

Pseudopeptidic Compounds for Biocompatible Gels: A Review

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KEY WORDS: *pseudopeptides, gels, organogelators, biocompatibility*

ABSTRACT: *Simple pseudopeptides derived from natural amino acids can be designed and prepared as efficient gelators for a variety of solvents, and with a high potential for biocompatibility. The appropriate selection of structural components, reviewed herein, shows how to produce gels with tailored properties, including high thermal stability.*

Gels are formed when a compound present in a solution self-assembles to form a highly cross-linked fibrillar network in which the solvent molecules remain entrapped. The resulting material has properties that are intermediate between those of liquids and solids. Usually, gels are classified according to the nature of the solvent involved.^{1,2} Thus, hydrogels refer to gels formed in the presence of water, while organogels are those in which organic solvents are involved.

Many different types of compounds have been developed and used either as hydrogelators or as organogelators; according to the foods industry, natural and nonnatural polymers originally were tested for the formation of gels. Nevertheless, the use of low molecular weight gelators has gained increasing importance in recent years. Since low molecular weight compounds possess a well-defined structure, their properties including self-assembling behavior can be more easily studied, which allows for the more efficient design and fine-tuning of gelating agents. As a consequence, a large number of technological applications have recently been reported for gels formed either in water or organic solvents through the

use of low molecular weight molecules.³ In particular, gel formulations are used as penetration enhancers for drug and cosmetic actives release. This is due to the fact that incorporating the active component in a gel matrix can control its release rate, increasing the application time and consequently, the corresponding activity.⁴

For applications in food, pharmaceutical and cosmetic industries, biocompatibility is an essential property to be considered.

In this regard, there are several aspects that must be taken into consideration. First of all, topical application in the form of gel increases the contact time, thus favoring the action of the active principles. In addition, it limits the application to the specific desired area, reducing the side effects on other areas, i.e., local irritation. Finally, the occlusion of the active principle in a complex matrix can control the release

rate of the active principles, and the capacity of the gelator molecules to interact with other compounds via supramolecular interactions can be used to regulate this capacity.

Three main properties can be used to define the efficiency of a given gelator: the minimum concentration of the compound in a given solvent at which the gel is formed; the solvents for which the compounds are able to act as the gelator; and the stability of the gel in the presence of external stimuli such as pressure, temperature and pH changes. In general, good gelators can act in concentrations as low as 1–5% w/w, or even lower. Hydrogelators and organogelators differ in that they usually possess different chemical structural motifs including specific groups such as amide, urea and carbamate. In the case of organogelators, most can act as such only for a limited number of solvents with related structures, e.g., toluene, dimethyl sulfoxide, *N,N*-dimethylformamide and methanol, and if one compound is a good gelator for alcohols, it is usually is not a good gelator for ethers. Hydrogelators, on the other hand, incorporate additional polar groups, e.g., carboxylic acids, hydroxy and amino, in their chemical structure, which increases their compatibility with water.

The stability of the gels formed in the presence of external stimuli is critical for practical applications, since gels provide the structure into which additional functionally active compounds are embedded. Thus, gels must be stable in the presence of active compounds as well as during the preparation conditions for the corresponding formula and its manipulation and use. In this regard, thermal stability is often a

limiting factor. Gels are usually formed by heating a solvent in the presence of the gelator and upon cooling, the gel structure spontaneously forms in a reversible process. Accordingly, many gels maintain their properties only at temperatures lower than 50–60°C.

For applications in food, pharmaceutical and cosmetic industries, three leading areas for the application of gels, biocompatibility is a fourth essential property to be considered. As in many other areas of science and technology, trial and error can be used to develop biocompatible gels but a more efficient strategy is to design gelators having structural features that could, in principle, favor their biocompatibility. Building organic molecules based on natural components and providing mechanisms for biodegradation is one of the most common approaches to achieving this target. For cosmetic applications, an important line of work involves using different lipids including cholesterol, and ionic and nonionic surfactants with an amphiphilic nature. This work led to the development by different companies of proniosomal gel formulations as penetration enhancers.^{5–10} However, it is important to take into account that some surfactants can damage epidermis membranes.¹¹

An alternative approach, described herein, is the use of peptides and pseudopeptide compounds of relatively low molecular weight to produce biocompatible gelators. Short peptides and pseudopeptides contain, in their structure, a large number of functional groups and can combine hydrophobic and hydrophilic domains according to the nature of the component amino acids and the structure of the non-natural components, in the

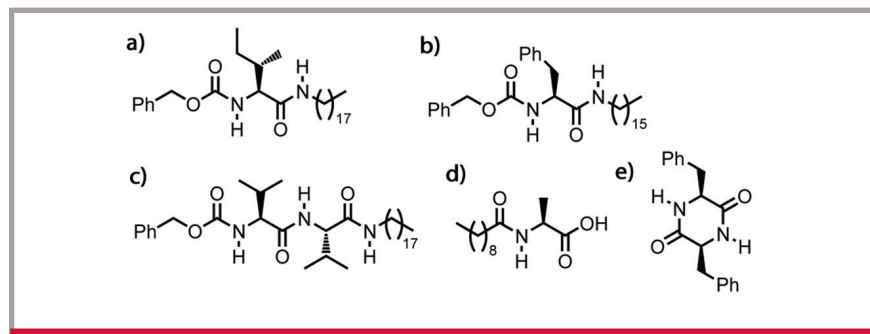


Figure 1. Examples of first generation amino acid-derived organogelators

case of pseudopeptides. These structural features provide the elements for hierarchically ordered supramolecular self-assembly, leading to the development of fibrillar networks required for the gelation process. In addition, the preparation of molecules based on the presence of peptidic bonds, i.e., amide functionalities, facilitates their biodegradation.

Peptidic and Pseudopeptidic Hydrogelators and Organogelators

Different gels based on short amphiphilic peptidic sequences have successfully been used in the area of regenerative medicine. For instance, the peptide $\text{CH}_3\text{CO-NH-(Arg-Ala-Asp-Ala)}_4\text{-CONH}_2$ has been applied for brain repair and has achieved a partial vision recovery in hamsters.¹² These peptides present an alternating sequence of cationic (Arg) and anionic (Asp) amino acids separated by a hydrophobic amino acid. The resulting self-complementary chain forms a β -sheet structure, where one peptidic chain is hydrogen bonded to two additional contiguous chains, giving place to a two-dimensional structure and forming a twisted sheet.

This β -sheet arrangement is the second form of regular secondary structure in proteins, and these sheet structures are able to further self-assemble into nanofibers, providing the formation of stable gels under physiological conditions.¹³ The same strategy has also been used to favor homeostasis, cartilage repair,¹⁴ growth of endothelial cells,¹⁵ angiogenesis¹⁶ and for drug delivery.^{17,18} In some of these cases, no side effects were observed in the animals six months after the introduction of the gelling agents, revealing the high biocompatibility of these types of systems.

The first examples of amino acid-based organogelators were obtained through modification of molecules containing a single amino acid subunit. Thus, long chain alkylamides of *N*-carbobenzyloxy amino acids such as compounds **a**) and **b**) shown in **Figure 1** were reported to act as organogelators for a variety of organic solvents, although in some instances, in particular with polar solvents like alcohols or *N,N*-dimethylformamide (DMF), relatively high concentrations ($> 10 \text{ g L}^{-1}$) were required for gelation at room temperature.^{19, 20} Similar behavior was observed with a similar structure derived from a dipeptide—i.e., long chain alkylamides of *N*-benzyloxy-

carbonyl-L-valyl-L-valine such as compound **c**), also shown in **Figure 1**.²¹ The related compound **d**) in **Figure 1**, in which the long aliphatic chain is bound to the amino acid moiety through acylation of the amino group and contains a free carboxyl group, showed more efficient gelling ability; the concentration required for the relatively apolar solvents studied were below 8 g L^{-1} .²² Cyclo(dipeptides) such as compound **e**) shown in **Figure 1**, also have organogelating properties but in general, only for a limited number of solvents.²³

In recent years, the authors have been involved in the synthesis and study of simple pseudopeptidic compounds based on the general structure **f**) in **Figure 2**. These compounds have a

large potential for diversity and their synthesis is relatively simple and can be achieved in high yields. The properties of the resulting pseudopeptides can be modulated through the proper selection of the spacer and amino acid. Additionally, they can be elaborated in order to incorporate other groups, e.g., R' in compound **g**) (see **Figure 2**), or to obtain macrocyclic structures such as **h**) and **j**), providing a higher degree of preorganization, thus facilitating a more efficient supramolecular interaction with other molecules, which clearly favors the formation of hierarchically ordered fibrillar structures implementing the trapping of different solvents in the resulting network of the gel.^{24, 25} A common feature of all structures in **Figure 2** is the presence of a high

degree of symmetry—i.e., C_2 symmetry associated to the presence of two identical component amino acids, which facilitates not only their synthesis, but also the understanding of their resulting properties and, accordingly, the proper design for the expected applications such as drug delivery, detection of amino acids and preparation of electronic devices.

The first examples applying the pseudopeptidic compounds described in **Figure 2** as organogelators were provided by Hanabusa and Bhattacharya as a step forward from initial structures **a**), **b**) and **c**) represented in **Figure 1**.^{20, 26} Such compounds are exemplarized by compound **k**) in **Figure 3**, which also corresponds to the general compound structure **b**) in **Figure 1**, with R' being the carboxybenzyl-protecting group (Cbz-protecting group), which is a carbamate commonly used as an amine-protecting group in organic synthesis and peptide chemistry. In this case, the hydrophobic fragment is provided by the aliphatic spacer. The compounds studied were good gelling agents for solvents of low polarity, although could also gelate some polar solvents at higher concentrations ($> 10 \text{ g L}^{-1}$). Interestingly, removing the Cbz-protecting group to yield the free amino group to provide compounds with the general structure **f**) in **Figure 2** resulted in a complete loss of the organogelating behavior.

A second class of open chain pseudopeptidic organogelators is represented by bis(amino acid) oxalyl amides, such as **m**) in **Figure 3**. For some of the compounds studied, a single molecule of gelator was able to retain up to 2,000 molecules of solvent, typically polar.²⁷ The role of preorganization provided by macrocyclic structures was clearly highlighted when simple compounds such as **n**) in **Figure 3** were studied.^{28–30} These compounds formed stable gels with a variety of organic solvents, in particular aromatic solvents and esters, providing materials that were stable under different conditions.³¹ The high level or hierarchical organization was revealed by the observation that the intrinsic chirality of the molecule was transferred to the macroscopic level in such a way that the fibers formed had a

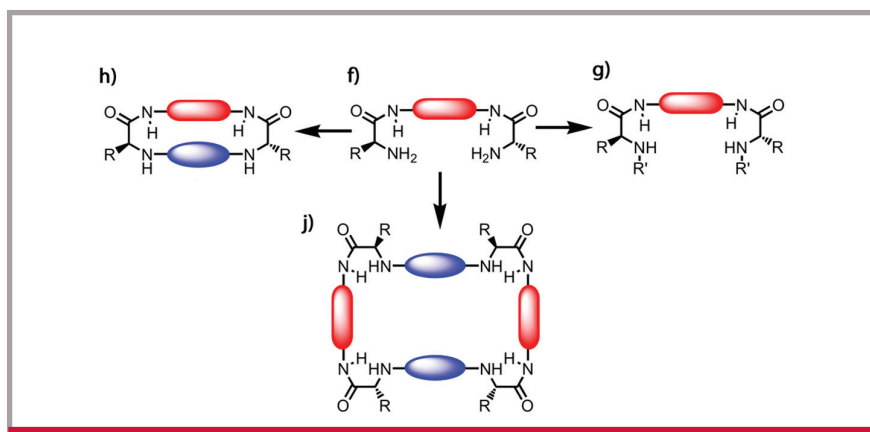


Figure 2. Examples of organogelating compounds with C_2 or C_3 symmetry

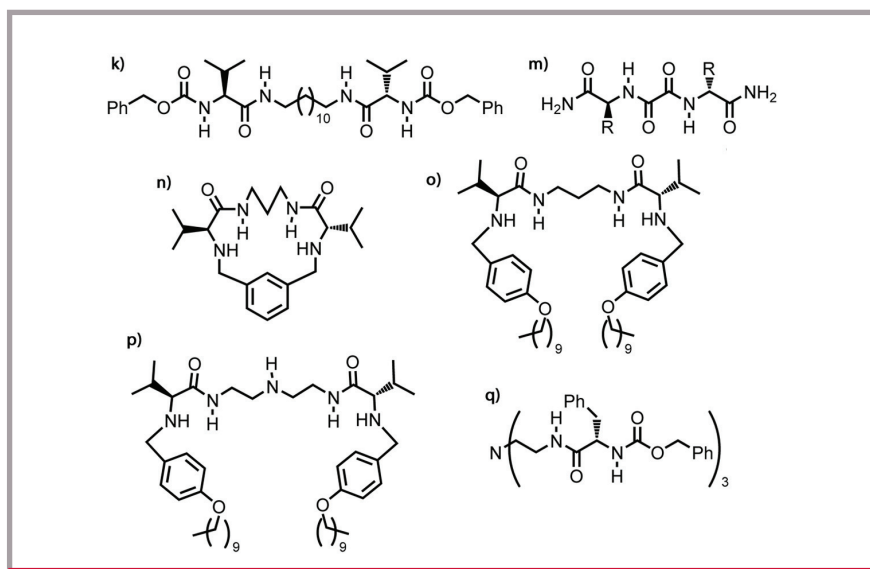


Figure 3. Examples of organogelating compounds

chiral helical structure. The possibility of incorporating active ingredients or drugs into such gels without disturbing their morphology was determined with the help of fluorescence techniques.^{32,33}

Although compounds with the general structure of **j**) (see **Figure 2**) showed interesting self-assembling properties in the solid state,³⁴ no gelling properties had been observed for them yet. The same happens for amphiphilic pseudopeptides like **o**) in **Figure 3**.³⁵ Rather interestingly, a small structural modification, with the introduction of an additional nitrogen atom in the middle of the central aliphatic spacer, see **p**) in **Figure 3**, provides an appropriate chemical structure for the formation of stable gels for a variety of water/ethanol mixtures.³⁶ Additionally, in this case, the gel is formed in situ by the addition of water over the ethanolic solution, without needing the usual heating and cooling cycle.

Very recently, tripodal pseudopeptidic structures such as **q**) in **Figure 3** have also been shown to have some organogelating properties for

aromatic solvents, even if relatively high concentrations were needed ($> 10 \text{ g L}^{-1}$).³⁷ It must be noted that the thermal stability of those gels was significantly higher ($T_g > 73^\circ\text{C}$) than that observed for most organogels. Based on the general structure **g**) in **Figure 2**, a new and interesting family of organogelating compounds is currently being studied.³⁸ These compounds are related to structure **o**) in **Figure 3** but incorporate a urea linkage between the hydrophobic tail and the pseudopeptidic moiety. Two main features define the properties of the resulting pseudopeptides. First, they are able to gelate a broad variety of organic

solvents ranging from polar (MeOH) to relatively apolar solvents (toluene), as shown for selected examples in **Table 1**. In addition, all the gels formed show very high thermal stability, with gel-sol transition temperatures higher than 80°C ; in some instances, it was observed that distillation of the solvent could be carried out without destroying the fibrillar structure of the gel.

As observed in **Table 1**, an almost universal organogelating character can be reached for some of these compounds, including with solvents such as dimethyl sulfoxide (DMSO), which has often been used in combination with different active components for

Table 1. Selected examples for the gelation behavior of bis-urea pseudopeptidic compounds in different organic solvents

Compound	DMF	DMSO	CH ₂ Cl ₂	MeOH	ACN	Toluene	CHCl ₃
g1)	G (3.1)	G (4.8)	G (4.7)	G (3.4)	G (3.4)	G (4.2)	G (3.5)
g2)	G (4.3)	G (6.0)	G (4.3)	G (3.9)	G (4.6)	G (3.7)	G (4.1)
g3)	G (5.3)	G (6.0)	G (5.9)	G (5.7)	G (6.3)	G (5.3)	G (5.0)

Note: G = gel, minimum gelator concentration (g L⁻¹); S = soluble; I = insoluble; ACN = Acetonitrile.



Figure 4. Gels with high transparency can be formed from pseudopeptidic structures

skin treatments.³⁹ It must be noted that in general, the organogelating behavior is associated with the presence of a central aliphatic spacer. This is in contrast with recent findings based on systems containing aromatic spacers but in these cases, the presence of additional functionalities on the aromatic groups seems to play a critical role for the properties of the resulting compounds.⁴⁰

Pseudopeptidic Gels and Cosmetic Applications

Specific applications for pseudopeptidic gels in cosmetic formulations include where products are applied as creams or gels, in order to increase contact time and facilitate their topical application only on desired areas. Different materials, waxes for instance, have traditionally been used as a base component for cream or gel formulations, however, their use has some drawbacks. For instance, these semisolid systems often have low transparency, which can make it difficult to achieve the desired appearance in some cosmetic products. Besides, waxes and related materials must be used in relatively high amounts, in some cases 40% or even higher, to impart the semisolid property to the resulting composition. This can produce a heavy feel, difficult application and high levels of residue on the skin after application. Other alternatives have been considered, e.g., the use

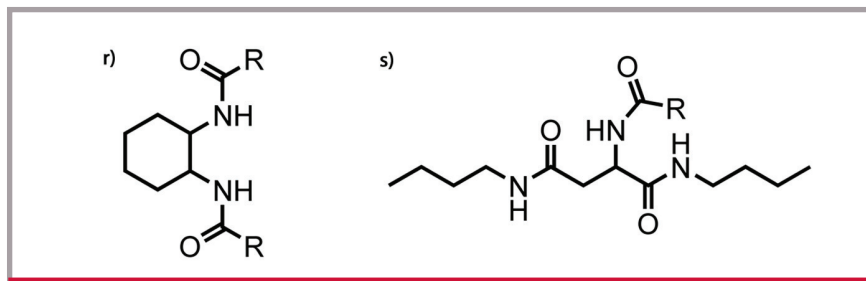


Figure 5. Examples of organogelating compounds with cosmetic and pharmaceutical applications

of emulsions or liposomes, but many of those approaches are limited due to cost constraints. Some of those limitations can be overcome by the use of organogelator and/or hydrogelator systems in place of the waxes and related materials to impart the appropriate rheological properties to the cosmetic composition.

Short peptides and pseudopeptides contain functional groups that can combine hydrophobic and hydrophilic domains, leading to the fibrillar networks required for gelation.

As noted, different advantages are associated with the use of pseudopeptidic gels and in general, a good gelator must function at relatively low concentrations—certainly below 10% w/w and, advisably, below 5%. In some cases, the authors have found the amount required to be as low as 1 g L⁻¹. This simplifies the cosmetic formulation since the gel greatly reduces the amount and variety of rheological additives required, as well as reduces residue and potential side effects. The gels obtained from low concentrations of gelating agent in particular are also very transparent and stable; the sample shown in **Figure 4** was prepared by the authors from a pseudopeptidic structure.

Although few instances of amino acid-derived gelating agents for cosmetic applications are currently cited

in the literature, some related structures have been used by companies in the field; for instance, in Japanese patents, the use of organogelators with a bisamide structure based on different diamines and a fatty acid, typically branched, is described.^{41,42} Although the initial compounds were acknowledged for a broad range of potential applications including cosmetics, specific applications also have been described. For instance, amides of stearic acid with ethanolamine or ethylene diamine have been used for the preparation of toilet oil bars that enable the release of oil when wetted with water.⁴³ The use of these diamides for other cosmetic and pharmaceutical applications also has been considered (see **Figure 5**); in particular, the preparation of new red lipsticks have been described using small amounts of compounds such as **r**) shown in **Figure 5** (< 10%).⁴⁴ More related to the pseudopeptidic structures considered here are the N-acyl amino acid amides like **s**) shown in **Figure 5**, which have been used as gelators for the preparation of antiperspirant gel sticks.⁴⁵

Conclusion

In conclusion, amphiphilic peptides and pseudopeptides of relatively low molecular weight are promising candidates for the development of biocompatible hydrogels and organogels for pharmaceutical and cosmetic applications. Of particular interest are the pseudopeptidic compounds, as the incorporation of non-peptidic components allows for an easier and more effective design, and for simpler—and therefore, more economic—synthesis, a factor that can be critical for practical applications at an industrial level. By

properly designing these materials, one can produce gelators for essentially all kinds of solvents and for very high stabilities, which is of great importance for facilitating the manipulation of the resulting gels and to avoid the loss of gel properties upon storing, transport or use.

The biocompatibility of peptide-based gels is well-documented, having been used for tissue repair on different animals. In the case of pseudo-peptides, preliminary studies on some of the described compounds also have revealed a very low level of toxicity for different microorganisms. Additionally, some compounds with the general structure **h**), in **Figure 2**, have efficiently been used as intracellular fluorescent pH probes.^{46, 47}

It can be expected that, in the near future, peptide-based organogels and hydrogels will also be important components of the cosmetic industry, improving the aesthetic and rheological properties of the resulting compositions, facilitating the application and the release of the active principles, and reducing significantly the amount of additives required for the corresponding formulation. In addition, the high potential of these structures for being designed according to the expected application represents a key advantage for their use. It may also be envisaged that gelating compounds may be developed to selectively interact with the different active principles in the composition in such a way than a selective

control of their individual release could be achieved. Finally, the development of gels with properties being regulated by external stimuli, i.e., the pH of the area of application or the presence of a specific compound, could produce intelligent cosmetic products that release the corresponding active principles only when they are required and just in the area where they are needed.

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