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REVIEW

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Low-molecular-weight gels from amino acid and peptide derivatives for controlled release and delivery

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Low-molecular-weight (LMW) gelators are a versatile class of compounds able to self-assemble and to form supramolecular materials, such as gels. The use of LMW peptides to produce these gels shows many advantages, because of their wide structure tunability, the low-cost and effective synthesis, and the *in vivo* biocompatibility and biodegradability, which makes them optimal candidates for release and delivery applications. In addition, in these materials, the binding of the hosts may occur through a variety of noncovalent interactions, which are also the main factors responsible for the self-assembly of the gelators, and through specific interactions with the fibers or the pores of the gel matrix. This review aims to report LMW gels based on amino acid and peptide derivatives used for the release of many different species (drugs, fragrances, dyes, proteins, and cells) with a focus on the possible strategies to incorporate the cargo in these materials, and to demonstrate how versatile these self-assembled materials are in several applications.

KEYWORDS
delivery, gels, peptides, release, self-assembly

1 | INTRODUCTION

Low-molecular-weight (LMW) gelators are small compounds able to form supramolecular materials.[1,2] Their assembly is usually driven by multiple noncovalent interactions, such as π-π stackings, hydrogen and halogen bonds,[3–5] Van der Waals forces, and electrostatic interactions,[6,7] and usually relies on a partial solubility of the gelator molecules in the chosen solvent system.[8,9] In recent years, peptide derivatives have been deeply investigated as LMW gelators for many reasons. First of all, the unique chemical and functional versatility of peptide molecules allows to easily tune their structures by changing the number and sequence of amino acids and of protecting groups, thus modifying the properties of the resulting materials.[10] In addition, these compounds interact by a variety of noncovalent bonds, are often biocompatible *in vivo*, and their proteolytic stability can be regulated depending on the chemical structure and configuration of the amino acids used.[11,12] These are some of the reasons why peptide-based LMW gelators have been explored for use as delivery carriers,[13–16] since they are more amenable to manipulation at the molecular scale than synthetic polymers, at the same time offering the ability to tune features such as the viscoelastic and mechanical properties. Gels are soft materials mainly composed by a solvent (water for hydrogels and organic solvents for organogels) or a mixture of solvents, and a tridimensional network of fibers entangled together, which can be even less than 1% w/v. All these types of gels will be discussed in the review. The highly porous structure of these materials allows the incorporation of many species with different sizes and shapes,[17–21] and their use in applications dealing with their release or adsorption.[22–27]

Among the possible types of supramolecular materials that can be obtained with LMW peptide gelators, gels are considered smart materials, because they can respond to a plethora of chemical or physical stimuli (light, pH, temperature, enzymes, solvents) useful for several applications. These materials conveniently respond to specific energy

inputs with a reversible conversion from solution to gel and *vice versa* (assembly/disassembly). This on–off switching of the self-assembly process can be used conveniently for the detection of a change in the environment (pH, concentration of analytes, redox state) as well as for the release of an entrapped component (drug, enzyme, crystals).[28–32] For instance, light-responsive gels contain molecules that change shape when hit by light, causing the gel to stiffen, soften, or even release molecules trapped inside. Light of specific wavelengths can stimulate a variety of responses, such as cleavage of crosslinks, diffraction shifts in the presence of analytes, biomolecule, and nanoparticle uptake and release.[33] Thermo-responsive gels, instead, react to temperature changes, and can both thicken or undergo gel-to-sol transition.[34,35] This makes them useful for controlled delivery or to create switches based on temperature. Some gels may exhibit a dynamic response to changes in the acidity of the surrounding environment. The incorporation of functional groups with ionizable moieties, such as carboxylic acids or amines, into the gelator molecules provides the basis for pH-sensitivity.[36] At a specific pH value, typically corresponding to the pK_a of the incorporated functional groups, a transition in the ionization state of the gelator occurs. This transition alters the intermolecular interactions between gelator molecules, leading to a change in the overall structure of the gel network.

Species can be loaded in the gel matrix by physical entrapment in the pores, or encapsulation, which results in the release by diffusion, or covalently bonded to the gelator and released by degradation thanks to proteases or specific stimuli. Many reviews already reported the use of LMW peptide gels especially for drug release applications, related to specific drugs[13] or proteins,[37] or to specific types of release.[38] For the majority of cases, a single LMW gelator is used to form the gels and this is defined as a single-component system. There are also a number of examples where at least two gelators are needed to form a specific 3D structure and are identified as multicomponent gels.[39–41] This review aims to describe recent papers about gels for the release of different cargos, from drugs, to dyes, cells and fragrances, focusing on the types of functionalized materials that can be obtained from peptide derivatives. The materials here reported would be thus divided into paragraphs. In the first part, the discussion will be focused on single component and multicomponent gels encapsulating the cargo; then, it will continue with gels containing fillers, such as polymers or inorganic particles, and will finish with systems based on gelators covalently linked to the cargo (Figure 1).

2 | CARGO ENCAPSULATION: SINGLE-COMPONENT GELS

By encapsulation of a specific substance (drug or cosmetic active agent), an enhancement in its stability against degradation and, at the same time, its controlled release to the medium can be achieved. The simplest method to prepare a gel for release applications is by mixing the gelator and the selected compound, thus obtaining its encapsulation in the gel matrix by coacervation. As the guest molecules are only physically entrapped inside the gel network, their diffusion rate depends on their molecular weight and dimension of the pores, as well as on the strength of noncovalent interactions with the gelator molecules.[26,36,42]

One of the first examples was reported by Vegners et al., which observed the formation of a gel from Fmoc-Leu-Asp and some dipeptide analogues, Fmoc-Ala-Asp e Fmoc-Ile-Asp, with the heating–cooling method.[43] Two LMW drugs, 3,5-dimethyl-1-adamantmamine hydrochloride (Ada2Me) and 5-methyl-1-adamantmamine 3-carboxylic acid (Ada-MeC) were incorporated in the Fmoc-Leu-Asp gel. The gels obtained were then injected into rabbits, and an increase in the production of specific antibodies against this drug was observed, without the need for additional adjuvant. This response was not observed in presence of the drugs alone.

Hamachi et al. reported thermally responsive *N*-acetyl-galactosamine-appended amino acid (GalNAc-aa) derivatives, able to shrink upon heating and reform upon cooling.[44] The release of species trapped in this gel matrix could be thus controlled with temperature changes. For instance, DNA may be discontinuously released upon the gel shrinkage. In contrast, bisphenol A, a hydrophobic water pollutant, is entrapped in the hydrophobic cavity of the gel and coprecipitated with the shrunken gel upon heating.

A lysine-based cyclic gelator, coupled with a fluorinated azobenzene, resulted to be a photochromic supramolecular gelator, able to release several unmodified drugs (antibiotics, anti-inflammatory, and anticancer drugs, proteins) upon green light irradiation.[45] Other examples of Lys-based gelators in biocompatible solvents, such as paraffin, 1-decanol, and 1,2-propanediol, were reported by Kaplan et al.[46] Their compounds can form gels in the presence of a high loading of naproxen (up to 166.6% as percentage of gelator) and releases the drug in a controlled fashion, depending on the gelator concentration and on the pH. Thermally stable and reversible gels were formed by the assembly of some open chain C_2-symmetry pseudopeptides containing a carboxylic pendant group in the spacer. Even in this case, the

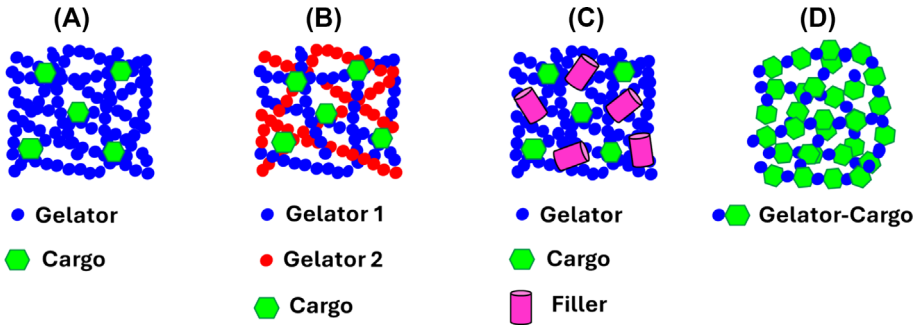

FIGURE 1 Schematic representation of the types of self-assembled gels that will be discussed: (a) single-component and (b) multicomponent gels with cargo encapsulation; (c) gels containing a cargo and a filler (polymeric or inorganic); (d) gelators covalently linked with the cargo.

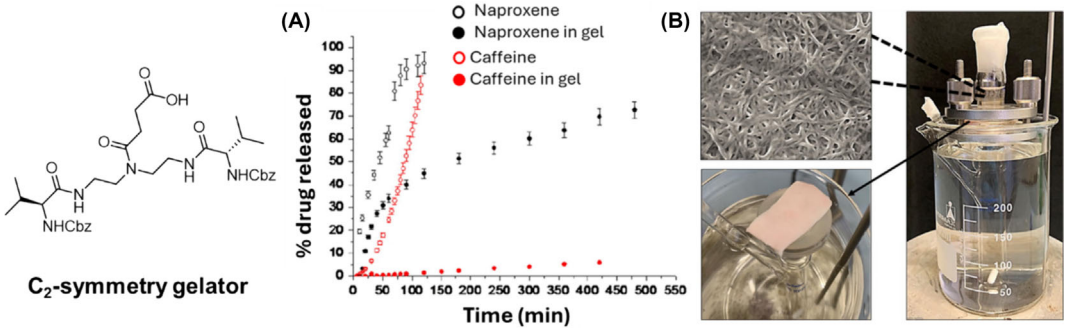

FIGURE 2 (a) Drug release profile in the absence (empty circles) and presence (full circles) of the C_2-symmetry pseudopeptide gelator (chemical structure on the left). (b) Image of the Franz cell and the pig skin membrane. Adapted with permission from ref.[47]

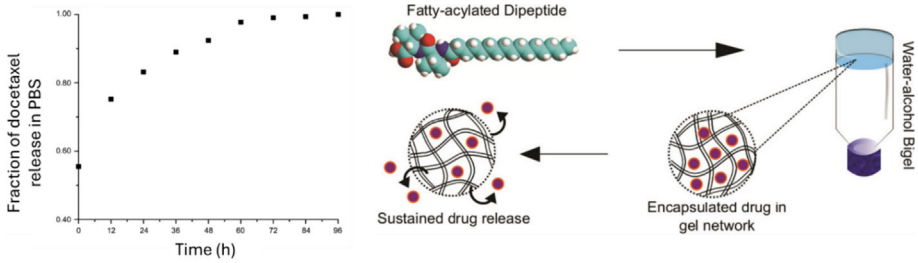

FIGURE 3 Release profile of docetaxel in PBS from a water/alcohol bigel and schematic representation of the drug encapsulation and release. Adapted with permission from ref.[49] Copyright 2020 American Chemical Society.

presence of the gel matrix significantly reduced the release of two model drugs (naproxen and caffeine), analyzed through pig ear skin in Franz diffusion cells (Figure 2).[47]

The addition of long alkyl chains deriving from fatty acids was also reported as a successful strategy to obtain amphiphilic amino acids,[14,48] leading to the formation of biocompatible materials, able to gel different solvents (vegetable oils, organic solvents, water/alcohol mixtures) and to release a cargo. Some water/alcohol bigels based on combinations of Leu/Ile/Val and fatty acids were reported for applications in the release of dyes and drugs (Figure 3).[49] These water/alcohol mixtures make it possible to encapsulate large amounts of poorly water-soluble drugs, and ensure a sustained drug release, as that of an anticancer compound released over 3 days in PBS (phosphate saline buffer).

The esters of some amino acids (Ala-Me, Glu-Me, Ser-Me, and Ala-Et), derivatized with C_{20} fatty acids, were reported to be organogelators for soybean oil and demonstrated a controlled release of risperidone over 7 days *in vivo*, when subcutaneously injected.[50] Llansola et al. described a Pro-Val dipeptide hydrogelator with a C_{12} chain[51] bearing a nucleophilic site that reacts in the presence of aldehydes, with the consequent disassembly of the gel network. This behavior leads not only to the visual detection of aldehydes but also to the controlled release of compounds entrapped within the gel, with a rate depending on the structure of the aldehyde used. Methylene Blue and ketoprofen were studied as simple models to evaluate the potential application of these hydrogels for drug delivery, in response to specific aldehydes. Other works related to the adsorption of pollutant dyes also reported the study of their release/removal to completely recover the pristine gel and reuse it in multiple cycles of adsorption.[52,53] Encapsulation of essential oils for flavors and fragrances is also of great interest.[54] These are volatile compounds synthesized by plants and having strong odors, often with antimicrobial, antioxidant, antiviral, and anti-inflammatory properties. Their encapsulation is a good strategy to avoid their degradation during storage or fast volatilization, allowing a controlled release.[55,56] In a recent study, urea-based LMW pseudopeptidic organogelators were successfully tested for their ability to encapsulate (R)-limonene.[57] The time needed for the release resulted to be almost 4.5 times larger for the gel than for pure (R)-limonene. Our group recently reported two studies on the comparison of fragrance release between solutions and gels made from L-Dopa (3,4-dihydroxyphenylalanine)[58] derivatives [Boc-L-Dopa $(Bn)_2$-OH and its methyl ester analogue]. In these works, we synthesized two families of profragrances, which are precursor of fragrances obtained by a covalent bond between two odorant molecules. These compounds can respond to specific stimuli, which break the bond and lead to the release of the fragrances.[59–61] In a first study,[62] we reported the controlled hydrolysis of four imines (or Schiff bases). Their entrapment in the gel medium reduced the hydrolysis rate, prolonging the release time of the odorant molecules. In a second study,[63] the lactonization of four esters derived from *o*-coumaric acid was studied in gels and solutions upon exposure to solar light. Even in this case, the release of coumarin and odorant alcohols was significantly reduced in the gel matrices, which allowed an increased stability and long-lastingness of the fragrances (Figure 4).

A part from drugs, dyes, and fragrances, the encapsulation method was also envisaged in few studies to entrap contrast agents, such as Gd(III) complexes,[64] even exploiting peptide amphiphiles.[65]

2.1 | Phe-based gelators

One of the most used gelator in the field of peptide-based LMW gels is the ultrashort unit, Fmoc-Phe. The self-assembly of this gelator was

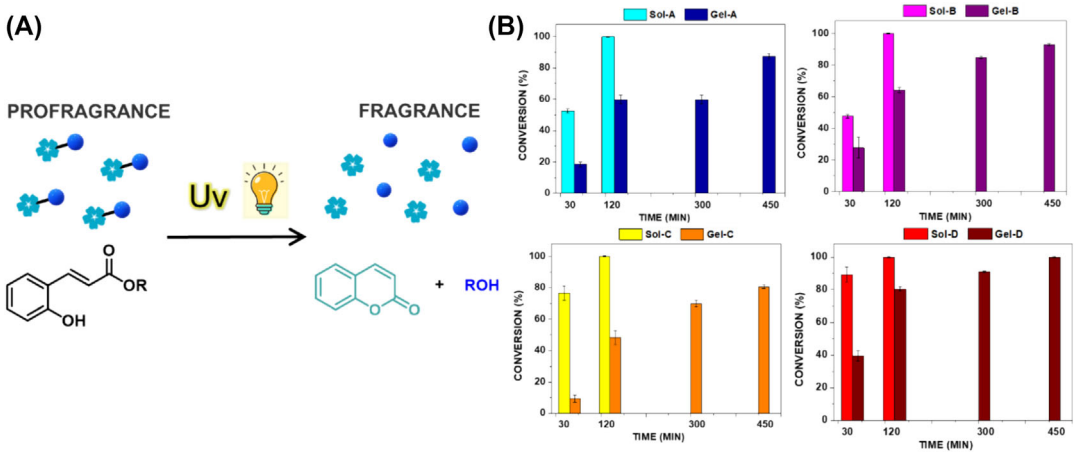

FIGURE 4 (a) Schematic representation of the release of fragrances from profragrances. The *o*-coumaric esters react under UV light, releasing odorant molecules (coumarin and alcohols). (b) Kinetics of the lactonization of profragrances A–D in solution (sol, lighter colors) and in gel (gel, darker colors) under solar light. Adapted with permission from ref.[63]

largely studied,[66] also in combination with other species (Table 1). Among them we can find drugs, such as doxorubicin, which is able to co-assemble with Fmoc-Phe, interacting by noncovalent interactions (H-bonding and π-π stacking). In this system, the release is dependent from the erosion and disassembly of the gel network.[67] Salicylic acid, a precursor of aspirin, was also added to Fmoc-Phe gels and released in a controlled fashion over days.[68] Sutton et al. have reported the use of Fmoc-Phe and a Fmoc-Tyr to obtain hydrogels for dye entrapment and release.[69] Dyes with different radii of gyration (see Table 1) diffuse from the hydrogels with similar diffusion coefficients, implying that the network is not specifically retaining even relatively large (5 nm) dyes. On the other hand, the diffusion of larger dyes is restricted from Fmoc-Tyr hydrogels, which have significantly higher storage moduli than those formed from Fmoc-Phe.

Singh et al. also offered a model for drug entrapment and release from Fmoc-Phe hydrogels, using Congo Red and Direct Red.[70] Nilsson et al. also investigated the release behavior of small and large molecules from supramolecular hydrogels, composed of Fmoc–Phe and Fmoc–Phe–DAP (DAP = diaminopropane) derivatives (see Table 1). First, they determined that the release rate of small molecules from their cationic hydrogels was correlated to the charge of the cargo, as positive and neutral molecules were rapidly released, while negative molecules were highly retained.[71,72] Then, they studied the release of four model proteins (ribonuclease A (RNase A), trypsin inhibitor (TI), bovine serum albumin (BSA), and human immunoglobulin G (IgG)) at different pH values, obtained by the addition of NaCl (pH ≈ 5) or DMEM, Dulbecco's modified Eagle's medium, (pH ≈ 7).[73] They found out that the hydrogels facilitate the release of proteins of varying size and charge, and release rates can be controlled by modifying the pH and ionic strength of the hydrogel network. Significantly, the proteins maintain native function within the hydrogel network and upon release from the network. Tiwari et al. investigated various Fmoc- and Boc-protected dipeptides containing Phe for the sustained release of several anticancer drugs (Figure 5), such as doxorubicin, curcumin, and 5-fluorouracil (5-FU).[74,75] The proteolytic stability of the gels was improved thanks to the presence in the gelator structure of γ- or δ-amino acids (such as Gaba = γ-aminobutyric acid and Ava = δ-amino valeric acid) and D-amino acids. The gels showed thermoreversible, injectable, and self-healing properties, and it was also demonstrated that the Boc-hydrogelators display mechanical strength comparable to the Fmoc-derivatives, with the additional advantage of a synthesis which does not imply the basic conditions that may lead to the racemization of the chiral amino acids.

The microscopic hollow cavities present in the fibrous network formed by Fmoc-Phe-Phe were also used as a reservoir for diagnostic/therapeutic material by Mahler et al.[76] Their study reports the self-assembly of the gelator in the presence of fluorescent particles of various molecular dimensions: fluorescein and insulin–FITC (FITC: fluorescein isothiocyanate). Some derivatives of Phe-Phe in combination with Lys (such as Nap-FFKK) to obtain a cationic peptide were also investigated as systems for ocular drug delivery.[77] These gels demonstrated improved efficacy compared to the anionic analogues containing Asp, in terms of *in vitro* cellular uptake and of adhesion and retention to the cornea, a convenient way to increase the retention of active drugs on eyes.

3 | CARGO ENCAPSULATION: MULTICOMPONENT GELS

In multicomponent gels, at least two gelators contribute to the formation of the fibrous network. This class of materials combines two gelators either because they are not able to form a gel when taken separately or to take advantage of their synergistic properties.[39–41] An example of peptide co-assembly is reported by Hansda et al.[78] Their multicomponent gel (Figure 6) is formed by two peptide amphiphiles (molecules A and B), where the peptides Val-Val

TABLE 1 Summary of the Phe-based gels discussed in Section 2.1

Gelator	- Concentration and solvent - Trigger	Cargo	Release: conditions, duration and type	Ref.
Fmoc-Phe	- 1% (w/v DMSO/H_2O) - Solvent mix	Doxorubicin	37°C, PBS, 10 h, diffusion/erosion	67
Fmoc-Phe	- 0.6% (w/v PBS) - Sonication and temperature	Salicilic acid	37°C, PBS vs. milli-Q water, 4 days, diffusion	68
Fmoc-Phe Fmoc-Tyr	- About 1% (H_2O) - pH (GdL)	Naphtol yellow, direct red, FITC-dextran$_{4K}$, FITC-dextran$_{10K}$, FITC-dextran$_{20K}$	25°C, water (pH 7 buffer), 6 h, diffusion (with different coefficients)	69
Fmoc-Phe	- 0.6% (in PBS) - Sonication and temperature	Congo red, direct red	PBS, 4/25/37/45°C 2–4 h, diffusion/erosion	70
Fmoc-Phe-DAP Fmoc-3F-Phe-DAP Fmoc-F_5-Phe-DAP	- 33.7mM (H_2O) - NaCl	Diclofenac	37°C, NaCl or H_2O, 4 days, charge dependent	71
Fmoc-Phe Fmoc-3F-Phe Fmoc-F_5-Phe Fmoc-Phe-DAP Fmoc-3F-Phe-DAP Fmoc-F_5-Phe-DAP	- 20mM (H_2O) - NaCl or GdL	Methylene blue, naphtol yellow S, caffeine	25°C, NaCl or PBS, 3 days, charge dependent	72
Fmoc-F_5-Phe-DAP	- 15mM (H_2O) - NaCl or DMEM	RNase A, TI, BSA, human IgG	37 °C, PBS, 3 days, charge and MW dependent	73
Fmoc-Gaba-Phe Fmoc-Ava-Phe	- 0.020% and 0.025% (w/v DMSO/H_2O) - Solvent mix	Curcumin	r.t., simulated intestinal medium (SIM), 3–4 days	74
Boc-δ-Ava-L-Phe Boc-δ-Ava-D-Phe	- 0.3% w/v (PBS) - Temperature	5-FU, curcumin, doxorubicin	r.t., SIM or PBS, 4 days	75
Fmoc-Phe-Phe	- 0.5% w/v (HFIP/H_2O) - Solvent mix	Fluorescein, insulin-FITC	r.t., milli-Q water, 24 h, size-dependent diffusion	76
Nap-Phe-Phe-Lys-Lys Nap-Phe-Phe-Asp	- 1% w/v (PBS) - pH or temperature	Levofloxacin	*In vivo* (rabbits), 8 h	77

and Lys-Phe-Phe are coupled with two amino-fatty acids (11-aminoundecanoic acid and dodecyl amine).

Different ratios of the two gelators form gels, with tunable mechanical properties, injectability, and biocompatibility. The 1:1 mixture is also able to encapsulate a variety of drugs, including anticancer drugs (doxorubicin) and antibiotics (amoxicillin and rifampicin), and sustaining their release over 3 days. In another case, the nanofiber formation of Fmoc-Phe was exploited to reinforce puerarin (7,4′-dihydroxyisoflavone-8-β-D-glucopyranoside, PUE) hydrogels and to introduce convenient antibacterial properties.[79] The mixed gel can efficiently inhibit *Staphylococcus aureus* by taking advantage of the synergistic effect of the gel matrix and an additional antibacterial agent added to the system, berberine hydrochloride. The release of this compound is pH dependent, because the PUE hydrogel network is sensitive to alkaline conditions: the weakening of the gel structure leads to an increase (Figure 7).

LMW peptide gels can also be prepared starting from gelators with a double function not only of structural component of the material but also for their specific bioactivity. This is for example the case of Fmoc-Leu and Fmoc-Lys, two anti-inflammatory agents. These compounds self-assemble forming a multicomponent gel when dissolved in a basic solution and subjected to a heating/cooling cycle, and may incorporate antineoplastic drugs, such as 5-fluoro-2′-deoxyuridine.[80] A slightly longer and phosphorylated gelator precursor based on Fmoc, Lys, and Tyr (Fmoc-KKYpYp) was mixed with the prodrug etoposide phosphate.[81] Both the prodrug and the gelator precursor are dephosphorylated in presence of the ALP enzyme (alkaline phosphatase), overexpressed in cancer cells, which transforms the precursor in the gelator, and the prodrug into the anticancer drug (Figure 8). The co-assembly of the two compounds formed nanostructures similar to those of the gelator alone, led to prolonged slow release of the drug, and slightly enhanced its anticancer effects. Multicomponent amphipathic tetrapeptides (based on combinations of Phe/Lys or Phe/Asp) assemble through the complementary charge interaction between acidic and basic residues. These easily spreadable gels were evaluated for transdermal release applications,[82] providing for a twofold enhancement in permeation of the drug in a time-dependent manner and at nontoxic concentrations.

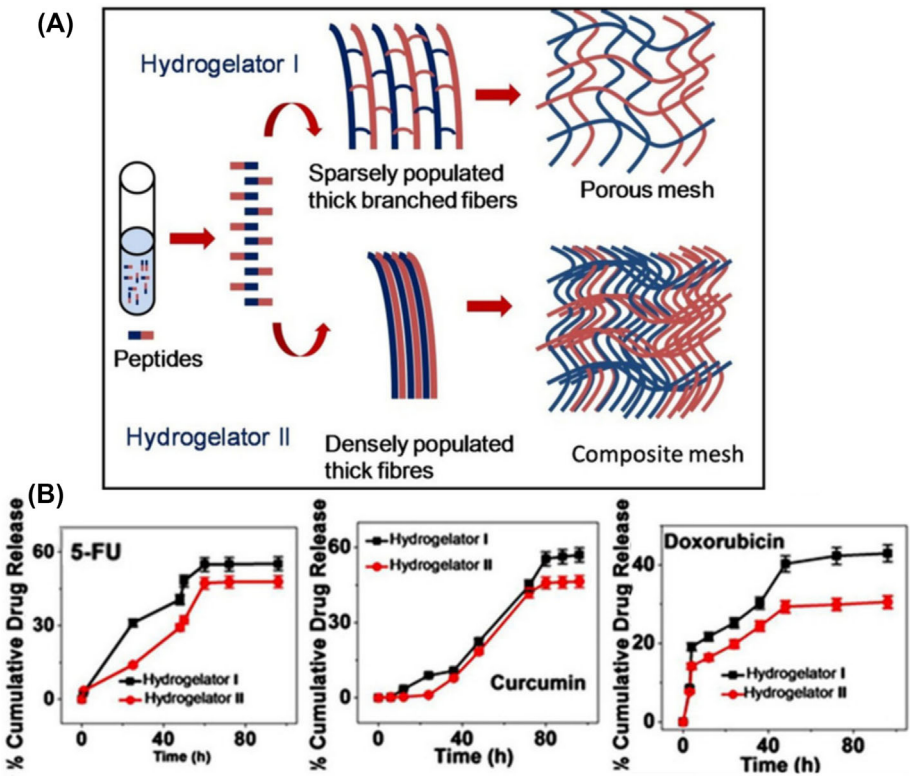

FIGURE 5 (A) A plausible mode of self-assembly of the hydrogelators based on SEM images. By increasing the concentration of hydrogelator I, thick branched nanofibers were gradually interconnected by a porous mesh, while for hydrogelator II composite mesh formation through multilayer segregation of multiple mesh aggregates was observed. (B) Release kinetics of different anticancer drugs from the matrices of the two hydrogelators. Adapted with permission from ref.[75]

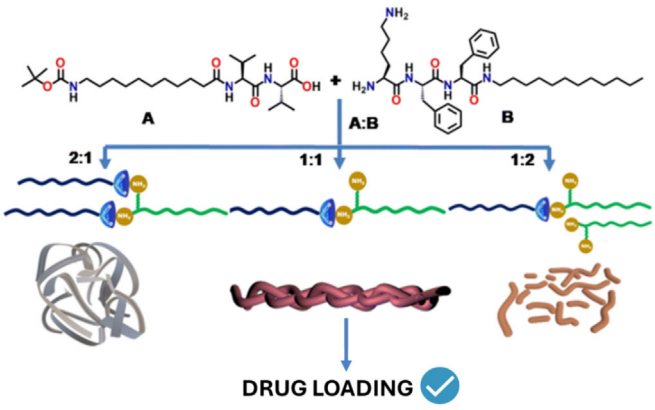

FIGURE 6 Molecular structure of gelator molecules A and B, and schematic diagram of their assembly pattern in different ratios. Adapted with permission from ref.[78]

Our group also reported a multicomponent gel for topical delivery applications.[83] The gel is formed by a robust gelator based on a derivative of L-Dopa,[18] Boc-L-Dopa $(Bn)_2$-OH,[19] which mainly provides the stiffness of the gel, and a tripeptide (Boc-Ala-Aib-Val)[84] which is not able to gel in water alone. By changing the ratio between the two gelators, we obtained gels with different final pH (5–7.4), in the range suitable for the delivery of drugs or cosmetic active molecules. The gels are also thixotropic and can reform even after many cycles of harsh shaking. We introduced in the gels two tripeptides known for their anti-age activity and analyzed their permeation through pig skin in Franz cells. A simple two-component gel based on a glutamine amide derivative and benzaldehyde, forming a reversible Schiff base, was reported for nasal delivery of neurologically active drugs, such as L-Dopa.[85] In this case, the gel was designed to have soft rheological properties and to show a fast release of the encapsulated drug, which is more desirable in nasal delivery applications. The gel formulation outperformed the L-Dopa solution, probably for its longer persistency in the nose cavity. Multicomponent photoresponsive gels made of Fmoc–Phe and 4,4′-azopyridine were reported by Dou et al.,[86] who assessed an enhanced release of the encapsulated sulforhodamine B dye molecules upon Uv light irradiation. Feng et al.[25] reported a multi-responsive hydrogel system co-assembled from a Phe derivative (LPF2) and an azobenzene derivative (PPI). The hydrogel is formed through hydrogen bonds between amide moieties/pyridine and carbonyl groups, and can respond to temperature, pH, host–guest interaction, and photoirradiation. The gels were able to encapsulate mouse embryonic fibroblast cells (NIH 3T3) and upon irradiation started to collapse, leading to a complete gel-to-solution phase transition and to the release of the cells during the disruption process (Figure 9). Since the entire procedure did not involve any destructive factors to the cells, such as enzyme degradation, the 3D scaffold provided a facile and biologically friendly platform for controlling cell encapsulation and release in the noncontact and remote modes.

3.1 | LMW gelators with other fillers

LMW gelator may also be mixed with fillers (polymeric or inorganic) which may confer specific properties to the hybrid gels obtained. An

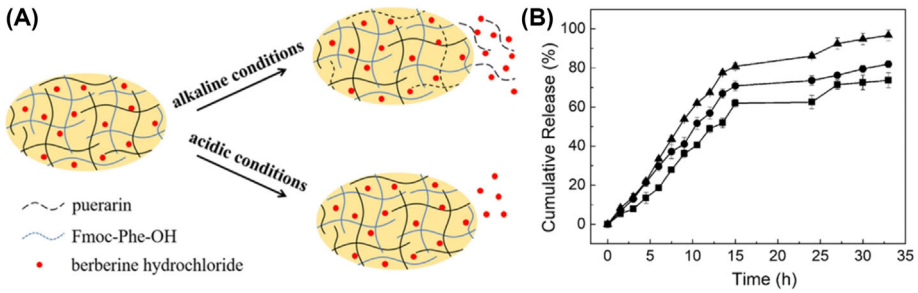

FIGURE 7 (a) Schematic representation of the release of berberine hydrochloride from the Fmoc/PUE hydrogels. (b) Release profiles of berberine hydrochloride from Fmoc/PUE hydrogels at 37°C in pH 5.8 (black square), 6.8 (black circle) and 7.4 (black triangle) PBS buffers. Adapted with permission from ref.[79]

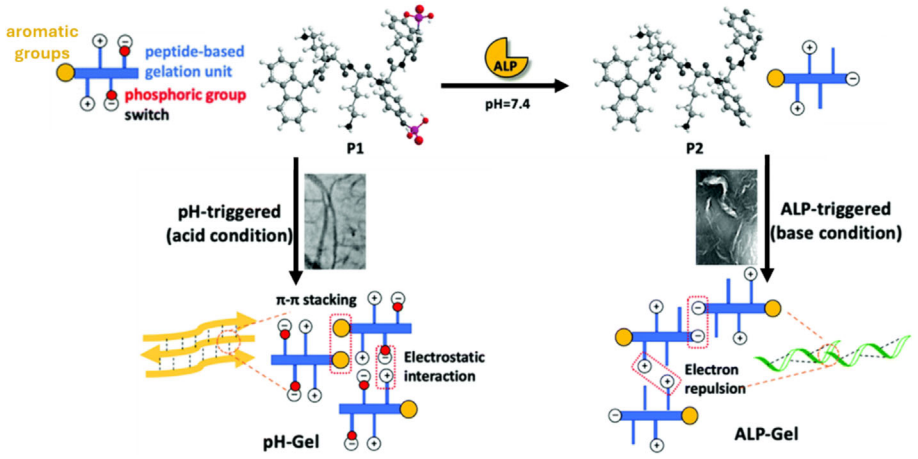

FIGURE 8 Illustration of the distinct self-assembly behaviour of the gelator described using different stimuli: pH (left) and ALP (right). Adapted with permission from ref.[81]

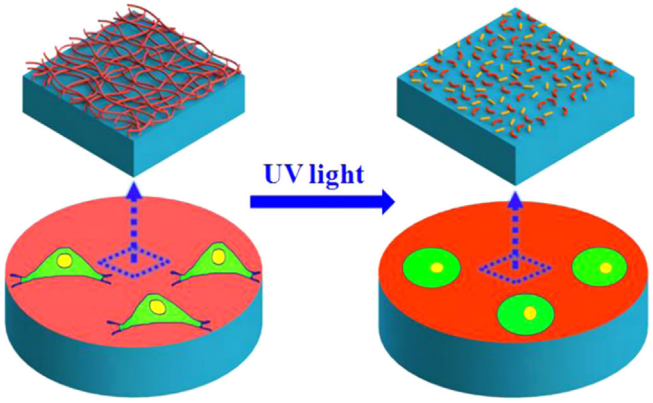

FIGURE 9 The panel shows a schematic view of the gel fiber coatings and NIH 3T3 cells adhered on the films before (left) and after (right) UV irradiation. The yellow rod represents LPF2, and the orange crook is Z-PPI. Adapted with permission from ref.[25] Copyright 2015 American Chemical Society.

example of such systems was reported by Hassan et al.[87] who mixed Fmoc-Phe-Phe and PEG (polyethylene glycol) with different molecular weights. The PEG/water mixture used to prepare these gels has the peculiar advantage that a larger variety of compounds can be co-dissolved and potentially encapsulated compared to the traditional hydrogels formed by the pH change methods, which also hampers the introduction of molecules not stable at specific pH values. This was exactly the case of the two poorly soluble anticancer drugs, Paclitaxel and Temozolomide, also unstable at a basic pH, which were successfully incorporated and then slowly released from the mixed polymer-peptide gel. Fmoc–Phe–Phe was also mixed with chitosan to study the delivery of doxorubicin, whose introduction contributed to increase the stability of the gel.[88] A much more complex system was reported by Wu et al.[89] In this study, the heptapeptide-based gel was chosen for its injectability, structural flexibility, and biocompatibility, and was reinforced by the coordination bonds with cisplatin, an anticancer drug. Alginate nanoparticles were also added to the matrix, to further improve the mechanical properties of the material through electrostatic interactions and also to encapsulate a second drug, irinotecan. With this method, a temporal control of the release of the two drugs was achieved, and the subcutaneous administration of the composite gel proved an efficient inhibition of tumor growth, not obtained with the same doses of the two individual drugs. Wang et al.[90] formed hybrid hydrogels from supramolecular gelators and agarose. Their research results demonstrated that their easily fabricated hybrid materials are highly elastic, with fracture stresses at least 20 times higher than those of supramolecular gels, and can be used for the purpose of long-term, controlled drug release, which was assessed with Congo red as a drug model.

Escuder et al.[91] reported the preparation of two-component hydrogels made by a well-known and biologically active polymer, hyaluronic acid (HA), and a dipeptide-based gelator, L-prolyl-L-valine dodecylamide (PVD). Their strategy consists of using HA, a soluble polymer which is not able to form hydrogels by itself, as an additive that may interact with the LMW gelator network and modify its physical properties.[92] Indeed, PVD is a dipeptide amphiphile that forms hydrogels and has been applied in the context of biomimetic

organocatalysis.[93] Unfortunately, PVD has shown a remarkable polymorphism highly dependent on the hydrogel preparation procedures, that is highly reduced by the addition of HA. The amount of HA integrated into the hydrogel is in line with the weight percentage reported for commercial cosmetics and pharmaceutical HA formulations. As a proof of concept, the prepared material has been tested for cell suspension, for applications where cell sedimentation should be avoided. Hydrogel-containing wells showed bundles of suspended cells surrounding the gel fibrillar network, whereas in control samples, all the cells were adhered to the bottom of the well. This behavior may offer opportunities for advanced cell culture and cell delivery techniques.

Another innovative strategy for delivery purposes relies on the preparation of supramolecular gels where inorganic components are added as fillers, to improve the properties of the material, its responsiveness to specific stimuli or to entrap and release a specific cargo. Liposomes loaded with hydrophilic drugs were entrapped in supramolecular gels together with silica-coated gold nanoparticles. This approach was envisaged to use photothermia as the trigger to stimulate and control the drug release, thus avoiding the passive release often occurring with the encapsulation of a hydrophilic cargo directly in the gel network.[94] Another example was provided by Rizzo et al.,[95] who reported gels containing Fmoc–Phe, with the addition of functionalized halloysite nanotubes (f-HNT) as a filler. These natural clays can easily incorporate the chemotherapeutic anticancer drug selected for the release study, camptothecin (CPT), and were further functionalized by covalently linking Fmoc–Phe on the outer surfaces of the tubes (Figure 10). A comparison of the data collected for the release from HNT and from the hybrid gels/HNT clearly evidenced a synergistic action of the HNTs and the gel matrix. The nanotubes allow a better drug dispersion in the gel, while the gel matrix contributes to a slower rate of drug release, resulting overall as a good alternative to delivery camptothecin in the body, providing a sustained release and preventing its hydrolysis.

Another type of hybrid system is provided by metallogels, where the peptide-based gelators are coordinated by metals. Dutta et al. obtained self-healing and thermoreversible gels using an aspartic acid-based gelator and Mn(II), and successfully used them to encapsulate the anticancer drug gemcitabine and the nonsteroidal anti-inflammatory drug (NSAID) indomethacin.[96] Phe-based bolaamphiphile metallo-gel formed in the presence of several divalent metal salts and demonstrated to be pH dependent, efficient systems to slowly release vitamin B12, and able to absorb various toxic dyes from water.[97]

3.2 | Covalent bond

Short peptides, oligonucleotides, and other synthetic biomolecules have shown remarkable advantages as therapeutic agents and also as carriers for active molecules.[98,99] Design and synthesis of biomolecules covalently tethered to a drug can be made target specific, and could be utilized to inactivate the drug, thereby reducing the side effects.[100] This is particularly important for cancer treatment, as most of the antitumor agents also show high cytotoxicity towards normal cells. This strategy can be also pursued with peptide-based LMW gels, by covalently linking the cargo to the gelator,[101] with or without the presence of a self-immolative spacer[102] between them. The covalent bond can then be selectively cleaved to reach a much controlled and stimuli-responsive release. An antiretroviral drug, zidovudine, was covalently conjugated to a gelator (NapFFKY(p)G-OH), and this approach led to a reduced release (47%) compared to the encapsulated analogue (70%).[103] Das et al.[104] prepared a peptide-prodrug conjugate by linking the drug 5-FU to the Phe–Phe dipeptide by a photo-cleavable linker (4-bromomethyl-3-nitrobenzoic acid). The covalent bond makes the drug cleavage selective upon stimulation, the dosage controlled, and the toxicity to unaffected cells reduced.

Yang et al.[105] synthetized two Phe–Phe–Tyr gelators capped with the synthetic phytohormone auxin 1-naphthylacetic acid (NAA). In the first gelator (NAA-G'FFY), a hydrolysable ester bond connects the NAA and the peptide, allowing a slow release of NAA by

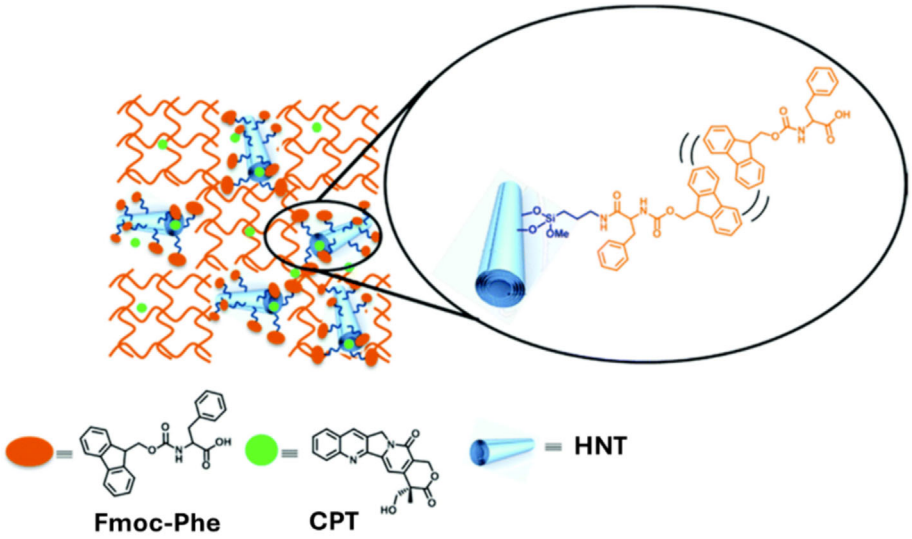

FIGURE 10 Representation of the Fmoc-Phe/f-HNT/CPT hybrid gel. Adapted with permission from ref.[95]

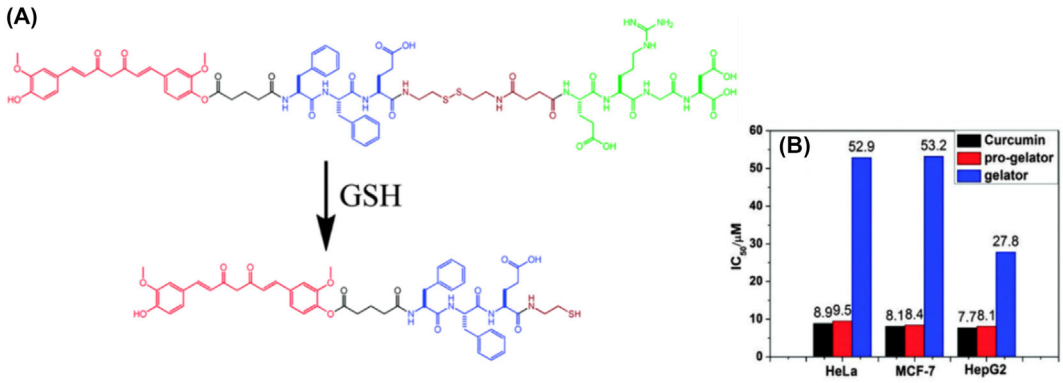

FIGURE 11 (A) The chemical structures of pro-gelator and possible gelator catalyzed by glutathione (GSH). (B) Cytotoxicity of the pro-gelator, the gel, and curcumin against HepG2, HeLa, and MCF-7 cells. Adapted with permission from ref.[106]

changes in environmental conditions, such as the pH. In the second gelator (NAA-GFFY), the NAA was conjugated by an amide bond, and therefore, it could only be released by enzymatic digestion. The first gelator was also mixed with a complementary component, Fmoc-GFFY to obtain coassembled gels, able to release NAA *in vivo* both temporally and spatially, promoting on-site auxin responses including primary root elongation and lateral root formation in the model plant.

It is also possible to form the gelator *in situ* after the cleavage of a specific bond, thus releasing the active cargo and at the same time comparing the efficacy of the pre-gelator and self-assembled gelator in inhibiting targeted processes. An example of this approach is the study of a Phe–Phe–Glu derivative coupled with curcumin,[106] where the addition of glutathione transforms the gelator precursor (pro-gelator), containing also an ERGD sequence, in the effective gelator, by a disulfide bond reduction. The gel sustained the release of curcumin over 24 h and showed higher cellular uptake *in vitro*, but overall, the pro-gelator demonstrated an enhanced *in vivo* efficacy in inhibiting tumor growth (Figure 11). Other examples are the L-amino acids (Hyp, Phe, Leu) bonded to the NSAID drug indomethacin (IND) and then reacted with the antiviral drug amantadine, forming gelator salts.[107] Some of these gelators have anti-inflammatory properties and are capable of cell imaging, while also acting as self-delivery system, and some show interesting mechanical properties such as shape sustaining, load-bearing and self-healing ability.

4 | CONCLUSIONS

The aim of this review article is to collect some recent papers that describe the application of supramolecular gels to the delivery of several cargos, including drugs, dyes, fragrances, proteins, and cells. In the reported examples, the high tunability of the gel systems has a pivotal role in tailoring the release kinetics, that may be also modified on-demand, responding to specific stimuli, thus implementing a spatial and temporal control over the release.

The properties of these gels are ascribed to their formation through the self-assembly of small molecules, called low molecular weight gelators. In this review article, we focused our attention on gelators consisting of small amino acids and peptide derivatives, because of their effective synthesis, biocompatibility, biodegradability, and adjustable proteolytic resistance. It should also be noticed that the chemical structure of the gelators is highly tunable, which is a major difference compared to polymeric systems. The gels may be formed by one gelator (single component) or by more than one gelator (multicomponent) or mixed with other fillers (as polymers or inorganic materials) to provide specific properties. The release profiles in these cases can be highly tuned by the density of the gel fibers and consequent porosity of the network, and by the affinity of the gelator molecule with the cargo. A final paragraph has been dedicated to special gels obtained using gelators covalently linked with the cargo, which is delivered after bond cleavage. This strategy is a powerful mean to achieve site-specific and sustained release over long time periods, drastically reducing for example the side-effects deriving from the burst release of some compounds.

We believe that a deeper investigation on the last two classes of gels, those mixed with polymeric and inorganic fillers and those covalently linked to the cargo, is necessary, since the examples reported in these fields seem very promising and are fewer compared to the classical encapsulation method. The first class allows to finely tailor the mechanical properties of the gels with the introduction of the fillers, and to incorporate cargos inside inorganic particles or nanomaterials, which may further control the release. The second class may instead lead to particularly selective release conditions, by choosing a covalent bond between the gelator and the cargo which could be cleaved in response to one or multiple stimuli. A detailed analysis on *in vivo* studies should also be addressed to assess the real applicability of these materials in practical uses.

With this review, we aimed at demonstrating the advantages of using LMW gels in delivery and release applications, highlighting the many desirable features of these materials, such as tunable viscoelastic properties, thixotropy, self-healing ability, thermoreversibility, and

injectability. We truly believe that self-assembled amino acids and peptide derivatives are a key tool to obtain versatile smart materials, responding to different inputs and environments, and useful for a plethora of applications.

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