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Current Opinion in Food Science

Molecular gels: improving selection and design through computational methods

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The supramolecular self-assembly of low molecular weight gelators (LMWGs) enables the formation and development of novel soft materials, sensors and smart delivery systems potentially useful for the food industry. Identification of effective LMWGs for food applications usually involves extensive, laborious, and time consuming screening of gelator/solvent combinations. The advancement of computational tools can reduce screening time, speed up the discovery of appropriate edible, nontoxic gelators for food applications and shed light on solvent–gelator interactions. The state of the art on computational techniques developed to advance the understanding, selection and rational design of LMWGs will be discussed herein.

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Current Opinion in Food Science 2016, **9**:84–92

This review comes from a themed issue on **Food physics and material science**

Edited by **Osvaldo Campanella**

For a complete overview see the Issue and the Editorial

Available online 6th October 2016

http://dx.doi.org/10.1016/j.cofs.2016.09.009

Molecular gels and low molecular weight gelators (LMWGs)

During the last two decades studies of molecular gels have become one of the most active areas of research in material science [1,2••,3•]. Molecular gels form via self-assembly of small amounts ($\geq$0.5%) of low molecular weight gelators (LMWGs) ($\sim$<3000 Da) into one-dimensional (1D) fibers through non-covalent interactions such as hydrogen bonds, π–π stacking, solvophobic and van der Waals interactions, among others [4,5•]. Subsequently, the 1D fibers entangle into continuous three-dimensional (3D) self-assembled fibrillar networks (SAFINs) capable of immobilizing organic and/or aqueous solvents [6,7••]. Molecular gels are dubbed organogels or hydrogels, depending on if they entrap organic solvents or aqueous solutions, respectively.

Common organogelators include: fatty acid derivatives, steroid derivatives, anthryl derivatives, gelators containing steroidal groups condensed onto aromatic rings, amino acid-type organogelators and organometallic compounds [8–10]. Urea, pyridine, amino acids, peptides and nucleobases derivatives as well as monosaccharide and oligosaccharide based compounds behave as hydrogelators [5•,11•]. Although most LMWGs perform exclusively as either organogelators or hydrogelators, ambidextrous gelators of both water and organic solvents have also been identified, for example, L-cysteine derived compounds [12]. The large structural diversity of the identified LMWGs explains the variety of physical properties and rheological characteristics of molecular gels that range from elastic to thixotropic, viscoelastic or pseudoplastic materials [7••,13]. The functionality and potential applications of molecular gels as delivery systems for drugs and bioactive components [13,14], sensors [5•,15–17], stimuli-responsive materials [18,19], reclamation agents for oil spills [20,21], and novel soft materials with tailored mechanical properties [22–25] also stem from their versatility and structural diversity. In the food industry, molecular gels offer promises as structuring materials of edible oil to: First, mitigate oil migration in multiphase systems such as chocolate confections, and Second, replace saturated and trans fatty acids with healthier alternatives [26]. Additionally, molecular gels have the potential to improve the stability of food emulsions and control the release kinetics of bioactive compounds in delivery systems [27]. Fatty acids [28•,29], waxes [30,31], lecithin, medium chain sugar amphiphiles [32], and combinations of β-sitosterol and γ-oryzanol [33] have been identified as feasible edible LMWGs for food applications in recent years.

The large pool of LMWGs available and the diversity of interactions that drive the assembly process have complicated the development of adequate models or computational techniques that can accurately and universally predict a molecular gelator/solvent state, that is, will the LMWG stay in solution, form a gel or precipitate when combined with a particular solvent or a mixture of solvents? Although systematic studies have been used to establish structure-function correlations and computational techniques, such as density functional theory (DFT) [34,35] or molecular dynamics [36–38], have been useful in devising molecular arrangements and gelation mechanisms at early stages of aggregation [2••], limited computational tools have been proven successful at describing and predicting gelation ability [39]. In the following sections computational advances that have resulted in successful predictions and the potential implementation of methodologies to improve predictive ability will be discussed.

Predicting molecular gelation

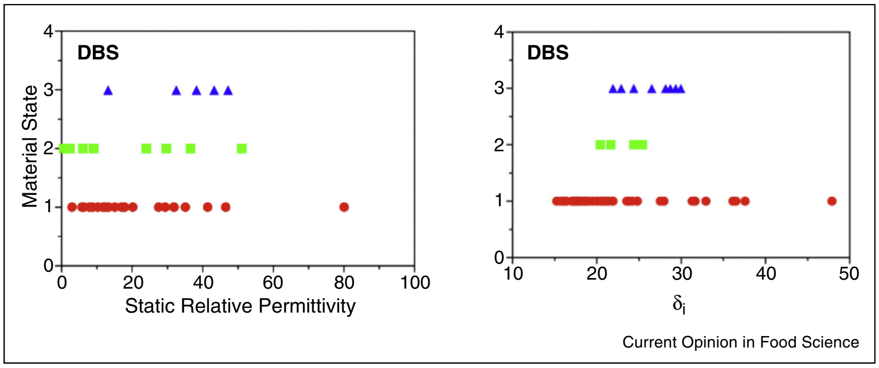
Molecular gelation is largely determined by the chemical structure of the LMWG, external environmental factors, solvent properties and interactions between the gelator and the surrounding solvent [40]. The interplay of these factors has an important role in the balance between solubility of the gelator and intermolecular forces that drive self-assembly, which ultimately results in the gelator dissolving completely in the solvent, the formation of a gel or the precipitation of the gelator out of the solution. As such, an adequate predictive tool should have as feasible outcomes all the aforementioned states so it can depict an accurate scenario and provide reliable results. Identifying the most relevant factors that drive molecular gelation is also crucial for computational purposes to allow researchers to move away from identifying new gelators based solely on serendipitous discovery.

Correlations between individual solvent properties (or gelator characteristics) and gelation behavior

Solvent properties, such as partition coefficients, Henry law constants, dielectric constant solvatochromic and thermodynamic parameters, affect gelator–gelator and gelator–solvent non-covalent interactions that drive the self-assembly processes. These parameters are readily available from the literature or can easily be estimated using standard procedures for a myriad of solvents [41–43]. However, one individual solvent property more often than not is ineffective at predicting molecular gelation. Several researchers [15,44,45] have correlated, with limited degrees of success, either single solvent properties or single gelator characteristics to gelation behavior. For example, Kaszynska *et al.* [46] have reported that a global physical parameter (i.e., dielectric constant) and a solvatochromic parameter (i.e., E_T) were useful in assessing solvent effects on the gelation of methyl-4,6-O-benzylidene derivatives of monosaccharides in organic solvents. This observation applied only to these modified monosaccharides, whose predominant aggregation and packing mechanisms are based on hydrogen bonding. Also, as reported by Zhu and Dordick [47], a thermodynamic solvent property, the Hildebrand solvent polarity parameter, correlates well with the gelation of trehalose diesters in organic solvents. In these systems, the authors verified that a balance between solvation, inter-gelator hydrophobic interactions and inter-gelator hydrogen bonding, which to some extent are represented by the Hildebrand parameter, affected the self-assembly process and the structure of the gels.

Lan *et al.* [48••] performed an extensive review on the ability of individual physical, solvatochromic and thermodynamic solvent properties to effectively account for gelation behavior. This analysis surveyed the performance of 22 molecular gelators and up to 80 solvents. Examples of the correlations obtained by this group are presented in Figure 1. As expected, in the vast majority of the cases it was impossible to differentiate gelation behavior (i.e., solutions, gels and precipitates) based on individual solvent parameters since they only provide a rough approximation of the interactions between the LMWG and the solvent [49]. However, some interesting trends could be identified. For example, gelators that have both the ability to form hydrogen bonds and undergo π–π stacking and van der Waals interactions were able to gel solvents with diverse dielectric constants . Conversely, gelators that rely mainly on hydrogen bonding gelled solvents with lower dielectric constant values and those that depend mainly on π–π stacking tended to gel solvents with higher dielectric constant values. When multiple term solvent properties, both solvatochromic and thermodynamic, were used an improvement in predicting ability was observed, presumably due to a more complete description of the interactions. The Kamlet Taft solubility parameters, a multi-term

Figure 1



Correlations between the ability of DBS to form gels, precipitates or solutions as a function of a physical (left) or thermodynamic (right) solvent property. Blue triangles correspond to solutions, green squares to precipitates and red spheres to gels. Reproduced from Ref. [45] with permission from Chemical Society Reviews.