Gels without Vapor Pressure: Soft, Nonaqueous, and Solvent-Free Supramolecular Biomaterials for Prospective Parenteral Drug Delivery Applications

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The engineering advantages of soft, nonaqueous, solvent-free supramolecular materials have resulted in their emerging transition and adoption from a predominantly food, cosmetics, and paint industry-driven technology to biocompatible matrices for parenteral drug delivery. Factors that have contributed to this trend are the drastic increase of hydrophobic and combination drugs in the pharmaceutical pipeline and the limitations of hydrated drug delivery materials with regard to poorly soluble drugs and biologics. This review highlights examples of nonaqueous, soft supramolecular materials, illustrates molecular engineering principles that may give rise to novel structures and unique properties, and explores emerging opportunities of application of these materials in parenteral drug delivery.

1. Introduction

1.1. Oleogels and Nonaqueous Systems

Polymer-based gels are 3D networks of physical and/or covalent crosslinks that percolate across the entire phase and can be used to entrap small molecules and macromolecules. Many thousands of synthetic gels have been published in the last century.[1–4] Many of these gels have high water content, that is, they are hydrogels, and have been widely used in biomedical applications including drug delivery and tissue engineering.[4–7] Despite the heavy research focus on the exploitation of synthetic hydrogels, many critical challenges remain in their translation to the clinic.[7,8] One key challenge lies in the use of synthetic gels for parenteral (or injection) drug delivery of hydrophobic small molecule drugs.[8–10] Hydrophobic, poorly water-soluble active pharmaceutical ingredients (APIs) have seen a dramatic rise in share of the pharmaceutical pipeline in recent years, now making up 90% of the drugs in development.[9] Since hydrogel matrices are predominantly hydrophilic with high water content, there may be limits in loading clinically relevant concentrations of poorly water-soluble APIs and achieving bolus-free, prolonged, zero or first-order release kinetics of these drugs over several weeks.[10] Further challenges include the mechanical fragility of many biodegradable hydrogels, dehydration over time, and nonideal drug release due to leakage or phase separation.[11] Although mechanical weaknesses of hydrogels may be overcome by several approaches such as introducing a second interpenetrating supramolecular or covalent network within the primary hydrogel matrix,[12] other problems due to the inherent presence of water have no straightforward remedy.

Given these current limitations in hydrogel technology, in particular those associated with the incompatibility of aqueous matrices with controlled release of poorly soluble drugs, some groups have explored whether nonaqueous matrices can overcome these challenges.[14,15] One alternative class of materials to hydrogels is organogels. A typical organogel is composed of a hydrophobic or amphiphilic gelator and an organic solvent, such as N-methyl-2-pyrrolidone (NMP) or dimethyl sulfoxide (DMSO).[3] A common strategy for the use of organogels in parenteral drug delivery is direct injection of polymer mixed with drug and added organic solvent for solubilization and viscosity reduction. Subsequent solvent leaching results in the formation of an implant in situ to release the drug over time.[14] However, compelling reasons against the clinical adoption of such materials exist, including the concern over safety of injecting organic-solvent loaded materials into patients with potentially harmful or unknown biological consequences.[3,16]

A highly promising subset of organogels that has seen limited adoption into drug delivery is called oleogels, which do not contain organic solvents, such as NMP, and consist of oligomers or polymer melts.[9] These materials are supramolecular analogues to soft, covalent elastomers. A key advantage of such polymer melt-based gels is their lack of any appreciable vapor pressure.[17] Such stability and lack of evaporation over time makes these materials quite distinct from hydrogels or organic solvent-based organogels. Whereas hydrogels can be left sealed on the benchtop or in the fridge and remain unaltered due to evaporation on the order of days, solvent-free gels are potentially stable for months to years. While the application of these...
materials in parenteral drug delivery is emerging, much effort currently has focused on molecular engineering novel structures and mechanistic understanding of structure–property relations. Biomedical application also dictates that the constituents of oleogels are either generally regarded as safe (GRAS) or with demonstrated biocompatibility. In this review, we highlight some examples of this relatively less-studied class of biomaterials that lack vapor pressure and are formed via supramolecular interactions. Supramolecular gels are heavily exploited in parenteral drug delivery, in particular supramolecular hydrogel systems, because their shear-thinning and shear-recovery properties enable their injectability and in situ recovery in vivo. Such an approach is promising as a less-invasive alternative to surgical implantation or as a way to improve epitalial engagement in postsurgically administered local adjuvant therapies, that is, improve the depot/tissue surface area and minimize empty space between drug-loaded material and tissue.\cite{17,18} Furthermore, in this review we are concerned with soft gels. The biomedical advantages of soft materials are clear.\cite{18–21} Particularly, stiffness mismatch can cause severe side effects in the drug delivery to many targets, including the brain and central nervous system.\cite{18} Herein, we generally define a soft material as one with stiffness on the order of 10 kPa or less, and focus on gels with dynamic moduli in this range.

In most cases, materials highlighted in this review can be considered structured polymer oils or more precisely supramolecular networks including or within polymer melts. We borrow this term from supramolecular chemistry\cite{22} but do not mean to imply that all systems described here contain directional, molecular-recognition type interactions, such as host–guest interactions with macrocyclic hosts,\cite{23,24} that have been critically important to the field over the last century.\cite{25} Rather, we widen this umbrella term to encompass systems formed because of well-defined, hydrogen-bonding-driven interactions between macromolecules and/or nanoparticles that drive self-assembly.\cite{25,26} A natural division among this class of materials includes systems where the polymer oil or melt participates in the percolation (i.e., formation) of the network (type A), and systems where the melt does not (type B), as depicted in Figure 1. Type A systems are necessarily considered solvent-free gels. In type B systems, some may argue that while the polymer melt matrix does not possess a vapor pressure, it does solvate a percolated supramolecular network, and is therefore a solvent (i.e., those gels are not solvent-free). Nonetheless, the advantages of such a system are also compelling: namely, lack of vapor pressure and the opportunity to provide a completely hydrophobic yet cytocompatible matrix remain. For some applications, type B systems may be more advantageous than type A, for example, if the melt is a functional or bioinert polymer not intended to bind to particles in vivo. In this review, we highlight both type A and B systems.

1.2. Unmet Needs in Parenteral Drug Delivery

Parenteral delivery (by injection) of drug depots is an attractive approach to achieve high local concentration of APIs while avoiding negative side effects and toxicity associated with systemic therapies that are administered via other routes of administration.\cite{14,15,19,27–29} Parenteral drug delivery facilitated by shear-thinning and shear-recovering biomaterials is also less invasive than surgically implanted depots.\cite{15,27} Clinical administration of a soft, shear-thinning material results in many advantages over systemic or stiff alternatives, not least of which include improved compatibility between the drug delivery system and biological tissues.\cite{18,19} Nonetheless, several unmet medical needs remain. Of these, the sustained delivery of hydrophobic small molecules, proteins, and combination therapies (multiple drugs with synergistic benefit) at clinically relevant concentrations on the time scale of months to years is particularly difficult. Development of biodegradable and soft matrices that remain in vivo and release drugs for greater than 30 d remains an elusive goal for parenteral drug delivery.
The delivery of hydrophobic, poorly soluble small molecules to disease targets without adverse side effects is a major challenge for modern medicine.[30] While 90% of the drugs in development are categorized as hydrophobic and poorly soluble, less than half of such drugs reach the market largely due to 0 in solubilization, stabilization, transport, and adsorption.[9]

In Section 1.1, the challenges in using high-water-content hydrogel matrices were discussed. The solubilization of clinically relevant concentrations of hydrophobic APIs in hydrogels and achieving controlled, sustained release is difficult.[11,30–32] Hydrophobic materials are attractive alternatives for at least two reasons. First, the ability to solubilize higher concentrations of hydrophobic drugs makes hydrophobic polymers ideal matrices for such drugs. Second, because of the stark difference in the bulk phases of hydrophobic matrices compared to biological tissue, the sustained release of these APIs is less of an engineering challenge. The controlled, bolus-free release of hydrophobic drugs from a hydrogel into tissue is challenging in part because the water content of both phases (i.e., the drug-loaded hydrogel and the biological tissue) is high. In this case, the partition coefficient between them reaches unity[33] and the release of small molecule drugs is diffusion-limited given the mesh size of hydrogels.[4] Some systems attempt to address this mesh size problem of hydrophilic small molecules via prodrug approaches, that is, covalently tethering drugs to the matrix,[34] but such an approach is more challenging to implement with hydrophobic drugs because of poor water-solubility and scalability.

The sustained release of peptide and protein drugs is another major challenge in parenteral drug delivery. Peptides and proteins are prone to denaturation and degradation, and have short half-lives in vivo. How to achieve sustained delivery over several months to years remains a subject of intense investigation.[27,35] Protein fragility in organic solvents is a major risk when
organogels are used, which is one reason that many research groups prefer hydrogels for local delivery of proteins. However, the presence of water in hydrogels still exposes proteins to various chemical attacks, and long-term sustained release of proteins from hydrogel matrices is often not attainable.

A unique challenge is the delivery of combination therapies, often including multiple hydrophilic small molecules (such as in the case of combination cancer chemotherapies[36,37]) as well as peptide or protein drugs, each with its own unique physiochemical properties (solubility, stability, etc.) and its own required optimal pharmacokinetics.[38-40] In combination drugs, the presence of one constituent may affect the solubility, stability, and mechanism of action of other constituents. The ability to modulate the release kinetics of combination drugs from a local drug delivery matrix independently of one another to match their therapeutic windows is probably beyond simple hydrophilic or hydrophobic matrices and would likely require composite materials with complex structures for spatiotemporal modulation of multiple APIs.

2. Molecular Mechanisms of Gelation

Many strategies exist for developing supramolecular gels without vapor pressure. A fundamental limitation in developing soft solvent-free gels where the polymer melt matrix necessarily participates in the gelation process is the polymer entanglement plateau modulus.[17] Such a problem was recently explored by Sheiko, Weitz, Rubinstein, and others.[43,44,45] The bottleneck results from intrinsically high entanglement moduli \( G_e \) that are often \( \geq 100 \) kPa, limiting the ability to develop gels whose stiffness is \( \leq 10 \) kPa (i.e., mechanical biomimicry of tissue[13]). \( G_e \) is inversely proportional to the square of the chain diameter \( (G_e \sim D^{-2}) \). However, the persistence length of linear polymers scales with diameter raised to the fourth power \( (\phi \sim D^4) \). Therefore, despite the potential reduction in \( G_e \) that may be achieved from increasing the chain diameter, a much more drastic increase in persistence length leads to more rigid chains, as shown in this excellent illustration by Sheiko and co-workers (Figure 2).[12] The authors take a clever approach of exploiting the retarded change in persistence length of densely grafted bottlebrushes \( (\phi \sim D) \) to extend the diameter of the chain while maintaining entropic flexibility. An increase in the diameter of a chain therefore resulted in a decrease of \( G_e \) without dramatic increases in rigidity, which resulted in the accessibility of soft stiffness regimes \( (\leq 1 \) kPa) in neat, solvent-free systems.

An alternative, more classical approach to bottlebrush-geometry design is to create nanocomposites consisting of nanoparticles in a polymer melt (Figure 1), such as the systems described by Macosko and co-workers.[43-48] The polymer chains form a strongly bound layer on the particles, and also “bridge” multiple particles to create a supramolecular network.[43,48,49] Much work has been done to determine what drives the formation of a mechanically robust gel in nanocomposites formed in melt and solvated systems.[43,50] For example, Appel et al. showed that in hydrogels formed via polymer/nanoparticle bridged flocculation interactions, the diameter of particles must be smaller than the persistence length of the polymer in order for percolation to occur.[50] Similar to hydrated nanocomposites, percolation and stiffness of solvent-free supramolecular nanocomposites are generally enhanced by smaller particle size, higher polymer molecule weight, and propensity of hydrogen bonding between the polymer chains and the surface of the nanoparticles.[43,47,50-52]

The story changes when the nanoparticles are grafted with polymer brushes.[52] If the brush molecular weight is below \( G_e \), steric repulsions contribute to the stabilization of particles in the melt and the reduction or complete removal of a supramolecular network. After the molecular weight crosses the \( G_e \) threshold, entanglement between brushes leads to the formation of a supramolecular gel due to these interactions.

Type B supramolecular networks (Figure 1) are not necessarily limited by \( G_e \), but not all of them use nanoparticles to form a network. Other methods of gelation include those that exploit the largely entropically based hydrophobic force, induce crystallization of a single component across the phase, or percolate a network via polymer entanglements.[51] We refer to the latter two processes[51] as supramolecular-like, as physical, non-covalent interactions contribute to the formation of a network, but not necessarily via strictly defined supramolecular interactions (crystallization, entanglement).

Other materials with such supramolecular features include clay-based nanocomposites, which have behavior distinct from particle-based supramolecular networks. Namely, these systems have exfoliated layers, unlike discrete and individual layers of silicate, and have superior mechanical properties than polymer-bridged silicate layers in the intercalated geometry.[52] The driving force of percolation of these supramolecular networks is the frictional forces between layers as opposed to bridged flocculation-type percolation sometimes seen in silica nanoparticle networks.[53]
3. Macromolecule- and Drug-Structured Oleogels

Many oleogels of type B (Figure 1) have been proposed for the food industry in part to generate edible gels with attractive texture while replacing and eliminating saturated and trans fats.\[55\] These materials commonly use heterogenous, commercially available, and safe biologically derived oils as the matrix, including safflower, mineral, and sunflower oils.\[53,55–62\] Here, we highlight a few recent examples of gel formation within these matrices.

Patel et al. recently reported a process to “structure” (i.e., embed a supramolecular network within) a Newtonian sunflower oil matrix with a protein/polysaccharide network consisting of gelatin and xanthan gum that could be dispersed in an oil phase.\[56\] The process begins with an oil-in-water emulsion that is then made solvent-free by drying the matrix via lyophilization or by heating in an oven. No major differences were found in the resulting microstructure or hardness between the drying techniques. An interesting feature of this system is that the dried product must be sheared to form a percolated oleogel network, resembling other reports in the literature of shear-induced flocculation in colloidal systems.\[63\] While the emulsion resulted in storage modulus ($G'$) values near 1 kPa, the dried product, whose final composition was <3% protein/polysaccharide combinations in a small molecule oil phase, was between 10 and 11 kPa.

Xanthan gum is a widely used thixotropic agent that has been used for many applications in biomedicine, for example, to make supramolecular, shear-thinning, and shear-recovering hydrogel inks for bioprinting.\[64,65\] In this system, hydrogen bonding and hydrophobic interaction drive the formation of a similarly thixotropic supramolecular network in a low-molecular-weight oil phase. Continuous flow rheological experiments suggest that this network exhibits classic supramolecular shear-thinning behavior.

Scholten and co-workers developed sunflower-based oleogels formed via protein-mediated assembly.\[55,60\] In these studies, a solvent-exchange process transitioning from aqueous solvent to organic solvent (acetone) to sunflower oil was required to form these gels (Figure 3), where the left is the denatured protein dispersed in the sunflower oil, and the right is the denatured protein in the sunflower oil matrix formed via solvent exchange. The weight fraction of the protein played a large role in the stiffness of the resulting gels, with storage moduli of ≈100 and 1000 Pa at 4.1 (left) and 6.1 wt% (right) loading (Figure 3).

Manzocco et al. also developed sunflower oil-based oleogels using a solvent exchange method.\[66\] In this work, a charged sulfated polysaccharide $\kappa$-carrageenan hydrogel was formed first into an aerogel via solvent exchange with ethanol solutions and supercritical CO$_2$ drying, followed by solvation with sunflower oil, though no rheological data were provided.

![Figure 3. An example of protein/sunflower oil-based oleogels by de Vries.\[60\] A) Images showing that solvent exchange converted a liquid dispersion of protein aggregates in sunflower oil (left) to an oleogel (right). B,C) Rheological characterization of the oleogels 4.1 and 6.1% protein loading. Closed symbols: storage modulus ($G'$). Open symbols: loss modulus ($G''$) Reproduced with permission.\[60\] Copyright 2017, Elsevier.](image-url)
Leroux and co-workers reported an in situ forming oleogel implant formed via a N-stearoyl l-alanine methyl ester (SAM) organogelator in a safflower oil matrix. While this material is not solvent-free in its clinical formulation because 10% w/w NMP was used as a solvent to reduce the viscosity of the parenteral formulation, the mechanical properties of the solvent-free supramolecular system were characterized. The drug-free system had a storage modulus of 8.3 kPa and a loss modulus of 1.49 kPa. Upon incorporation of the API rivastigmine hydrogen tartrate, an FDA approved drug for Alzheimer’s disease, the stiffness increased by more than an order of magnitude ($G' = 142$ kPa, $G'' = 19.2$ kPa). The ability of drugs to percolate the system and result in a network is an interesting phenomenon that could potentially be exploited to simplify drug delivery systems and link the characteristic timescale of drug elution to that of material degradation in vivo. In follow-up studies, the authors determined that tyrosine-derived oleogels yielded stiffer matrices with a reduced bolus release compared to other amino acids such as phenylalanine and tryptophan (Figure 4). They then injected this tyrosine-based oleogel as a locally administered, in situ forming depot loaded with rivastigmine into rats. The authors found this depot could release the loaded API for at least four weeks postinjection, though with a strong initial bolus release (Figure 4). The authors also screened the activity of acetylcholinesterase, the enzyme inhibited by rivastigmine, and found its activity to be most inhibited in the hippocampus for up to two weeks with implications for treating Alzheimer’s disease. These elegant studies highlight the potential advantages of sustained local delivery over systemic approaches using organogels consisting of small-molecule gelators.

Lukyanova et al. explored cell proliferation in 12-hydroxystearic acid structured soybean oil or caprylic/capric triglyceride oleogels. While dynamic moduli versus amplitude or frequency were not reported, the cytocompatibility of these systems was found to be excellent.

Dewettinck and co-workers recently reported on the formation of a sunflower oil oleogel derived from the self-assembly of a mixture of sucrose esters, which cannot be dispersed in or percolate a hydrophobic phase, with amphiphilic phospholipids. The authors screened gels consisting of 10 wt% constituents in sunflower oil, and changed the ratio of the sucrose esters to the phospholipids. The authors contrast the gelation of these constituents with a similar system that required the use of alcohol solvent mixtures. The bulk rheological properties of these gels were measured at 5 °C and were highly dependent on the ratio of the substituents. When the ratio of sucrose esters (SE) and the phospholipid sunflower lecithin (SFL) was 7:3, the resulting gel was the most stiff with a complex modulus $G^*$ of 11 kPa at 10 rad s$^{-1}$ and 5 °C, which reduced to 1000 Pa at 20 °C. Yet, a sol-gel transition occurred at 37 °C, with $G^*$ dropping to ~1 Pa. The authors attribute the percolation of the network at lower temperatures to the entropic hydrophobic effect between SE and SFL.

Patel et al. reported the formation of supramolecular networks of shellac in rapeseed oil. Shellac is an insect-derived polymer resin. When shellac was introduced into the rapeseed phase, heated, and then cooled, gelation occurred via the crystallization of shellac and entrapment of the oil phase. Gelation could occur at 2 wt%, with a stiffness between 500 and 1000 Pa at low angular frequencies and between 1000 and 3000 Pa at higher frequencies. This material also exhibited shear-thinning and shear-recovery properties. Particularly attractive about this material system is its robustness in formation and its durability even in the presence of water. At 20 wt% water, the system still exhibited gelation, with stiffness for both the 2 and 4 wt% samples between 1000 and 3000 Pa.

Almeida and Bahia reported on cholesterol and sorbitan monostearate structured oleogels in liquid paraffin and sweet almond oil for topical drug delivery. The authors observed a critical gelation concentration for cholesterol in liquid paraffin was 1.5 wt%, while that of sorbitan monostearate in almond oil was 17 wt%. At concentrations of 3.5 and 19 wt%, the authors reported soft gels with stiffness on the order of 1 kPa at room and physiological temperatures. The gels were stable for at least
three months at room temperature, but did show signs of instability on the timescale of one month at 40 °C. These gels could be easily prepared by simply mixing the constituents at elevated temperature for 30 min. However, their instability may cause challenges at physiological temperature of 37 °C, so perhaps more or alternative constituents are needed to use this system for sustained drug release in vivo.

Sánchez, Franco, Núñez, and colleagues reported a series of studies on the development and characterization of oleogels structured with cellulose, sorbitan monostearate, chitin, chitosan, or derivatives. In one study, the authors highlight the potential environmental advantage of using these types of biodegradable materials as alternatives to traditional lubricants. While these systems were too stiff to be compatible with soft biological tissue, an interesting observation was made that castor oil templated with sorbitan monostearate was less stiff than castor oil templated with glycerol monostearate at the same weight fractions, which one again demonstrates that slight chemical changes in one constituent may have profound impact on the bulk properties of the oleogels.

These sorbitan monostearate/castor oil (SMS) oleogels could be prepared simply by mixing under elevated temperatures for 1 h to yield noncovalent gels with dynamic moduli between 10 Pa and 10 kPa. An obvious advantage of these systems is the use of renewable ingredients to form the oleogels. While materials in medicine are not currently limited to renewable feedstocks or, in many cases, low cost, such consideration may become more important to translational application of materials in the future and should continue to be a worthy research direction.

4. Nanoparticle-Structured Oleogels

Silica nanoparticle-infused polymer melts are among the best-known nanocomposite materials. Various types of silica particles have been introduced in poly(ethylene glycol) (PEG), poly(dimethylsiloxane) (PDMS), and other polymers in the melt state. Silica nanoparticles are important nanomaterials in biomedicine for drug delivery. A protein or small molecule drug can be loaded into the pores of mesoporous silica nanoparticles, and these will be systemically or locally delivered as standalone therapies or in combination. Non-mesoporous silica—namely, fumed silica and colloidal silica—have seen tremendous use as fillers for polymer melts in biomedical fields (i.e., oral formulations) and other industries such as paints and cosmetics. Fumed silica nanoparticles are high-surface-area aggregates comprised of primary particles (<5 nm in size) covalently fused into secondary structures between 100 and 300 nm in size which tend to agglomerate into structures >1 μm in diameter. Colloidal silica nanoparticles, on the other hand, lack such extremely high-surface-area structure, and as a result, the particle–particle interactions are not as strong nor as consequential when forming supramolecular systems consisting of silica particles and free polymer chains.

Zhang and Archer reported the rheological properties of a supramolecular network based on colloidal silica nanoparticles in a relatively high-molecular-weight (≥45 kDa) neat PEG melt at elevated temperatures. While clearly such a system will have a glass transition temperature (Tg) above physiological temperatures, it does illustrate the difference in supramolecular gel formation of colloidal silica versus fumed silica nanoparticles, which we ascribe as type A and type B, respectively (Figure 1). The supramolecular networks formed with the colloidal silica systems were identified to be driven by polymer–particle interactions as opposed to the dominant particle–particle interactions found in fumed silica gels. Sternstein and Zhu reported on the rheological behavior of fumed silica composites in high molecular weight homo- and copolymers of poly(vinyl acetate) and poly(vinyl acetate)-co-poly(vinyl alcohol) at elevated temperatures with low fumed silica volume fractions. In these lower volume fractions (below percolation limit), the authors reported that the dominant driving force of matrix stiffness was not particle–particle interaction but instead a combination of polymer entanglement and particle–polymer interactions. Since all these systems use high molecular weight polymers that are not melts at room or physiological temperature, they cannot be directly useful for parenteral drug delivery. Nonetheless, these results demonstrate important principles that can be applied to systems that are viscoelastic gels at these lower temperatures. Multiple factors, including the type of particle, strength of particle–particle versus particle–polymer interactions, volume fraction, and presence or lack of polymer entanglements all play significant roles in determining the nature of the supramolecular gel (i.e., type A or type B). Such fundamental polymer and colloidal physics questions are consequential in molecular engineering of biomaterials for parenteral drug delivery because such parameters can affect the characteristic timescales and overall release kinetics of drugs. It is conceivable that if a drug is loaded in the melt and another is loaded in the particles, the particle–particle or particle–polymer interactions will affect whether cells are exposed to drug combinations with overlapping or lagged timescales. Combination drugs often have independent therapeutic windows and require precise control of release rates. Silica-polymer melt-based systems offer an interesting opportunity to potentially meet the pharmacokinetic requirements of a drug cocktail by tuning the interactions between the melt and the nanocarrier.

Our group has recently developed supramolecular, solvent-free gels based on a novel biodegradable block copolymer melt of PEG and poly(caprolactone) (PCL) embedded within bridged networks of nanoparticles of mesoporous silica, fumed silica, and proteins. We demonstrated that the release kinetics of hydrophobic versus hydrophilic drugs from the amphiphilic matrix are distinctly different, and that particle–particle interaction was the primary driving force for percolation, with particle–polymer interactions playing a secondary role. This led to favorable drug release conditions in an in vitro setting. We also examined the effect of nanoparticle surface chemistry on network formation and found that hydrogen bonding between silanol groups on the silica nanoparticle surface and ethylene glycol segments of the polymer melt was a more prominent driving force than hydrophobic interactions between alkoxy-functionalized silica and hydrocarbon segments of the polymer.

Sugino and Kawaguchi recently reported on networks of hydrophilic silica nanoparticles in a mineral oil phase.
this report, the percolation and stiffness of the resulting supramolecular networks were studied in the context of surface silanol density. Networks based on the flocculation of fumed silica nanoparticles were contrasted with those of precipitated silica, which had a similar diameter (16 nm vs 19 nm), but nearly twice the surface silanol density (2.2 nm² vs 4 nm²). Amplitude sweeps of these networks at different volume fractions indicated that at a volume fraction of 0.017, the fumed silica network resulted in a soft gel at room temperature with \( G' \approx 700 \text{ Pa} \) and \( G'' \approx 100 \text{ Pa} \), on par with biological tissue. In contrast, the precipitated silica, which lack the high-surface-area nanostructure of fumed silica, did not form a gel at the same volume fraction. At volume fraction of 0.035, the fumed silica resulted in a gel with \( G' \approx 11 \text{ kPa} \) and \( G'' \approx 1 \text{ kPa} \), whereas the precipitated silica formed a soft gel with \( G' \approx 700 \text{ Pa} \) and \( G'' \approx 100 \text{ Pa} \). These data suggest that the strength of particle–particle interactions determined the bulk stiffness of the supramolecular gel. The authors further explore this concept by plotting the storage modulus in the linear viscoelastic region \( (G'_0) \) and the critical oscillatory shear strain \( (\gamma_c) \) where the response becomes nonlinear (Figure 5).

While the storage modulus of both systems increases with increasing particle volume fraction, \( \gamma_c \) decreases with volume fraction for fumed silica, whereas it increases in precipitated silica. These data together suggest that interactions of silica particles within a floc (or a local agglomeration of particles) are stronger than between flocs for the precipitated silica (weak-link gel), and that interactions between flocs are stronger and more elastic than intrafloc interactions for fumed silica. This result demonstrates that the length scales of interactions and the strength of intra- versus interfloc interactions play a key role in determining the bulk stiffness of the supramolecular networks.

Silica particles in PDMS melts have been explored\cite{47, 86, 91} The entanglement molecular weight \( M_e \) of PDMS is \( \approx 32 \text{ kDa} \)\cite{86} Ma et al. recently reported on solvent-free supramolecular gels of fumed silica in PDMS in the melt at molecular weights below and above \( M_e \), with varying silica surface chemistries, and different aging times of samples\cite{86}. The 2 kDa melt with up to 15% loading resulted in soft gels with similar stiffness regimes to that of biological tissue. At 5% loading, the stiffness of the 88 kDa system interestingly decreased, an exception to the trend that higher molecular weight results in stiffer systems. They observed that short chains exhibit accelerated gelation, consistent with other reports and our own observations that improved chain mobility results in more rapid formation of networks\cite{10, 63}. Furthermore, the silica with hydrophobic surface functionalization resulted in more stable particles and consequently less stiff, sometimes nonpercolated materials. Interestingly, in this work, the rheological properties changed over the course of a few weeks. For PDMS with molecular weight 2–51 kDa, aging resulted in a decrease in both \( G' \) and \( G'' \), with the 2 kDa gels undergoing a gel-to-sol transition, while the higher molecular weight 21 and 51 kDa gels underwent dynamic moduli reductions to the point of becoming critical gels \( (G' = G'') \). Conversely, for the 88 kDa matrix, under the same aging time (one month), the composites thickened, and in the case of the \( \approx 5\% \) wt/wt sample, the system underwent a sol-to-gel transition. The authors suggest a potential explanation of this phenomena is bridged flocculation interactions in the higher molecular weight system. These differences between the 2–51 kDa systems and the 88 kDa systems for the hydrophilic fumed silica particle systems are interesting because they suggest a transition from a type A to type B system. These data agree with a report by Sun and Butt\cite{48} who studied bridged flocculation of PDMA (18 kDa), poly(ethylmethysiloxane) (i.e., PEMS) at 16.8 kDa, and block polymers PDMS-b-PEMS (15.1 kDa) on silicon oxide using atomic force microscopy (AFM) (Figure 6). PDMS at this molecular weight was not found to exhibit a strong tendency to bridge two silicon oxide surfaces, whereas PEMS and PDMS-b-PEMS did\cite{48}. The authors hypothesize that PEMS exhibited more tendency to

![Figure 5. Rheological properties of oleogels consisting of silica nanoparticles and structured mineral oil by Sugino and Kawaguchi\cite{57}. Linear viscoelastic region storage modulus (\( G'_0 \)) and critical oscillatory shear strain (\( \gamma_c \)) plotted versus hydrophilic silica nanoparticle volume fraction (\( \Phi \)) in a mineral oil phase, to demonstrate the effects of particle–particle and polymer–particle interactions on bulk stiffness. Fumed silica (FS) was compared to precipitated silica (PS). Reproduced with permission under the terms of the CC-BY 4.0 license\cite{57}. Copyright 2017, the authors, published by MDPI.](https://www.advancedsciencenews.com/doi/10.1002/adhm.201800908)

![Figure 6. An AFM experiment reveals the states of polymer chains in the melt with respect to silica surfaces, by Sun and Butt\cite{48}. Some polymer chains (gray) are entangled in immobilized layers on the surface of silica particles, whereas other polymer chains (black) mediate bridging flocculation of the particles. Reproduced with permission.\cite{48} Copyright 2004, American Chemical Society.](https://www.advancedsciencenews.com/doi/10.1002/adhm.201800908)
bridge multiple particles compared to PDMS because PEMS was not bound as strongly, and at these molecular weights, the higher binding toward a single surface retards the ability of a chain to penetrate through the immobilized layer.

5. Practical Issues of Material Administration and Biocompatibility

5.1. Injectability of Oleogel Systems

A key parameter that must be considered in parenteral drug delivery systems is their syringeability—the ability of being injected through syringe needles.[106] The material systems described here generally exhibit shear-thinning and shear-recovery behaviors, allowing the networks to be temporarily disrupted and the viscosity (or complex viscosity) reduced for long enough time to inject the formulation before recovery commences in the human body in situ. The fluid mechanics of these complex materials can have important biological consequences. The shear-thinning properties of the oleogel networks can also be exploited to protect precious cargo such as proteins and cells (Figure 7). Heilshorn and co-workers explored such a phenomena in aqueous supramolecular materials used for applications including direct-write 3D printing of cells, a transport process which resembles parenteral drug delivery.[64,107–109] The mechanical (shear or extensional) forces experienced during injection can have negative consequences on protein drugs or other biologics. Shear-thinning along the edges allows the dissipation of this force to occur in the form of breaking noncovalent bonds instead of disrupting cargo structure.

The lack of aqueous or organic solvents present in the systems outlined in this review indeed results in innately higher viscosity regimes which make their injectability more challenging. For target diseases where high-gauge (small) needles are required, creative injection strategies will need to be implemented in order to use oleogels for treating these diseases. At least two shear-thinning strategies exist that make injection possible. Namely, the bulk material can be sheared and subsequently injected, or simply sheared in the process of injection (Figure 7). In the latter case, two phases with distinct fluid velocity profiles emerge, with the center phase remaining gel-like and exhibiting plug flow behavior. For some medical applications, such as local drug delivery of adjuvant therapies against glioblastoma or low grade gliomas,[19] where injection can be carried out using low-gauge (large) needles or even without any needle, no such limitation in injectability exists.

5.2. Bulk Hydrophobicity and In Vivo Evaluation

This review has focused on soft materials that are compatible with the stiffness of biological tissues. Critically, the materials described here have bulk hydrophobicity, which are distinct from the predominantly water-based materials that comprise the physiological environment. This phase mismatch does not disqualify such materials from long-term use in vivo. There are several examples of hydrophobic, biologically inert materials that are well-tolerated in vivo for years.[110–114] Rather than matching bulk phase hydrophilicity, which is a common goal of hydrogel development, the oleogel materials capture the value of soft materials and are more suitable for delivery of hydrophobic drugs. Nonetheless, long-term residence and fate of these soft hydrophobic matrices will need to be evaluated in appropriate animal models and should be a point of future research. Furthermore, quantitative elucidation of acute and chronic (if any) inflammatory responses toward these soft hydrophobic matrices in vivo is needed so as to establish biocompatibility in animals and ultimately in humans. Leroux and co-workers observed a bolus release profile in one such system,[64] suggesting that even if a fibrous tissue layer forms on the material surface as part of the foreign body reaction, it does not prevent mass transfer of drug molecules into the local tissue. Additionally, the degradation kinetics of the oleogel systems after full release of the cargo is of paramount concern to biocompatibility and should be evaluated in future animal studies. As was previously mentioned, gelling a system with the active ingredient directly is one promising approach to potentially linking the drug release and material degradation timescales. In principle, much can be done to modulate the kinetics of material degradation through manipulating the nature of noncovalent bonding between the constituents of the oleogel networks, which opens up a range of possibilities of novel material design strategies.

Some of the constituents of the material systems highlighted in this review may raise some safety concerns. For example, silica nanoparticles that can structure certain oleogels (Section 4) have potential toxicity as reported in some in vitro and in vivo studies.[115–117] Nonetheless, these particles have been widely adopted into biomedicine and drug delivery.[118] The oleogel systems have largely leveraged commercially available polymer melts or oils and structuring agents. One promising alternative approach is to develop functional synthetic polymers and functionalized, monodisperse nanoparticles or...
Structuring agents that are made of FDA-approved ingredients. While such a strategy has been adopted in the hydrogel literature,\textsuperscript{[7]} synthetic chemistry tools have not been widely available for the development of biocompatible oleogels. Much of the research until now has focused on understanding how intermolecular interactions can dictate dynamic bulk properties of the oleogel networks. Going forward, there is a large opportunity to use synthetic chemistry tools to create more biocompatible and functional oleogels and to advance the practical use of these materials in various drug delivery applications and beyond.

6. Conclusion and Future Outlook

Nonaqueous, solvent-free polymer melt-based supramolecular gels are an exciting class of materials with strong potential and many unexplored opportunities in parenteral drug delivery. These systems can potentially address challenges in the solubilization of hydrophobic small molecule drugs and combination therapies. Based on some of the molecular engineering principles discussed in this review, strategies exist for using these systems to tune the release kinetics of combination drugs independently of one another. Nonetheless, many opportunities exist to showcase the biomedical promise of these materials.

Future research efforts may focus on expanding the chemical toolbox available to develop such gels, including synthesis of novel polymer melts and nanoparticles using biocompatible and biodegradable building blocks. Substituting biologically derived oils with well-defined and monodisperse synthetic polymer melts via controlled polymerization is another potential interesting approach. Furthermore, combining polymers with bottlebrush geometries, which allows the accessibility of low-stiffness regimes, with nanocarriers to form supramolecular gels may prove to be an effective way to tune polymer/particle-derived structural properties to achieve ideal drug release kinetics.

Exploring the impact of APIs on the molecular structures and rheological properties of these gels is another topic of interest. Obtaining a deeper understanding of drug–matrix interactions could allow for more precise molecular engineering of therapeutic materials and selection of ideal excipient materials tailored to the physical and chemical properties of the drug. Furthermore, the stability and retention of activity of proteins drug in these nonaqueous, solvent-free matrices remain potential limitation of these systems and should be addressed in the future.

Finally, the performance of these supramolecular networks should be evaluated for safety, biocompatibility, and efficacy in cells and in appropriate animal models. The structure–property relationship of the materials and the mechanism for drug release in vivo remains largely unknown at the moment and must be elucidated in the future. Applying first principles from polymer and colloidal sciences to molecular engineering of novel materials, as illustrated here with examples of nonaqueous, solvent-free supramolecular networks, will lead to the creation of unconventional biomaterials that may enable more efficacious drug therapies.

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Conflict of Interest

The authors declare no conflict of interest.

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