Polymer Bulletin 28, 569–576 (1992)

Polymer Bulletin

Monodisperse polymer beads as packing material for high-performance liquid chromatography

Fine control of pore structure of macroporous beads

Q. Ching Wang, Frantisek Svec, and Jean M. J. Fréchet*

Department of Chemistry, Baker Laboratory, Cornell University, Ithaca, NY 14853-1301, USA

Abstract

A novel approach to monodispersed porous polymer beads allowing accurate control over a broad range of pore size distribution has been developed. It involves the use of monodispersed template particles which are used as polymeric porogens in the suspension polymerization of monomers such as styrene and divinylbenzene. The size uniformity of the template particles is retained by the final porous beads. The porous properties of the final beads are determined in large part by the characteristics of the porogenic mixture such as its composition, the molecular weight of the polymeric porogen, as well as the relative amount of monomers, polymeric and low molecular weight porogens used.

Introduction

Suspension polymerization is the only preparative technique that is applicable to the production of spherical bead polymers with sizes in the micrometer to millimeter range. In most cases, the polymerization is carried out in a stirred reactor using water as the suspending medium, though the use of organic media or is also possible (1). Suspension polymerization techniques afford beads with a broad distribution of sizes. In contrast, size-monodispersed beads with diameters several micron in size can be obtained by techniques such as dispersion (2) or seeded suspension techniques. In particular, Ugelstad introduced the activated swelling and polymerization method which has been used to prepare monodispersed beads with sizes suitable for application in high pressure liquid chromatography (3, 4). With this method, porous beads can be obtained through the use of polymerization mixtures that contain monomers, crosslinkers and porogenic solvents. A patented process (5) suggests the use of toluene as a porogen. However, this approach involving the use of pure solvents as sole porogenic diluents sets narrow limits to the types of porous structures than can be obtained. Only a few solvents are suitable as their solubility in water must be carefully controlled since the solvent has to be transferred from "reservoir" droplets to the seed particles through the continuous water phase before the suspension polymerization starts.

In this paper, we suggest another method which provides great versatility for the control of pore size distribution in uniformly sized porous beads.

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*Corresponding author

Results and discussion

The activated swelling and polymerization method of Ugelstad (3-5) is very similar to classical suspension polymerization except for the use of uniformly sized seed particles that are enlarged by incorporation of the polymerization mixture consisting of monomers and organic solvents, then polymerized. The sole advantage of the technique is that it affords uniformly sized beads, rather than the polydisperse mixture of beads of different sizes obtained in the simple unseeded suspension polymerization process. This is of value for applications in chromatographic media where bead size uniformity is desired.

Another important consideration in the preparation of porous beads for chromatographic applications is the pore size distribution. As described by Ugelstad (5) the method offers little flexibility in this area. It is our objective to develop novel suspension polymerization methods which combine reproducibility with the ability to control bead size uniformity as well as pore-size distribution.

We have recently discovered (6) that a previously unknown feature of the swelling and polymerization technique is that it provides a small but significant shift in the pore size distribution towards larger pores when compared to classical suspension polymerization under similar conditions (Figure 1). A detailed analysis of the two processes reveals that the only difference between the two polymerizations is the presence of about 1 % of dissolved polymer originating from the monodispersed seeds. This suggests that even a very low amount of polymer can act as a powerful porogen (6) in suspension polymerization processes.

Though studied earlier (7,8), polymeric porogens have not received much attention and their mechanism of action has not been fully elucidated. It would be desirable to devise a new approach to porous materials that combined the size monodispersity of the activated swelling method with the porous characteristics that can be achieved with polymeric porogens. The activated swelling method itself, in which the porogen must diffuse through the water phase, is not suitable for use with a polymeric porogen.

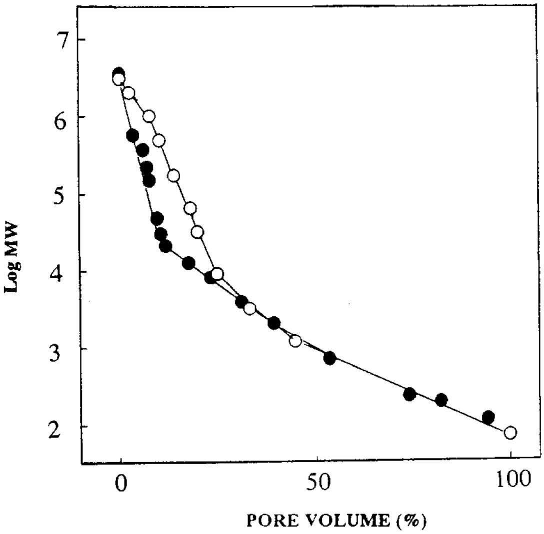

Figure 1
Size-exclusion chromatography calibration curve of 5.6 µm monodispersed porous beads prepared by two-step swelling and polymerization technique (o) and 3-7 µm beads prepared by standard suspension polymerization (●) (Polystyrene standards in THF)

It effectively precludes the introduction of any external polymer to be used as a porogen. On the other hand, the amount of polymer seed that is present in the swelling and polymerization method cannot be varied effectively over a broad range as it remains around 1%.

Our approach is therefore to prepare sufficiently large monodispersed polymeric particles that will act both as porogens and as shape-templates. These large porogen particles are then used as a medium for the polymerization of the desired mixture of monomers. For example, the preparation of porous 7 µm beads with 50% porosity requires the use of 5.6 µm size-monodispersed porogen particles, if polymer is to be the sole porogen. This technique is very versatile as the percentage of polymeric porogen can be varied at will, not only through adjustments in the ratio of polymeric porogen to monomers, but also through the addition of solvent.

Monodispersed polymer particles can be obtained in sizes up to about 10 µm by techniques such as dispersion polymerization (2), or multi-step successive seeded polymerization (9,10). In practice, it may be convenient to proceed in two steps from readily available smaller particles. In the first step, the monodispersed small particles act as shape-templates in the preparation of the larger polymeric porogen particles. These porogen particles can then be used directly, without isolation step, in combination with monomer and crosslinker to prepare the final porous beads.

For example small uniformly sized latex polymer particles with diameters up to 1-2 µm are easily obtained by emulsifier-free emulsion polymerization. A detailed study of the emulsion polymerization of styrene, methyl methacrylate, and glycidyl methacrylate was published recently (11).

Therefore, the polymeric porogen is prepared in the form of non-porous beads by swelling with the monomer or with a monomer-solvent mixture containing the required amount of initiator. The composition, size, and molecular weight of the porogenic polymer can be varied by simple adjustments in this polymerization reaction.

The key step is the final polymerization of monomers within the enlarged polymeric porogen template. This results in porous uniformly sized beads after the soluble polymer molecules of the porogen are removed. This is important in determining the inner chemistry of the final beads as only the monomers polymerized in the last step, and not the polymeric porogen, are used to create the porous matrix.

The same qualitative result, with a different distribution of pore sizes, is achieved using mixtures of polymers and solvents in the final polymerization. In all cases the pore-size distribution of beads obtained with a significant amount of polymeric porogen shows a considerable component corresponding to large pores.

Table 1 documents the preparation of 7.4 µm beads from a variety of uniformly-sized porogenic particles using a constant fraction of porogen. In all cases a two-step preparation is used with the polymeric porogen prepared *in situ* from 1.1 µm shape-template particles (11). In experiment A, the polymeric porogen particles (still containing a small amount of 1-chlorodecane) are of a size (5.3 µm) sufficient to represent about 40% of the final volume of the 7.4 µm particles. In all other experiments, some dibutyl phthalate was used as a co-porogen. In experiment F, the porogen particles are so small that they only contribute to less than 1 % of the porogenic mixture. A remarkable break in properties is seen for beads prepared in experiments A and B. Addition of even a small volume of dibutyl phthalate to the mixture results in a large increase in mean pore diameter. The results of experiments with combined porogens (B - F) document the gradual shift in pore size

TABLE 1. Preparation and properties of 7.4 μ m porous beads: effect of composition of porogen mixture

Experiment	A	B	C	D	E	F
Preparation of porogen beads[a]						
Styrene, ml	6.40	5.10	3.80	2.60	1.30	0
Bead size, μm	5.3	5.1	4.7	4.2	3.6	2.5
Preparation of porous beads [b]						
Polymer beads, %[c]	100	80	60	40	20	0
Dibutyl phthalate, ml	0	1.30	2.60	3.80	5.10	6.40
Polymer in porogen, %[d]	91.5	73.1	54.7	37.7	19.2	0.8
Properties of porous beads						
Pore volume [e], ml/g						
< 10 nm	0.16	0.12	0.10	0.13	0.12	0.14
10 - 50 nm	0.30	0.25	0.31	0.36	0.38	0.38
> 50 nm	0.37	0.53	0.51	0.37	0.15	0.19
d_m [f], nm	37	66	53	43	21	23
S_g [g], m^2/g	17	18	57	50	250	341

[a] 0.06 g of shape template particles (1.1 μm), 0.60 ml 1-chlorodecane, and benzoyl peroxide (5 wt.% with respect to styrene) added ; [b] 5 ml styrene, 5 ml divinylbenzene and 0.1 g benzoyl peroxide added; [c] Volume percentage of polystyrene porogen beads in the mixture with dibutyl phthalate; [d] percentage of polymer in total porogens including 1-chlorodecane and polystyrene shape templates used in the preparation of the porous beads; [e] Fraction of the pore volume contained in pores within the limits; [f] Median pore diameter (both [e] and [f] according to Hg porosimetry); [g] Specific surface area (according to B.E.T.)

distribution as the percentage of polymeric porogen is decreased. Figure 2a illustrates this difference for beads prepared with 80% polymeric porogen by our method (polymer B), and with less than 1% polymeric porogen by a method somewhat similar to Ugelstad's (polymer F).

The high values of the specific surface areas for the beads of experiments E and F are explained by an increase of volume of micropores that is not detected by Hg porosimetry. Beads D were found to be the best suited for application in size-exclusion and reversed-phase chromatography (12).

The pore size distribution of the beads can also be controlled by varying the molecular weight of the polymer porogen. This can be used in combination with changes in the percentage of polymer porogen to fine-tune the porous properties of the beads. Table 2 shows the effect of changing the molecular weight of the polymer porogen on porous properties for three different preparations, all involving 40% of polymer porogen. The median pore size decreases from 283 nm for the porogen polymer with M_w = 517 000 to 49 nm for the polymer porogen with a molecular weight 22 times lower. The lower the molecular weight, the more similar the polymer is to a porogenic solvent, and the lesser its effect on porous properties.

TABLE 2
Preparation and properties of 7.4 µm porous beads: effect of molecular weight of the polymeric porogen on properties of porous beads

Experiment	G	H	I
Preparation of porogen beads[a]			
Benzoyl peroxide, %	1	2.5	10
$M_w . 10^3$	517	86	23
$M_n . 10^3$	204	61	5.2
M_w/M_n	2.5	1.4	4.6
Properties of porous beads[b]			
Pore volume [c], ml/g			
< 10 nm	0.07	0.03	0.12
10 - 50 nm	0.17	0.29	0.44
> 50 nm	0.89	0.74	0.48
d_m [d], nm	283	92	49
S_g [e], m^2/g	8	112	122

[a] 0.07 g shape template particles (1.1 µm), 0.20 ml dibutyl phthalate and 4.4 ml styrene added, swollen bead size 4.3 µm; [b] 5 ml styrene, 5 ml divinylbenzene, 3.4 ml dibutyl phthalate, and 0.1 g benzoylperoxide was added to dispersion of porogen beads; [c, d, e] Same as in Table 1

However, the effect is most clearly seen in the location of the maximum of the pore size distribution curve in the area of large pores. The beads of experiment G (Table 2) provide a distinct maximum at a pore size of 400 nm, in experiment H the maximum is at 150 nm, while in experiment I it is at 60 nm only. In all cases, the biporous character of the beads is preserved. As an example, Figure 2b shows the pore size distribution curve for the polymer prepared in experiment G.

Incompatibility of the polymeric porogens with the polymerizing media may also make a significant contribution to pore formation and be useful in the fine-tuning of porous properties (8). The extent of incompatibility depends on the chemical composition of the polymers. Therefore the chemical structure of the porogenic polymer particles is expected to be an important variable, capable of providing a high degree of control over the porous properties of the final beads. The flexibility of our method (12) allows the simple preparation of copolymers to be used as porogenic beads.

The use of copolymers of styrene and methyl methacrylate of varying compositions, but similar molecular weights as porogen produces effects similar to those resulting from increases in the molecular weight of the polymer porogen.

For example, the use of 40% of methyl methacrylate and 60% styrene in the polymer porogen shifts the distribution curve maximum in the macroporous range to a diameter of more than 500 nm while the volume of mesopores decreases as shown in curve L in Figure 2b. The volume of pores with diameters larger than 50 nm increases from 31% for a pure polystyrene porogen to 55% for a 60:40 copolymer of styrene and methyl methacrylate as measured by Hg-porosimetry. In contrast, the volume of pores with sizes ranging from 10 to 50 nm decreases from 54%

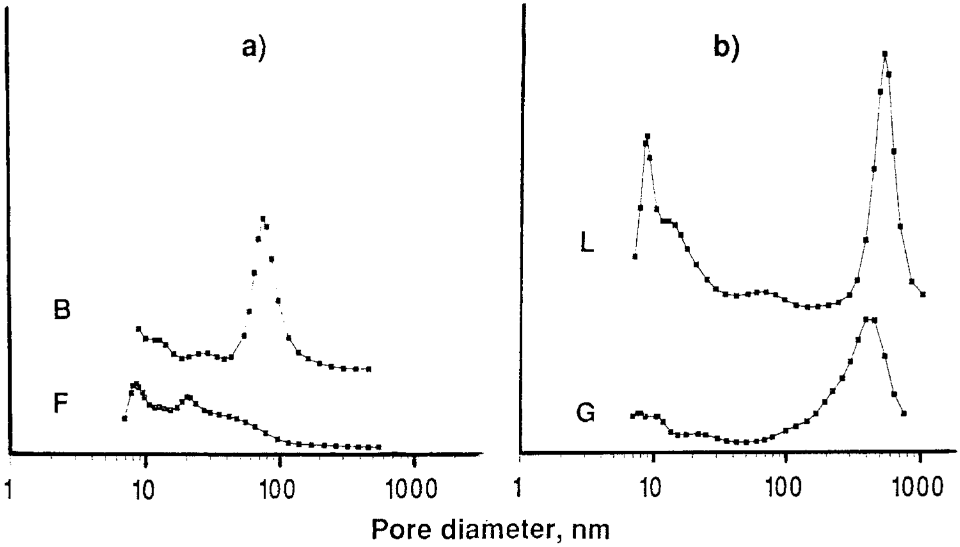

Figure 2 Differential pore volume curves of the porous beads prepared in experiments B, F, G, and beads prepared under the conditions of experiment G except for addition of 8.9 ml styrene and 6.0 ml methyl methacrylate to shape-template particles in preparation of polymer porogen (L)

to 30%. The volume of pores with sizes below 10 nm (not monitored by mercury porosimetry), is essentially unaffected. This is confirmed by the modest increase in the specific surface area of the beads from 81 m^2/g (polystyrene only) to 102 m^2/g(60:40 copolymer of styrene and methyl methacrylate). This 20% increase is much lower than those shown in Tables 1 and 2 reporting the effects of changes in amount and molecular weight of the polymer porogen.

Conclusion

The use of *in situ* prepared polymer porogens provides a powerful tool for the fine control of the porous properties of uniformly sized porous beads. The volume fraction of the polymer porogen and solvent in the porogenic mixture, as well as the molecular weight and composition of the polymer porogen have a great influence on the pore size distribution of the final beads. As each of these variables affects the pore size distribution in a different manner, their combination allows the design and preparation of particles with porous properties closely related to the expected use. An obvious example is the application of the uniformly sized porous beads in HPLC (12).

Experimental

Standard suspension polymerization method. The organic phase consisting of 7 ml styrene, 9.5 ml divinylbenzene (55% DVB), 25 ml toluene, 3.2 ml dibutyl phthalate and 0.3 g benzoyl peroxide was stirred in a 2 wt % aqueous solution of poly(vinyl alcohol)(Aldrich, M.W. 85 000-146 000; 88% hydrolyzed) at 70 °C for 10 hours. The beads were washed with methanol and THF, dried, and packed in a column without size classification .

Swelling and polymerization method. Monodispersed polystyrene particles prepared according to ref.(11) (1.5 µm diameter, 7.2% solid in water, 7 ml) were swollen with a solution of 0.3 g benzoyl peroxide in 3.2 ml dibutyl phthalate emulsified in 20 ml of water containing 0.15 g sodium dodecyl sulfate (SDS). In the second swelling step, 16.5 ml of emulsified monomers (7 ml styrene, 9.5 ml divinylbenzene (55% DVB) and 25 ml toluene (porogenic diluent) in 170 ml water containing 3.4 g poly(vinyl alcohol) were added to the dispersion resulting from the first swelling step. The polymerization was carried out in a glass reactor (Buchi BEP 280) at 70 °C for 10 hours. The workup of the beads was done as described above.

Preparation of porous beads with polymer porogen. Monodisperse polystyrene particles prepared according to ref. (11) (1.1 µm diameter, 12% solid in water, 0.50 ml) were swollen by absorption of 0.6 ml 1-chlorodecane or dibutyl phthalate emulsified by sonication in 0.25 wt % aqueous SDS solution. The swelling was allowed to proceed at room temperature for 30 hours. An emulsified mixture containing varying amounts of styrene or styrene/methyl methacrylate and benzoyl peroxide was added to the dispersion resulting from the previous step and the swelling was continued for another 5 hours. To the dispersion of swollen particles was added 5% solution of poly(vinyl alcohol) to adjust to 1 wt % the total concentration of poly(vinyl alcohol) and the mixture was deaerated by purging with nitrogen. The polymerization was carried out in a glass reactor (Büchi BEP 280) at 70 °C for 24 hours. To the resulting dispersion of the polymer porogen particles was added emulsified mixture of 5 ml styrene, 5 ml divinylbenzene (80% DVB, Dow Chemical Co., Midland), dibutyl phthalate, and benzoyl peroxide in 0.25 wt % aqueous SDS solution. The mixture was stirred at room temperature until all of the emulsified liquid was transferred into the shape-template particles. This process was checked by an optical microscope and took about 5 hours. The mixture was deaerated again and the reactor sealed. The polymerization was allowed to proceed at 70 °C for 24 hours. The beads were washed by repeated decantation in water and methanol. The polymeric porogen was removed by extraction with toluene for 48 hours in a Soxhlet apparatus. The porous beads were washed with methanol again and dried in air.

Characterization of the properties. The specific surface area was calculated from B.E.T. isotherm of sorption and desorption of nitrogen, the pore size distribution was determined by mercury porosimetry (Combined BET Sorptometer and Mercury Porosimeter, Porous Materials Inc., Ithaca, NY). The size exclusion HPLC was performed in THF in a stainless steel column 150 x 4.6 mm i.d. with benzene and polystyrene standards with molecular weights ranging from 1250 to 2 950 000 (6).

Acknowledgements

Financial support of this research by the National Institutes of Health (GM 44885-01) is gratefully acknowledged. Thanks are also due to the Cornell Materials Science Center supported by the National Science Foundation (DMR-8818558) for the use of its polymer characterization facility, and to the Institute of Macromolecular Chemistry, Czechoslovak Academy of Sciences for granting a leave of absence to F.S.

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Accepted April 21, 1992 K