicolaou and Guy, 1994; Vemula et al., 2009). Gels are identified through the following criteria: (1) the solid-like rheological behavior, despite being predominantly liquid in composition; (2) the continuous microstructure with macroscopic dimensions (Escuder and Miravet, 2013). The continuous phase can be any fluid, including water, organic solvent and air, corresponding to the hydrogel, organogel and aerogel, respectively (Yu et al., 2013).

The formation of a gel usually required a specific trigger, including changing the solvent polarity (Dudukovic and Zukoski, 2014; Raeburn et al., 2015), changing the pH (Adams et al., 2009; Tang et al., 2009), cleaving functional groups of compounds by certain enzymes (Yang et al., 2008), and lowering the temperature of the binary solution (Raeburn et al., 2013). When cooling the hot solution, the molecules dissolved in the solvent start to aggregate, and three situations would occur: (1) a random aggregation giving rise to amorphous precipitate, (2) a highly ordered aggregation resulting in crystals, and (3) an

aggregation process between the two cases, generating a gel (Wang et al., 2008). Therefore, the gel results from the inhibited precipitation or crystallization. Upon cooling below the solution-gel transition temperature (T_{gel}), molecular recognition and self-assembly of LMWGs in one or two dimensions lead to the formation of fibers, and subsequently the anisotropic fibers entangle into a continuous and porous network, which traps the liquid phase by capillary force and surface tension allowing it to support its own weight without collapsing (Fig. 1). These cross-links between fibers are driven by non-covalent interactions in nature such as π - π -stacking, H-bonding, hydrophobic forces, and electrostatic attractions (Xing et al., 2002; Yu et al., 2013), which means that the gels are often thermally reversible, that is, they can be melted at high temperature and be reformed again upon subsequent cooling (And and Hamilton, 2004).

With the help of microscopy techniques (e.g., scanning electron microscope (SEM), transmission electron microscope (TEM) and atomic force microscope (AFM)) (Bühler et al., 2003; Buhler et al., 2003; Rong et al., 2000), gels are usually observed to have Cayley-like fractal structures, which are self-similar and characterized by the fractal dimension (Grahame et al., 2011; Lam et al., 2010; Liu and Sawant, 2002a,b). And some key parameters of the network, such as the degree of branching, the average thickness of fibers, and the type of crosslink,

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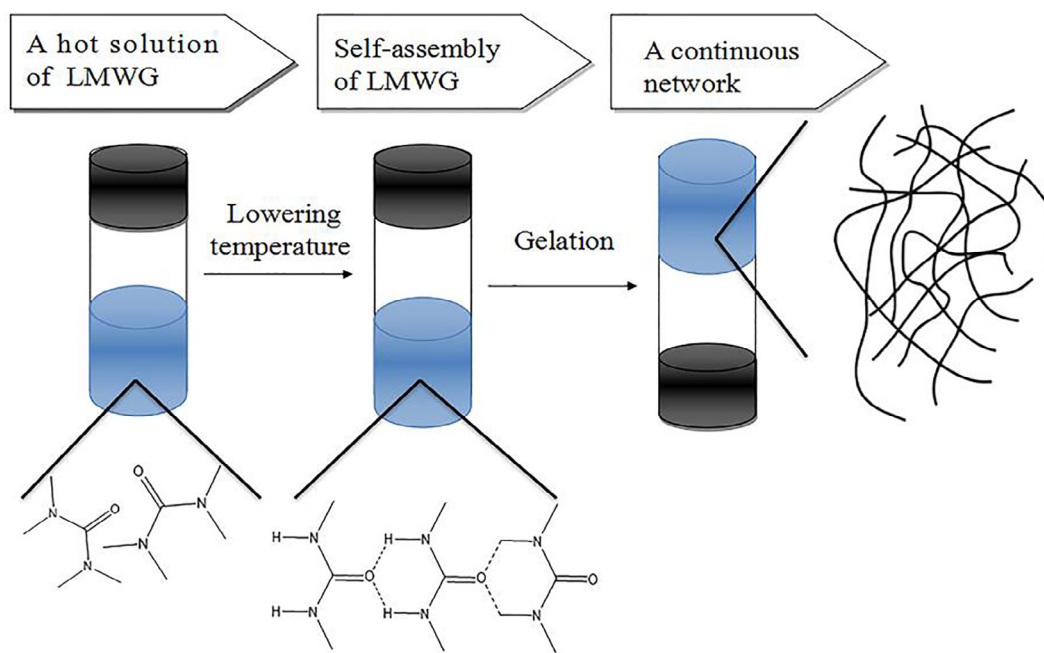


Fig. 1. Schematic of the self-assembly of a gelator leading to the self-supporting gel with fibrous network.

have an important effect on the rheological properties of gels (Liu and Sawant, 2002b; Raeburn et al., 2013; Wang et al., 2006), and these properties will determine how effective they are for the specific applications. Although the experimental and theoretical approaches attempt to understand the nature of the gelation process, the limited number of studies still have not provided a clear mechanism for the formation of the fibrous network.

Puerarin (7,4'-dihydroxyisoflavone-8- β -D-glucopyranoside, PUE), is one of the major active ingredients in the root of the plant *Pueraria lobata*. It has a broad application prospect in treating various diseases, such as cardiovascular disorders, diabetes, and cancer (Cheng et al., 2015; Huang et al., 2012; Yu and Li, 2006). Its chemical structure (Fig. 2) contains the hydrophilic sugar moiety and the hydrophobic aromatic group, which may achieve the balance between the molecule's ability to dissolve or self-assemble in water. In the present paper, we found surprisingly that PUE could gelate water to form hydrogel upon cooling its heated solution. This encouraged us to make an attempt to investigate the properties and formation mechanism of PUE hydrogel, mainly including the driving force for PUE self-assembly and relationship between the gelation and crystallization. We demonstrated that the C=O $\cdots\pi$ interaction played a key role in the aggregation process of PUE molecules in water. In addition, we not only monitored the dynamic forming process of the fiber network via polarizing microscope, but also combined its rheological properties, 3D nucleation model and Avrami equation to conclude the nucleation process and the types of fiber growth. And then we presented an explanation for the formation mechanism of the gel on the basis of crystallographic mismatch branching

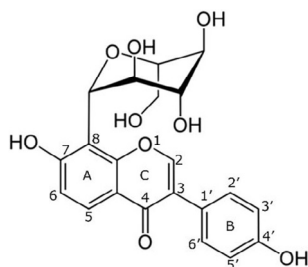


Fig. 2. Molecular structure of puerarin.

theory.

2. Materials and methods

2.1. Materials

Puerarin (monohydrate, purity of 99.9%) was kindly gifted by Zhejiang Zhenyuan Pharmaceutical Co., Ltd. (Zhejiang, China). Puerarin dihydrate (PUEDH) was prepared by stirring supersaturated solution of puerarin monohydrate (PUEMH) at 37 °C for 72 h (Zhong et al., 2017). Then the precipitate was collected and dried in the vacuum oven at 25 °C for 48 h, and subsequently characterized by thermogravimetric analysis (TGA, Fig. S1), differential scanning calorimetry (DSC, Fig. S2) and powder X-ray diffraction (PXRD, Fig. S3). Additionally, the kinetic solubility comparison of PUEMH and PUEDH was investigated (Fig. S4). Methanol of HPLC grade was purchased from E. Merck (Darmstadt, Germany).

2.2. Gelling behavior

To test the gelling ability of PUE, PUE solutions in the concentration range of 1.0–3.0% were prepared by dissolving PUE powders into water in 80 °C water bath, followed by incubating the solution in 30 °C water bath overnight. Then, the glass vials were inverted to test the states of solutions. If no flow was observed, the solution was recognized as a gel. The xerogel was prepared by drying the hydrogel in the vacuum oven at 25 °C for 96 h. And in order to study the effect of incubation temperature on gelation, the heated PUE solutions (80 °C) were incubated at 30, 35, 40 and 45 °C, respectively. In addition, the gelation temperature (T_{gel}) for 2% PUE hydrogel was measured by “dropping ball” method (Takahashi et al., 1980). A steel ball (ca. 0.35 g and ca.0.3 cm diameter) was placed on the surface of gel contained in a glass vial (ca. 5 cm length and 0.7 cm diameter). The gel was heated at a rate of 3 °C/min and the temperature at which the ball fell to the bottom of the vial was taken as T_{gel} .

2.3. Stability experiment

Stability experiment was performed to clarify whether PUE had some degradation during the heating process. 1 mg/mL PUE solution

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