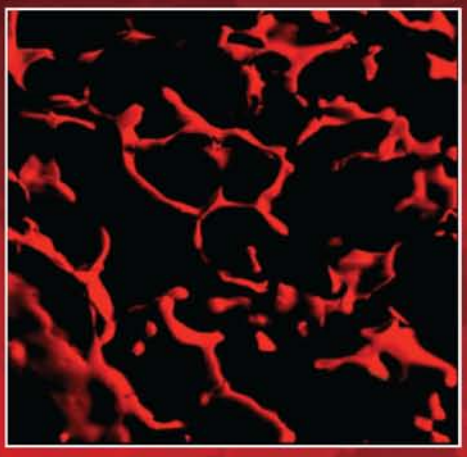
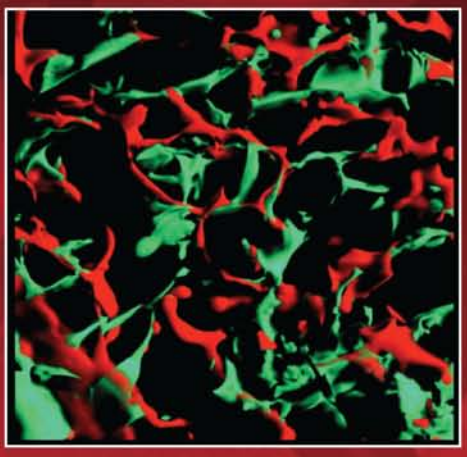
MACROPOROUS POLYMERS

Production Properties and Biotechnological/Biomedical Applications





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Ashok Kumar
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Contents

Section II Characterization of Macroporous Polymers

Section III Application of Macroporous Polymers

Introduction

According to the International Union of Pure and Applied Chemistry (IUPAC) definition, macroporous polymers have pores in the range of 50 nm to 1 μm (http://goldbook.iupac.org/MT07177.html). Recently, however, much attention has been brought to the materials with pore sizes between 1 μm and 100 μm, and beyond. Such polymers, sometimes called supermacroporous polymers, are the main target of this book. As the border between these two types of materials is very diffuse, both names *supermacroporous* and *macroporous* are used in the book describing polymer systems with pores of micrometer sizes.

Macroporous hydrogels as a separate class of macroporous polymers are represented by materials composed of three-dimensional hydrophilic polymer networks that in most cases are biocompatible. These macroporous gels offer new and interesting possibilities in biotechnology and biomedicine due to their heterogenic structure, namely the pores filled with solvent and surrounded by relatively thin walls composed of polymer phase. The polymer nature, pore sizes and pore size distribution, pore connectivity, and pore tortuosity are factors that strongly influence the properties and possibilities for success in various applications within the life science area. Access to materials such as macroporous hydrogels has meant that a range of new challenges in life science research can be met. Development in the area is at present intense, both with regard to designing new and better materials and also concerning new applications.

This book gives an up-to-date compilation of modes of production of macroporous hydrogels, characterization of such materials, and applications with regard to both biotechnology and biomedicine. As microbial or mammalian (including human) cells are of the same size as pores in such materials, cells can be handled with macroporous gels and this opens up possibilities with regard to immobilization, separation, and cultivation of cells. The former alternatives are traditionally regarded as biotechnological applications while cultivation of mammalian cells is classified as biomedicine. The porous structure and the compatible properties form a basis to meet challenges in tissue engineering as well as cultivating mammalian cells in bioreactors. With large pores it is possible to modify the surface by grafting, for example, and still have enough pore lumen to allow cells to penetrate or pass.

One can produce macroporous hydrogels using different approaches and from different polymers, biodegradable as well as chemically stable polymers. In biomedicine biodegradability may be desired, while in some industrial applications, such as wastewater treatment processes, it might be more advantageous to use nondegradable robust materials.

The introduction of macroporous hydrogels is one example of polymer chemistry offering interesting solutions to biological problems. By combining the technique of making macroporous gels with other recent advantages in polymer chemistry (stimuli-responsive polymers, polymer brushes, controlled radical polymerization, reversible addition–fragmentation chain transfer (RAFT) polymerization, click chemistry, etc.), new dimensions can be reached.

Under one cover, the editors have done their best to collect chapters written by the scientist most active in the production and study of macroporous polymers and their applications. The intent of the book is to be considered state of the art and will provide further development in the area by attracting fresh recruits, both polymer chemists capable of developing new advanced polymers and biotechnologists ready to use these polymers for new applications. The editors hope that the volume will stimulate the minds of the readers to actively consider this new group of materials as interesting possibilities when addressing different challenges in life science and other areas.

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Section I

Production of Macroporous Polymers

1

Production of Macroporous Polymeric Materials by Phase Separation Polymerization

Oguz Okay

CONTENTS

1.1 Introduction

Polymer hydrogels are cross-linked materials absorbing large quantities of water without dissolving. The ability of hydrogels to absorb water arises from their hydrophilic functional groups attached to the polymer backbone while their resistance to dissolution arises from cross-links between network chains (Tanaka 1981; Shibayama and Tanaka 1993). If such a conventional hydrogel is dried by heating, the polymer network obtained has no voids (pores) in its structure. However, as the polymer network swells again in water, the space between the network chains increases so that a type of porosity called *molecular porosity* appears. Thus, molecular porosity in conventional gels depends on the degree of swelling and the distance between the polymer regions is in the range of a few nanometers. In contrast, however, macroporous hydrogels refer to materials having a permanent porous structure that persist even in the dry state (Dusek 1982). According to the IUPAC, material having pores of larger than 50 nm are called macroporous (Sing et al. 1985). Some researchers define macroporous gels as opaque materials with a measurable specific surface area and absorbing nonsolvents in their dry states (Millar et al. 1963; Rabelo and Coutinho 1994).

Macroporous gels contain nanometer to micron size liquid channels separated by cross-linked polymer regions, which provide sufficient mechanical stability. There are two basic techniques to obtain cross-linked polymers with a macroporous structure (Okay 2008). The first technique is the use of inert templates in the hydrogel preparation. By this technique, the polymer formation reactions are carried out in the presence of templates; a macroporous structure in the final hydrogel matrix appears after extraction of template materials. For example, by the cryogelation technique, the polymer formation reactions are carried out below the bulk freezing temperature of the reaction system (Lozinsky 2002). A macroporous structure in the final material appears due to the existence of ice crystals acting as a template for the formation of the pores. Another technique to create a macroporous network structure is the reaction-induced phase separation (i.e., phase separation polymerization). This technique involves the cross-linking copolymerization of the monomer and the cross-linker mixture in the presence of an inert diluent, which is soluble in the monomer mixture (Okay 2000). In order to obtain macroporous structures, a phase separation must occur during the course of the network formation process so that the two-phase structure formed is fixed by the formation of additional cross-links. After the polymerization, the diluent is removed from the network, leaving a porous structure within the highly cross-linked polymer network.

This chapter provides an overview of the formation mechanism of macroporous networks by phase separation polymerization and their characteristics under various experimental conditions. Some examples are also presented to demonstrate the correlation between the preparation conditions and the structure of macroporous hydrogels.

1.2 Formation Mechanism of Macroporous Structures

Macroporous networks are mainly prepared by free-radical, cross-linking copolymerization of vinyl–divinyl monomers in the presence of an inert diluent (Seidl et al. 1967; Guyot and Bartholin 1982; Okay 2000). The diluent, which is a solvent, a nonsolvent, or a linear polymer, is included in the reaction system as a pore forming agent, and plays an important role in the design of the pore structure of cross-linked materials. The diluent is initially soluble in the monomer mixture. At low cross-linker contents and in the presence of solvating diluents, the diluent remains in the gel throughout the reactions so that an expanded network structure is obtained. The expanded gels thus formed collapse during the removal of the diluent after their synthesis and therefore, they are nonporous in the dry state. Heterogeneities in the network structure start to appear and become permanent if the diluent separates out of the gel phase during polymerization.

If the cross-linker content is above a critical level, the reaction mixture of cross-linking copolymerization initially remains homogeneous as long as the growing polymer network is able to absorb all the available monomers and the diluent. As the reactions proceed, that is as the cross-link density of the network increases, a critical point is passed, at which the equilibrium degree of swelling of the network in the diluent becomes equal to its degree of dilution. At this point, since the dilution of a homogeneous network cannot be greater than its equilibrium degree of swelling, the reaction system will separate into two: the network phase and the separated phase. Thus, the condition for incipient phase separation during gelation is given by

$$q_v/q_v^0 \leq 1, \tag{1.1}$$

where q_v is the equilibrium volume swelling ratio of the network in the reaction system and q_v^0 is its dilution degree (reaction volume/volume of polymer network). To test the validity of Equation 1.1, gelation reactions were carried out using the styrene (S), divinylbenzene (DVB) comonomer system and using di-2-ethylhexyl phthalate (DOP) as the diluent (Okay 1986; Okay 1988). Figure 1.1A shows how the q_v/q_v^0 ratio varies with the cross-linker (DVB) concentration used in the network synthesis. The q_v/q_v^0 ratio decreases below unity between 18 and 22 wt % DVB, which is the phase separation condition of Equation 1.1. Indeed, the porosity P% of the networks starts to increase between the same DVB concentrations (Figure 1B). In Figure 1C, the volume swelling ratio q_v of the networks in toluene is shown as a function of the DVB concentration. The filled and open symbols represent q_v values of the networks prepared with and without using a diluent, respectively. The networks formed below 18 wt % DVB are in a swollen state (i.e., they swell much more than the corresponding, conventional networks prepared without using a diluent). This indicates that the diluent used in the synthesis remains in the gel phase during the reactions so that expanded gels form. However, above 18 wt % DVB, q_v rapidly decreases and approaches to that of homogeneous networks, indicating separation of the diluent out of the network phase. Figure 1.1 supports the relation between equilibrium swelling and the conditions of porosity formation during gelation reactions as expressed in Equation 1.1.

Phase separation during cross-linking can be induced by increasing the cross-linker concentration, (ν-induced syneresis) or by decreasing the solvating power of the diluent (χ-induced syneresis; Dusek 1965; Seidl et al. 1967; Dusek 1982). In both cases, the growing polymer network or the polymer chains cannot absorb all the available solvent in the reaction system. Thus, the reaction de-swells (or collapses) to form reaction particles (microspheres) within the separated continuous liquid phase. As the reaction proceeds, new microspheres are continuously generated due to the successive separation of the growing polymers. The agglomeration of the microspheres

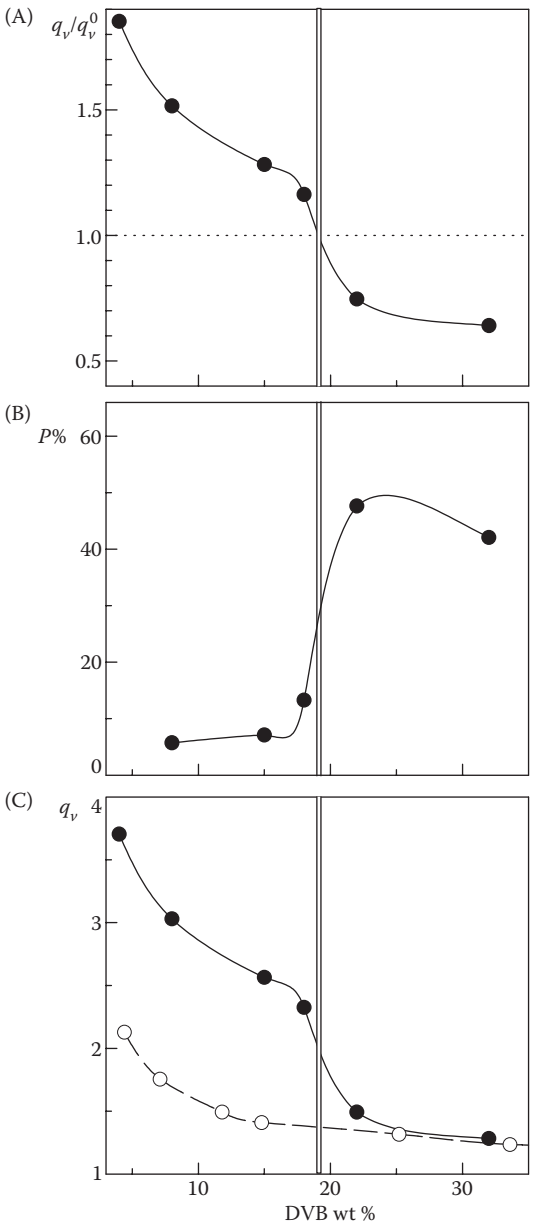

FIGURE 1.1
q_v/q_v^0 ratio (A), the total porosity *P*% (B), and the swelling ratio in toluene q_v (C) of S-DVB networks plotted as a function of the cross-linker (DVB) concentration. Diluent = di-2-ethylhexyl phthalate (DOP). Initial monomer concentration = 52 v/v %. The open symbols in (C) represent the swelling ratio of the networks prepared without using a diluent. (Reprinted from Okay, O., *Prog. Polym. Sci.*, 25, 711–79, 2000. With permission from Elsevier.)

results in the formation of a heterogeneous gel consisting of two continuous phases: a gel phase and a diluent phase. Removing of the diluent from the network creates voids (pores) of sizes from 1 nm up to 1 μm when measured in the glassy state of a polymer system. Compared to the χ-induced syneresis, the mechanisms of ν-induced syneresis results in a more ordered pore structure consisting of smaller agglomerates rather than formed in the former mechanism.

Almost all macroporous networks formed by phase separation are characterized by a relatively broad pore size distribution ranging from micropores having widths up to 2 nm to macropores having widths greater than 50 nm. Figure 1.2 illustrates typical morphology of a macroporous network formed by phase separation polymerization. The polymer network consists of agglomerates of particles of various sizes that look like cauliflowers. The pores are irregular voids between agglomerates that are typically interconnected. From the scanning electron micrograph (SEM) image in Figure 1.2, one may distinguish microspheres of about 10^2 nm in diameter. The agglomerates of microspheres have sizes between 10^0–10^1 μm. Meso- and macropores having widths in the range 2–200 nm constitute the interstices between the microspheres while larger pores appear between the agglomerates of the microspheres.

As mentioned above, expanded hydrogels collapse during the removal of water and therefore, they are nonporous in the dry state. However, if an expanded hydrogel is freeze-dried after preparation, its expanded network structure is partially preserved so that a porous network can also be generated. For example, Figure 1.3 shows the SEM image of a porous poly(acrylamide) PAAm network prepared by the freeze-drying process. It is seen that the morphology of the network consists of polyhedral large pores

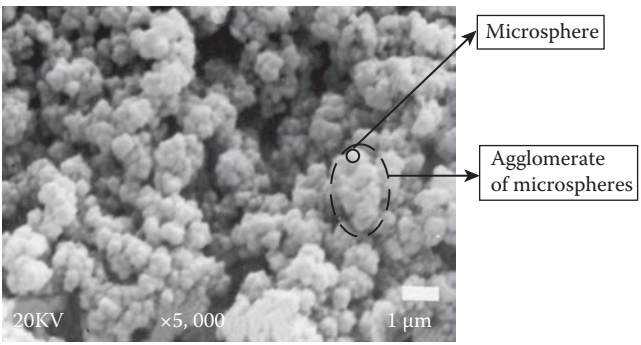

FIGURE 1.2
SEM image of poly(N-isopropylacrylamide; PNIPA) network at ×5000 (1μm bar in the lower right corner). Initial monomer (NIPA) concentration = 20 w/v %. N,N′-methylenebis(acrylamide) content = 30 wt % (with respect to the monomer). Polymerization temperature: 22.5°C. Diluent: Water.