A Brief History of Polymeric Cryogels

Vladimir I. Lozinsky

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Abstract Polymeric cryogels, the gels formed in moderately frozen gelling systems, have been empirically known for many decades, but systematic scientific research on various cryogels and the peculiarities of cryotropic gel formation only commenced at the beginning of the 1980s. This historical review briefly describes the principal stages of the studies on these very interesting gel materials. It also discusses some mechanisms of their formation, as well as summarizes published data on the main representatives of chemically crosslinked (covalent), ionically linked, and noncovalent (physical) cryogels.

Keywords Polymeric cryogels • Cryogel history • Moderately frozen gelling systems • Cryotropic gelation processes

V.I. Lozinsky (✉)
Laboratory for Cryochemistry of (Bio)Polymers, A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Vavilov Street 28, 119991 Moscow, Russian Federation
e-mail: loz@ineos.ac.ru

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1 Introductory Remarks

Polymeric cryogels are the gel systems formed via the cryogenic treatment (moderate freezing—frozen storage—thawing) of solutions or colloidal dispersions of the appropriate precursors [1]. On a microscopic level, moderately frozen molecular or colloid solutions are heterophase systems containing both solids (i.e., the polycrystals of frozen solvent) and some unfrozen fraction called "unfrozen liquid microphase" [2], where the solutes are concentrated. Thus, gelation can only occur within the latter unfrozen regions of the system while the crystals of frozen solvent act as porogens. Such specific conditions of gel formation are the key factors in determining the rather unusual heterophase macroporous morphology of the resulting polymer materials, the whole set of their physicochemical characteristics and, as a consequence, their operational capabilities. The present volume deals with the diverse aspects of preparation, properties, structure, and practical implementation of various cryogels based on synthetic organic or inorganic polymers, as well as on natural biopolymers. Taking into account the fact that the number of the works published in this field has grown almost exponentially during recent years (Fig. 1a), it is reasonable to first give a brief historical overview of these gel systems, which are very interesting both from the fundamental and applied viewpoints. Moreover, the authors of some recent publications devoted mainly to the applied aspects often seem to be unaware of the pioneering studies and main scientific sources. It is hoped that this chapter will also contribute to a better understanding of the developments achieved in cryotropic gel formation over the past three decades.

In many cases, it is difficult to indicate which exactly was the very first communication on some experimentally observed phenomenon, especially if it was discovered many years ago in the pre-electronic era, and the report appeared in an issue hardly available now, or if it was patented locally in a language not commonly used. The present brief historical information certainly has no claim to be an exhaustive review of all the early pioneering publications on cryogenically produced gel matrices. Nevertheless, we can assert that the term "cryogel" was most probably applied for the first time in a paper published in 1984 to designate polymeric materials prepared via chemical crosslinking of macromolecular precursors in moderately frozen organic media [4]. The term was created by combining "cryo" (from the Greek *kryos*, meaning frost or ice) and "gel," thus highlighting the specific formation conditions for the gels of this family. Besides the mentioned article, different terms were used for gels formed in frozen systems (mainly, aqueous ones): cryocoacervates [5], cryocoagulates [6], cryo-concentrated gels [7, 8], anomalous gels [9], freeze–thaw gels [10], etc. However, since the end of the 1980s the term "cryogel" has become more and more popular (Fig. 1b).

It should also be noted that several other materials are currently called "cryogels." Specific examples are as follows:

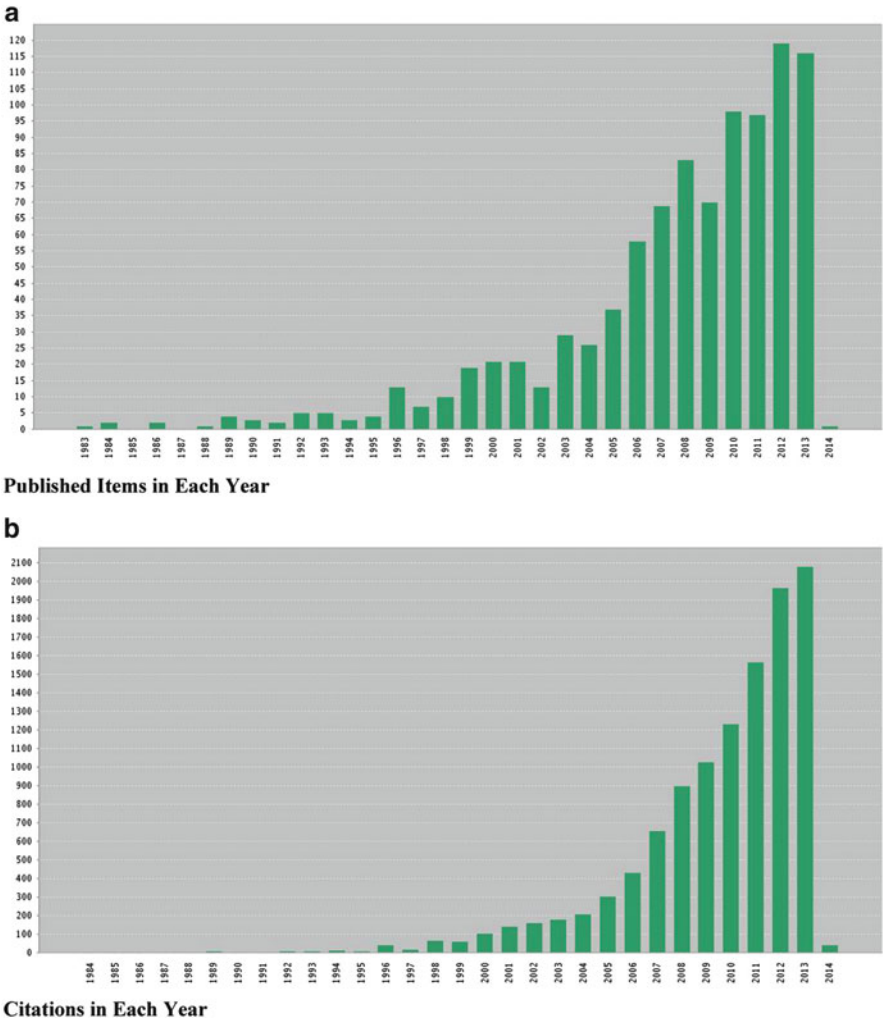

Fig. 1 The number of publications (**a**) and citations (**b**) with keywords "cryogel" or "cryogels" from 1980 to 1 November 2013 according to the ISI Web of Knowledge portal [3]

1. Commercially available jelly-like medical liniments causing a cooling-down effect when spread on the skin surface [11]. It is evident that this has no relation at all to gel formation under frozen conditions.
2. The proteinaceous water-swollen coagulates that are formed upon low-positive-temperature chilling of blood plasma taken from the patients with rheumatoid arthritis or some complex immune diseases [12, 13]. Since no freeze–thaw treatment is applied to the precursor liquid in order to induce the formation of such coagulates, the use of the term "cryogel" for this protein matter appears unjustified.

3. The so-called "carbon cryogels" prepared by swelling of certain crosslinked organic polymers, e.g., swelling of phenol–formaldehyde resins in crystallizable organic solvents such as benzene, followed by freezing of the swollen matter and finally freeze-drying to obtain a macroporous polymeric texturate, which is then subjected to high-temperature carbonization with the formation of activated carbon (charcoal) possessing specific macroporosity [14–16]. It is also obvious that such final materials (i.e., "carbon cryogels") are not gels at all, because gels are 3D networks constructed from organic or inorganic polymers and necessarily contain immobilized low molecular weight solvate liquid (i.e., water in the case of hydrogels).
4. Some authors have named the polymeric matrices fabricated via conventional freeze-drying by the term "cryogels." Certainly, freezing of polymeric solutions or colloidal dispersions causes solid–liquid phase separation, and the subsequent sublimation of the solidified solvent crystals "fixes" the system thus structured [17, 18], but no gelation occurs during these consecutive steps. Therefore, it is more correct to call such freeze-dried polymeric matrices "cryostructurates" or "cryotexturates" rather than "cryogels."

Taking into account the above considerations, one can conclude that the polymeric and biopolymeric materials mentioned above are not related directly to proper cryogels and that they are probably named by such a term rather accidentally.

2 Types of Initial Systems Capable of Being Precursors for the Preparation of Cryogels

Numerous studies on various aspects of cryotropic gelation phenomena have demonstrated that cryogels can be prepared, similarly to the traditional gels formed at positive temperatures, from precursor systems that fall into the following categories (see review articles [1, 18–29]):

- *Colloidal dispersions*: Freezing of colloid sols and the resulting cryoconcentration effects cause reinforcement of the interparticle interactions, leading to the formation of tight particle-to-particle contacts. These contacts are stabilized either by the cohesion forces or, if some reactive auxiliary substances are present, by the formation of chemical links between the grains of particulate matter. It seems likely that the freeze–thaw structuring and gelling of colloid systems is the oldest example of cryotropic gelation and has been known for many decades, especially by people who deal with the frozen storage of foodstuffs (some particular instances are given below).
- *Solutions of monomeric precursors*: Chemically or radiation-induced crosslinking polymerization or polycondensation in moderately frozen aqueous or organic media (depending on the chemical nature of the monomers) results in

covalently crosslinked gel materials that generally possess a wide-pore spongy morphology.

- *Solutions of high molecular weight precursors*: Covalent crosslinking, i.e., curing of macromolecules either with chemical agents or by irradiation (gamma-rays, electron beams, UV irradiation, photolysis in the presence of a suitable photoinitiator) in non-deeply frozen systems, results in chemically crosslinked highly porous matrices. The characteristics of the porosity of such gel materials (i.e., their macroporous or supermacroporous sponge-like texture) are governed by the freezing conditions, by the amount of freezable solvent, and by the size of porogen particles, namely, solvent polycrystals.
- *Solutions of so-called self-gelling polymers*: Such precursor systems are capable of forming physical (noncovalent) gels upon "worsening" of the thermodynamic quality of the solvent [1, 30] or by the addition of a solute that induces a change in the conformation of the macromolecular chains, e.g., a protein denaturant [31, 32].
- *Solutions of polyelectrolytes containing low molecular weight or polymeric crosslinking counterions*: These precursor systems are able to form sufficiently stable ionic bridges between the polyelectolyte chains. Such kind of gel formation is a relatively rare variant of the cryotropic gelation case, since the ion-exchange reactions are fast processes and, thus, it is technically difficult to freeze the precursor solution prior to its gelation. Therefore, some special methods must be implemented to overcome the mentioned impediments, that is, to shift the onset of gelation beyond the freezing of the reaction solution. For instance, an ionic crosslinker can be introduced in the feed solution in the form of a solid powdered salt having a negative temperature coefficient of solubility, i.e., its solubility rises with lowering of the temperature. In this way, the feed can first be frost-bound, and ionotropic gelling will then occur within the moderately frozen bulk system [33, 34].

The above classification of the precursor systems is also convenient for an overview of the "cryogel story," since different types of polymeric cryogels at the early stages of their history have been discovered virtually independently. This situation continued at least until the beginning of 1980s, when general approaches for the preparation of covalently crosslinked cryogels based on both monomeric and polymeric precursors were elaborated and patented [35]. The listed variants are considered here in the same sequence.

However, one important remark should be made first regarding the definitions of "positive" and "negative" temperatures. In the subsequent discussion, the freezing/melting point of the feed system is taken as "zero" in the temperature scale; therefore, the processes under the thermal conditions above this point occur at positive temperatures, while gel formation below this point occurs at negative temperatures. Further, in this context, we also use the terms "non-deeply frozen" or "moderately frozen" to designate frozen systems that are not completely solid at the corresponding negative temperature, and in which some fraction of unfrozen liquid microphase still exists. As a rule, such temperatures lie not lower than several tens of centigrade under the freezing/melting point of the corresponding feed solution [1, 2].

2.1 Polymeric/Biopolymeric Cryogels Formed by Freeze–Thaw Aging of Colloid Sols

Perhaps the earliest example of a technologically realized process in which freeze–thaw-induced gel formation was employed is the manufacture of the food product named "kori-tofu," which has been known for centuries and is still very popular in Japan [36]. The starting material for the fabrication of this soybean-protein foodstuff is the soya curd "tofu," a colloid-type dispersion of the salting-out coagulate of 11S globulins. Tofu is subjected to freezing, during which the SH groups of cysteine residues of the neighboring macromolecules are coupled into intermolecular disulfide bridges, thus resulting in the formation of a 3D supramolecular network of protein particles [37–40]. Another example of cryotropic gel formation of colloidal dispersions is the freeze–thaw-caused structuration of minced meat and pastes of myofibrillar protein isolates, e.g., those extracted from various kinds of fish, shrimp or Antarctic krill [41–48]. Since the major myofibrillar proteins, actin and myosin, are rich in cysteine, chemical crosslinking of proteinaceous colloid particles in non-deeply frozen systems is accompanied by the formation of interparticle covalent SS-bonds with the participation of air oxygen dissolved in the unfrozen liquid microphase. This gelation mechanism was elucidated using studies on the cryogel formation of model thiol-bearing polymers [49–52].

Cryotropic crosslinking of discrete particles of colloidal dispersions in the presence of a crosslinking agent to produce 3D macroporous polymeric materials has also been reported. The preparation of cryostructured collagen sponges [53–55] or the process of fabrication of leather-like materials from milled tanned leather wastes [56–58] are examples of such type of cryogel formation. In these cases, the respective dispersion was mixed with a crosslinking agent (e.g., glutaraldehyde) and then this heterophase reaction mass was frozen and kept in the frozen state for a necessary period of time and finally defrosted, resulting in spongy matter built of a supramolecular framework of chemically bound polymer particles. The same approach was also employed in subsequent years for the creation of macroporous materials based on covalently linked particulate matters like latexes [59, 60], microbial cells [27, 61], or small gel particles [27, 62, 63].

As well as covalent freeze–thaw gels derived from colloid dispersions, noncovalent cryogels with aligned macroporous morphology have also been prepared from particulate precursors. These include protein-containing systems [64–69], cryogels fabricated from the colloid solutions of gelatinized starch [5, 70–78], and cryostructured polymer matrices formed as a result of the freeze–thaw treatment of frost-sensitive latexes [79–84]. The nature of the interparticle links in the first case is a combination of hydrogen bonding, ionic interactions, and hydrophobic interactions. Multiple H-bonds are responsible for gelation of the starch-based systems, while the hydrophobic associations are the basis of particles "glueing" in the latex examples. The macroporous morphology of the resulting polymer materials and their physicochemical properties are determined by the initial

concentration of the dispersed particles; their size, shape, and chemical structure; and by the conditions of the freeze–thaw process. All these parameters must be taken into account in order either to prepare certain cryogels/cryostructurates or to prevent their formation when it is undesirable, as in the case of staving off the cryocoagulation phenomena in latex dispersions at negative temperatures [85].

2.2 Cryogels Prepared from Monomeric Precursors

The following three points are of principle significance for the preparation of cryogels from solutions of monomeric precursors:

1. The chosen solvent must crystallize rather than vitrify under the cryostructuring conditions; otherwise, if the solvent undergoes a glass transition, the unfrozen liquid microphase will not form and, hence, no cryo-concentrating effects will take place. This requirement is also valid for any other precursor system to be gelled cryogenically.
2. The solubility of the monomers should be high enough not only at positive temperatures, but also in the unfrozen liquid microphase. If the solubility of the monomer decreases drastically with decreasing temperature, the monomer concentration in the reaction medium becomes insufficient for the formation of a spatial network; that is, the critical concentration of gelation will not be reached. Various cryogels have been synthesized by using low molecular weight monomeric precursors, as in the majority of the reported cases, or macromonomers (macromers) such as the methacrylated derivatives of gelatine and chondroitin sulfate [86, 87], or poly(vinyl alcohol) [88, 89]. In the latter cases, the properties of the resulting gel matrices depend, along with common factors such as the monomer concentration or the freezing conditions, on the molecular weight of the macromonomer and on the amount of unsaturated groups in its molecule.
3. The crucial problem in the case of cryotropic gelation via free radical polymerization is the performance of the initiator system at negative temperatures. Chemical initiators such as peroxides that generate primary radicals owing to thermal decomposition are not suitable for cryopolymerization. Therefore, redox initiating systems capable of generating radicals at reduced temperatures are commonly employed [1, 26, 35, 90, 91]. Nonetheless, some rare cases are also known, where the “high-temperature” radical cryopolymerization of vinyl monomers has been carried out using thermally decomposed initiators. One such example is the 2,2′-azoisobutyronitrile-initiated copolymerization of styrene and divinylbenzene at 50 °C in the medium of crystallized naphthalene having a crystallization temperature of about 80 °C [35, 91, 92]. In the case of radiation-induced cryopolymerization, the above-discussed problem of the temperature-dependent activity of chemical initiators is virtually absent. The efficiency of radiation-induced processes is mainly a function of the applied radiation dose but not of the temperature, as demonstrated in the pioneering

studies conducted in Japan (see, e.g., [19, 93–100]). Yet another possibility for the preparation of cryogels of the polymerization type is the use of electron beams [101] or photoinitiation [102–104]. An essential point in this case is that the penetration capability of both these kinds of radiation is not very high, which limits the thickness of the samples. Therefore, the simplest approach, applicable in most laboratories, for the synthesis of polymerization-type cryogels is the use of a suitable chemical initiator system, where no specific radiation source is required and the amount of the added initiating substances can easily be controlled.

In the context of historical aspects of the development of polymerization-type cryogels, Table 1 summarizes the reaction components, e.g., the monomers, crosslinkers, initiator systems, solvents, and the temperature for cryogelation reactions starting from monomeric precursors. The data were taken from the pioneering reports on such gelation systems as well as from the most significant studies revealing the basic mechanisms of the key processes or ascertaining specific properties of the corresponding cryogels. Naturally, this selection is subjective, from the viewpoint of the author, and some works of good quality might have been missed.

Cryogels synthesized via polycondensation reactions are also known. These are mainly inorganic cryogels prepared by the sol–gel transformation in non-deeply frozen precursor systems, where the condensation of certain hydroxides accompanied by water liberation leads to the formation of polyoxides, as detailed in [173]. Polycondensation-type organic cryogels have also been reported in a few publications. Obviously, the first examples of such cryogels are those synthesized in frozen aqueous medium at −15 °C from the mixture of lysine (a trifunctional amino acid bearing two NH_2 groups and one COOH group) with water-soluble carbodiimide or from the mixture of lysyl-lysine (a dipeptide having three NH_2 groups) with glutaraldehyde [35]. In any case, the basic principle is that one of the precursors must be at least trifunctional or higher in order to ensure the branched 3D character of the forming polymer and its crosslinking. One recent example realizing this principle is the polycondensation-type cryogel prepared via the reaction of three-arm amino-terminated oligo(ethylene glycol) star polymers with dithio-bis (maleimido)ethane in the medium of non-deeply frozen dioxane at −8 °C [174]. Here, a 3D polymeric network forms as a result of the Michael addition of the primary amino groups to the double bonds of maleimide residues.

2.3 *Preparation of Cryogels by Covalent Crosslinking of High Molecular Weight Precursors*

As for the systems discussed in Sect. 2.2, the requirement of a good solubility of the high molecular weight precursors in the medium of the unfrozen liquid microphase is also important. If a decrease in the temperature and resulting freezing of the

Table 1 Examples of systems for the preparation and study of polymerization-type cryogels

Monomers and crosslinkers	Solvent[a]	Initiating system	Temperature of cryotropic gelation (°C)	What was done and reported	References
I. Chemical initiation					
Acrylamide + *N*,*N*′-methylene-bis-acrylamide	Water (T_0 = 0 °C)	APS + TMEDA	−10 to −30	Preparation of sponge-like poly(acrylamide) cryogels	[35, 90, 91]
				Study of the influence of cryostructuring conditions on the physicochemical and structural characteristics of resulting gel materials	[91, 105–114]
				Study of the gel formation dynamics	[108, 115, 116]
	Formamide (T_0 = +2.9 °C)		−8	Preparation of poly(acrylamide) cryogels in organic medium	[90, 91, 106]
	Water/dimethyl sulfoxide mixtures		−18	Preparation of poly(acrylamide) cryogels, study of their swelling behavior, mechanical properties, and porous structure	[117, 118]
Acrylamide + allyl glycidyl ether + *N*,*N*′-methylene-bis-acrylamide	Water	APS + TMEDA	−10 to −30	Preparation of epoxy-containing poly(acrylamide) cryogels, study of their properties and porous structure	[91, 119–125]
Acrylamide + 2-acrylamido-2-methylpropane sulfonic acid + *N*,*N*′-methylene-bis-acrylamide	Water-in-oil emulsion	APS + TMEDA	−4	Preparation and study of pH-responsive cryogel microbeads	[126]
Acrylamide + 2-acrylamido-2-methylpropane sulfonic acid + *N*,*N*′-methylene-bis-acrylamide	Water	APS + TMEDA	−18	Preparation of pH-responsive cryogels, study of their pH-dependent swelling behavior and wide pore morphology	[127]

(continued)

Table 1 (continued)

Monomers and crosslinkers	Solvent[a]	Initiating system	Temperature of cryotropic gelation (°C)	What was done and reported	References
N-Isopropylacrylamide + *N*,*N*′-methylene-bis-acrylamide	Water	APS + TMEDA	−11 to −40	Preparation of thermoresponsive poly(*N*-isopropylacrylamide) cryogels, study of their temperature-dependent swelling behavior, mechanical properties and porous structure	[128–132]
	Dimethylsulfoxide (T_0 = +18.4 °C)	APS + TMEDA	−20		[133, 134]
	Water or water/dioxane mixtures	DDMBAPS + TMEDA	−8 to −12	Preparation of fast-thermoresponsive cryogels, study of their temperature-dependent swelling behavior and wide pore morphology	[135, 136]
N-Isopropylacrylamide + *N*,*N*-di-*n*-propylacrylamide + *N*,*N*′-methylene-bis-acrylamide	Water/dioxane (4:1)	APS + TMEDA	−28	Preparation of hydrophobically modified thermoresponsive poly(*N*-isopropropylacrylamide)-based cryogels, study of their temperature-dependent swelling behavior and wide pore morphology	[137]
N-Isopropylacrylamide + acrylic acid + *N*, *N*′-methylene-bis-acrylamide	Water	APS + TMEDA	−22	Preparation of thermo- and pH-responsive cryogels, study of their temperature- and pH-dependent swelling behavior, as well as of the wide pore morphology	[138, 139]
N-Isopropylacrylamide + itaconic acid + *N*, *N*′-methylene-bis-acrylamide					[140]

N-Isopropylacrylamide + *N*,*N*′-bis-(acryloyl)-cystamine	Water	APS + TMEDA	−15	Preparation of thermoresponsive cryogels with entrapped oily emulsions, study of the temperature-dependent swelling behavior and emulsion release	[141, 142]
N-Isopropylacrylamide + *N*-[3-(*N*,*N*′-dimethylamino)propyl]-acrylamide + *N*,*N*′-bis-(acryloyl)-cystamine	Water	APS + TMEDA	−10	Preparation of thermoresponsive cryogels molecularly imprinted by ibuprofen, study of the bonding/release thermodynamics	[143]
N,*N*-Diethylacrylamide + *N*,*N*′-methylene-bis-acrylamide	Water	APS + TMEDA	−10	Preparation of thermoresponsive poly(*N*,*N*-diethylacrylamide) cryogels and study of their temperature-dependent swelling behavior	[144]
2-Acrylamido-2-methylpropane sulfonic acid + *N*,*N*′-methylene-bis-acrylamide	Water	APS + TMEDA	−22	Preparation of pH-responsive cryogels, study of their pH-dependent swelling behavior and the wide pore morphology	[145, 146]
N,*N*-Dimethylacrylamide + oligoethylene glycol diacrylate	Water	APS + TMEDA	−12	Study of the gel formation dynamics	[147, 148]
N,*N*-Dimethylacrylamide and its mixtures with polar uncharged or ionic vinyl comonomers	Water	APS + TMEDA	−5 to −40	Preparation of cryogels exhibiting superabsorbent properties	[149]
N,*N*-Dimethylacrylamide + 2-(diethylamino)ethyl methacrylate + *N*,*N*′-methylene-bis-acrylamide	Water/ethanol (1:1)	APS + TMEDA	−26	Preparation of pH-responsive cryogels, study of their pH-dependent swelling behavior and the wide pore morphology	[150]

(continued)

Table 1 (continued)

Monomers and crosslinkers	Solvent[a]	Initiating system	Temperature of cryotropic gelation (°C)	What was done and reported	References
Methacrylic acid + oligoethylene glycol diacrylate	Water	APS + TMEDA	−20	Preparation of macroporous ion-exchange continuous chromatographic bed	[151]
2-Hydroxyethylmethacrylate + different crosslinking agents	Water or water/dioxane (2:1)	SPS + TMEDA	−8 to −13	Preparation of poly(2-hydroxyethylmethacrylate) cryogels and study of their properties	[152, 153]
2-Hydroxyethylmethacrylate + *N*,*N*-dimethylacrylamide + *N*,*N*′-methylene-bis-acrylamide	Water	APS + TMEDA	−12	Preparation of copolymeric cryogels, study of their swelling characteristics and the wide pore morphology	[154]
2-Hydroxyethylmethacrylate + *N*,*N*′-bis-(methacryloyl)-L-cystine	Water	APS + TMEDA	−12	Preparation of copolymeric cryogels, study of their swelling characteristics, wide pore morphology, and possibility to be dissolved upon action of added thiols	[155]
2-Hydroxyethylmethacrylate + *N*-vinyl imidazole + ethylene glycol dimethacrylate	Water	APS + TMEDA	−16	Preparation of imidazole-bearing cryogel, study of its physicochemical properties, porous structure, and metal-absorbing capacity	[156]
2-Hydroxyethylmethacrylate + *N*-methacryloyl-(L)-histidine methyl ester + *N*,*N*′-methylene-bis-acrylamide	Water	APS + TMEDA	−16	Preparation of the histidine-bearing bioaffinity matrix	[157]

2-Hydroxyethylmethacrylate + vinyl-phenyl-boronic acid + oligoethylene glycol dimethacrylate	Water	APS + TMEDA	−12	Preparation of affinity matrix for the boronate affinity chromatography	[158]
N-Vinyl-caprolactam + oligoethylene glycol diacrylate	Water/dimethylsulfoxide mixtures	APS + TMEDA	−12	Preparation of temperature-responsive cryogels, study of their properties and the wide pore morphology	[159]
II. Initiation with radiation					
2-Hydroxyethylmethacrylate	Water	γ-rays	−24 to −196	Preparation of carriers for the immobilization of enzymes and cells, study of the properties and morphology of resulting cryogels as dependent on the cryopoly merization conditions	[93–98, 160, 161]
2-Hydroxyethylmethacrylate + acrolein	Water	γ-rays	−14 to −78	Preparation of aldehyde-bearing carriers for the immobilization of proteins	[99, 162]
2-Hydroxyethylmethacrylate + *N*-vinyl-pyrrolidone	Water	γ-rays	−78	Preparation of polymeric carriers for the immobilization of cells	[163]
2-Hydroxyethylmethacrylate + glycidyl methacrylate	Water	γ-rays	−78	Preparation of epoxide-bearing carriers for the immobilization of enzymes	[164]
Diacrylates or dimethacrylates of oligoethylene glycols	Water	γ-rays	−78	Preparation and study of physicochemical properties and macroporous morphology of respective cryogels	[95, 165]
Methoxyoligoethylene glycol methacrylates	Water	γ-rays	−78	Preparation of polymeric carriers for the immobilization of cells, study of properties and porosity of the resulting cryogels	[166, 167]

(continued)

Table 1 (continued)

Monomers and crosslinkers	Solvent[a]	Initiating system	Temperature of cryotropic gelation (°C)	What was done and reported	References
Acrylic acid + methylmethacrylate + oligoethylene glycol	Water-in-oil emulsion	γ-rays	No definite data	Preparation of polymeric carriers for the immobilization of enzymes	[168]
Olygoethylene glycol methacrylate + tetraethyleneglycol diacrylate	Water	β-beams	−5 to −30	Preparation and study of physicochemical properties and macroporous morphology of respective cryogels	[101]
III. Use of photoinitiation					
Acrylamide (or *N*-iso-propylacryamide, or 2-hydroxyethylmethacrylate) + oligoethylene glycol diacrylate	Water	H_2O_2 + UV irradiation	−20	Preparation and study of physicochemical properties and macroporous morphology of resultant cryogels	[102, 103]
Acrylamide + *N*,*N*′-methylene-bis-acrylamide	Water	1-[4-(2-hydroxyethyl) phenyl]-2-hydroxy-2-methyl-1-propane-1-one + UV irradiation	−13	Preparation of quickly swelling spongy poly(acrylamide) cryogels, study of their properties and wide pore morphology	[169]
		H_2O_2 + UV irradiation	−20	Synthesis and study of the poly (acrylamide) cryogel matrices for the immobilization of enzymes	[170]
N-Isopropylacrylamide or *N*,*N*-dimethylacrylamide + *N*,*N*′-methylene-bis-acrylamide + carbon nanotubes	Water	H_2O_2 + UV irradiation	−20	Preparation and study of cryogels with entrapped carbon nanotubes	[171]

Ethoxytriethylene glycol acrylate (or 2-hydroxy-ethylmethacrylate, or *N*, *N*′-methylene-bis-acrylamide)	Water	H_2O_2 + UV irradiation	−20	Synthesis and study of cryogel-based drug release matrices	[104]
Urethane diacrylate + poly(L-lactic acid)	Dioxane (T_0 = +11.3 °C)	Diphenyl-(2,4,6-methyl-benzoyl)-phosphine oxide + UV irradiation	−25	Preparation of macroporous honeycomb cryogel and study of its properties and pore structure.	[172]

APS ammonium persulfate, *SPS* sodium persulfate, *TMEDA* *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, *DDMBAPS* dodecyl dimethyl benzyl ammonium persulfate

[a]T_0 is the freezing/melting temperature of the neat solvent

initial solution causes a loss of solubility and therefore precipitation/coagulation of the polymer, no crosslinked product can be obtained after thawing of the system, especially when the concentration of the crosslinking agent is relatively low. In addition, a rather important parameter is the molecular weight of the polymeric precursor, which determines both the initial viscosity of the feed solution prior to freezing and the viscosity in the reaction zone, i.e., within the volume of the unfrozen liquid microphase. Due to the generally high molecular weight of the polymeric precursors, very high viscosity of the reaction zone significantly reduces the segmental and translational mobilities of the polymer chains, thus preventing the occurrence of gelation reactions. Therefore, some preliminary experiments are often required to select the optimum molecular-weight characteristics of the corresponding polymeric precursor [1, 175, 176].

Cryogels prepared by chemical crosslinking of proteins were the first cases that exploited a scheme for producing immobilized biocatalysts. These were microbial or plant cells entrapped in a spongy carrier composed of serum albumin or gelatine cured with glutaraldehyde or formaldehyde, respectively [177–181]. In these early works, the factors influencing the gelation process and the properties of the final cryogels were not studied. Specific features inherent in this kind of cryotropic gelation and its mechanisms were basically established later using polymers chemically simpler than proteins, namely homopolymers or plain AB-copolymers, where the process of interest is not sophisticated by the numerous secondary interactions. Such a "modeling" approach found a series of significant effects that turned out to be characteristic for the formation of various cryogels. For instance, it was shown that cryogels in both aqueous [50, 182] and organic [4] media can be prepared at considerably lower initial concentration of precursors as compared to their gelation at positive temperatures. Thus, the effect of an apparent decrease in the critical concentration of gelation is inherent in the gel formation processes occurring in the non-deeply frozen reaction systems [1, 91]. The reason for such an effect is the cryo-concentrating phenomenon, which makes the concentration of the gelling agents considerably higher than that in the initial liquid feed. The same phenomenon generally causes the acceleration of cryochemical reactions in moderately frozen solutions over a certain range of negative temperatures [2, 183, 184] and is also observed during cryotropic gelation through covalent crosslinking of macromolecular precursors with suitable crosslinking agents, (see, e.g., [1, 91]). For instance, the oxidation of SH groups in thiol-containing poly(acrylamide) induced by water-dissolved air oxygen and leading to the formation of disulfide-crosslinked 3D polymeric network was at least five times faster in a frozen system at −15 °C than in a solution at +15 °C. Moreover, the gel-point was reached about 1 h after freezing of the feed solution in the former case, whereas in the latter case the time was about 1 day [52].

Examples of the majority of the reported covalent cryogels prepared from macromolecular precursors are given in Table 2. These data show that such cryogels based on natural and synthetic polymers can be synthesized by chemical crosslinking or by irradiation techniques in frozen aqueous, organic, or mixed water–organic media. Thus, the chemical structure, physico-chemical properties,

Table 2 Examples of covalent cryogels prepared by crosslinking of macromolecular precursors in moderately frozen systems

High molecular weight precursors	Crosslinking agent	Solvent[a]	Temperature of cryotropic gelation (°C)	What was done and reported	References
I. Crosslinking with chemical agents					
Serum albumin	Glutaraldehyde	Water ($T_0 = 0$ °C)	−25	Preparation of macroporous carrier for the immobilization of thylakoids	[178]
			−20 to −25	Preparation of macroporous carrier for the immobilization of bacterial cells.	[179, 180]
			−20	Preparation of macroporous carrier for the immobilization of submembrane fraction of plant cells	[181]
Serum albumin	Cysteine	Water + urea	−3 to −78	Preparation of macroporous albumin cryogels	[31]
Gelatine	Formaldehyde	Water	−28	Preparation of macroporous carrier for the immobilization yeast cells	[177]
	Glutaraldehyde		−12	Preparation of macroporous scaffolds for tissue engineering	[185]
Gelatine + acrylonitrile	Glutaraldehyde, *N*,*N*′-methylene-bis-acrylamide	Water	−12	Preparation of composite cryogel via combination of polymer crosslinking and radical polymerization	[186]
Gelatine + fibrinogen	Glutaraldehyde	Water	−12	Preparation and study of covers on wounds	[187]
Gelatine + laminin	Glutaraldehyde	Water	−12	Preparation and study of macroporous scaffolds for tissue engineering	[188]
Collagen	Dialdehyde starch	Water	−15	Preparation and study of properties and macroporous morphology of resulting cryogels	[189]

(continued)

Table 2 (continued)

High molecular weight precursors	Crosslinking agent	Solvent[a]	Temperature of cryotropic gelation (°C)	What was done and reported	References
Collagen + hydroxyapatite	Water-soluble carbodiimide	Water	−18	Preparation and study of macroporous scaffolds for bone tissue engineering	[190]
Casein	Enzyme—transglutaminase	Water	−12	Preparation of macroporous scaffolds for tissue engineering	[185]
Thermo-coagulated soy protein isolate	Enzyme—transglutaminase	Water	−15	Preparation of macroporous protein scaffolds for tissue regeneration	[191]
Silk fibroin	Ethyleneglycol diglycidyl ether	Water	−5 to −22	Preparation and study of properties and macroporous morphology of resulting cryogels	[192]
SH-containing poly(acrylamide)	Water dissolved O_2	Water	−5 to −30	Study of the formation mechanisms of cryogels on the basis of thiol-containing polymers	[35, 49–52, 91]
Poly(β-D-glucose amine) (chitosan)	Glutaraldehyde	Aqueous acetic acid	−8 to −30	Preparation and study of physico-chemical properties and macroporous morphology of chitosan cryogels	[35, 50, 175, 182, 193, 194]
	Dialdehyde-dextran	Aqueous acetic acid	−32		[195]
Chitosan + gelatine	Dialdehyde-dextran	Aqueous acetic acid	−12		[196]
Poly(vinyl alcohol-*co*-vinyl acetate)	Epichlorohydrin	Water–NaOH solutions	−10	Preparation of macroporous polymeric cryogels	[35, 91]
Highly methoxylated pectin			−14		
Dextran			−9		
Cellulose	Epichlorohydrin	Water–NaOH–urea solutions	−20	Preparation and study of cryogels based on the cryogenically dissolved cellulose	[197]

Poly(vinyl alcohol-*co*-vinyl acetate)	Glutaraldehyde	Water–HCl solutions	−12 to −18	Preparation and study of physico-chemical properties and macroporous morphology of resulting cryogels	[91, 198]
Poly(vinyl alcohol-*co*-vinyl acetate) + particles of activated carbon			−12	Preparation and study of carbon-filled cryogels	[199, 200]
Poly(acrylamide)	Glutaraldehyde	Water-alkaline solutions	−5 to −20	Preparation and study of physico-chemical properties and macroporous morphology of resulting cryogels	[176, 201]
Chitosan + ovalbumin	Glutaraldehyde	Aqueous acetic acid	−18	Preparation of cryogel matrices for enzyme immobilization	[202]
Chitosan + gelatine	Glutaraldehyde	Aqueous acetic acid	−12	Preparation and study of physico-chemical properties of resulting cryogels	[203]
Chitosan + gelatine + hydroxyapatite			−20	Preparation and study of macroporous scaffolds for tissue engineering aims	[204]
Chitosan + agarose	Glutaraldehyde	Aqueous acetic acid	−20	Preparation of macroporous chromatographic matrices	[205]
Chitosan + gelatine + polypyrrole			−12	Synthesis and study of electroconducting cryogel matrices	[206]
Desoxyribonucleic acid	Ethylene glycol diglycidyl ether	Water–alkaline solution	−18	Preparation of DNA-cryogels, study of their properties, microstructure, and functional activities	[207–209]
Heparin + NH_2-end 4-arm star poly (ethylene glycol)	Water-soluble carbodiimide + *N*-hydroxysulfo-succineimide	Water	−20	Preparation and study of wide pore scaffolds for cell culture	[210]

(continued)

Table 2 (continued)

High molecular weight precursors	Crosslinking agent	Solvent[a]	Temperature of cryotropic gelation (°C)	What was done and reported	References
Poly(styrene-*co*-maleic anhydride)	Benzidine	Dimethylsulfoxide (T_0 = +18.4 °C)	+9	Preparation and study of physico-chemical properties of resulting cryogels	[35, 91]
Poly(*N*-vinyl-pyrrolidone-*co*-maleic anhydride)	4,4′-Diamino-diphenyloxide		+2 to −8		[4, 35, 50, 91]
Polystyrene	*p*-Xylylene-dichloride	Nitrobenzene (T_0 = +5.5 °C)	−4 to −27	Preparation and study of physico-chemical properties of resulting cryogels	[4, 35, 91]
Poly(iso-butylene)	Sulfur monochloride	Benzene (T_0 = +5.5 °C)	−18	Preparation of "single-hole" macroporous cryogel particles and study of their properties and microstructure	[211, 212]
Poly(iso-butylene) + silica nanoparticles			−5 to −15	Synthesis of butyl-rubber spongy composites and study of their properties	[213]
Poly(iso-butylene) + silica nanoparticles		Cyclohexane (T_0 = +6.5 °C)	−2;−18	Preparation of spongy composite butyl-rubber-cryogels and study of their physicochemical properties and porous morphology	[214]
II. Crosslinking by radiation					
Poly(vinyl alcohol) + poly(*N*-vinyl-pyrrolidone) + aloe vera	γ-rays	Water	−70	Preparation and study of hydrogels for wound dressing	[215]
III. Photo-induced crosslinking					
Poly(ethylene oxide)	UV irradiation + (4-benzoyl)benzyltri-methylammonium chloride	Water	−25	Preparation and study of physico-chemical properties of resulting cryogels	[216]
(Hydroxypropyl)methyl-cellulose or 2-hydroxyethyl-cellulose, or methyl-cellulose			−10 to −30		[217–219]

2-Hydroxy-ethylcellulose + poly (ethylene oxide)	−30	[220]
Poly(ethylene oxide) + sodium alginate + chitosan	−40	[221]
Poly(glycidol-*co*-ethyl glycidyl carbamate	−20	[222]

[a]T_0 is the freezing/melting temperature of a neat solvent

and porous morphology of cryogels discussed in this section can be varied over a very wide range, so that their potential applications are many. Judging from the published information, biomedical and biotechnological applications are the primary uses for the cryogels prepared from polymeric precursors. In addition, some other promising implementation fields also exist for such cryogels, including the employment of rubber-based "cryosponges" developed in Turkey as a reusable sorbent for the removal of oil spill from water surfaces [211, 212, 214, 223], crosslinked chitosan cryogels for the absorption of radionuclides from waste water [224, 225], crosslinked and partially saponificated poly(vinyl alcohol) cryogel composites containing activated carbon particles for the absorption of dyes [29, 199, 200], and so forth.

2.4 Physical (Noncovalent) Polymeric Cryogels

The publications on this group of cryogels are the most numerous and include several well-known and very informative reviews. The majority of these studies are related to poly(vinyl alcohol) (PVA) cryogels, which have been known since the 1970s [226–231]. The formation mechanisms of PVA cryogels [1, 29, 232–237] and their applications in various fields have been investigated extensively. These gel materials are used in medicine [1, 232, 235, 238–251], in biochemistry and biotechnology [1, 234, 252–262], in environmental protection [1, 263], in construction in the permafrost regions [1, 264, 265], etc. Such popularity of PVA cryogels is due to the combination of a set of remarkable features they possess, such as excellent physico-mechanical properties, a high thermal endurance compared with other physical hydrogels, a high resistance to abrasive erosion, a macroporosity that ensures good diffusion characteristics, the availability and relatively low cost of PVA itself, and a comparatively simple procedure for the preparation of such cryogels. In addition, PVA cryogels have a high biocompatibility and are nontoxic for biological objects.

Noncovalent cryogels based on other "self-gelling" synthetic and natural macromolecules have also been described for more than 40 years. In 1971, it was demonstrated that freezing of a 17 % solution of poly(acrylonitrile) in dimethylformamide/water (95–97:5–3, v/v) mixtures at −78 °C leads to the formation of physical gels that are stable at room temperature [266]. Later, the freeze–thaw-induced formation of noncovalent cryogels was also reported for other polymeric systems. For instance, freezing of an aqueous solution of syndiotactic poly(methacrylic acid) and poly(ethylene oxide) mixture at −78 °C, followed by its defrosting at room temperature, results in noncovalent cryogels [267]. Similarly, freezing of semidilute aqueous solutions of agar-agar or A-type gelatine at −10 °C for 24 h followed by thawing at 25 °C leads to the formation of biopolymer cryogels [30]. The cryogels thus obtained possess macroporous morphology, whose characteristics mainly depend on the type of polymeric precursor and its initial concentration in the feed. The cryogels formed from gelatinized starch [5, 70–78]

(mentioned in Sect. 2.1) as well as those based on starch-polysaccharides [268, 269] are also noncovalent cryogels that are stable at room temperature, but can be fused upon heating to 70–90 °C.

There is also a special case of the formation of physical cryogels where the self-gelation processes occur at a high rate even at positive temperatures. The aqueous solutions of >1 wt% agarose or >5–10 wt% gelatine belong to this category of gel-forming systems. When such solutions are being frozen at a moderate negative temperature, the ice is formed inside the already formed polymeric gel rather than in the liquid feed solution. As a consequence, the cryo-concentrating processes will not be realized to a significant extent, and the growing solvent polycrystals can even destroy the primary gel structure. The preparation of cryogels based on such quickly self-gelling precursors requires that freezing of the initial polymer solution should occur before the onset of the gelation. Principally, there are two possible ways to achieve this goal (1) freezing the initial hot solution very rapidly, e.g., in a liquid nitrogen bath, or (2) decreasing the self-gelation rate of the precursors by using specific additives capable of partially inhibiting the sol-to-gel transition. These two options were examined in detail in gelation systems containing agarose as a polymeric precursor [270, 271]. It was shown that the first option results in rather brittle gel materials with micrometer-sized pores. For the second approach, that is, to reduce the self-gelation rate of the precursor system, some solutes capable of partially interfering with H-bond formation between agarose chains were introduced into the initial feed solutions. This resulted in agarose cryogels with porosity and operational properties suitable for various applications, e.g., as wide-pore scaffolds for culturing of animal or human cells, including stem cells [271–277], and as supermacroporous continuous chromatographic beds for manipulation of particulate sorbates like viruses, cell organelles, and whole cells [272, 278]. It was found that the most convenient method of decelerating self-gelation in agarose solutions is to shift the pH so that some of the agarose hydroxyl groups are ionized, thus creating charges of the same sign along the chains, which causes certain repulsion between the chains [271].

Examples of various physical cryogels are summarized in Table 3, where the data are categorized according to the nature of the polymeric precursors, namely, polysaccharides, proteins, and synthetic polymers. The data for PVA cryogels are given separately due to the large number of papers published on these cryogels.

The history of PVA cryogels is also interesting because such gel systems have been discovered twice, as it were. First, there were mainly empiric recordings on the formation of these cryogels [230, 231] and the first patents were issued on the "virtual" applied possibilities of such materials [226–229]. Almost 10 years later, two approaches for increasing the strength of PVA cryogels were reported, namely, multiple freeze–thaw processing [299, 365–370] and the partial dehydration of frozen specimens *in vacuo* [9, 300, 301, 371]. These findings initiated numerous fundamental studies due to the amazing combination of cryogel properties and their macroporous structure. The investigations of frozen PVA solutions by nuclear magnetic resonance (NMR) and electron spin resonance (ESR) allowed better understanding of the fine details of the gelation processes inside frost-bound

Table 3 The examples of systems for the preparation of noncovalent (physical) cryogels

Polymeric precursor (its concentration in the feed)	Solvent	Conditions of cryotropic gel formation				What was done and reported	References
		Freezing temperature (°C)	Frozen storage duration (h)	Thawing rate (°C/min)	Number of freeze–thaw cycles		
I. Polysaccharides							
Agar-agar (0.25–1.0 wt%)	Water	−10	24	~0.2	1	Sponge-like cryogels with a rather brittle macropore walls were obtained	[30, 91]
Agarose (2–3 wt%)	Aqueous solutions of different pH values	−5 to −30	23	~0.3	1	Preparation of agarose-based cryogels, study of their physicochemical properties and peculiarities of the wide pore structure	[270–272]
Amylopectin Amylopectin + amylose (0.5–2 g/dL)	Water or 0.35 M NaCl solution	−6 to −24	18 18	3.00; 0.30; 0.03	1	Preparation of polysaccharide cryogels, study of the influence of cryogenic process regimes on the properties of final cryogels, demonstration of synergism of the amylopectin and amylose interactions upon the gel formation	[268] [74]
Carboxy-methylated curdlan (0.5–3 wt%)	Acidified water (pH 0.76–2.40)	−18	24–48	–	1–5	Preparation of the CM-curdlan-based cryogels, study of their swelling behavior and of the nature of interchain linking	[279]

Cress seed gum (1–7 wt%)	Water	−18; −30	24; 15	–	1	Preparation of the gum-based cryogels and evaluation of their rheological characteristics	[280]
β-Glucans from cereal sources (1–3 wt%)	Water	−18	24	–	1–12	Preparation of the β-glucan-based cryogels, study of their physicomechanical and thermal properties as depended on the source of polysaccharide isolation, molecular-weight parameters of gelling polymer, its initial concentration and conditions of cryogenic processing	[281, 282]
(3 wt%)	Aqueous solutions of glucose, fructose, sucrose, xylose or sorbitol	−15	24		14–22	Study of the influence of polyols on the physicochemical properties and macroporous morphology of resulting cryogels	[283]
Locust bean gum (0.5–5.1 wt%)	Water	−15	18–24	–	1–5	Preparation of the gum-based cryogels, study of the influence of freezing rate and freeze/thaw cycles number on the physicochemical properties of resulting cryogels	[284–287]

(continued)

Table 3 (continued)

Polymeric precursor (its concentration in the feed)	Solvent	Conditions of cryotropic gel formation				What was done and reported	References
		Freezing temperature (°C)	Frozen storage duration (h)	Thawing rate (°C/min)	Number of freeze–thaw cycles		
Locust bean gum (0.5–3 g/dL)	Water; aqueous solutions of urea, NaCl, Na_2SO_4	−10 to −30	18	3.00; 0.30; 0.03	1	Study of the nature of interchain links in the junction knots of 3D polymeric network; revealing the influence of the cryogenic process conditions on the physicochemical properties of final cryogels	[288]
(2 wt%)	Water	−20 to −60	1.5	1; 3; 7; 10	1	Study of the freezing and thawing rates influence on the mechanical properties of the gum-based cryogels	[289]
(1 wt%)	Aqueous solutions of glucose, fructose, sucrose or sorbitol	−20	24	–	1	Study of carbohydrates influence on the rheological properties of the gum-based cryogels, evaluation of the gum molecular weight influence on the physicochemical characteristics of resulting cryogels	[290]

Hyaluronic acid (1 wt%)	Aqueous HNO_3 solution (pH 1.5)	−20	15–72	–	1	Preparation of the hyaluronate-based matrices, study of their physicochemical and biomedical properties	[291–293]
Maltodextrin (0.1–15 g/dL)	Water	−6 to −24	18	3.00; 0.30; 0.03	1	Preparation of the maltodextrin-based cryogels and study of their physicochemical properties as dependent on the cryotropic gelation conditions	[269]
Xanthan (0.2–2 wt%)	Water	−20; −80	24	–	1–2	Preparation of xanthan cryogels and study of their rheological and thermal properties	[294, 295]
II. Proteins and peptides							
Gelatine, A-type (0.5–1.5 wt%)	Water	−10	24	~0.2	1	Sponge-like cryogels were prepared; the fragility of macropore walls increased with the growth of initial polymer concentration	[30, 91]
Gelatine B-type (0.2–2 g/dL)		−30	24	0.5	1–4	Preparation of gelatine-based cryogels and study of their rheological properties as dependent on the cryogenic processing conditions	[87]
Gelatine, B-type (10 g/dL) + montmorillonite	Water-formamide mixture	−20	24	–	1	Preparation of composite cryogels and study of their properties and microstructure, revealing the effects of montmorillonite exfoliation	[296]

(continued)

Table 3 (continued)

Polymeric precursor (its concentration in the feed)	Solvent	Conditions of cryotropic gel formation				What was done and reported	References
		Freezing temperature (°C)	Frozen storage duration (h)	Thawing rate (°C/min)	Number of freeze–thaw cycles		
Ovalbumin (0.25–5.0 wt%)	Water + urea (0.125–5.0 mol/L)	−8 to −32	24	~0.3	1	Preparation of soft spongy cryogels, whose wide pore structure was governed by the freezing temperature, the thermal pre-history upon freezing, and the protein and urea concentration in the initial solutions	[31, 32, 185]
Dipeptide Fmoc-Phe-Phe (2–20 mmol/L) + glucono-lactone	Water or 0.1 M K_2SO_4 solution	−12	72	–	1	Preparation of cryogels based on the self-assembled dipeptide molecules, study of rheological properties and macroporous morphology of resulting cryogels	[297]
III. Synthetic polymers							
Poly(acrylo-nitrile) (~17 wt%)	Dimethylformamide/water (97–95/3–5, v/v)	−78	24	–	1	The gel's strength markedly grew with increase in water fraction in the composition of initial mixed solvent	[266]

Poly(methacrylic acid) + poly(ethylene oxide)	Water	−78	–	–	1	The polymeric phase of final heterogeneous material was composed from the interpolymer complexes; the phase had fibrillar structure, and the thickness of the fibrils depended on the poly (ethylene oxide) molecular weight	[267]
Poly(*p*-phenylene-vinylene) or poly(*p*-phenylene-ethynylene) (9.1 wt%)	Naphthalene (T_0 = +80.4 °C)	−78; +10; +45	6	–	1	Preparation of wide pore π-conjugated polyphenylene matrices, study of their properties and porous structure	[298]
IV. PVA cryogels[a]							
80/98 (3–9 g/dL)	Water	−75 to −80	2 min	–	1–6	Apparently the first report on the empiric observation of the fact of PVA cryogel formation	[230]
88.8/99.3 (2.5–15 wt%)		−20	45–150 min	–		The study of the temperature-dependent turbidity of water–PVA systems, the registration of the freeze–thaw-caused gel formation	[231]
105.6/99.6 (15 wt%)		−15	24–120	–	Multiple	Preparation of PVA cryogels and evaluation of their rigidity as	[299]

(continued)

Table 3 (continued)

Polymeric precursor (its concentration in the feed)	Solvent	Conditions of cryotropic gel formation				What was done and reported	References
		Freezing temperature (°C)	Frozen storage duration (h)	Thawing rate (°C/min)	Number of freeze–thaw cycles		
						depended on the number of freeze–thaw cycles	
105.6/99.6 (10–15 wt%)		−20 to −40 and partial lyophylization	12–24	–	1	Preparation of PVA cryogels via polymer solution freezing with the additional partial lyophilization; evaluation of mechanical strength of final gel species	[9, 300, 301]
66/99 (10–16 wt%)	DMSO (T_0 = +18.4 °C)	−10	20	–	1	Apparently the first report on the possibility of PVA cryotropic gelation in frozen organic medium	[30]
69/99 (10 wt%)	Water	−15	12	–	1	Evidence of the noncovalent nature of intermolecular links in PVA cryogels	[302]
90/98 (8 wt%)		−10	24				
110/97.5 (6 wt%)		−20	18; 240				
95.6–110 or 98–99 (0.003 g/dL)		−25; −196	24		1–9		[303, 304]
*i*PVA: 660/99.9 (9 wt%)	Water	−20	20	–	1–4	Evidence of the key role of H-bonding for	[305–307]

*a*PVA: 74.8/99.9 (9 wt%)						intermolecular linking in PVA cryogels via the interactions of OH groups of neighboring chains	
*s*PVA: 66/99.9							
*a*PVA: 74.8/99.9 (3 wt%)	D_2O or DMSO-d_6	−50	–	–	1		[308]
*i*PVA:49.7/100 or 400/100 (3 wt%)							
37/98 (2.5 wt%); 69/99 (2.5 wt%)	Water	−20	25	–	1		[309]
160/98 (0.001–8 g/dL)	Water	−25	24	–	1	Finding the critical concentration of gelation for the PVA cryogels case	[310]
138/100 (0.1–1.0 g/dL)		−10; −20; −30		3.00; 0.30; 0.03			[311]
154/99.8 (15 wt%)	Water	−15	23	–	1–14	Experimental proving (using various methods of physicochemical analysis) that junction knots in PVA cryogels are microcrystallites	[312]
88/– (3–9 wt%)		200 K (ca. −73)	–	5 or 10 K/min	1		[313]
18.5 to 78.8/99.8 (2–35 wt%)		−20	12	–	1		[314]
35.7/99; 64/99; 88.9/99.8 (7–15 wt%)		−20	8	–	3–7		[315]
89–98/99 (10–35 wt%)		−20	21	–	1–10		[316]
61.6/98.7 (9–29 wt%)		−15	12	–	1		[317]
115/98–99 (11 wt%)	D_2O	−22	4–20	–	1–10		[318–323]
115/98–99 (5 and 10 wt%)		−13	0–6.5	–	1		[324]
115/98–99 (5.03; 10.11; 14.22 wt%)			0–2	–	1		[325]

(continued)

Table 3 (continued)

Polymeric precursor (its concentration in the feed)	Solvent	Conditions of cryotropic gel formation				What was done and reported	References
		Freezing temperature (°C)	Frozen storage duration (h)	Thawing rate (°C/min)	Number of freeze–thaw cycles		
69/99 (7–14 wt%)	Water	−1 to −30	24	1.00; 0.20; 0.02	1	Revealing the significance of the defrosting rate for the formation of PVA cryogels, in general, and for the properties of the gels when those are formed.	[326, 327]
PVA 138/100 (0.1–1.0 g/dL)		−10, −20, −30		3.00; 0.30; 0.03			[311, 328]
81.7/98.5 (10 g/dL)		−18	18	0.20; 0.02			[329]
69/99; 86/100; 115/100 (8–12 g/dL)		−10; −20; −30; −40	24	0.30; 0.03; 0.003			[330, 331]
81.7/98 (10 wt%)	Water	−1 to −10	0–0.5	1.0	1	Studies on frozen PVA solutions	[332]
69/99 (14 wt%)		−10 to −30	1–10				[333, 334]
90/98 (10 wt%)	H_2O–D_2O mixtures	0 to −66	1	–			[335]
*a*PVA: 74.8/99.9 (3 wt%)	D_2O or DMSO-d_6	−50		–			[336]
*i*PVA: 400/100 (3 wt%) –/98.5 (20, 30, or 50 wt%)	H_2O or D_2O	0.25–2		–			[337]
69/99 (7–14 wt%)	Water	−1 to −30	24	1.00; 0.20; 0.02	1	Studies on the microstructure and porosity	[326, 333]

69/99; 86/100; 115/100 (8–12 g/dL)		−10; −20; −30; −40		0.30; 0.03; 0.003		characteristics of PVA cryogels.	[330, 331]
69/99 (10, 14, or, 16 wt%)		−10; −20	24–240	–			[338]
77/99.5 (10, 20, or 30 wt%)		−20	24	–			[339]
160/99.3 (4, 8, or 12 wt%)	DMSO or DMSO–water mixtures	−20; −60	15	–			[340, 341]
82/98 (10 wt%)	Water	−20	24	0.2			[342]
145/99.4 (19 wt%)		−20	0.5	5.0	1–24		[343]
69/99 (12 g/dL)		−20	18	0.30; 0.03	1		[344]
72/97.5–99.5 (10–12 wt%)		−25	10	0.5	1–14		[345]
69/99 (8, 10, or 12 g/dL)	Water	−20	19	0.3	1–5	Studies on microstructure and porosity characteristics of PVA cryogels	[346]
88/98 (10 wt%)		−10	20	–	2		[347]
146–186/99 (10 wt%)	D_2O	−20	1	0.1	1–6		[348–350]
94/99 (10–20 wt%)		−32	1–12	–	1–16		[351]
22/98.5; 44/98.5; 74.8/98.5; 105.6/98.5; 74.8/96; 74.6/97.5; 74.8/99.9 (all 15 wt%)	Water	−60	6	0.389	1–20	Preparation of PVA cryogels and study of their properties as dependent on the cryotropic gelation conditions	[352]
74.8/98.5 (7.5–20 wt%)		−20	23	–	1		[353]
80/98 (15 wt%)		−25	16	–	1–4		[354]
35.4/99.6; 72.2/99.6 (both 10 or 15 wt%)		−20	1–24	–	1–9		[355, 356]
48/99; 103/99 (15 or 20 wt%)	Water	−20	6 or 12	–	2–5	Preparation of PVA cryogels and study of their properties as	[310]
108/99.7 (5 or 10 wt%)		−15	24		1–13		[357]

(continued)

Table 3 (continued)

Polymeric precursor (its concentration in the feed)	Solvent	Conditions of cryotropic gel formation				What was done and reported	References
		Freezing temperature (°C)	Frozen storage duration (h)	Thawing rate (°C/min)	Number of freeze–thaw cycles		
				0.083; 0.11-1; 0.333		dependent on the cryotropic gelation conditions	
PVA 81.7/98 (10 wt%); 110/99.5 (9.4 g/dL)		−80	3	–	4		[358]
83/100(–)		−16; −20	–	–	1		[359]
31–50/98–99 (5 or 10 wt%)		−18	12	1.7	1		[360]
*a*PVA: 84/99.9 or 342/99.9; *s*PVA:74.4/99.9 or 353/99.9 (2–8.8 g/dL)		−38	72	–	1		[361]
88/99 or 94/99 (20 wt%)		−20	12	–	3		[362]
Mixtures of *a*PVA: 84/98 and *s*PVA: 35.2/99.8; 48.4/99.8; 193/98 (5 wt%)	Water	−30	10	–	3	Preparation of PVA cryogels and study of their properties as dependent on the cryotropic gelation conditions	[363]
130/– (15 or 20 wt%)		−20	12	–	1		[364]

In the above boxes related to PVA cryogels, see the data of [30, 328, 330–333, 338, 346] that also contain information on the influence of the cryotropic gelation conditions on the properties of resulting PVA cryogels

Dash means no data; *aPVA* atactic polymer; *iPVA* PVA rich in isotactic fragments; *sPVA* syndiotactic-rich polymer

[a]For PVA cryogels the values of the polymer molecular weight (in kDa) and the deacylation degree (in %) are given in Column 1 as a vulgar fraction, when the data are available from the relevant publications

heterophase PVA–solvent systems [308, 332–337]. Features of the microstructure of PVA cryogels were ascertained using various microscopy techniques [330, 331, 333, 338–346] and other physicochemical analysis methods [237, 326, 347–351].

In these studies, the following five principal facts were established:

1. The nodes in the 3D supramolecular network of PVA cryogels have a noncovalent nature. Therefore, such cryogels can be fused upon heating above the gel melting temperature with the formation of a polymer solution without any change in the characteristics of PVA molecular weight compared to that before freezing [30, 302–304]. This feature is observed provided that the used polymer is pure, i.e., it contains no reactive admixtures, frequently present in industrial PVA specimens.
2. Intermolecular H-bonding via the interactions of OH groups of the neighboring PVA chains plays a key role in the formation of PVA cryogels [305–309].
3. The junction knots in these cryogels were experimentally proven to be PVA microcrystallites [312–317]. A series of works conducted by a team of Italian researchers on this topic [318–325] is very impressive; the same can be said about the precision study by a Japanese team who found that each junction knot in PVA cryogels includes, depending on the gel formation conditions, about 2–3 chains with around 24–120 segments [314].
4. The defrosting rate of frozen PVA solutions plays a significant role in the formation and properties of PVA cryogels [234, 311, 326–331].
5. The molecular weight of PVA, chain tacticity, amount of residual O-acyl groups, and PVA concentration, as well as the conditions of freezing, frozen storage, and thawing have a significant effect on the properties and macroporosity of PVA cryogels [1, 9, 10, 23, 29, 30, 232–236, 254, 258, 299–301, 310–316, 326–331, 333, 338, 346, 352–364, 366–372].

Because the number of publications dealing with the relationships between the preparation conditions of PVA cryogels and their properties is large, Table 3 summarizes only the most important of them, from the viewpoint of the author of this review. Apart from PVA cryogels formed from simple two-component feeds (e.g., from systems composed of PVA dissolved in a neat solvent), a large amount of data is also available in the literature on PVA cryogels that contain soluble foreign additives, both of low and high molecular weights. In the former case, the corresponding cryogels can be classified as those prepared from PVA dissolved in a mixed solvent, whereas in the latter case a more suitable term is “complex PVA cryogels.” It should also be noted that there are also extensive studies on “composite PVA cryogels” that contain various discrete fillers. Different soluble and insoluble additives have been introduced in the initial PVA solutions to obtain complex and filled PVA cryogels, respectively. It was shown that the type of additives can affect, more or less, the properties and the microstructure of the resulting cryogels. Since the character of such an influence is very diverse and the observed effects can be multidirectional, such examples are not cited in Table 3. However, readers interested in the principal studies in these fields can find the corresponding references in the following reviews and recent experimental articles:

PVA formed in mixed solvents [1, 20, 23, 234, 264, 373], complex PVA cryogels [1, 234, 239, 374], and composite PVA cryogels [1, 20, 23, 29, 234, 236, 237, 252, 254, 265, 375–377].

2.5 *Ionic (Ionotropic) Cryogels*

As pointed out above, the accomplishment of gel formation through crosslinking of polyelectrolyte chains with suitable counterions within the space of the unfrozen liquid microphase is a difficult task because of the high rate of the ionic processes. As a rule, conventional ionotropic gelation occurs before freezing of the gelling system. This is the reason why there is only a limited number of successful examples of preparation of ionically crosslinked cryogels by this "direct" route (e.g., [33, 34]). However, the cryogenically structured macroporous gel-like matrices can be fabricated by using roundabout pathways.

One way is the freezing of the partially (incompletely) formed gel, followed by its frozen storage in order to complete the ionic crosslinking, and then sublimation of the frozen solvent crystals. Such a sequence of operations results in macroporous dry cryostructurates that are transformed upon swelling in macroporous gels. This approach was used, for instance, for the preparation of Ca-alginate-based wound/burn dressings [34], or wide-pore scaffolds for tissue engineering [378–380].

Another method includes freezing the polyelectrolyte solution, followed by the removal of frozen solvent crystals without their thawing. The latter can be done either via freeze-drying, or via cryoextraction, i.e., by rinsing the frozen sample at a negative temperature with a liquid that acts as a solvent for the crystalline phase but a nonsolvent for the polyelectrolyte. The resulting macroporous cryostructurate is then treated with an agent capable of either ionically crosslinking the polymeric chains, or recharging their ionogenic groups. This stage is also carried out in a nonsolvent for the macromolecular material. A macroporous gel is obtained upon subsequent swelling of the resulting material in the respective solvating liquids. This approach was employed for the fabrication of wide-pore cryostructured matrices based on both polyacids and polybases [1]. For example, in order to prepare Ca-alginate sponges, the initial aqueous sodium alginate solution was frozen, and ice polycrystals were then removed via vacuum sublimation or via cryoextraction with cold ethanol. The resultant cryogenically structured polymer was then immersed in an ethanolic solution of calcium salt for ionic crosslinking leading to water-insoluble sponge-like Ca-alginate cryogel [381]. Such sponges possessing a system of interconnected gross pores of capillary size are of interest as cell culture scaffolds in biotechnological systems [382–384]. The preparation of cryostuctured polyelectolytes through recharging of their ionic groups can be exemplified by chitosan-based sponges. Here, after removal of ice crystals from the frozen chitosan–aqueous acetic acid system, the resulting cryostructurate was treated with alkaline acetone, thus causing formation of water-insoluble unprotonated

chitosan base [385]. Wide-pore sponges of this material were also used as scaffolds for the 3D culturing of animal cells [386].

Thus, there are wide opportunities for the creation of diverse polyelectrolyte-based cryostructured gel-like matrices, whose properties and porous morphology can be varied in desired directions by an appropriate choice of the polymeric precursor and the respective counterions, their concentrations, by the freezing conditions, and by the procedure for the removal of frozen solvent.

3 Concluding Remarks

Fundamental studies and applied research on cryotropic gelation and various polymeric cryogels have been in progress for more than 40 years. As a result, numerous interesting observations have been made, mechanisms of the processes contributing to the formation of cryogels have been established, a series of cryogels possessing remarkable properties have been developed, and diverse practical applications have been realized (see reviews [1, 18–29, 184, 232–265, 387–404]).

It is evident that this part of polymer science did not start from a "clean slate." First of all, there were different empiric observations on the freeze–thaw-caused gelation in systems like the above mentioned kori-tofu case. Second, it is necessary to emphasize the key role of the knowledge accumulated on the specific features of various chemical reactions in non-deeply frozen multicomponent solutions. In this respect, the pioneering studies that revealed the occurrence per se of such reactions in the moderately frozen systems were of great significance (see, e.g., [405–408]). These studies identified the existence of an unfrozen liquid microphase, and gave quantitative descriptions of the kinetic peculiarities of the relevant cryochemical reactions [2, 409–412]. Third, another important basis for the development of research on cryotropic gel formation was information on routes for the preparation of conventional covalent and noncovalent gels, their properties, and the factors that influence them. Moreover, a series of studies on frozen polymer–solvent systems should also be noted (e.g., [413–417]). The results of these studies allow a deeper understanding of the important fact that, in moderately frozen macromolecular solutions and even in frozen gels, the chain segments do not lose a certain degree of mobility and, hence, interaction of such segments can cause further transformations within the system up to the formation of a spatial polymeric network. Therefore, all the listed sources can be considered as the roots that supplied the "tree of polymeric cryogels" with the necessary primary "nutrients" available at the time when intense studies on cryotropic gel formation began. The subsequent growth and branching of this tree produced fine fruits, these being both new fundamental knowledge and the development of such wonderful gel materials as polymeric cryogels with their multitudinous practical applications, which are discussed in some of the subsequent chapters of this volume.

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