

# Porous Polymer Particles – A Comprehensive Guide to Synthesis, Characterization, Functionalization and Applications

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## Abstract:

This review is written to fulfill the need of a comprehensive guide for the manufacture of porous polymer particles. The synthesis section discusses and for the first time compares microfluidics, membrane/microchannel, suspension, dispersion, precipitation, multistage polymerizations and a few other less known methods, microfluidics being in greater detail. The comparison includes on one hand simplicity, scaling-up possibilities and the ability to yield nonspherical particles for these methods and on the other hand size, size monodispersity, pore characteristics and chemical functionality of the obtained particles. This extensive comparison certainly makes this review also useful for the preparation of nonporous particles. In addition, functionalization/characterization techniques and applications of porous particles are also discussed, including some visionary recommendations. The review is expected not only to enable individual experts of each field to compare their methods with the other ones, but also to be a handbook for the newcomers to this field to guide them from the synthesis to the applications.

## Abbreviations:

AIBN, 2,2'-azobis(2-methylpropionitrile); ASTM, American Society for Testing and Materials; CuAAC, Cu(I) catalyzed azide-alkyne cycloaddition; CV, coefficient of variation defined as  $(\sigma/D_p) \times 100$  where  $D_p$  is the number average diameter and  $\sigma$  is the standard deviation on the diameter; DSC, differential scanning calorimetry; DVB, divinylbenzene; EGDMA, ethylene glycol dimethacrylate; EtOH, ethanol; Fmoc, fluorenylmethyloxycarbonyl; GMA, glycidyl methacrylate; HEMA, 2-hydroxyethyl methacrylate; HIPE, high internal phase emulsion; HPLC, high performance liquid chromatography; MeOH, methanol; MMA, methyl methacrylate; MW, molecular weight; O/W, oil-in-water emulsion; PDMS, poly(dimethylsiloxane); PEO, poly(ethylene oxide); PMMA, poly(methyl methacrylate); PS, polystyrene; PVA, poly(vinylalcohol); SDS, sodium dodecyl sulfate; SEC, size exclusion chromatography; SEM, scanning electron microscopy; SPOS, solid phase organic synthesis; SPPS, solid phase peptide synthesis; SPG, Shirazu porous glass; TEM, transmission electron microscope; TGA, thermogravimetric analysis; THF, tetrahydrofuran; UV, ultra violet; W/O, water-in-oil emulsion.

**Keywords:** Microgel, beads, porosity, porogen, microfluidics, membrane/microchannel emulsification, suspension-dispersion-precipitation-seeded polymerization, click chemistry

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## 1. Introduction

Porous polymer particles, especially the ones that are spherical in shape, have been utilized in numerous applications for decades. They have been classified as macro-, meso- and microporous depending on the size of the pores, respectively > 50 nm, 50-2 nm and < 2nm. Two main features, their porous nature and higher crosslinking degree, differentiate them from gel-type polymer particles. These differences give rise to different characteristics such as high surface area, ability to uptake various solvents with different polarity and increased brittleness. Size, size dispersity, chemical nature and functionality can be mentioned as the other features that porous particles share with their nonporous counterparts, the gel-type particles. The variety of applications requires different combinations of the mentioned features. For instance, while chromatography requires highly monodisperse (uniform in size, low coefficient of variation (CV)) sub 5  $\mu\text{m}$  beads, solid phase peptide synthesis (SPPS) is usually conducted with 100-200  $\mu\text{m}$  beads and monodispersity is not that crucial. On the other hand, functionality is a must for SPPS but can be undesired for chromatography.

In general, polymer particles are produced by heterogeneous polymerizations using the immiscibility of two or more liquids. Suspension, dispersion, precipitation, multistage, membrane/microchannel emulsification and microfluidic polymerizations are the main techniques to form porous particles. In all cases, the application should be kept in mind prior to choosing the method of production.

With this review about porous polymer particles, we would like to fulfill the need for a comprehensive guide, not only for the experts but also for scientists that are new in this broad field. The closest review on this topic by Okay in 2000 [1] deals more with particle characteristics, explains the methods of production and characterization briefly and lacks discussion about applications. Although in literature there are several reviews for polymer particles (not specifically porous),

the older ones [1-3] merely cover the conventional methods (suspension, emulsion, dispersion, precipitation, seeded) while the new ones [4-6] only focus on the new methods (membrane/microchannel emulsification and microfluidics). To the best of our knowledge, we gathered in this review for the first time all the manufacture methods, including some less known methods. Novel explanations are delivered about these techniques by making use of schematic descriptions. Moreover, we focused more on the chemistry viewpoints using basic phenomena, rather than highlighting the technical aspects of the mentioned methods.

The review also includes detailed characterization, functionalization and application sections. The functionalization section has the intention to give a summary of what is flourishing in polymer science as efficient chemical transformation methods, including click chemistries. This section also includes surface- and pore-size-specific functionalization. Together with current usage areas, future recommendations are given in the applications section. Last but not least, nonspherical particles are also discussed throughout the text since this is an immature field for porous particles with lots of opportunities waiting to be exploited to our belief.

Porogens are the substances yielding the porous nature of particles. Throughout the text, we will avoid using the widely applied term 'porogenic solvent' since gasses and solids can also be used as porogens. The term 'inert diluent' is also not proper to our understanding since we believe that there is room for innovations by making use of reactive porogens and that immiscible porogens cannot really dilute a monomer mixture. It is also worth to mention that the term 'monomer' will not necessarily exclude crosslinkers; all polymerizable species can be denoted together as the monomer mixture in this text. Moreover, we will focus on particle formation via vinyl polymerization, which constitutes the largest part of the field. Inorganic, hybrid and non-crosslinked polymer particles (produced via precipitation from polymer solutions) are kept out of the scope of this manuscript.

## 2. Synthesis

### 2.1. An introduction to the Production of Porous Polymer Particles

For decades chemists learnt how to use physical principles to design their reactors, rather than chemical principles. Temperature, pressure, viscosity, stirring and fluid dynamics are the important principles to be mentioned first. Liquid immiscibility is another 'tool' that chemists are familiar with and make it serve to their quests, for instance to produce regular particulate materials. From daily life, we all know that oil and water are immiscible and will phase separate. When it is desired to form a dispersion of one of the two liquids in the other, which is called an emulsion, a sufficient amount of emulsion stabilizer should be added together with applied shear. The words emulsifier, surfactant, surface active molecules and many more are all used to describe emulsion stabilizers that are readily present in our everyday life, such as soap and detergents. Emulsifiers are molecules that have both hydrophilic and hydrophobic parts, recognized by water and oil, respectively. When oil and water are mixed in the presence of such an emulsifier, the emulsifier molecules cover the surface of the dispersed phase droplets by reducing the interfacial tension. Milk is a well known example of a stable emulsion in nature where oil (butterfat) droplets are dispersed in water by the aid of phospholipids and proteins.

Already in 1912, chemists realized that an emulsion can be utilized to produce polymer particles [7]. Keeping water as the continuous phase, the discrete phase could be droplets of hydrophobic monomeric species, which can be converted into polymer particles after polymerization. The emulsion stabilizer can be a soap molecule, a polymeric stabilizer or a natural surface active material such as gum, starch or gelatin. A free radical polymerization initiator is used and can be added to either phase. These ingredients and their immiscibility are the basis of heterogeneous polymerizations (also called heterophase polymerizations), with the exception of dispersion and precipitation polymerizations where the initial mixture starts from a completely homogeneous solution, which will be discussed later in this section. It is also worth to mention that water soluble monomers can be polymerized as discrete phase droplets in an organic solvent (the oil phase). These types of W/O systems are generally denoted as inverse heterogeneous polymerizations.

The importance of controlling the interfacial tension is already discussed in the introduction paragraph.

However, it is also necessary to stress that the spherical shape of the monomer droplets is caused by this interfacial tension. Indeed, the sphere is the shape with the lowest surface to volume ratio, which is the reason why in most cases polymer particles are spherical in shape, thus explaining the difficulty to make regular nonspherical particles.

Emulsion polymerization, mini- and microemulsion polymerization, suspension polymerization, dispersion polymerization, precipitation polymerization, membrane emulsification and microfluidics are the techniques utilized for polymer particle manufacture. With exception of emulsion, miniemulsion and microemulsion polymerizations, all these polymerization methods will be covered by this review as emulsion polymerization is not readily used to form porous particles [8]. This is ascribed to its unique mechanism where the location of initiation, chain growth and largest monomer presence are all different from each other [3].

Nevertheless, emulsion polymerization is widely (but not only) utilized as the first stage of seed polymerizations that can be defined as multistage heterogeneous polymerization techniques where almost any combination of the aforementioned techniques can be used. In this two stage approach, first nonporous 'seed' particles are produced, which are the initial relatively small monodisperse particles. These seed particles are subsequently enlarged in a second stage. As a result, seed polymerization techniques will also be covered. As mentioned before, this review will also cover microfluidics in detail since this is the most recent among all heterogeneous polymerization techniques and allows the synthesis of unprecedented structures such as regular nonspherical forms or core-shell structures. This is an area of research in which also our own research group has been contributing recently [9-10]. The following sub-section describes suspension polymerization together with all main pore formation mechanisms/methods, which are also applicable in the other techniques including microfluidics.

### 2.2. Suspension Polymerization and General Pore Formation Techniques

In terms of physical categorization, whereas an emulsion denotes a liquid/liquid dispersion, a suspension denotes a solid/liquid dispersion. However, this does not apply for heterogeneous polymerizations since both emulsion and suspension polymerizations start with liquid/liquid mixtures in the beginning and end up as solid/liquid dispersions. A suspension polymerization starts with

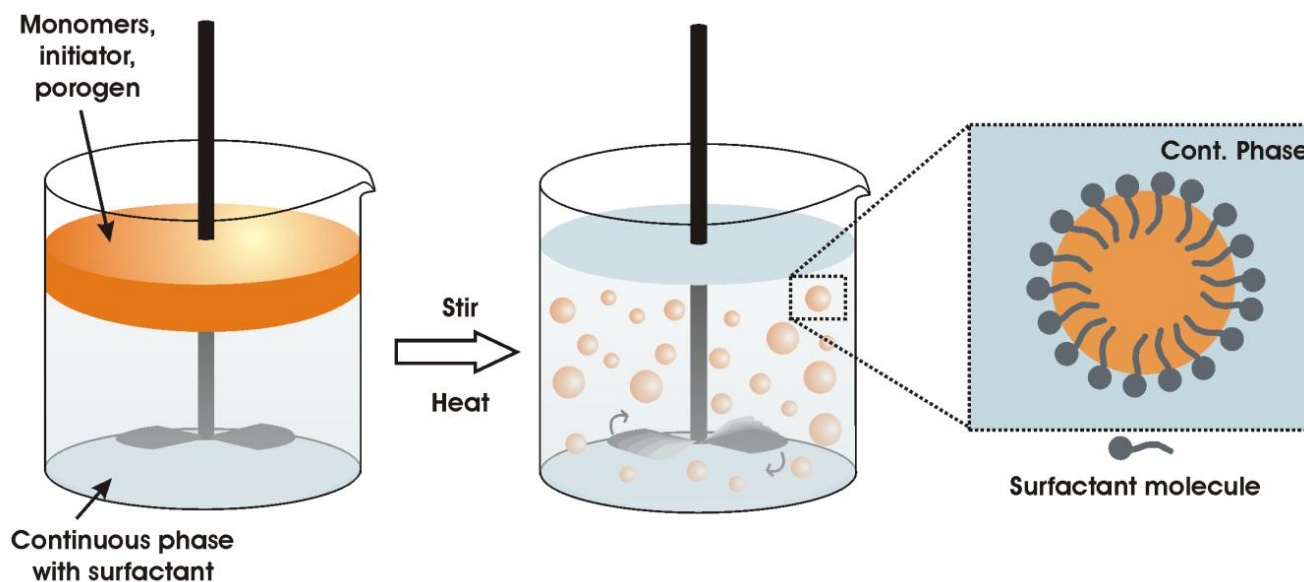


Fig. 1. Basic depiction of the suspension polymerization technique.

dispersing monomer droplets in a continuous phase with the aid of surfactants such as sodium dodecyl sulfate (SDS) (Fig. 1). A monomer soluble initiator is added, aiming to drive both initiation and chain growth inside the monomer droplets. This is the main difference with the emulsion polymerization where a continuous phase soluble initiator is used so that the mechanism completely changes, for which we refer to other literature [3]. Moreover, radical trapping species such as  $\text{NO}_2^-$  salts, can also be added to suspension polymerization recipes [11] to prevent nucleation in the continuous phase [12].

Suspension polymerization can be considered as the least complicated heterogeneous polymerization technique in terms of its mechanism. As depicted in Fig. 1, there are the discrete phase droplets with monomeric species (monomers and crosslinkers), initiator and porogen on one hand and there is the continuous phase with dissolved surfactant and/or polymeric stabilizers on the other hand. The molecular transfer between the two phases needs to be minimized in suspension polymerization because initiation and propagation all take place in the monomer droplets. Two parameters are of utmost importance: solubility of monomers in the continuous phase and the role of surfactants and stabilizers. The monomer solubility in the continuous phase becomes an important issue in systems where the monomer to continuous phase ratio is low. If there are no phase transfer limitations, a significant amount of monomer would be present in the continuous phase at the start of the polymerization reaction and will transfer back to discrete phase droplets by time since polymerization consumes the monomers in these droplets. This process may result in retardation of the

polymerization. Also the porous nature of the final particles would be affected since porosity depends very much on the concentration difference between monomers to porogen(s). Nevertheless, a porogen can also be used to increase the partition of a water soluble monomer in the discrete phase droplets where the continuous phase is water. For example, Fréchet and co-workers managed to polymerize a completely water soluble crosslinker in a "classical" suspension polymerization by using cyclohexanol as the porogen [11].

In suspension polymerization, continuous mechanical agitation with a constant speed is applied throughout the whole process to keep the monomer droplets well dispersed (Fig. 1). However, droplet collision and break-up cannot be prevented. Since the droplet formation is governed by the chaotic agitation and since droplet collision/break-up takes place continuously throughout the process, particles obtained via suspension polymerization are almost always polydisperse. Notwithstanding the fact that this polydispersity is the main drawback of suspension polymerization, this technique is widely applied in industry because of the low cost and upscaling possibilities. The obtained particles are sieved to specific size ranges when needed. The agitation speed and the shape of both the reactor and the mechanical stirrer are the main factors influencing the size distribution and size of final particles, without forgetting the importance of the viscosity values of both phases and surfactant concentration that tunes the interfacial tension.

Here we will discuss the general pore formation mechanisms which can be directly applied to the other techniques as well, especially membrane/microchannel

emulsification and microfluidics. Other techniques about pore formation, which are not applicable to suspension polymerization, are discussed within the relevant sections.

### 2.2.1. Using a Good Solvent as the Porogen ( $v$ -Induced Syneresis)

Polymerization of styrene in water can be accepted as a text-book example of the suspension polymerization. As an example, the discrete phase may consist of styrene (monomer), divinylbenzene (DVB, crosslinker), 2,2'-azobis(2-methylpropionitrile) (AIBN, initiator) and toluene (porogen), whereas the continuous phase can be an aqueous poly(vinylalcohol) (PVA, emulsion stabilizer) solution. Toluene is a thermodynamically good solvent for the polymer, which means that it can readily swell the final crosslinked beads. A good solvent is characterized by a Hildebrand solubility parameter close to that of the polymer [2]. Inside every discrete phase monomer droplet, a continuous network grows by addition of monomer and after a certain time, the network becomes incapable of absorbing more toluene due to an increasing amount of crosslinking. A precipitation or deswelling (phase separation) occurs at this point, which is after the gelation point of the network. It is this phase separation that yields the porous nature of the particles. The amount of crosslinker is of great importance as it determines the time of precipitation and the extent of porosity. Micro- and mesopores are predominant, resulting in beads with high surface area values but low pore volumes [2]. This type of pore formation is called  $v$ -induced syneresis [1].

### 2.2.2. Using a Nonsolvent as the Porogen ( $\chi$ -Induced Syneresis)

On the other hand, if a nonsolvent for the final polymer is used as a porogen, such as *n*-heptane [13] instead of toluene in the previous case, pore formation occurs via  $\chi$ -induced syneresis [1]. In this case, phase separation occurs before the gelation point since heptane cannot swell/dissolve the growing polymer chains. At the start of the initiation, separated smaller particles of polymer (nuclei) grow as a discontinuous phase (early phase separation due to the nonsolvent) inside every discrete monomer phase droplet. These nuclei agglomerate via inter-nuclei crosslinking and the final bead is formed. In contrast to the previous case, macropores are predominant, resulting in particles with a significantly lower surface area but larger pore volumes [2]. Moreover, suspension polymerization of monomers like vinyl chloride and acrylonitrile yields intrinsically

macroporous particles without the addition of an external nonsolvent due to the fact that these monomers cannot dissolve/swell their corresponding polymers [7, 14]; this could be referred to as the 'self-porogen' effect.

### 2.2.3. Using Linear Polymers as the Porogen

Various polymers and oligomers can also be used, generally together with a solvent, as the porogen. Also in this case pore formation occurs via  $\chi$ -induced syneresis [1]. Examples of polymers and oligomers used as porogens include poly(methyl methacrylate) (PMMA) [15], PS [16], poly(ethylene oxide) (PEO) [17], poly(propylene oxide) [18] and poly(dimethylsiloxane) (PDMS) [18]. It is important to note that Okubo et al. [19-20] reported that the amount and the nature of polymeric porogen may either induce a porous or a nonporous hollow final structure. The pioneers of methacrylate based porous particles, Svec and Horák, reported the differences between the use of a good solvent (toluene), nonsolvent (dodecanol) and a polymeric porogen (polystyrene in toluene, 15%) for the synthesis of a copolymer of glycidyl methacrylate (GMA) and ethylene glycol dimethacrylate (EGDMA) [2]. In the order of good solvent, nonsolvent and polymeric porogen, the specific surface area decreases below 1 m<sup>2</sup>/g whereas the size of microglobules and total pore volume increase (Fig. 2).

Macintyre and Sherrington [18] reported that a bimodal pore size distribution can be obtained in some cases by using a mixture of toluene (good solvent, inducing micropores) and PDMS (polymeric porogen, inducing macropores) for a bead composed of DVB alone. Although it should be against expectations that from a single porogen the combination of high surface area and high pore volume could be reached, Li et al. [21] found out that polyDVB particles exhibit a surface area equal to 720 m<sup>2</sup>/g, together with a very high pore volume of 68%, when prepared in the presence of 1-chlorodecane alone, which is a nonsolvent for polyDVB. However, the authors were unable to explain this unexpected behavior.

An important problem of using a nonsolvent as the porogen is the possibility of the formation of a dense and often impermeable polymer layer on the surface of particles, although the internal structure is highly porous. In literature, this nonporous layer is referred to as either a "skin" [22-25] or "shell" [26-27]. As mentioned before, a nonsolvent should possess a solubility parameter value that significantly differs from that of the polymer. However, when the difference in the solubility parameter is too large, "skin" formation is promoted, as reported in detail by Kumacheva and co-workers [28]. In their case, the difference in the solubility parameter was increasing

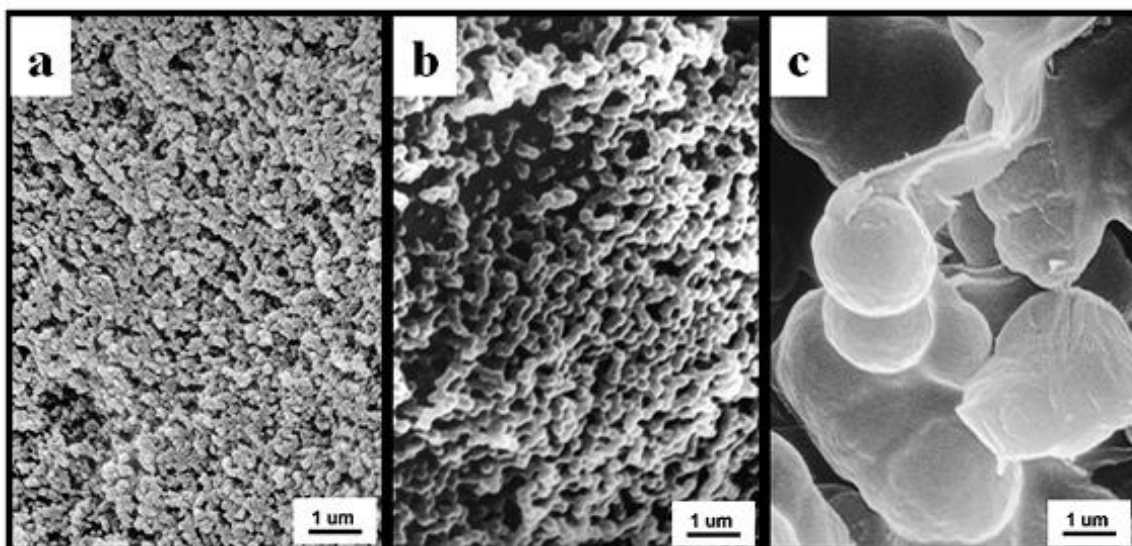


Fig. 2. Scanning electron microscopy (SEM) images from surface of EGDMA-GMA (24%-16) beads prepared by using different porogens at 60% ratio: (a) toluene (good solvent), (b) dodecanol (nonsolvent), (c) PS solution in toluene (polymeric porogen, 50000 g/mol, 15%). From left to right, pore size increases and total surface area decreases. Reproduced from [2] with permission. Copyright 2005 Wiley-VCH Verlag GmbH & Co. KGaA.

by a decreasing polarity of porogen. Since the continuous phase was water in their system, highly nonpolar porogens disliked to be present in the water/oil interface due to the high interfacial tension. Thus, the interface became rich in monomer and polymer, resulting in a "skin" layer, while the interior was porous. On the other hand, more polar solvents resulted in "skin"-free macroporous particles. Moreover, they provided an excellent solution to this problem by decreasing the interfacial tension without changing the highly nonpolar porogen. They lowered the interfacial tension by decreasing the polarity of the continuous aqueous phase or by adding a specific surfactant next to a polymeric stabilizer. However, it should be noted that this solution avoiding the skin formation may not be valid for every monomer/continuous phase system since the interfacial tension and solubility parameters may not follow the same trend. Although the technique utilized was microfluidics in this case [28], these results should also be applicable to suspension polymerization. The similarities between the two techniques will be discussed further on in the microfluidics section.

#### 2.2.4. Using Water as the Porogen

Unlike a nonsolvent, solvent or a polymer, a porogen that is even immiscible with the initial monomer mixture can also be utilized to obtain porous particles. The most common example of such strategy is using water as the porogen. A water-in-oil-in-water (W/O/W) double emulsion is formed by adding oil soluble surfactants to the discrete monomer (oil) phase. Water is absorbed

from the continuous water phase by the monomer droplets as a result of the stabilizing effect of the oil soluble surfactants [29]. Although porogen water droplets should have been separated initially inside the monomer phase, highly porous polymer beads with pore sizes around 80 nm and surface area values reaching up to 200 m<sup>2</sup>/g (proving the interconnectivity of pores) are obtained after polymerization. The same authors also published that a combination of surfactants can produce hollow porous beads (Fig. 3(B)) [30]. Although produced by a uniquely facile template-free approach, such hollow porous particles were not further discussed in their paper [30]. However, the same authors published later that hollow porous particles can also be obtained via addition of a W/O emulsion (the oil being the monomer phase) into a second water phase [31], thanks to ripening.

#### 2.2.5. HIPE Technique

The highest amount of a liquid dispersed as monodisperse spherical droplets in another liquid can be 74 vol% [32]. However, by a careful choice of the surfactant and dropwise addition of the internal phase over a vigorously stirred continuous phase (including the surfactant), high internal phase emulsions (HIPE) can be obtained with internal phase volumes exceeding 99% [33] because of the nonspherical packing of internal phase droplets [32]. When the continuous phase is polymerized, a poly(HIPE) is obtained, i.e. a very light, highly porous material with fully interconnected pores exceeding 10 μm in diameter [32-33]. Particulate poly(HIPE) with regular shapes has been a challenge for

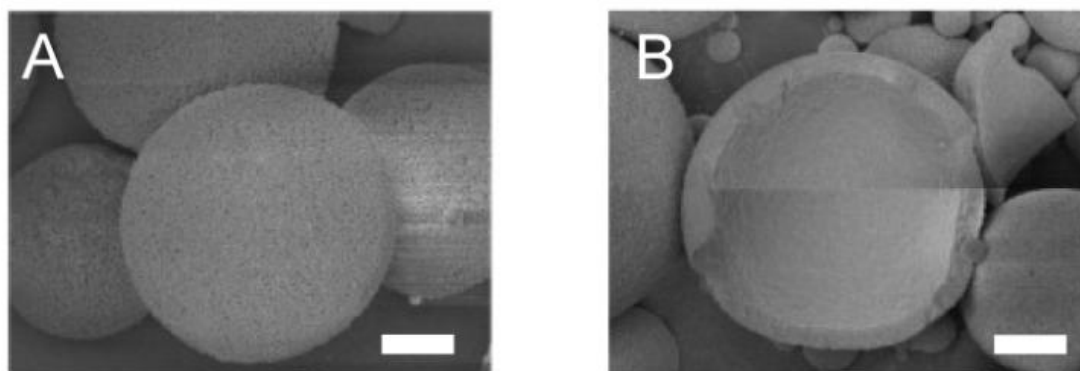


Fig. 3. (A) Porous and (B) hollow porous particles prepared by aqueous suspension polymerization, utilizing water as the porogen with the aid of various monomer soluble surfactants. Monomer soluble surfactants captured water from the continuous phase, resulting in the hollow and/or porous structure. The hollow core only formed with specific surfactants. Scale bars indicate 10  $\mu\text{m}$ . Adapted from [30] with permission. Copyright 2007 Elsevier.

scientists due to the difficulties faced during forming HIPE droplets in a second continuous phase (double emulsion). Nevertheless there are few reports in patents [34-35] and in open literature [36-39] of polymerizing HIPE formulations in a suspension media yielding polydisperse beads with ultra large pore sizes (Fig. 4(A)). Deleuze and co-workers reported [36] a surface area value of 124  $\text{m}^2/\text{g}$  when they added 20% petroleum ether (a volatile porogen) to the monomer phase of the HIPE whereas the surface area was 20  $\text{m}^2/\text{g}$  in the absence of petroleum ether. This is another example where a combination of porogens is utilized to obtain different pore sizes. Based on the W/O/W double emulsion approach, Nelissen and co-workers [40] prepared water absorbed PS beads. The obtained beads were heated above their glass transition temperature in order to use the entrapped water molecules as blowing agents, which resulted in pores reaching up to 100  $\mu\text{m}$  (Fig. 4(B)). In this example water replaces the traditional blowing agent pentane [41], which results in avoiding the use of volatile organic compounds.

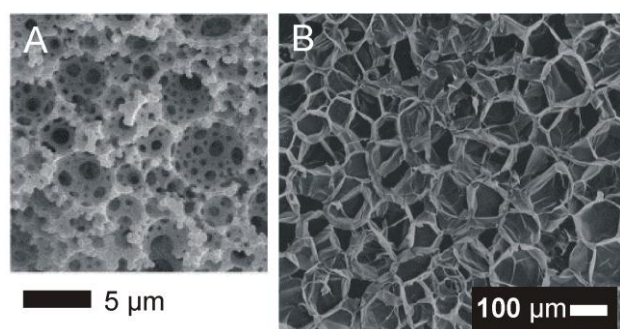


Fig. 4. The surface of (A) a poly(HIPE) bead [36] and (B) a water expanded PS bead [40] both prepared by suspension polymerization using water as the porogen. While the largest pore is only  $\sim 5 \mu\text{m}$  for the poly(HIPE) bead, the water expanded PS bead possesses pores as large as 100  $\mu\text{m}$ . Adapted from [36, 40] with permission. Copyright 2002 Elsevier; Copyright 1999 Elsevier.

### 2.2.6. Using Solids as the Porogen

Another type of immiscible porogens can be a solid instead of water, which results in the realization of solid-in-oil-in-water (S/O/W) dispersions. Pores are formed after the removal of solid particles embedded on polymer beads via washing or etching. Washing is also needed to reveal the porous structure in the previous cases where a liquid porogen is used, with the exception of volatile solvents, which can be removed via evaporation. As an example for S/O/W dispersion, Wu and Pang dispersed  $\sim 0.8 \mu\text{m}$   $\text{CaCO}_3$  particles in a EGDMA-GMA monomer mixture and suspension polymerized this S/O dispersion in water [42]. After removal of  $\text{CaCO}_3$  via HCl etching, the beads exhibited pores as large as 10  $\mu\text{m}$  and a surface area value of 79  $\text{m}^2/\text{g}$ . In another report [43], a mixture of solid ( $\text{CaCO}_3$ ), nonsolvent (dodecanol) and good solvent (cyclohexanol) porogens are utilized all together for the suspension polymerization of the same EGDMA-GMA monomer mixture. Together with a total surface area of 91  $\text{m}^2/\text{g}$ , the formation of a bimodal distribution of micropores (10-90 nm) and macropores (180-4000 nm) is observed. We would like to stress here that, in principle, also gas forming reactive porogens can be used to obtain larger pores but no example was reported to the best of our knowledge.

For the above described strategies on pore formation in suspension polymerization, the continuous phase was water in every single case. Water soluble monomers are also suspension polymerized but in that case the continuous phase is an organic solvent. Thus the overall medium should be a W/O emulsion, which is also referred to as an inverse suspension polymerization. The aforementioned porogen types are applicable (at least theoretically) to inverse suspension polymerization under the condition that the porogen is chosen accordingly [44-46].



For the above mentioned pore formation techniques, the comparison of the size of the particles follows the trend of their pore sizes. Whereas porous beads in the size range of a few microns [2] can be prepared via syneresis techniques, poly(HIPE) beads need to be over 100  $\mu\text{m}$  [36] and water expanded polystyrene beads were prepared with a diameter range above millimeter scale [40] and pores as large as 100  $\mu\text{m}$ . As a rule of thumb, particles prepared via suspension polymerization (in the range of 5-2000  $\mu\text{m}$  [3]) are always larger than those prepared via other techniques. However, it is possible to provide smaller diameters via microsuspension polymerization. In this case, after the ingredients are mixed, a high shear force such as ultrasonification is applied prior to the start of polymerization, forming finer monomer droplets [22, 47].

We would like to note that in suspension polymerization, every single monomer droplet behaves like a microreactor of a bulk polymerization if a porogen is absent. These droplets will become microreactors of a solution polymerization where a good solvent is added as porogen. Addition of a poor solvent will make the droplets microreactors for precipitation polymerization. In the case of HIPE, droplets can be regarded as microreactors of monolith polymerization.

### 2.3. Precipitation and Dispersion Polymerizations: Homogeneous at the Start

In contrast to all other techniques described in this review, dispersion and precipitation polymerizations start as completely homogeneous solutions. However, they are still classified as members of heterogeneous polymerizations since phase separation takes place in an early stage as a result of the polymerization. Although the two techniques have similar mechanisms, there are two main differences: 1) a stabilizer is used in dispersion polymerization but not in precipitation polymerization, 2) a crosslinker is necessary and used in large proportions in precipitation polymerization, while crosslinkers are most of the cases omitted in dispersion polymerization. As a result of the second reason, dispersion polymerization is mostly used for non-crosslinked, nonporous particle production. On the other hand, precipitation polymerization is more suitable for highly crosslinked and porous particles. The most important and common feature of the two techniques is the production of monodisperse particles in the range of 0.1-10  $\mu\text{m}$

#### 2.3.1. Precipitation Polymerization

As depicted in Fig. 5(A), precipitation polymerization starts as a homogeneous solution of crosslinker and initiator in a medium composed of a near  $\Theta$ -solvent (for the crosslinker) and porogen(s). The near  $\Theta$ -solvent later becomes the continuous phase as the precipitation of particles starts. Precipitation polymerization requires a high amount of crosslinker and in many cases DVB is polymerized alone [48-49]. It should be noted that commercial DVB is technical, composed of either 55% or 80% DVB with the rest being mostly ethyl styrene monomer. Methacrylate crosslinkers are also polymerized via precipitation polymerization with a low percentage of added monomer [50-51]. As a result, precipitation polymerized particles are rich in remaining double bonds that can be efficiently utilized in post-functionalization [52] (see further functionalization section).

As the polymerization starts, oligomers and nuclei are being formed (Fig. 5(B)). Whereas the oligomers are still soluble in the medium, the nuclei precipitate resulting in a heterogeneous mixture. The nuclei are swollen by porogen (shown as the yellow background) and the medium (the continuous phase) becomes less rich in porogen. Although no stabilizer is used, the nuclei are stabilized by a layer of oligomers that are swollen by the medium. The polymerization continues at the particle-continuous phase interface [53]. The nuclei do not overlap but only grow by adding fresh monomer and oligomers from the medium (Fig. 5(C)). The porogen that is initially absorbed by the growing nuclei phase separates from the particle and forms the pores. As a result of the fact that the nuclei do not overlap, highly monodisperse particles, generally in the size range of 1-5  $\mu\text{m}$ , are obtained [54]. Recently, monodisperse nanoparticles are also reported [50]. As one of the unique properties of this technique, particles grow constantly and the polymerization can be stopped when the desired particle size is reached.

It has been reported earlier that, whereas a good solvent as the porogen gives only small pores (below 10nm) and thus very high surface area values (800  $\text{m}^2/\text{g}$ ), a poor solvent results in larger pores and thus lower surface area values [48]. This theory seems to overlap with the  $v$ -induced and  $\chi$ -induced synereses, as explained in the previous section. However, a latest report on precipitation polymerization of DVB does not coincide with the initial results. In this paper, 1-decanol resulted in a surface area as high as 419  $\text{m}^2/\text{g}$  and lower pore sizes (2.7 nm), which were 29.8  $\text{m}^2/\text{g}$  and 5.9 nm respectively when toluene was used [55]. The effect of porogens on

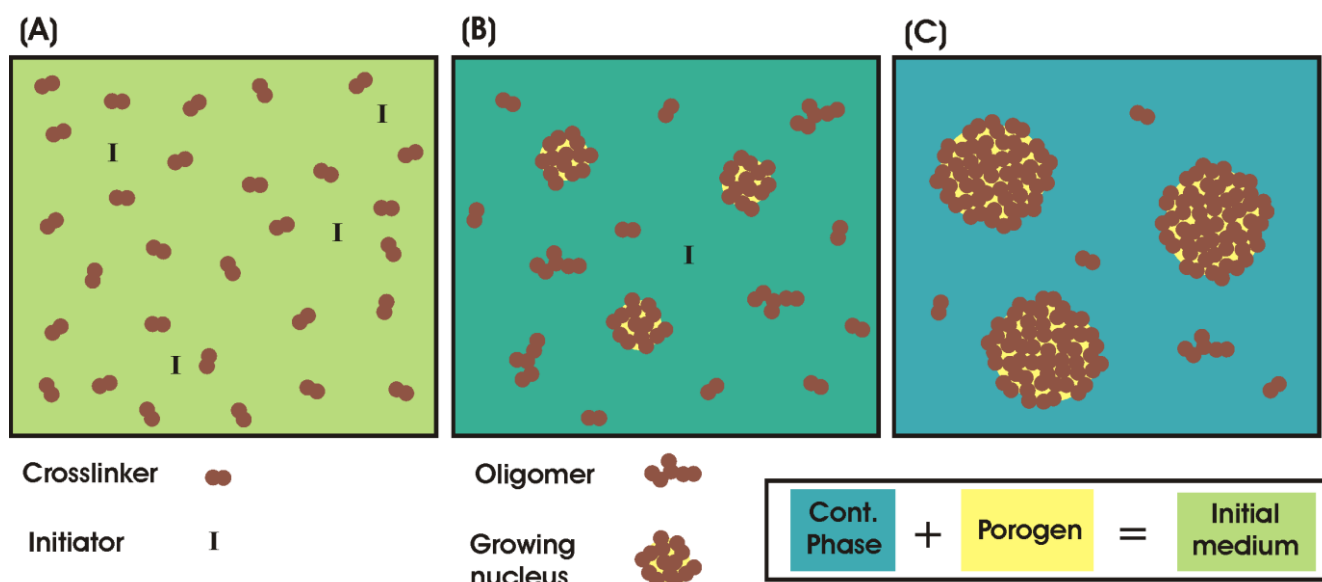


Fig. 5. Schematic description of the stages of precipitation polymerization for porous particle production. (A) Initially, only crosslinker and initiator molecules are in the medium. (B) Oligomers and nuclei are being formed because of radical polymerization. (C) As the reaction continues, nuclei grow by adding monomers and oligomers from the medium. In reality, there is a swollen layer of oligomers around the nuclei.

prepared from DVB/vinylbenzyl chloride mixture can be observed from Fig. 6 [56].

Precipitation polymerization needs highly diluted monomer concentrations (2-5%), i.e. a high amount of continuous phase, which is a drawback of this method. However, Li and Stöver reported the repeated usage of the continuous phase for subsequent precipitation polymerizations while still obtaining monodisperse particles [48]. The polymerization is rather slow due to the high monomer dilution in comparison to suspension polymerization, where high local monomer concentrations are achieved. It is also important to note that only gentle stirring or shaking is applied to avoid coagulation.

Polymerization of DVB in an acetonitrile/toluene mixture together with AIBN [48, 57] could be considered as the basic procedure for precipitation polymerization. Acetonitrile is the mostly used continuous phase in precipitation polymerization, next to the other solvents [58-59]. Toluene is the porogen, which can form up to 40% of the continuous phase [48]. In addition, depending on the crosslinker and monomer, the porogen can be a solvent, a non solvent or even a polymer [55-56]. Whereas the thermal initiation is the most applied route, there is a recent report about ultraviolet (UV) initiated precipitation polymerization [55] to obtain porous particles.

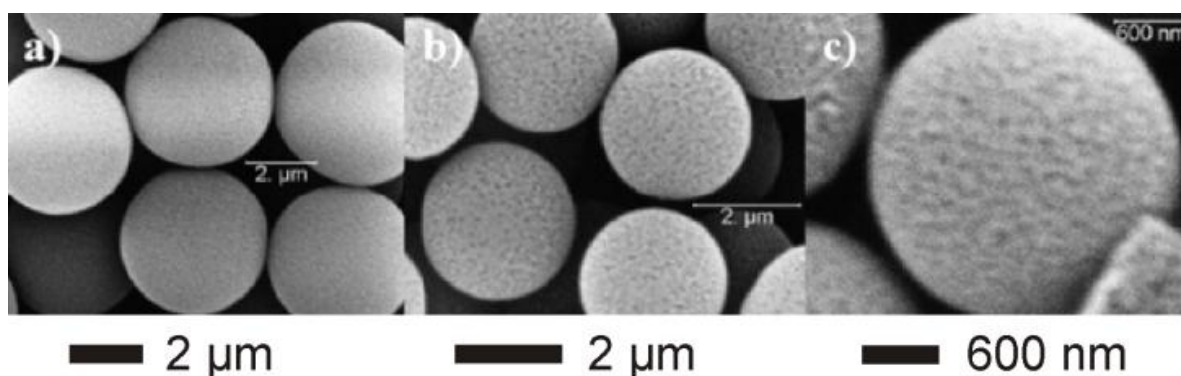


Fig. 6. Effect of the media on porosity of DVB/vinylbenzyl chloride (56/44) particles prepared via precipitation polymerization. (A) Acetonitrile/toluene 80/20, (B) acetonitrile/toluene/cyclohexanol 70/15/15, (C) acetonitrile/toluene/dodecanol 70/15/15. Reproduced from [56] with permission. Copyright 2008 Elsevier.

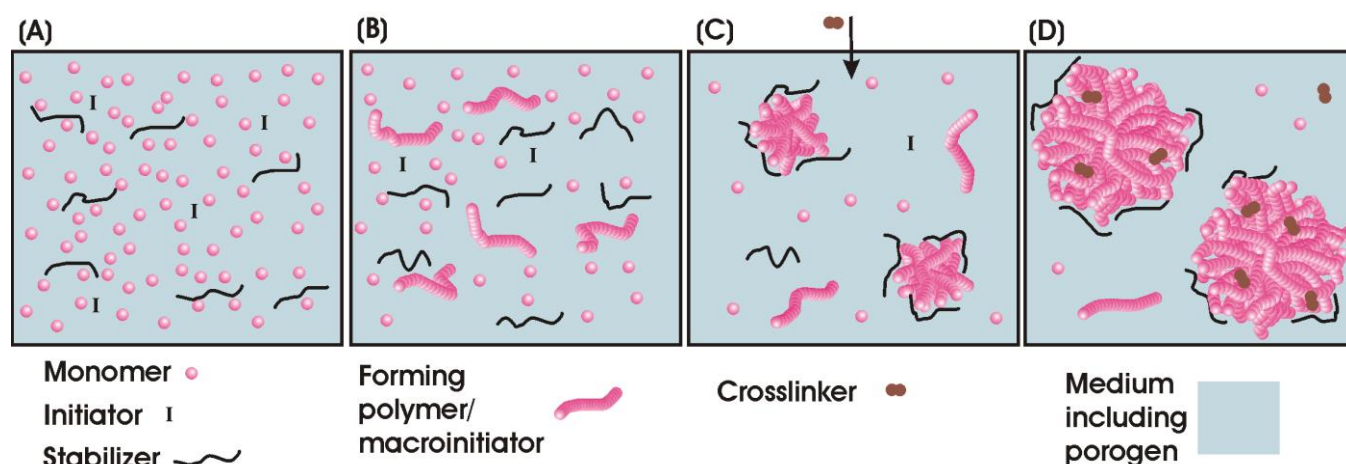


Fig. 7. Schematic description of the stages of dispersion polymerization. A) Initially monomer, initiator, porogen and polymeric stabilizer are dissolved in the medium. B) Oligomers are forming, which are still soluble in the medium. C) Nucleation stage at 1% monomer conversion. As their length increase, polymer chains precipitate and form the nuclei that are stabilized by the polymeric stabilizer. At this stage, a crosslinker may be added if desired. D) Particles grow by capturing monomers and oligomers from the medium.

### 2.3.2. Dispersion Polymerization

Dispersion polymerization is generally used to obtain non-crosslinked and nonporous particles [60-63]. As seen from Fig. 7(A), a monomer, initiator, porogen and a polymeric stabilizer is dissolved generally in an alcohol with mechanical stirring, such as in the case of the suspension polymerization setup (Fig. 1). With the start of heating, the initiator decomposes to form radicals and oligomers start to form, which are still soluble in the media (Fig. 7(B)). This homogeneous mixture becomes cloudy as the oligomers grow and precipitate, forming the nuclei of the final particles (Fig. 7(C)). The nuclei are stabilized by the polymeric stabilizer added in the beginning of the reaction. If no external intervention is made at this stage, such as addition of other species, nuclei grow by capturing new monomers and oligomers/polymers from the medium. The crosslinker should be added only after the nucleation stage (Fig. 7(C)), which corresponds to less than 1% monomer conversion [64]. By the addition of crosslinker, porogen swollen particles continue to grow and crosslink (Fig. 7(D)), resulting in porous particles.

The reason that the crosslinker should be introduced later is well explained by Winnik and coworkers.[64] They reported that crosslinkers and polar monomers significantly influence the particle growth and the monodispersity may be lost in such cases. The most important stage for the monodispersity of final particles was found to be the nucleation step. After the nucleation, crosslinker and polar monomers can be added and perfectly monodisperse crosslinked particles are obtained.

The medium is an alcohol such as EtOH and MeOH in dispersion polymerization procedures, although other possibilities have been recently reported [61]. In a report on the preparation of porous poly (methacrylic acid) particles via this route [65], 11 wt% of methacrylic acid was polymerized in a chloroform/EtOH mixture ( $\sim 5/1$ ). The obtained porous particles were then crosslinked [65-66]. The monomer concentration is much higher in the medium compared to the precipitation polymerization procedures because of the high amount (6.5 wt%) of polymeric stabilizer used.

## 2.4. Multistage Heterogeneous Polymerizations

### 2.4.1. Seeded Suspension Polymerization

Ugelstad et al. [67] discovered in the late 70's that polymer particles can absorb slightly hydrophilic molecules up to 100 times of their own volume and form stable emulsions. An important observation was that the final droplet size and size distribution were completely determined by the initial polymer particles, the so called "seeds". A polymerization in the second stage yields much larger monodisperse latexes provided that the seeds are monodisperse. This is the basis of so called seeded (also called templated) suspension polymerizations today.

Seeds need not only to be monodisperse but also non-crosslinked to allow swelling in the second stage. (Soap free) emulsion and dispersion polymerizations are readily utilized to obtain seeds. Since emulsion prepared seeds are generally in the submicron range, they are suitable for obtaining particles up to 10  $\mu\text{m}$  in diameter after the

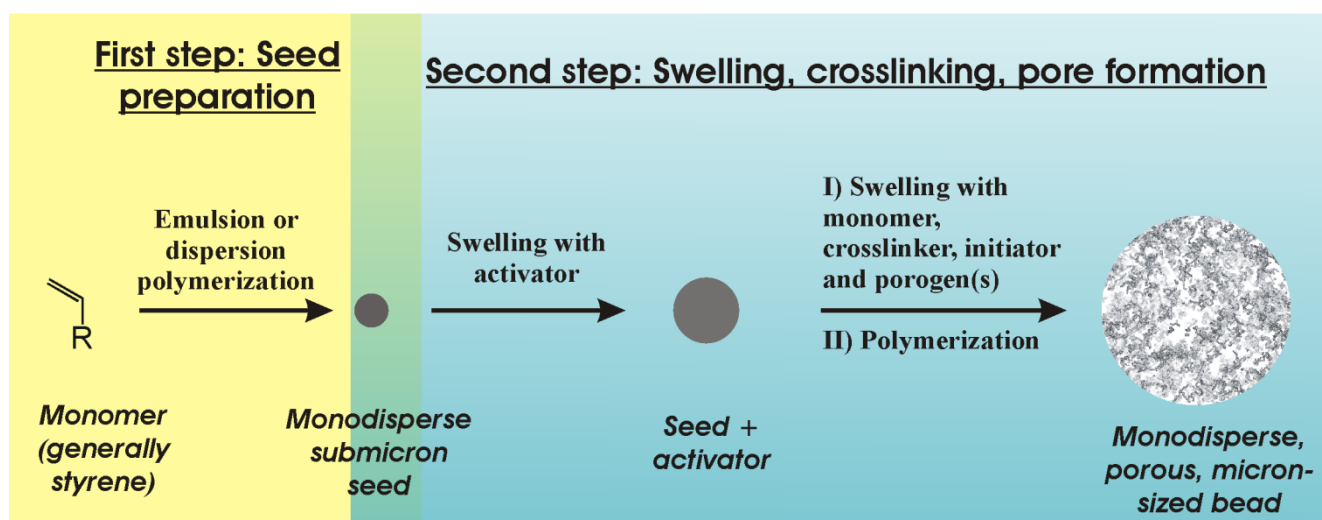


Fig. 8. Schematic description of seeded suspension polymerization for obtaining porous particles. In the first stage, submicron seeds are prepared from styrene by emulsion or dispersion polymerization. In the second stage, that is being suspension polymerization, seeds are first swollen with an activator (i.e. dibutyl phthalate) and then swollen with new monomer, crosslinker, initiator and porogens. Polymerization results in larger, porous and monodisperse particles.

suspension polymerization stage [68-69]. On the other hand, dispersion polymerized seeds can be in the range of 1-20  $\mu\text{m}$ , thus 10-200  $\mu\text{m}$  particles can be obtained in the suspension polymerization stage [70-79]. Note that a volume enlargement of  $10^6$  times would be needed for a 1  $\mu\text{m}$  seed to be swollen by the new monomer(s) to 100  $\mu\text{m}$ .

The approach of Fréchet and co-workers [12] is a good example of seeded suspension polymerization as depicted in Fig. 8. Polystyrene seeds with a diameter of 560 nm were first prepared by emulsifier-free emulsion polymerization. In the second stage, these seeds are first swollen by dibutyl phthalate in an aqueous emulsion, which is necessary to "activate" [2] the seeds prior to swelling them with the monomers. The amount of activator used was 6-7 times higher in volume compared to the seeds. Finally, these activated seeds were added to a new aqueous emulsion where the dispersed phase consisted of propargyl acrylate and EGDMA as monomers, a mixture of cyclohexanol/dodecanol (9/1) as solvent and nonsolvent porogens respectively and AIBN as the thermal initiator. The aqueous phase contained PVA as the stabilizer, SDS as the surfactant and  $\text{NaNO}_2$  as the radical trapping species. At the end of this successful second suspension polymerization stage, 5  $\mu\text{m}$  monodisperse functional (alkyne groups) beads were obtained with surface area values reaching up to 243  $\text{m}^2/\text{g}$  and a pore size of 10 nm. In this example, a volume enlargement of 794 times is achieved without sacrificing the monodispersity. In addition, it is also reported by Margel and coworkers [80-81] that porous particles can be prepared by just dissolving the PS seeds after the second stage. In this case the swelling medium included DVB however excluded the use of any porogen. A surface

area of 630  $\text{m}^2/\text{g}$  is obtained since PS chains distributed in the DVB network acted as a polymeric porogen.

The power of seeded suspension polymerization is that the advantages of two techniques can be combined, i.e. the monodispersity of emulsion/dispersion polymerizations with porosity-functionality-larger size of suspension polymerization. On the other hand, this is ultimately a multi-step approach and thus needs the knowledge and experience of the two applied polymerization techniques in order to obtain the desired particles.

#### 2.4.2. Supraballs: Seed Assembly

Supraballs are spherical colloidal crystals obtained via assembly of monodisperse seeds (0.1-2  $\mu\text{m}$  latex) into larger spheres [82-83] (Fig. 9). To achieve those structures, droplets of concentrated seed suspensions are generally formed in a continuous phase [84-85] or even on a superhydrophobic surface [86]. Drying (often spontaneous) yields unique assemblies of the latex. Spherical [87], dimpled [85], hollow [84], toroidal [88], eyeball [89] and patchy [88] colloidal crystal particles were prepared by the pioneering work of Velev et. al. It should be noted that these supraballs are unique in the sense that the globular inner structure and pores are perfectly monodisperse, which is not the case for the other beads prepared by any other method. This "globular monodispersity" may lead to interesting performances such as in chromatography.

The above mentioned examples of supraballs are assembled only via drying, which makes them unstable against physical manipulation or solvents. In this respect,

Weitz co-workers reported the preparation of colloisodomes [90]. PS seeds were assembled in the water/oil interface and merged by sintering at 105 °C for 5 min. The obtained colloisodomes were hollow since a low concentration of seeds was utilized. The size of the pores on the colloisodome shell was controlled by sintering time and the size of the seeds used. The authors also showed that these colloisodomes selectively allow other particles to enter the core if they are smaller than the pores. These colloisodomes were physically stable but not stable against organic solvents. Later, Sherrington and co-workers [91] managed to assemble 200 nm styrene/MAA latex seeds into aggregates in the second stage where toluene is the continuous phase (with an added surfactant). The water phase inside the seed aggregates was removed at 105 °C by Dean-Stark distillation, which yielded melt fusion of the nano-seeds into ~30 µm polydisperse supraballs. Although the seeds were non-crosslinked and no chemical reagent and monomer were added in the second stage, the obtained supraballs were stable, both mechanically and towards several solvents. This was explained by the authors as a result of a crosslinking process taking place during the heat treatment. Surface area values of 9-16 m<sup>2</sup>/g and pore size values of 3-12 nm have been reported.

In yet another contribution [92], the Sherrington group also managed to assemble 1 µm particles into larger supraballs where the possession of –OH groups was necessary for the seeds. The authors have taken the advantage of the reactive groups of the seeds to further crosslink the supraballs to improve their stability. Undesired inter-supraball crosslinking also occurred. Lower surface area values and comparable pore sizes are obtained in this second study. A recent paper from another group [83] applied the same approach, together with the help of an ink-jet apparatus and obtained rather monodisperse and smaller supraballs with regular spherical shapes (Fig. 9). The seeds used were crosslinked in this study.

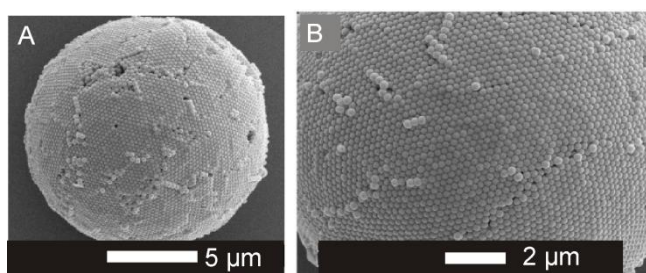


Fig. 9. SEM images of supraballs obtained via nano to micro assembly. Seeds are hexagonally packed resulting in uniform pores and uniform inner structure. Adapted from [83] with permission. Copyright 2009 Elsevier.

### 2.4.3. Davankov Approach: Hypercrosslinking the Phenyl Rings

Another approach that will be briefly discussed in this section is called the Davankov approach [93]. This approach is based on the formation of extensive post-crosslinking between the phenyl groups on the PS resin via Friedel-Crafts reactions [94]. A bis-halide such as dichloroethane is needed together with the catalyst FeCl<sub>3</sub> to form the bridges between the phenyl groups of pure PS resins [95] and FeCl<sub>3</sub> alone is sufficient for post-crosslinking PS resins containing 4-(chloromethyl)styrene comonomer [96]. The first stage can be any heterogeneous polymerization such as emulsion [97], suspension [98] or precipitation polymerization [99] while the second stage involves the Friedel-Crafts hypercrosslinking where the seeds are simply swollen in dichloroethane and heated in the presence of FeCl<sub>3</sub>. These hypercrosslinked resins are commercially available from various manufacturers [94] because of their high surface area values reaching up to 2000 m<sup>2</sup>/g [100], resulting in very different sorption characteristics [101]. In the case of emulsion polymerized seeds [97], monodisperse beads as small as ~500 nm with a surface area of 1200 m<sup>2</sup>/g are successfully prepared, which has never been achieved via another approach to the best of

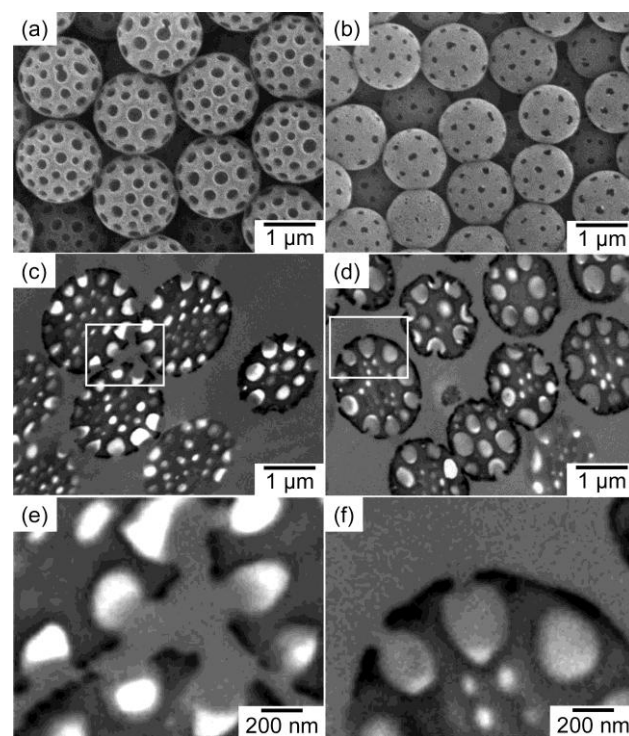


Fig. 10. "Golf ball-like" particles by Okubo et al. via a triple stage dispersion polymerization approach. Dodecane used in the last stage resulted in the dimples instead of an interconnected porous network. (a,b) SEM and (c-f) TEM images of microtomed beads. Image e and f are the enlargement of white rectangles on image c and d, respectively. Reproduced from [105] with permission. Copyright 2008 American Chemical Society.

our knowledge. Although vinylpyridine-based resins were also hypercrosslinked [102] and post-modification of hypercrosslinked PS resins is possible [103], to our knowledge this method is only applicable to aromatic resins, PS being the prime example.

#### 2.4.4. Other Multistage Heterogeneous Polymerization Approaches

This section will be finalized by discussing few other individual multistage approaches before an overview is given at the end. The first example is a triple dispersion polymerization for the preparation of "golf ball-like" particles. Okubo and co-workers [104-105] first prepared PS seeds and then enlarged these seeds by sodium styrene sulfonate monomer in the second dispersion polymerization stage. As discussed previously in dispersion polymerization section, polar monomers may result in polydisperse particles in dispersion polymerization if present at the initial mixture. Finally, these new hydrophilic seeds were swollen with butyl methacrylate and dodecane in the third dispersion polymerization stage and polymerized. Removal of the dodecane resulted in dimples but not interconnected pores (Fig. 10).

Another triple-stage heterogeneous polymerization approach to obtain "walnut-like multihollow" particles is proposed by Ge et al. [106]. The authors first prepared PS seeds by dispersion polymerization and used these seeds in a following suspension polymerization stage to form  $\sim 3 \mu\text{m}$  monodisperse crosslinked but still nonporous styrene-DVB particles. After sulfonation, these crosslinked seeds are swollen by the styrene monomer, again in water without the addition of any stabilizer, surfactant, initiator or porogen. A final exposure to  $\gamma$ -ray irradiation for polymerization resulted in walnut-like multihollow particles. Such as the previously mentioned "golf balls-like" particles, these ones also lack a truly porous structure, where pores are interconnected. However, both structures may be inspiration points for the development of novel porous particles with complex structures in the future.

The final example of this section is the "cage-like" particles that are basically hollow particles possessing huge pores (Fig. 11), also reported by Ge and co-workers. [107-109]. The Pickering emulsion route was utilized where emulsions are stabilized by particles instead of surfactants [110] similar to the colloisodomes that have been previously explained. They first prepared polydisperse sulfonated PS particles and used these

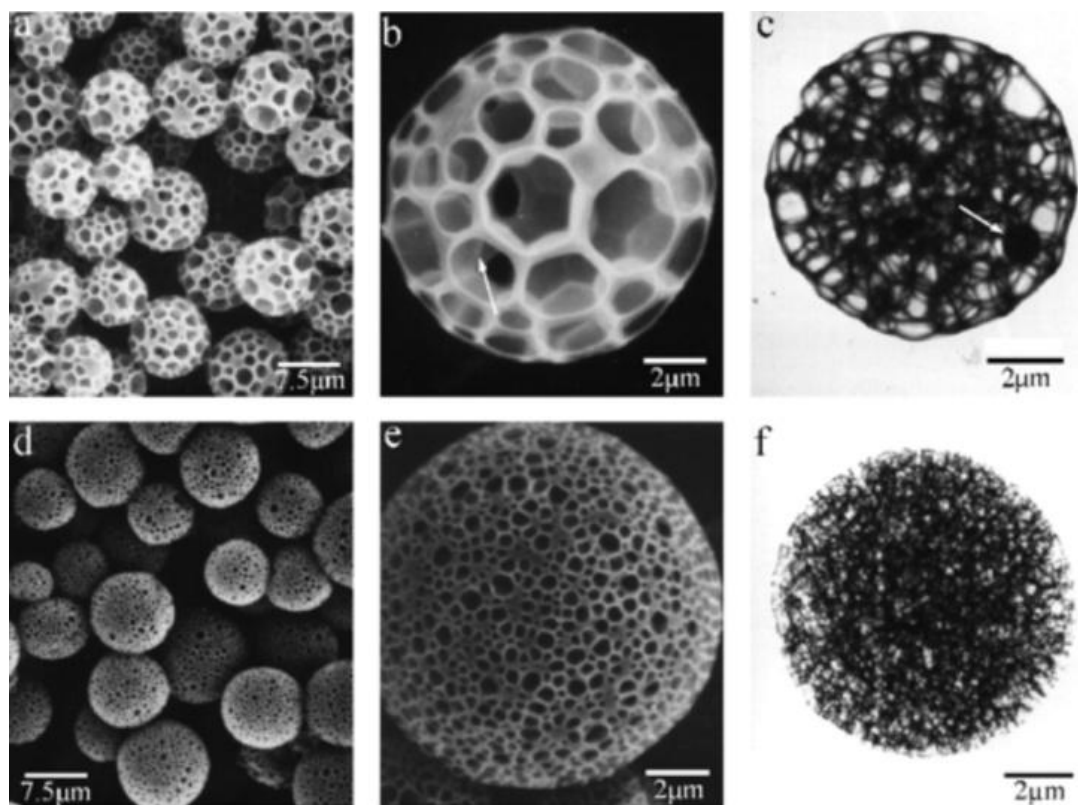


Fig. 11. SEM (A, B, D, E) and TEM (C, F) images of hollow core, porous shell ("cage-like") particles prepared by a combination of Pickering emulsion approach and  $\gamma$ -ray polymerization of additional monomer that are swelling these seeds (see Fig. 12 for the mechanism). (A-C) PMMA, (D-F) poly(vinylacetate). Adapted from [107] with permission. Copyright 2005 American Chemical Society.

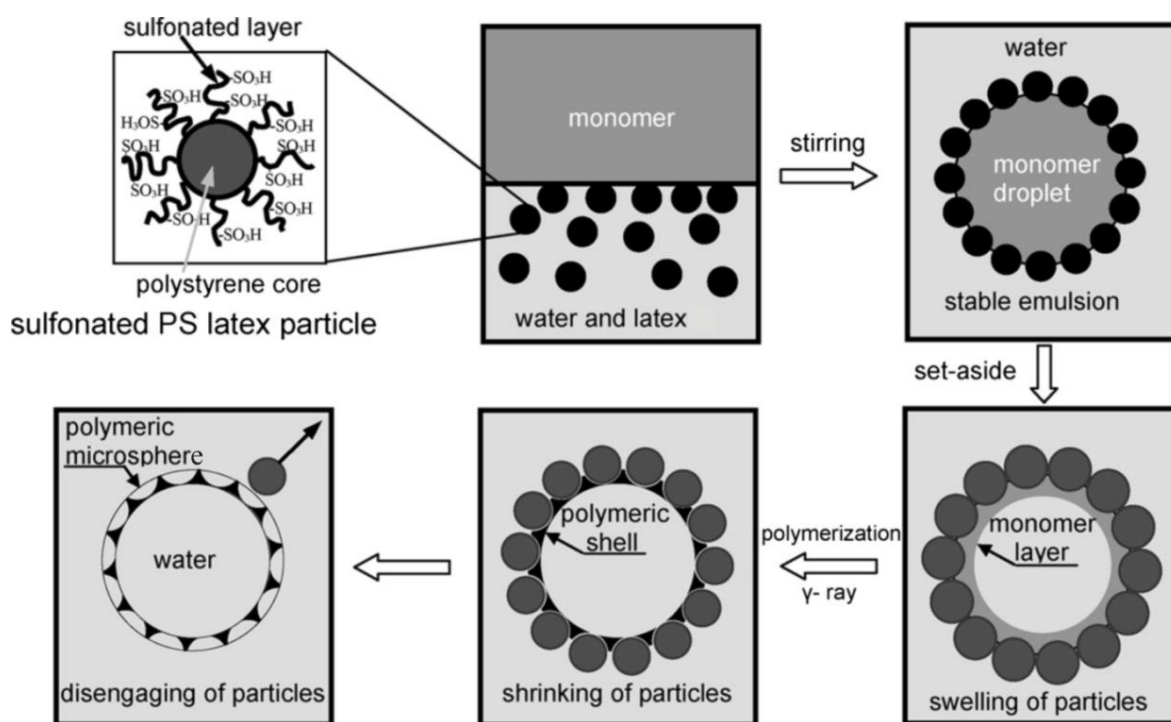


Fig. 12. Mechanism of the formation of "cage-like" particles shown in Fig. 11. Adapted from [107] with permission. Copyright 2005 American Chemical Society.

particles to stabilize an O/W emulsion where the oil phase is either methyl methacrylate (MMA) or vinyl acetate. A stable emulsion is formed after stirring owing to the sulfonated PS particles, which covered the surface of the monomer droplets (Fig. 12). These PS particles were allowed to swell the monomer phase, which is the reason for the hollow core formation. Shrinkage of the new polymer phase via  $\gamma$ -ray polymerization resulted in the removal of the seeds. Consequently, the space initially occupied by the seeds, turned into huge pores of the final porous hollow particles, which are referred to as cage-like particles by the authors.

It was our aim to highlight in this section the power of multistage heterogeneous polymerizations. By a careful selection and control of the different stages of the polymerization, it is possible to achieve polymer particles with any desired size, monodispersity, porosity, pore size distribution, hollowness and functionality. On the other hand, moving away from the spherical shape still does not seem to be achievable. Fig. 13 provides an overview of the multistage approaches discussed above. We believe that there are still opportunities for further developments, especially in the second stage.

## 2.5. Membrane/Microchannel Emulsification: Controlling the Droplet Formation

It was discussed in the previous section that seeded suspension polymerization leads to monodisperse particles provided that the seeds are monodisperse. Thus, it is clear that the control of the final size dispersity in a suspension polymerization is merely connected to controlling the initial droplet size distribution. As a matter of fact, the invention of the Shirasu porous glass (SPG) with uniform pore sizes, leading to uniform emulsions, paved the way for controlled suspension polymerizations [111].

The name membrane emulsification is appropriate for such a technique and low CV (around 10%) porous beads with diameters ranging from 1 to 100  $\mu\text{m}$  can be easily prepared in a single stage avoiding seed preparation and swelling steps. However, particles prepared via SPG are generally not monodisperse since the CV of the SPG pores varies between 10-17% (Fig. 14(B)) [112]. Later, other ceramic membranes have also been invented next to SPG [113-114]. Moreover, researchers developed microchannel emulsification for which every hole (channel) for discrete phase droplet formation is custom made. Silicon [115-118], metal [119-120] and polymer [121-122] based highly uniform microchannels have been used for monodisperse (CV <5%) particle manufacture [123]. The difference between membrane and microchannel emulsification is the fabrication of the emulsification material, which in turn affects the pore size distribution. Microchannels (Fig. 14(C)) are manmade uniform holes on a suitable material while a membrane

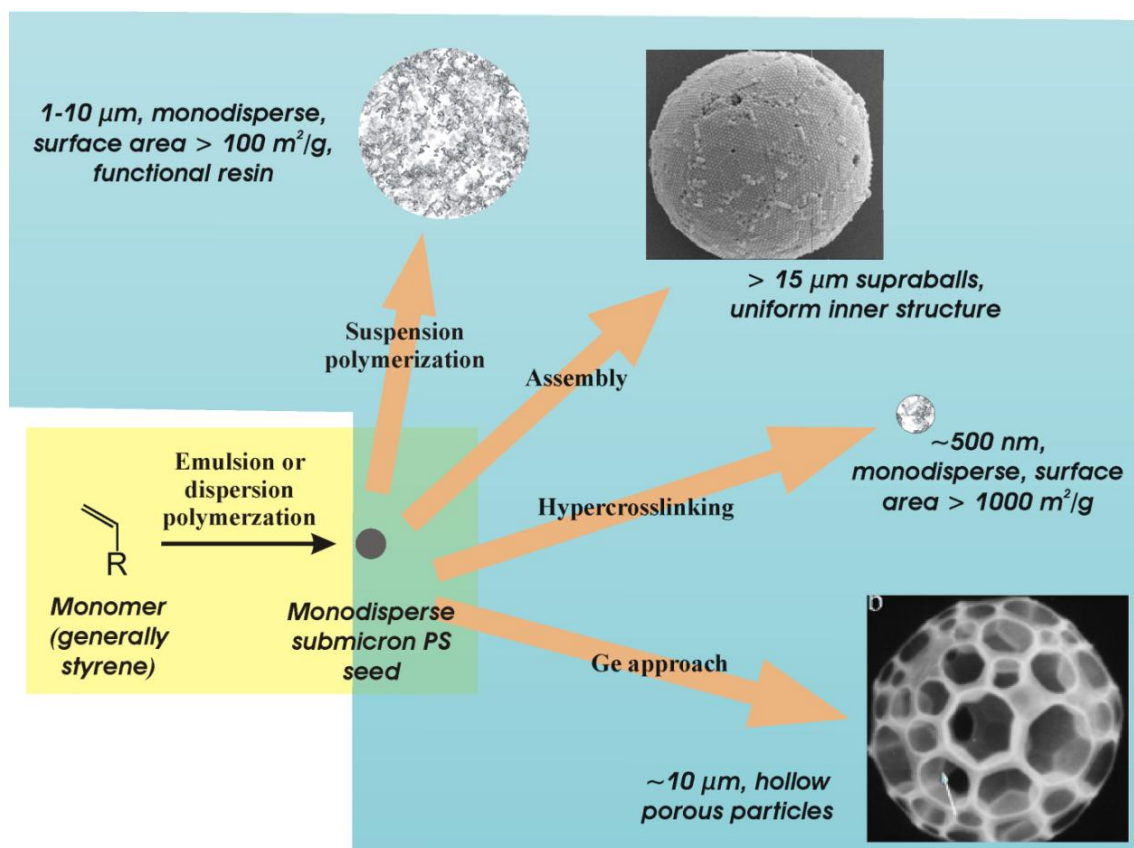


Fig. 13. Overview of multistage approaches with the monomer styrene as an example. In the first stage (yellow background), monodisperse submicron seeds are prepared. The second stage (blue background) can be either suspension polymerization to obtain larger and porous particles, or assembly to obtain supraballs, or hypercrosslinking to obtain very high surface areas or a combination of assembly and polymerization (Ge approach) to obtain cage-like particles.

(Fig. 14(B)) is a material where the production method is controlled in a way to reduce the polydispersity of the pores. In this review, the two techniques have been combined in the same section since they are basically the same. However, we kept the given names to indicate the difference, especially with regard to monodispersity and cost. Microchannels offer highly monodisperse particles but need to be custom-made, which can be expensive and may require a lot of experience.

Particle production using membrane/microchannel emulsification is depicted in Fig. 14(A). A discrete monomer phase is pumped through the membrane towards the continuous phase to form uniform droplets to be polymerized. A representative case from a published report is as follows: The discrete phase consisted of GMA, DVB, benzoyl peroxide and a mixture of solvating and non-solvating porogens while the continuous phase was an aqueous solution of  $\text{NaNO}_2$  and emulsion stabilizers [125]. This recipe can be transferred exactly to a basic suspension polymerization reactor to obtain porous particles. A propeller helps the monomer droplets to pinch off from the membrane surface. However, in literature many reactor designs are proposed that do not necessitate the usage of a propeller or a stirring bar [120]. Although thermal initiation is

utilized in this report [125], photopolymerization is mostly applied [126] in continuous flow membrane/microchannel emulsification reactors.

Most of the membranes and microchannels are hydrophilic such as SPG [123]. The nature (hydrophilic or hydrophobic) of the membrane/microchannel is quite important with regard to the quality of the emulsions in terms of their size dispersity. Emulsions prepared by SPG (hydrophilic) from styrenic monomers (hydrophobic) are more uniform compared to the ones prepared from more hydrophilic monomers such as acrylates, which will wet the membrane. This drawback has been overcome by an approach [127-128] that is very similar to Ugelstad's seed swelling method [67] discussed in the previous section. Since the obtained emulsions from methacrylate monomers (hydrophilic) were not sufficiently monodisperse by using SPG (hydrophilic) alone, hydrophobic monodisperse seed droplets were prepared by SPG first [127]. In this report by Ma and co-workers, uniform SPG emulsified seed droplets were composed of toluene, EGDMA, hexadecane and benzoyl peroxide while the non-uniform emulsion (prepared by ultrasonic emulsification) was a mixture of 2-hydroxyethyl methacrylate (HEMA), EGDMA and hexanol (Fig. 15). Via the continuous water phase, these super-hydrophobic



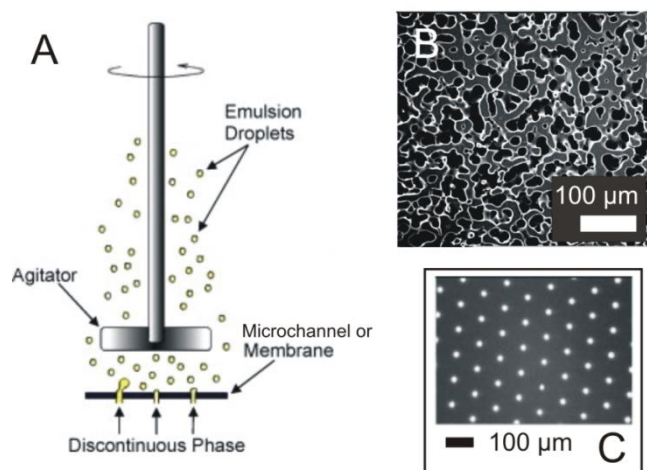


Fig. 14. (A) Representation of membrane/microchannel emulsification process [124]. The monomer phase (discontinuous phase) is pumped from the bottom through a microchannel network or a membrane towards the continuous phase. An agitator helps the droplets to pinch off. These monodisperse droplets are then polymerized to obtain particles. (B) SEM image of a SPG membrane with a mean pore size of 15  $\mu\text{m}$  [112], (C) circular pore microchannel network [124]. Adapted from [112, 124] with permission. Copyright 2007 Elsevier; Copyright 2009 Elsevier.

droplets absorbed hydrophilic methacrylate monomers (HEMA and porogen hexanol) in the swelling step. Finally, thermal treatment allowed them to obtain rather monodisperse poly(HEMA) beads with varying porous nature.

A report from Gong and co-workers [129] further demonstrated the importance of the hydrophobicity of the monomer phase by studying the effect of the porogen nature. In a study with 6 different porogens, it has been shown that the CV of DVB emulsions can be reduced from 23.7 to 8.8% when tetrahydrofuran (THF) and heptane were used respectively. It has also been shown in the same report that the total pore volumes can be doubled and specific surface areas can be significantly increased (from 481 to 987  $\text{m}^2/\text{g}$ ) by hypercrosslinking the obtained beads via the Davankov approach, which was discussed earlier. In another paper by Ma and co-workers [130] the use of porogens such as heptane, paraffin oil, hexadecane and lauryl alcohol for DVB was reported: from these solvents, not only porous but also hollow particles were obtained.

## 2.6. Microfluidics: The Ultimate Control

An ultimate control of droplet formation is achieved by the youngest particle production technique, called microfluidics. This technique can be considered as the miniaturized version of microchannel emulsification where flow plays a crucial role. Monomer droplets of

uniform size are pinched off from an orifice that is generally located in the middle of a flowing continuous phase (see Fig. 16). Spherical particles with CV below 2% can readily be produced by various microfluidic setups [131-135]. It is the elaborate chip design that allowed researchers not only to miniaturize microchannel emulsification reactors and prepare narrowly monodisperse spherical beads but also to achieve unprecedented control over structure and shape of particles. This unique capability of control resulted in the realization of perfectly controlled multiple emulsions [136-145], Janus particles [146-156], regular nonspherical shapes [157-166] and even gas bubbles [167-171], almost all of which were impossible to achieve before.

### 2.6.1. Types of Microfluidic Devices

It was the introduction of a soft lithography technique for the design of PDMS devices by Whitesides in the late 90's [172-173] that popularized the studying behavior of fluids at laminar flow in fine channel dimensions, which is referred to as microfluidics today. Since then, PDMS based chips became the most popular devices, also for microfluidic particle production. This technique is basically based on consecutive steps of molding, casting and curing steps, which is out of the scope of this review. Soft lithography allows an easy way to manufacture an unlimited number of 2D device designs including T-junction [174], co-flow [153] and flow-focusing [110, 175] geometries (Fig. 16). Multiple emulsification points [137, 140] to obtain multiple emulsions can also be easily fabricated. However, PDMS is not compatible with several organic solvents, mainly due to swelling [176]. The most important alternative to PDMS based microfluidic devices is the assembled glass capillaries introduced by Weitz and co-workers. [143, 177-178]. In this approach, chemical and solvent resistant glass capillary tubes are fitted in each other to form truly 3D

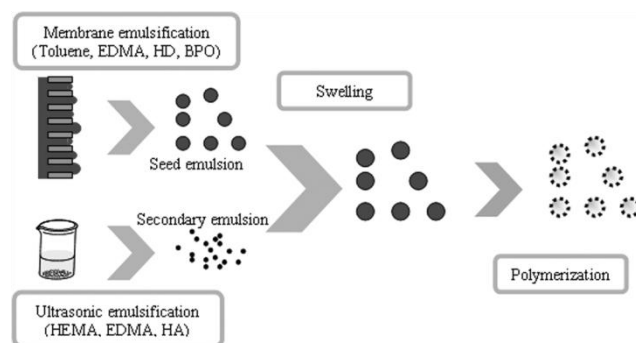


Fig. 15. Seed emulsion swelling method proposed to prepare monodisperse beads containing HEMA monomer. Reproduced from [127] with permission. Copyright 2008 American Chemical Society.

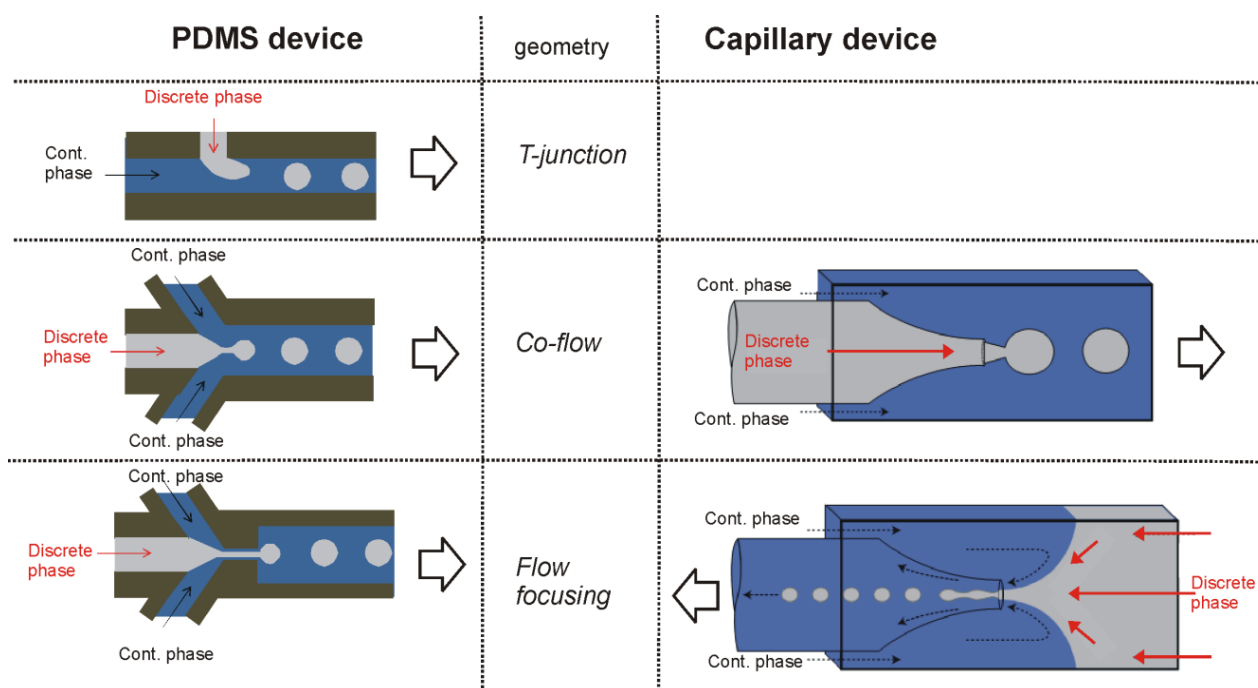


Fig. 16. T-junction, co-flow and flow-focusing geometries for PDMS and glass capillary microfluidic devices for comparison. The lighter liquid is the monomer phase while the darker one is the continuous (cont.) phase. Both phases are pumped at constant rates by the use of syringe pumps. Largest arrows point the direction of total flow and droplets. Capillary device graphics are adapted from [178] with permission. Copyright 2007 Materials Research Society.

microfluidic geometries including co-flow [179] and flow-focusing [180] (Fig 16). Droplets, hence particles, smaller than the orifice can be fabricated in a flow-focusing glass capillary device compared to a flow-focusing PDMS device (Fig. 16). However, Weitz-type glass capillary device preparation can be tedious and requires expertise. Recently, Weitz and co-workers proposed a route to coat inner walls of PDMS devices with glass [181-182], thereby merging the easiness of soft lithography with the inertness of glass. Other studies exist in which pure glass [183] or organic polymers [184-186] are used instead of PDMS for the chip manufacture.

In connection to these two mainstream microfluidic devices, a few other setups are also drawing the attention. The first one is the so called 'simple' microfluidic device [187-188] where the microchannel is as simple as a commercial transparent polymer tubing and the discrete phase orifice is a blunt needle punched into this tubing. Syringes, syringe pumps and a UV source are also needed like in the case of PDMS and glass capillary setups. In this device, chip preparation is avoided and even highly monodisperse double emulsions [189] can be prepared together with particles [190]. Later, Du Prez and co-workers reported [191] that the bending of the discrete phase needle transformed the device from a T-junction to a co-flow geometry (Fig. 17(A)) and more reproducible results are obtained for a viscous aqueous phase emulsified into an oil phase. This

simple device can perform as good as the PDMS and capillary based setups as soon as the blunt needle is well placed in the middle of the tubing. For this simplified setup, two main drawbacks are present. First, commercially available tubing is generally hydrophobic, which can be problematic in terms of wettability (see upcoming section for details) in case that mainstream hydrophobic monomers are used. Second, the smallest needle available has an internal diameter of 110  $\mu\text{m}$  (32G). The smallest porous beads that we were able to prepare with such needle in the aforementioned simple microfluidic system were about 150  $\mu\text{m}$  in diameter, which seems to be the limit for such device. Nevertheless, such simple setup is very attractive and nearly costless for researchers wishing to step into this research field.

Another co-flow device, similar to this simple setup, was reported by Serra and co-workers [192-193] utilizing a steel tee to fix the discrete phase needle (Fig. 17(B)). This design was important as it allowed further development by using capillaries instead of the discrete phase needle [157, 160, 194-195]. Theoretically, monodisperse particles with few  $\mu\text{meters}$  in diameter should be possible to achieve via this type of devices since down to 2  $\mu\text{m}$  internal diameter capillaries are commercially available. Few other type of devices are also reported in the literature [196-198].

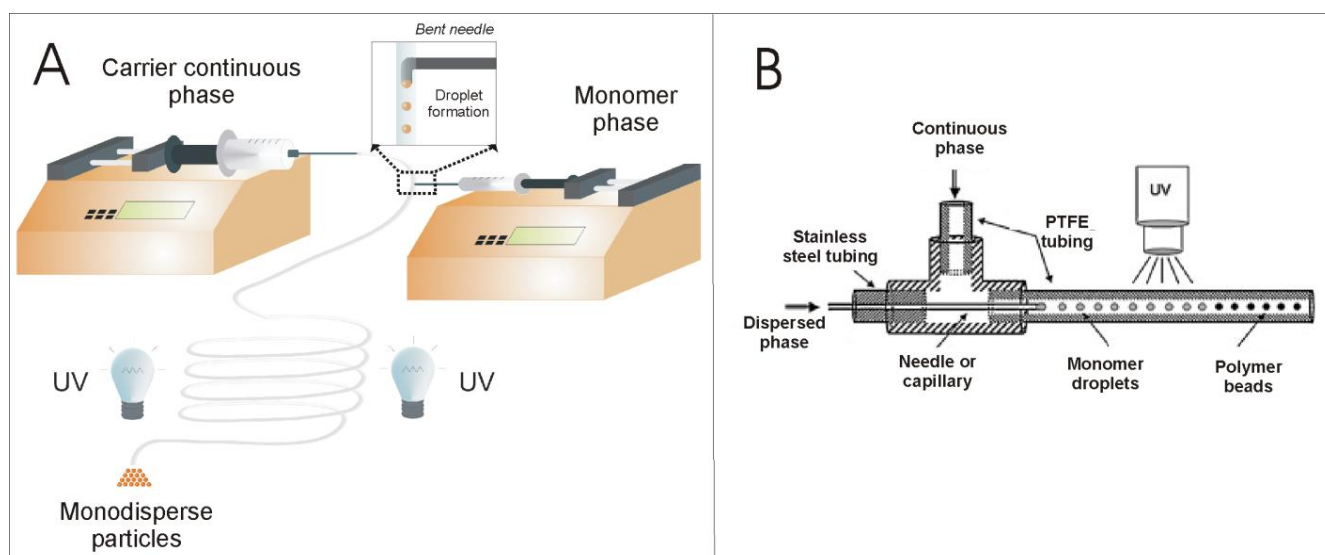


Fig. 17. (A) Tubing-needle based microfluidic co-flow device [9]. Note the bent needle in the droplet formation inset of the schematic drawing. Droplets are pinched off from the tip of the needle by the carrier continuous phase flow and photochemically polymerized downstream the tubing. (B) The latter developed tubing-needle/capillary device. The needle or capillary are fixed by using a commercially available tee [192]. Smaller particles are obtained in this way due to the usage of capillaries. Adapted from [9, 192] with permission. Copyright 2009 American Chemical Society; Copyright 2008 Elsevier.

### 2.6.2. Droplet Formation in Microfluidic Channels

The core of microfluidics is the droplet formation. To this extent, the dripping-jetting transition is of great importance for low CV particle production and satellite formation. The droplet formation mechanism in microfluidic emulsification will be discussed on a co-flow device (Fig. 16), which is the mostly utilized geometry in microfluidics. Dripping-jetting transition is generally explained by dimensionless numbers such as capillary, Weber and Reynolds numbers, for which we refer to other literature [179, 199-201]. In this review however, we would like to explain dripping-jetting transition by using parameters that are familiar to chemists, such as flow rates, polarity differences, viscosity, wettability and channel dimensions. In a co-flow microfluidic device (Fig. 16), the orifice of the dispersed phase is located in the middle of the surrounding continuous phase and the flow directions of either liquid phase are the same. As mentioned earlier, the continuous phase flows around the dispersed phase and provides the droplet breakup from the dispersed phase orifice. Droplet breakup can take place either in the dripping regime (Fig. 18 upper image) or jetting regime (Fig. 18 bottom image). The latter is characterized by the inner liquid forming a long thread before breaking up into droplets. The dripping regime is desired for the formation of low CV spherical particles. However, the production of low CV [143] and smaller particles (compared to particles prepared in the dripping regime) is reported in the jetting regime and

once the jet is stabilized [202], uniform fibers [158] and tubes [166] can be obtained.

In co-flow (Fig. 18) both the inner and the outer liquids are pressurized with constant flow rates, generally by the aid of syringe pumps. It is the immiscibility between the two liquids, hence the interfacial tension, that allows the discrete phase droplet to grow at the tip of the orifice. More inner liquid fills the droplet in the first stage, resulting in the growth of the droplet. Thus the growing droplet occupies more and more space from the available microchannel, hence the pressure of the surrounding outer liquid increases. By the time that a critical size for the droplet is reached, the pressure of the outer liquid overcomes the interfacial tension and forces the droplet to pinch off from the orifice, which is the second and the last stage of droplet formation in microfluidics.

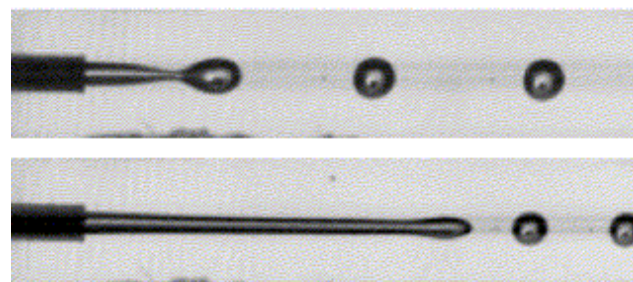


Fig. 18. Real time images of dripping (above) and jetting (below) regimes in a co-flow device [199]. The long thread of the inner phase is called the jet. Droplet break-up is often irregular in the jetting regime. Adapted from [199] with permission. Copyright 2004 Elsevier.

Flow rates are important in terms of the dripping-jetting transition. Indeed, when the flow rate of the outer liquid is too high (which means high pressure), it suppresses the proper droplet growth, so that the first stage is blocked. On the other hand, for too high flow rates of the inner liquid, this liquid adds more and more discrete phase into the forming jet and thus does not let the outer liquid to narrow the thread, resulting in the blockage of the second stage of the droplet formation. Consequently, there is a safe zone, the dripping regime, where both flow rates are low. Fischer and co-workers [199] showed this trend by plotting a graph (Fig. 18) showing the relationship between two flow rates and discussed about a 'critical jetting velocity' for the continuous phase where the jetting regime is reached above this velocity. It is important to note that the authors mentioned that this critical jetting velocity may slightly vary depending on the starting regime, which was also experienced by ourselves.

As mentioned above, it is crucial to work in the dripping regime to form droplets with CV below 2%. However, low flow rates have certain issues that cannot be neglected. First of all, a low flow rate for the discrete phase logically means a lower droplet production rate, hence a lower particle production rate, which is the main drawback of microfluidics. On the other hand, an increase in the discrete phase flow rate will generally increase the size of the final particles, which may not be desired for the application. The continuous phase flow rate can be increased (without exceeding the critical jetting velocity) to keep the particle size lower, without decreasing the

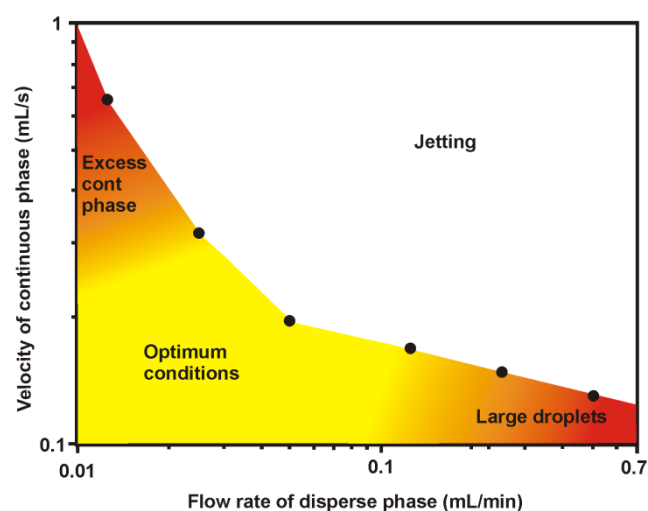


Fig. 19. Critical jetting velocity of the continuous phase as a function of the rate of discrete phase for an O/W emulsion in a co-flow microfluidic device. The plot is divided into 3 imaginary sections for this review. Optimum conditions are reached when both of the flow rates are low. Adapted from [199] with permission. Copyright 2004 Elsevier.

discrete phase flow rate. However, an increase in the continuous phase flow rate would result in a higher consumption of continuous phase liquid, and more importantly in a higher ratio of continuous phase over discrete phase droplets. This dilution is certainly problematic when more hydrophilic monomers are emulsified in water. This has been experienced in our research group with the observation of high losses of glycidyl methacrylate (GMA) into the continuous water phase. By taking these facts into consideration, the dripping-jetting transition figure from reference [199] was divided into 3 imaginary parts for this review (Fig. 19): large droplets (red), optimum conditions (yellow) and a large amount of the continuous phase (red).

Next to the flow rates, another important factor effecting dripping-jetting transition is the polarity of both phases. For an O/W emulsion, the effect of polarity can be very prominent for porous particles. Since it is the interfacial tension, hence the polarity difference between two phases, that allows droplet growth at the tip of the inner liquid orifice, an increase in polarity of the monomer phase will lead to smaller droplets and a smaller value of critical jetting velocity (undesired). We have often observed that addition of non-solvating porogens, such as long-chain alcohols, to methacrylates significantly decreases the droplet size due to an increase in polarity. In other words, polar porogens narrow the polarity gap between the two phases, resulting in a drop of the critical jetting velocity. On the other hand, addition of a hydrophobic porogen such as hexadecane should increase the droplet size if desired. Finally, addition of salts to the continuous phase increases its ionic strength and thereby increases the polarity difference between the two phases, which then increases the droplet size and critical jetting velocity, i.e. salt-out effect [203].

The last 'internal' factor affecting dripping-jetting transition discussed here will be the viscosity before switching to 'external' factors arising from the device itself. A highly viscous inner liquid would prefer jetting instead of dripping [199, 202] due to the viscous attraction of inner liquid molecules, thus suppressing the breakup. This behavior can also be explained by the stabilization of the interface between the two phases.

As an example, stable jet pieces were formed by us instead of droplets due to the high viscosity of a discrete HIPE phase, when pressurized into the continuous carrier water phase [9]. The only solution to achieve spherical droplets in our case was found to be decreasing the viscosity of the HIPE phase. Some reports emphasized the effect of continuous phase viscosity on droplet formation [204], but others also figured out that it does not have a significant effect [205]. Viscosity is found to be playing a

role [206] in the formation of undesired satellites too, which can be defined as the formation of much smaller droplets accompanying the larger monodisperse droplets [151, 153, 155, 207-209]. Kumacheva and co-workers reported for O/W emulsions that there are larger and narrower safe ranges (no satellite formation) of flow rate ratios for different viscosity values of oils emulsified [206]. It is also important to mention that the jetting regime is one of the main reasons of satellite formation [210]. However, a high viscosity of the jet can suppress satellite formation [211], again due to the viscous attraction.

When considering the effect of the microfluidic device on droplet formation, two main factors will be encountered: channel dimensions and wettability. As in the case of membrane/microchannel emulsification, the continuous phase should preferably wet the channel walls for a proper droplet breakup. In the case of opposite wettability, the monomer phase may form a flowing thin layer on the channel walls and let the continuous phase flow in the middle. Since most monomers of interest are hydrophobic, O/W systems are considered and hydrophilic channels are needed.

Two mainstream microfluidic devices differ on such issue. While Weitz-type glass capillary based devices are inherently hydrophilic, Whitesides-type PDMS devices are hydrophobic and generally treated prior to use [212], with a plasma [213] for instance, to change its wettability. In the case of W/O emulsions, the glass capillary device needs to be adapted which can be easily done via chemical treatment by silanes [214]. In terms of channel dimensions, the rule of thumb is 'the smaller the better', provided that the wettability is adjusted. Less amount of continuous phase will be needed for the same flow rate if the channel is narrower, which is important for monomer transfer and cost issues as discussed earlier. Wettability will be more prominent when miniaturizing the channel since the inner liquid droplets will become closer to the channel walls.

A last issue to be discussed in this sub-section is the effect of the initiation on porosity. Although few exceptions exist [153], microfluidic particle synthesis is almost completely based on fast UV curing, whereas the other manufacturing techniques mostly employ thermal initiation. Thermal initiation is much slower in terms of monomer conversion. Temperature also has an effect on the porosity [215], i.e. due to the change in solvating power of the porogen. Polymerization in UV initiated droplets is so fast that the phase separation process should be different compared to a thermally initiated polymerization. Moreover, although the temperature locally increases in a UV initiated droplet due to the

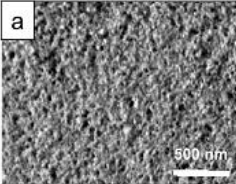
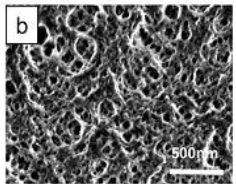
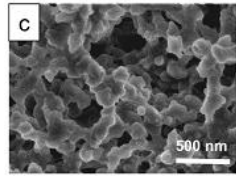
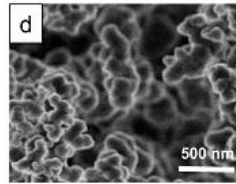
exothermic polymerization [216], this temperature should not reach 60-70 °C, which is typically the temperature used in suspension polymerization. This should theoretically influence the porous nature of the final particles since all the theory of porosity is mainly based on phase separation and solvating power of the porogen. To the best of our knowledge, the comparison between thermal and photo initiation in terms of porosity for a given system was not reported yet.

### 2.6.3. Examples of Microfluidic Particle Production

To start with the examples of porous particle production in microfluidics, we should state that the discussion on suspension polymerization in section 2.2. is the starting point to understand the pore formation in microfluidics. The reader will find out that most of the approaches mentioned in that section can be easily adopted to microfluidics since the latter can be considered as an advanced version of suspension polymerization. Moreover, microfluidics enables the formation of not only monodisperse particles but also of regular nonspherical porous particles, which is virtually impossible to achieve by suspension polymerization. Few approaches that are still not applied in a microfluidic channel will probably be exploited soon.

To the best of our knowledge, the first porous polymer particles synthesized via microfluidics appeared in literature in 2005 [217]. By using a PDMS based flow-focusing device, Whitesides and co-workers prepared porous particles of ~250 µm in diameter with a mean pore size of 0.90 µm. They photopolymerized tripropyleneglycol diacrylate mixed with 20% dioctyl phthalate (non-solvating porogen) in which the continuous carrier phase was 2% SDS in water. There were no further data about the surface area of the particles. Later, Kumacheva and co-workers studied the effect of 4 different phthalates as porogens for an EGDMA-GMA monomer mixture [218]. In the order from a solvating to a non-solvating phthalate, the pore size increased and the specific surface area decreased for the final particles (Table 1). CV values as low as 0.83 and particle diameters as low as 60 µm were reported. The authors also conducted suspension polymerization for the same mixtures and concluded that the particles prepared by microfluidics have a finer porous structure. In a following work, Kumacheva et al. [28] also reported that after scaling up, a skin layer was observed on a portion of beads when dioctyl phthalate and diisodecyl phthalate were used as porogens. The solution proposed was to change the continuous phase instead of the

Table 1. Comparison of the effect of porogenic phthalates on EGDMA-GMA particles. From left to right, the alkyl chain of the phthalate increases, the solubility parameter decreases, so that the gap between solubility parameters of polymer and porogen increases. As a result, pores become larger but the total surface area decreases. The solubility parameter of the polymer was calculated to be  $24 \text{ (MPa)}^{1/2}$  by the authors. Adapted from [218] with permission. Copyright 2008 American Chemical Society.

Surface of the obtained bead				
Porogen	Diethyl phthalate	Diisobutyl phthalate	Dioctyl phthalate	Diisodecyl phthalate
Solubility parameter $(\text{MPa})^{1/2}$	20.5	19.0	16.2	14.7
Surface area $\text{m}^2/\text{g}$	28.7	13.9	6.6	3.4

discrete phase, which has already been discussed in the suspension polymerization section of this review.

In another study, Kumacheva co-workers [216] reported the fabrication of beads with an acrylate-urethane interpenetrating network structure. The heat generated from the photopolymerization of the acrylic crosslinker triggered the formation of a urethane network. It has been shown that porous beads can be obtained when a lower amount of urethane precursors is used, thereby suggesting that the urethane chains act as a polymeric porogen for the acrylate. Zourob et al. [219] made use of a solvating porogen to obtain particles with the highest surface area prepared in a microfluidic reactor. A specific surface area of  $201 \text{ m}^2/\text{g}$  with a mean pore size of  $8.1 \text{ nm}$  was realized upon addition of acetonitrile to the monomer mixture. A polycarbonate based chip was fabricated and different batches of beads in the size range from  $10$  to  $120 \mu\text{m}$  with CV values below 2% were achieved. In another work [220] the effect of initiator on morphology of the beads was studied in a capillary device. While the continuous phase was water, the discrete phase was a mixture of HEMA and MMA monomers, as well as a porogen, 1-octanol. A macroporous morphology was only obtained when an oil soluble initiator is used. On the other hand, a water soluble UV initiator resulted in nonporous but hollow particles. The waterborne radicals started the polymerization from the periphery towards the core and 1-octanol stayed inside, forming the hollow core for the final beads.

Very recently, Ravoo and Du Prez et al. also used 1-octanol as the porogen for preparing EGDMA-GMA beads

via tubing-needle based microfluidics. This porogen was found to be the most successful porogen among others in yielding skin-free macroporous particles [221]. More interestingly, these isotropic particles underwent a reactive “sandwich” microcontact printing procedure, which produced anisotropic beads with two different faces, referred to as Janus particles [222]. By using an epoxy-amine reaction, the authors managed to covalently print either two different fluorophores, or two different biomolecules, or a fluorophore and a batch of magnetic nanoparticles. In this approach, monodispersity of the beads was crucial since sandwich microcontact printing necessitated a bead monolayer of uniform height. This type of porous Janus particles may have totally different applications [223-224] compared to the isotropic counterparts.

In terms of using water instead of miscible porogens in microfluidics, we did not find a report using monomer soluble surfactants that capture water droplets from the continuous carrier phase (see section 2.2 for suspension polymerization example). Nevertheless, HIPE formulations were successfully pressurized in a tubing-needle microfluidic device and unique structures are obtained due to the uniformity of W/O/W double emulsions. Du Prez and co-workers [9] prepared W/O HIPE formulations and emulsified them once more in the second carrier aqueous phase via the simple microfluidic device in which the middle oil phase consisted of the monomers with an added photo initiator. Beads with a diameter of  $\sim 400 \mu\text{m}$  were prepared (Fig. 20(A)), which are the smallest monodisperse poly(HIPE) beads reported so far. The obtained beads possess huge pores, as large

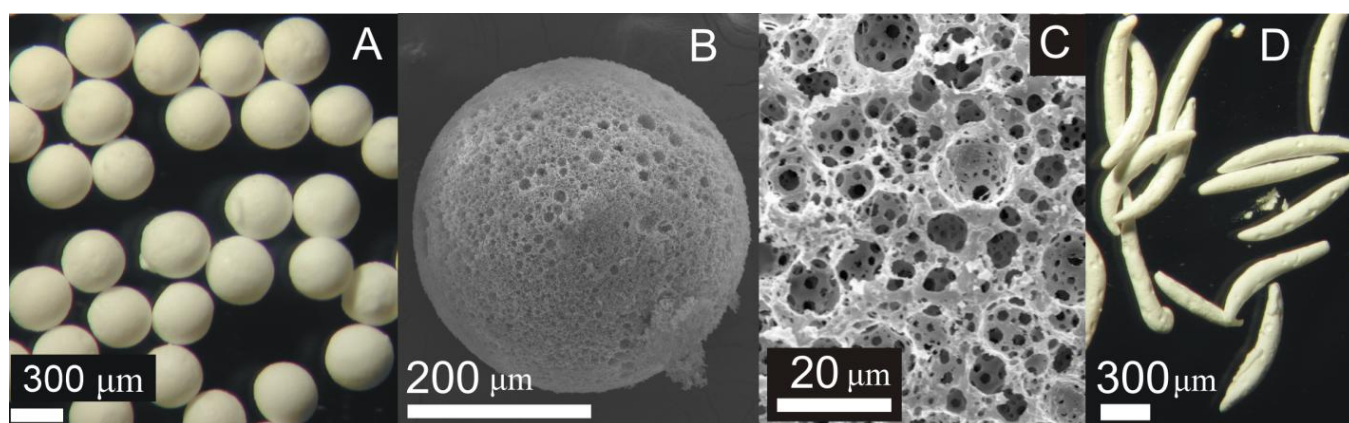


Fig. 20. Uniform poly(HIPE) beads and rods prepared via a tubing-needle microfluidic device. (A) Light microscopy image of beads showing monodispersity. (B) SEM image of a single poly(HIPE) bead. (C) SEM surface close-up of a poly(HIPE) bead. Pores are reaching up to 15  $\mu\text{m}$  and all interconnected. (D) Poly(HIPE) rods prepared from a more viscous HIPE mixture. Adapted from [9] with permission. Copyright 2009 American Chemical Society.

as 15  $\mu\text{m}$  (Fig. 20(C)) reminiscent of the water droplets and a surface area of 16  $\text{m}^2/\text{g}$  suggesting the presence of mesopores. The authors also prepared a batch of "classical" macroporous beads from the same monomer mixture by using a cyclohexanol-dodecanol porogen mixture and obtained a surface area of 49  $\text{m}^2/\text{g}$ . Although exhibiting a threefold less surface area, poly(HIPE) beads surpassed the performance of classical beads in both steps of a "click"-click modification, which demonstrates the importance of huge pores (see section 4 for click chemistry).

More strikingly was the production of poly(HIPE) rods of the same composition, except for the molar mass of the surfactant used in the HIPE preparation. A higher molecular weight (MW) surfactant increased the viscosity and the inner HIPE phase formed a jet instead of drops in the microfluidic setup. However, jet breakup was proper thanks to the bent needle and as a result poly(HIPE) rods (Fig. 20(D)) were fabricated. This viscosity driven nonspherical particle production is also unique of its kind since all the other approaches make use of confined channel geometries forbidding the formed droplets to relax into a spherical geometry [217]. It is also worth to mention that monodisperse poly(HIPE) beads were also obtained before but with a size of 2 mm by using a technique called sedimentation polymerization [225].

An approach realized exclusively by microfluidics is using gas bubbles instead of any liquid or solid porogen. Stone and co-workers [226] were able to capture a controlled number of gas bubbles in an aqueous monomer phase, which was then emulsified in the carrier oil phase, thus forming G/W/O double emulsions. Upon solidification of the monomer phase,  $\sim 20 \mu\text{m}$  sized beads with uniform spherical cavities were formed. It is worth to mention that the interior of the obtained beads were in closed-cell

foam structure (Fig. 21(A)), which designates the absence of interconnectivity between the cavities.

Another unique approach made use of a gas forming reactive porogen. Small droplets containing  $\text{H}_2\text{O}_2$  molecules were captured in bigger oil phase monomer droplets flowing in a carrier aqueous phase [227]. UV exposure not only solidified the oil phase but also decomposed  $\text{H}_2\text{O}_2$  molecules exhausting gas species, similar to the blowing agent strategy discussed in section 2.2. A controlled number of voids is reported, however interconnectivity within the porous structure is poor (Fig. 21(B)) in comparison to the poly(HIPE) structures (Fig. 4(A) and Fig. 20). Nevertheless, we believe that these two reports should inspire researchers to exploit the usage of bubble capture or gas forming porogens to obtain very light polymer particles with well interconnected pore structure. The combination of a liquid porogen with bubble capture/formation may lead to porous particles possessing ultra large voids connected to each other through smaller pores in the future. Moreover, selective functionalization of those pores depending on their size (see section 4.2) may pave the way to novel particles with unique properties.

It is important to mention that the solidification was not only based on vinyl polymerization but also on a commercial photo-curable thiol-ene adhesive in the latter report [227]. The addition of thiol radicals to alkene or alkyne bonds (thiol-ene and thiol-yne reactions, respectively) has recently gained considerable interest as novel metal-free 'click' reactions among polymer scientists [228-230]. We recently exploited thiol-ene/yne chemistries for producing functional porous beads via microfluidics [10]. A tetra-thiol was mixed with a di-yne or a multi-ene and the final functional groups of the particles were provided by adding amino, hydroxyl or carboxylic compounds possessing ene, yne or thiol

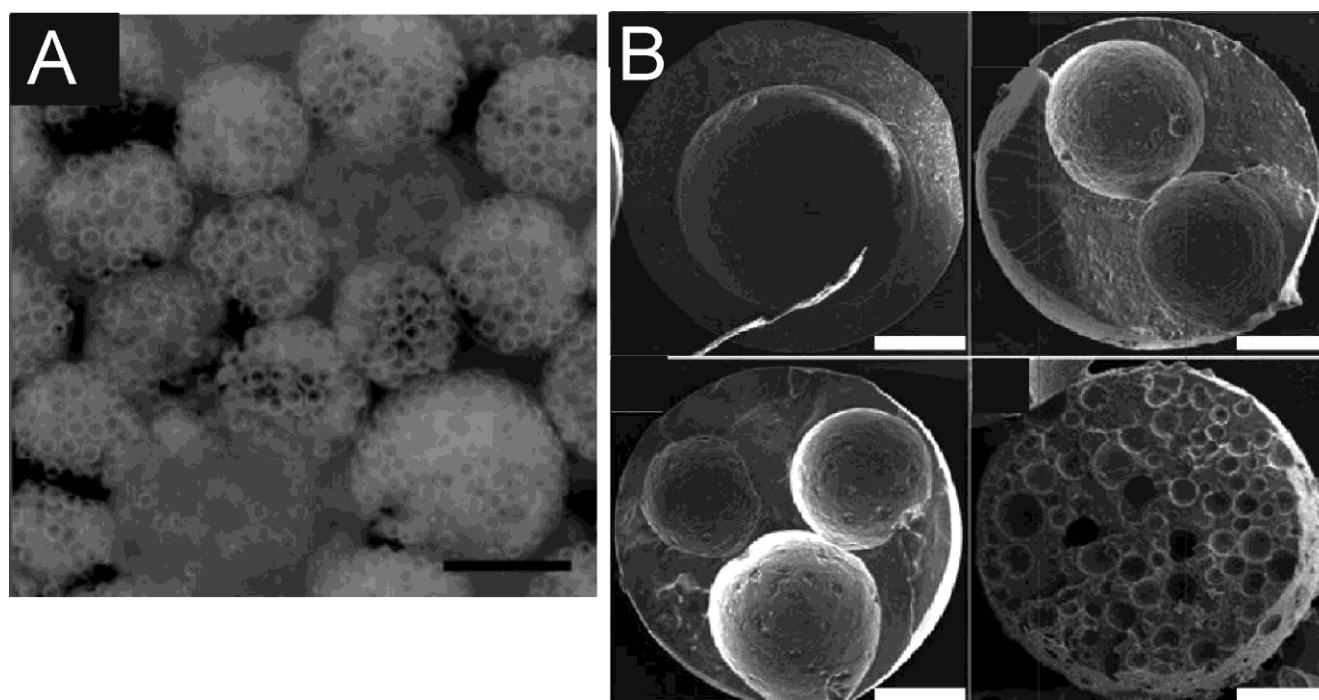


Fig. 21. Gas foamed particles prepared by PDMS chip based microfluidics. The number of internal cavities can be controlled in both cases; (A) Hydrophilic polyacrylamide particles prepared from a G/W/O emulsion. Scale bar represents 200  $\mu\text{m}$  [226]. (B) Hydrophobic particles made from a mixture of commercial thiol-ene resin and gas forming  $\text{H}_2\text{O}_2$ . Scale bars represent 50  $\mu\text{m}$  [227]. Adapted from [226-227] with permission. Copyright 2008 Wiley-VCH Verlag GmbH & Co. KGaA; Copyright 2009 American Chemical Society.

groups. A maximum surface area of 35.6  $\text{m}^2/\text{g}$  was reached. Together with size monodispersity, very uniform inner globules were obtained in one case where xylene was utilized in a thiol-yne formulation.

As previously mentioned, the fabrication of nonspherical particles is one of the distinctive capabilities of microfluidics devices. Next to the poly(HIPE) rods [9], porous Janus fibers [231] are formed from a photocurable polyurethane resin in a co-flow PDMS chip by making use of a stabilized jet. The inner jet, composed of the polyurethane resin, reacted with the continuous aqueous phase, thereby releasing  $\text{CO}_2$  and forming pores only on one side of the fiber. The effect of the water was proven by replacing it with glycerol, which led to the formation of nonporous fibers. Another approach was based on gas bubble capture in a stable aqueous monomer jet to form hydrophilic polymer threads with ordered, embedded uniform gas bubbles [232]. Although fibers are out of the scope of this review, these approaches may inspire particle synthesis since jets can break up into particles once the parameters such as flow rates are adjusted.

Microfluidics has also been utilized to form monodisperse supraballs, consisting of an assembly of smaller particles to form larger aggregates. As early as 2002, Pine and co-workers [233-235] reported the assembly of nanoscale spherical polymer beads into monodisperse ( $\sim 5 \mu\text{m}$ ) supraballs (Fig. 22) using a co-flow PDMS chip and a tubing/pipette tip device. Similar

results were reported by Gu and co-workers later on [236]. In both cases, nano-sized seed particles in aqueous suspension droplets were emulsified in oil and the assembly was realized via the removal of water. These approaches are actually multistage heterophase polymerizations in which the second stage is microfluidics. The first stages, namely seed preparation, were either dispersion [234] or emulsifier-free emulsion [235-236] polymerizations.

## 2.7. Other Techniques

In addition to all aforementioned mainstream production methods, few other techniques deserve to be included in this section which were not yet truly exploited for porous particle production. The first one is called aerosol

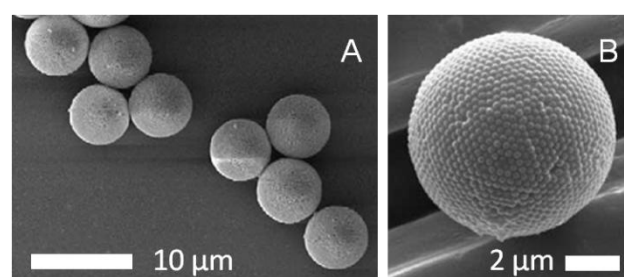


Fig. 22. (A) Monodisperse supraballs (spherical colloidal crystals) achieved via assembly of uniform nano-seeds in microfluidics; (B) single supraball exhibiting its nature. Adapted from [235] with permission. Copyright 2003 Elsevier.



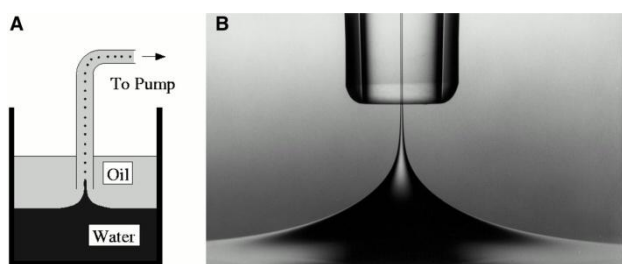


Fig. 23. Selective withdrawal for particle production. Water on the bottom is the source of the dispersed phase and oil on top is the continuous phase. Withdrawing from the right distance forms uniform droplets of the bottom phase. Reproduced from [251] with permission. Copyright 2001 American Association for the Advancement of Science.

polymerization [237], which utilizes a gas, for instance air, as the continuous phase instead of a liquid. The interfacial tension between monomer droplets and the surrounding gas also renders the former spherical, such as in the case of rain droplets. Although this seems to be a very efficient method, reports are scarce in the open literature [238-241]. For instance, Ray and co-workers [241] described the photopolymerization of a commercial multiacrylate resin via aerosol polymerization in a recent paper. The resin was dissolved in EtOH and atomized,

also referred as nebulized, by an aerosol generator. EtOH was quickly removed thanks to the  $N_2$  current and droplets were rapidly cured by UV. The particle size varied from 14 to 22  $\mu\text{m}$  with CV values below 1%. All particles were half the size of the orifice diameter due to the removal of EtOH. This kind of atomization is a very well known technique and is commonly used in industry in spray drying processes used for drying laundry detergent for instance. Another paper described the usage of a simple airbrush for atomization [242].

A similar technique to the aerosol polymerization is the electrospray method, where a high voltage is applied between the aerosol generator and the collection substrate. It is extensively used for the synthesis of non-crosslinked particles via precipitation of polymers from their solutions [243-247], and a limited number of reports describe monomer polymerization [248-250], all of which being about nonporous particles. Loscertales et al. [248] successfully electrified a coaxial jet composed of two immiscible liquids, the outer one being a commercial photo-polymerizable resin. Jet breakup resulted in monodisperse compound droplets and UV curing gave uniform submicron capsules with a liquid core. Like in the

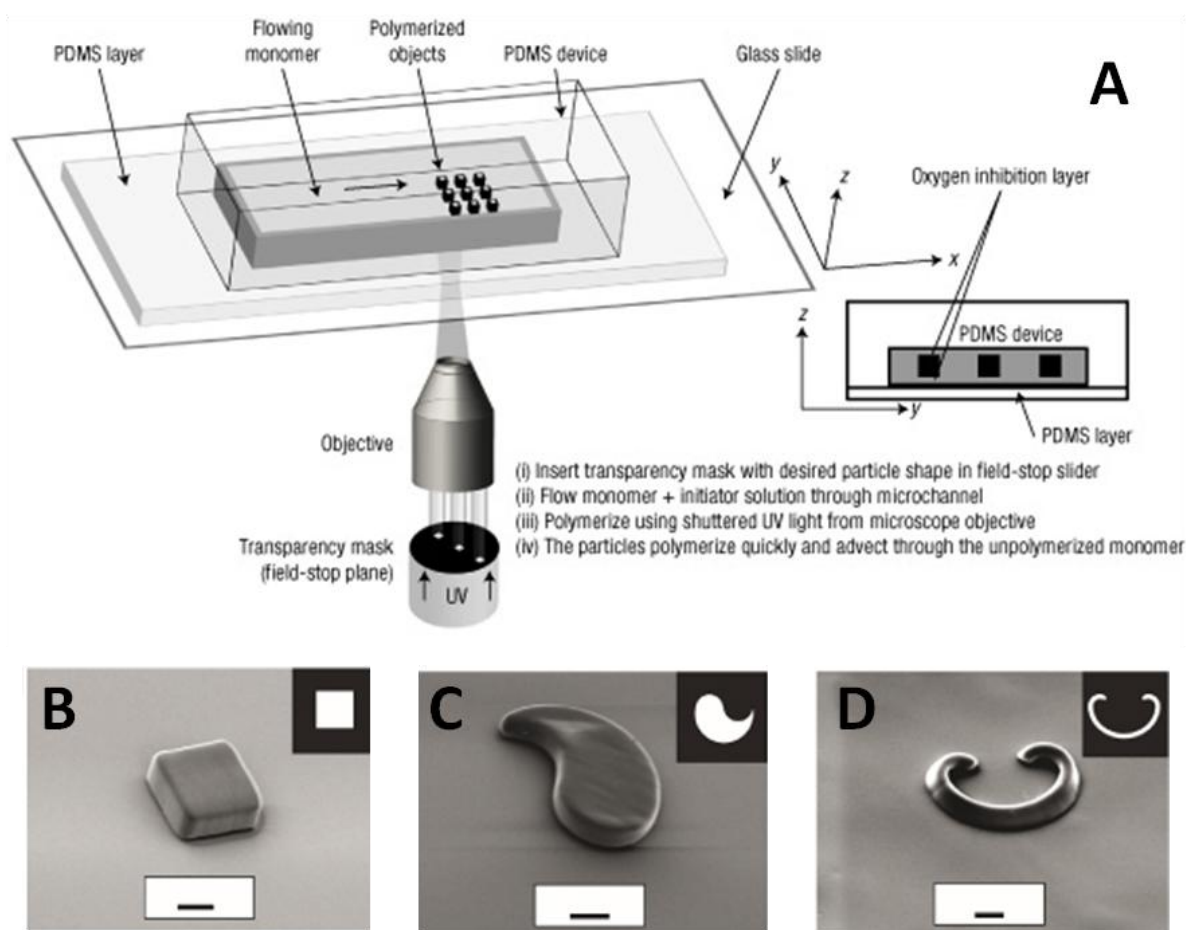


Fig. 24. (A) Schematic representation of the flow lithography technique. The device is composed of a single PDMS channel where monomer-photoinitiator solution flows. Particles are obtained by on-flight fast curing. (B-D) The obtained non-spherical particles by using different UV masks. Each scale bar represents 10  $\mu\text{m}$ . Adapted from [260] with permission. Copyright 2006 Nature Publishing Group.

previous case, addition of a porogen to make porous particles needs to be exploited.

Another technique waiting to be used for porous particle production is called selective withdrawal [251-255]. Reported initially by Nagel and co-workers [251], the bottom liquid, which is going to be the dispersed phase, is withdrawn just from the interface by a tube where the continuous phase liquid is on top (Fig. 23). The formed liquid cone breaks up into regular droplets inside the microchannel. The setup looks very similar to microfluidics, however it does not necessitate any tedious device preparation. Nevertheless, few parameters such as viscosity and tube distance to the lower phase are of importance.

Finally, flow lithography techniques pioneered by Doyle and co-workers [256-259] have drawn attention as a potential technique for porous particle production. Although generally being considered as a microfluidic technique, there are distinct differences. First of all, there is no immiscible carrier phase. The monomer mixture flows as a single homogenous phase in a PDMS channel and polymerization is done in seconds via UV light masked with a template (Fig. 24(A)). Polymerization near the PDMS channel is inhibited thanks to the high O<sub>2</sub> permeability of PDMS [260], which avoids clogging of the channel. The non-polymerized monomer flow basically acts as the carrier phase for the polymerized particles. The shapes and resolution of particles (Fig. 24(B-D)) achieved with flow lithography techniques [259-266] are

certainly unmatched by any other technique.

## 2.8. Final Comparison of Heterogeneous Polymerizations for Porous Particle Production

In this section, we aim to give an overview of all the techniques that can be used for porous particle production. We explained the basics for each individual technique by giving recipes but tried not to exclude creative reports that deviated from the mainstream approaches within each technique. We suggest that one should consider several points to decide which technique to use for the manufacture of porous particles. First of all, depending on the type (i.e. size, size-dispersity, pore size) of the particle needed there should be an initial selection from the techniques. For instance, if nonspherical porous particles are targeted, one will probably be directed to microfluidic approaches. However, it does not mean that it is impossible to obtain nonspherical porous particles with other techniques, just because it has not been realized so far. For sure, scientists will continue to challenge the limits of techniques in the near future.

In Table 2 we compare the mainstream techniques discussed above. Monodispersity, average particle diameter, functionality, extent of porosity, shape and certainly the cost should be considered all together. For instance, if the final application does not require

Table 2. Comparison of several heterogeneous polymerization techniques.

	Discovery	Diameter of beads (μm)	Minimum CV of beads produced	Ability to scale up	Chemical functionality	Shape variation	Multiple emulsions/core-shell structures	Easiness/cost	Reviews published
Suspension polymerization	20's	5-2000	Generally very high	✓	✓	X	Only mult. emulsions	Easy and cheap	[1-3, 267-270] [1, 271-272]
Precipitation polymerizations	Early 90's	0.1-8	2-3 %	~	✓	X	Only core-shell	Easy but can be costly	
Dispersion polymerization	70's	0.1-20	2-3 %	~	✓	X	X	Easy and cheap	[1, 3, 63, 273]
Seeded suspension polymerization	Early 80's	0.5-200	2-3 %	✓	✓	X	✓	Cheap but can be time consuming	[1-2, 270]
Membrane/microchannel emulsification	90's	10-1000	10 % (membrane) 2-3 % (μchannel)	✓	✓	X	Only mult. emulsions	Membrane/μchannel can be costly	[4-5, 123, 274-275]
Microfluidics	2000's	10-1000	<1 %	~	✓	✓	✓	Tedious/costly device preparation	[4-6, 178, 275-277]

✓ : Facile

~ : Possible but not easy

X : Not achieved so far

monodisperse particles, there may not be a need for membrane/microchannel emulsification or microfluidics. If a bimodal pore size distribution is aimed, using dispersion or precipitation polymerizations may be quite challenging for that purpose. From the economic viewpoint, suspension polymerization is probably the most attractive one but is limited for certain applications with regard to size and size dispersity.

### 3. Characterization

#### 3.1. Size and Size Dispersity

Perhaps the first 'label' to define a batch of spherical particles (also nonporous) will be the size and size dispersity. Size can be easily measured from microscopy images, especially in the case of monodisperse particles. Sieving and sedimentation are the methods still used in industry to fractionate particles and also to determine size range. There are several ways to determine a CV value for both monodisperse and polydisperse particles. One way is analyzing microscopy images via various available software [218, 241], which will also calculate the average size. Light scattering [278-280] and electrical sensing zone (also called Coulter counter) [45, 281-282] are rather sensitive instrument-based methods to determine size and size distribution. Microscopy and image analysis combination can be considered as the easiest method.

#### 3.2. Porosity: Surface area, Total Pore Volume and Pore Size Distribution

Surface area, total pore volume and pore size distribution data define the porous nature. These characteristics can be measured by N<sub>2</sub> sorption and Hg intrusion techniques, which both depend on penetration of the mentioned fluids into the pores. N<sub>2</sub> sorption is more suitable for determining micro- and mesopores and gives less data about macropores. On the other hand, Hg intrusion is only able to provide data about macropores and mesopores but not about micropores [18]. This is attributed to the higher ability of N<sub>2</sub> gas to penetrate into smaller pores compared to Hg [1]. Consequently, these methods are complimentary to each other and the proper one should be chosen depending on the type of the particle. The surface area is generally calculated from N<sub>2</sub> sorption isotherms by using the BET method. Commercial instruments measuring N<sub>2</sub> sorption isotherms include the necessary software. The total pore

volume in the dry state is measured by using both methods but again the size of the pores should be taken into consideration. It should be noted that both techniques require a minimum amount of 200-300 mg of particles, which could be difficult to collect via some low yielding manufacturing techniques such as microfluidics. Higher amounts of material give more reproducible results. In addition, N<sub>2</sub> sorption is a nondestructive method while Hg intrusion is destructive.

Besides N<sub>2</sub> sorption and Hg intrusion, other techniques [283] exist for quantifying the pore size distribution such as thermoporometry, inverse size exclusion chromatography and analysis of microscopy imaging [284]. It is important to note that inverse size exclusion chromatography is performed intrinsically in a solvent, so that the data can be considered as swollen state porosity [285]. To our viewpoint, N<sub>2</sub> sorption analysis stands as the most straightforward method since it gives quite reliable data for surface area, total pore volume and pore size distribution unless the pores are extremely large. We also would like to note that there are reports with equations to calculate several aspects of porosity by using density measurements as the only variable [286-287].

The effect of the washing solvent, used prior to drying, on dry state porosity is also important [288]. Indeed, a fraction of the pores can collapse if the particles are dried from a good solvent. However, these pores 'reopen' after drying from a poor solvent.

#### 3.3. Surface Charge

The surface charge of particles becomes important when the particle size is below 10 μm. In this range, a high surface charge will help the formation of more stable dispersions of particles in a liquid medium. Oppositely, surface charge is not desired for self-assembly purposes [289]. Charged particles are generally obtained by using acid [50] or base [191] monomers, yielding negative or positive charge, respectively. pH of the medium is also important: a carboxylic acid particle will not be charged at low pH. Adding a salt to the medium also suppresses particle charge [289]. Finally, surface charge can be induced by adding anionic surfactants to the medium, forming a charged polymer layer around the particles.

The zeta (ζ) potential is generally used as the measure of surface charge. Zeta potential is theoretically defined as the electric potential between the dispersed phase and the boundary fluid layer that is permanently attached to the particle. Particles with a zeta potential higher than

+30 mV or lower than -30 mV can be considered as highly charged [290]. Zeta potential is calculated from electrophoretic mobility that is measured by several commercial instruments, using methods such as laser Doppler electrophoresis or electrophoretic light scattering.

### 3. 4. Swelling/Solvent Uptake

Swelling is one of the important differences between porous and nonporous resins. Although swelling is crucial for nonporous resins, it may not be expected from porous (especially macroporous) resins. In the case of nonporous resins, reagents can only reach the inner reactive sites if they swell reasonably in the solvent used. For that reason, those resins are fabricated by using very low amount of crosslinkers, for instance 1% for the Merrifield resin (the word 'resin' is used interchangeably with the word 'bead' especially in the field of SPPS). On the other hand, a high amount of crosslinker is needed for producing a macroporous resin to facilitate the phase separation between the polymer and porogen during the synthesis, as discussed in section 2.2. High crosslinking densities limit the degree of swelling of porous resins. However in this case, the pores also 'accommodate' some solvent, a process that is better referred to as 'solvent uptake'. The presence of pores thereby greatly facilitates the diffusion of both reagents and solvents inside the particles, even though they are not swelling the particles.

The swelling degree (solvent uptake) can be expressed either in volume or weight expansion [11]. In the former case, a weighed sample of dried resin is swollen by a solvent and the excess of the solvent is removed after the equilibrium swelling is reached. The swelling degree is the ratio of the swollen weight over dry weight. In the latter case, dry beads are packed into a volumetric syringe fitted with a frit at the tip, then swollen by a solvent and the volume difference is recorded as the swelling degree.

### 3. 5. Mechanical Strength

Perhaps the weakest point of porous, especially macroporous resins is the lower mechanical strength compared to nonporous ones. For this reason, it is not advised to use a magnetic stir bar when a resin (even nonporous) is treated with reagents. Exposing particles to magnetic stirring and checking if particles preserve their shape is even used as a method to measure

mechanical strength [291]. Several shakers are being used and rotary evaporation is useful when heating is also needed [12].

Several methods are used to determine mechanical strength of particles. First of all, there are dedicated instruments measuring several mechanical parameters (tensile strength, elongation at break, D hardness) of particles according to ASTM standards [292]. Mercury intrusion porosimetry curves can also be used. A slope instead of a plateau for the second zone of the curves indicates low mechanical strength [13, 293]. In addition, combination of TGA and DSC is also proposed as a method of mechanical strength measurement [72-73]. These methods are suitable for particles of any shape, size and size distribution.

Another common way to analyze mechanical strength of particles with sizes down to 2  $\mu\text{m}$  in diameter is via compressing a single particle between two plates and measuring the deformation [294-297] by several ways such as microscopy [298] or weighing [299]. This technique is more suitable for monodisperse spherical particles since the measurement is generally performed on a single particle.

The final way to understand mechanical stability of particles is utilizing them for the desired application and observe if any change in morphology takes place due to the stress generated for this specific application. Particles prepared for chromatography columns are packed into columns and back pressure is measured as an indication of mechanical strength for instance [300].

### 3. 6. Chemical Analysis

The chemical nature of the particles is of utmost importance for some applications where functionalization is needed. Analytical techniques used to characterize other materials (i.e. nonporous particles, bulk polymer materials and inorganic particles) are to some extent applicable to porous particles. Most suitable techniques for the analysis of porous particles are elemental analysis, IR and color based essays, which are briefly described herein.

Elemental analysis can provide information about functional groups that carry atoms different from the backbone. For instance, halogen, azide and thiol groups will be nicely detected for a C, H, O based particle but not C-C triple bonds. If the function to be monitored possesses elements that are also present in the backbone, derivatization can be a solution.  $-\text{NH}_2$  groups on a N based resin is such an example. Elemental analysis will give the total amount of N present in the resin. If free

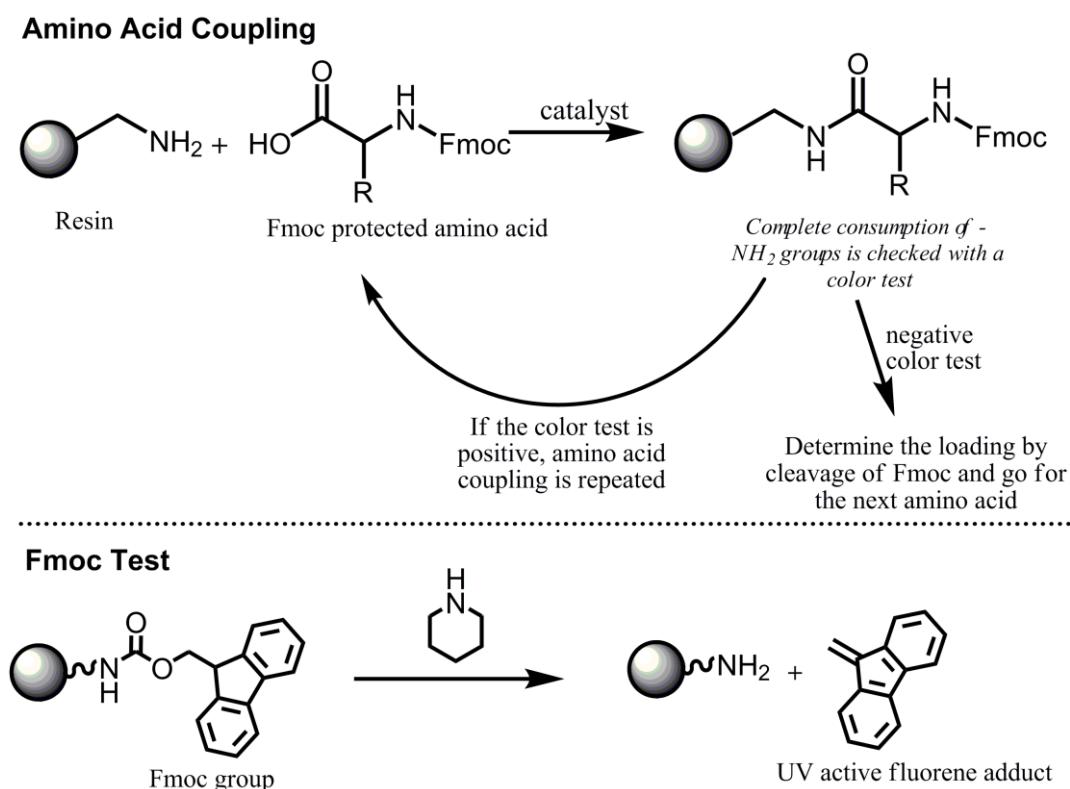
$\text{-NH}_2$  groups are completely capped (for instance) with a  $\text{-Cl}$  containing isocyanate, the amount of Cl atoms in the final resin will give the desired information about the accessible  $\text{-NH}_2$  groups of the initial batch. It is worth to be mentioned that the sample should obviously be totally free of any residual reagents or solvents.

Infrared (IR) analysis is probably the most facile instrument based method to detect functional groups (such as  $\text{-OH}$ ,  $\text{-NH}_2$ ,  $\text{C=O}$ ,  $\text{C=C}$ ,  $\text{C}\equiv\text{C}$ ,  $\text{-SH}$  and  $\text{-N}_3$ ) and monitor the evolution of reactions on particles [9, 218, 301]. IR spectrometers are abundant and analysis time is short. In addition, the decrease of a reagent due to the reaction with the present particles in a well sealed flask can also be followed by real-time IR measurement. As a complementary method to IR, Raman spectroscopy can reveal other functional groups (such as  $\text{C-Cl}$  and  $\text{C}\equiv\text{N}$ ) that can be difficult to detect by IR [302-303]. Moreover, solid state [304-305], gel phase [306-307] and high-resolution magic angle spinning (HRMAS) NMR [308-311] techniques can be quite successfully applied to detect the functional groups and monitor reactions on particles. Availability of probes, operator experience and need of a suitable solvent for the analysis can be the parameters to tackle.

Real time monitoring of reactions taking place on particles can be realized by several spectroscopy methods [312]. NMR, IR, UV-Vis and fluorescence spectroscopy techniques will give qualitative data on reaction kinetics in this way. Once the flask is well

isolated, decrease of a reagent due to the reaction with the present particles will enable online monitoring. However, one should be careful not to conclude that all the functional groups on the polymer are consumed when the consumption of the followed reagent is stopped. Mostly there are inaccessible functionalities on the polymer, which will give a positive signal when analyzed. This is generally troublesome since it is very difficult to quantify remaining functional groups.

It was the fact that reliable quantification of remaining functional groups on particles is rather difficult, stimulated solid phase peptide synthesizers to develop highly efficient coupling strategies [313]. These strategies will be further discussed in the next section. In solid phase synthesis, color tests [314-320] are the equivalence of thin layer chromatography for solution phase organic synthesis. Once a resin undergoes a chemical transformation with a reagent, a small portion of the resin is treated with a dye that is highly reactive for the chemical function that has to be consumed in the actual reaction. Lack of coloring of the resin judged by the naked eye designates the completeness of the main reaction. In the classical fluorenylmethyloxycarbonyl (Fmoc) based solid phase peptide synthesis (Scheme 1), a resin possessing  $\text{-NH}_2$  or  $\text{-OH}$  groups is treated with an Fmoc protected amino acid in the presence of some well known organic catalysts [321]. Here the completeness of the reaction is checked with a color test, i.e. ninhydrin. If the amidation/esterification is complete, the Fmoc group



Scheme 1. Solid phase amino acid coupling and Fmoc test for chemical analysis of particles.

can be released by piperidine and quantitatively detected by a well established UV measurement [322]. This in turn will give reliable data for initial  $-\text{NH}_2/-\text{OH}$  loading (amount of a functional group on a resin generally expressed as mmol/g) of the resin. Finally, titration [323-324] can also be used for quantitative analysis.

## 4. Functionalization

### 4.1. General Particle Functionalization

This section will briefly discuss the strategies employed for particle functionalization. As in the case of characterization, strategies used for monoliths, nonporous gels, surfaces and so on can be applied to porous particles in many cases. Consequently, references given here will not strictly include porous particles. It should be known beforehand that reactions on solid phase are much slower and yields are generally lower in comparison to homogeneous reactions. In addition, quantitative detection of unreacted remaining groups may not be straightforward as already mentioned in the previous section. Moreover, in some cases it is not possible to use excess of an expensive reagent to drive the reaction to completion. These constraints necessitate the use of high yielding reactions on solid phase. "Click chemistry" [325] is the term coined almost a decade ago to describe reactions basically running with high yields in mild conditions and without any offensive by-products. Thus, click type reactions should be well appreciated for functionalization of particles. For this reason, this section will mainly discuss click type reactions. It is important to mention that by-products or excess of the reagents generally do not constitute a problem for solid phase functionalization since purification is done by some washing steps.

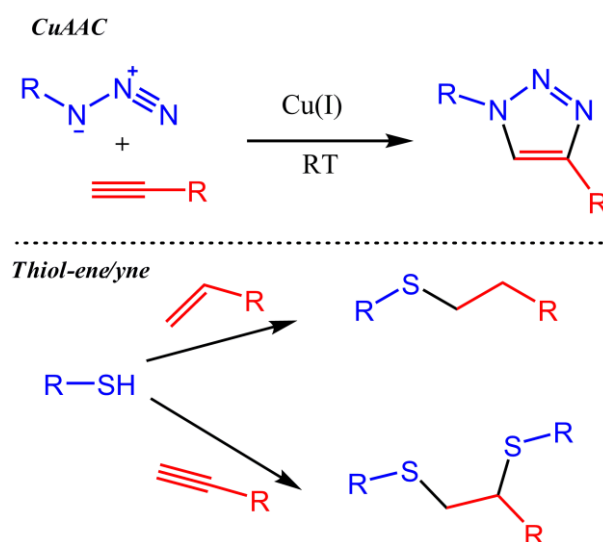
From the several proposed click type reactions in the literature [326-327], two of them received much attention within the polymer society: Cu(I) catalyzed azide-alkyne cycloaddition (CuAAC) [328-332] and the addition of a thiol radical to olefins (thiol-ene and thiol-yne) [230, 333-334] (Scheme 2). There is a huge number of publications utilizing CuAAC since the first report in 2002 and thio-click reactions are recently becoming very popular. Obviously, one of the reactive groups should be present on the solid support and the complementary one(s) in solution for these click reactions to take place. The presence of azide or thiol on the support and not in the solution should be considered for practical reasons. Low MW azide compounds can be seriously explosive [325, 335] while low MW thiol compounds generally have a deterring smell. Moreover, there are color tests to

detect remaining amounts of both azide [320] and thiol [314] groups. As mentioned in the previous section, azide, alkyne, alkene and thiol groups can be easily followed by IR spectroscopy which makes these reactions further attractive on solid phase.

#### 4.1.1. Cu(I) Catalyzed Azide-Alkyne Cycloaddition (CuAAC)

Although there are numerous studies on CuAAC functionalization of nonporous polymers [280, 298, 328, 336-351], silica [352-354] and metal particles [355], the amount of publications on porous polymer particles is limited. Finn and co-workers [356] described the click functionalization of a commercial porous agarose resin for affinity chromatography. In two parallel experiments, amino agarose beads were treated with azide and alkyne carrying activated esters respectively (Scheme 3). The interesting point of the approach was that the azide/alkyne carrying ester released the UV active *p*-nitrophenol group upon amidation, thus the azide/alkyne loading could be determined by online spectroscopic techniques in a similar way to the Fmoc test. Several compounds of interest were subsequently clicked on these agarose beads and the coupling efficiency was shown by clicking a fluorophore. More studies about clicking onto commercial agarose beads are reported [357-358] but information about the nature (porous or not) of the beads is missing.

The preparation of custom made porous azide and alkyne beads for chromatographic applications was later published by Fréchet and co-workers [12] utilizing a multistage seed swelling approach. Alkyne bearing beads were prepared in a straightforward fashion by using an alkyne monomer for the second swelling stage. For the azide bearing beads however, an epoxy monomer was



Scheme 2. CuAAC and thiol-ene/yne click chemistries.

used for the second swelling stage and azide introduction was realized in another step. Although the authors do not mention the reason for the need of another step instead of utilizing an azide monomer for swelling, we believe that it is due to the loss of azide groups during the polymerization of double bonds as recently reported by Perrier and co-workers [359]. We also experienced that azide groups are not only sensitive to temperature but also to UV. The UV triggered self crosslinking ability of azide groups is even used as a strategy to obtain networks [360]. Nevertheless, Chan and co-workers [339] recently reported a one-pot preparation of azide carrying nano-beads by a delayed addition of azide monomer into their inverse microemulsion polymerization batch.

Another strategy to introduce azide groups on a porous resin was published by Oyelere et al. [361], i.e.  $\text{NH}_2$  groups on commercial Argopore resin have been converted to azides via diazo-transfer reaction by using triflyl azide and further clicked with nucleosides. Despite the handling difficulties of triflyl azide (explosive, needs to be freshly prepared each time), this method should be widely applicable since there are numerous amino resins available on the market. Finally, Du Prez and co-workers [9] compared the clicking of phenyl acetylene onto self-prepared macroporous and megaporous (micron sized pores) poly(HIPE) particles composed of the same monomers. The effect of the pore size was shown to be more important than the surface area, which was proven by a better performance of the poly(HIPE) beads.

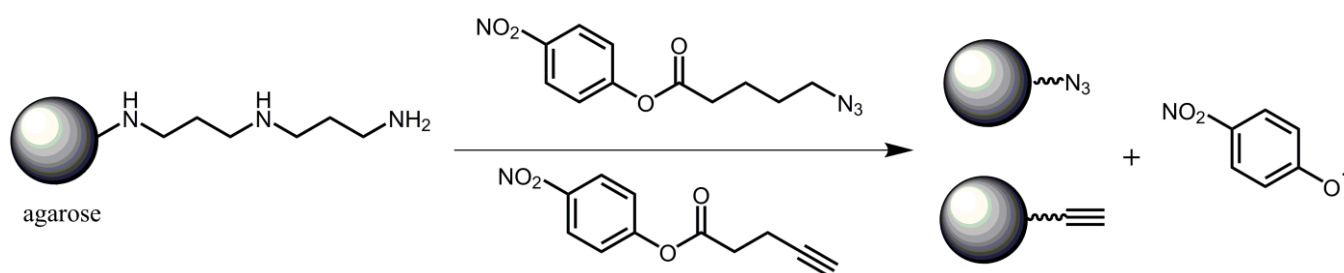
#### 4.1.2. Thio-Click Modifications

A combination of thiol-ene and CuAAC click reactions on nonporous polyDVB particles was published by Müller and co-workers [52]. Remaining double bonds of precipitation polymerized polyDVB particles first underwent thiol-ene click by treatment with 1-azidoundecan-11-thiol. In a second step, the azide functions have been treated with an alkyne terminated linear polymer. The same strategy was applied to metal doped nanoparticles by Hawker and co-workers [362].

The efficiency of the thio-click reaction was shown by the change in dispersing ability of the particles in THF after grafting thiol terminated PEG chains. Addition of thiol groups onto (meth)acrylate [363-364] or epoxy groups [365] of porous and nonporous particles has also been published. Our group also recently contributed to this field by preparing both thiol- and yne-functionalized nonporous beads by changing the ratio between the two building blocks: a tetra-thiol and a di-yne [366]. The yne bead was separately treated with a thiol and an azide for comparison and it was found that thiol-yne is faster than CuAAC for specific conditions. Moreover, the thiol bead was treated with 9 different click reagents in parallel and the ranking is found as follows based on fastest conjugation kinetics: isocyanate > norbornene > acrylate  $\approx$  isothiocyanate > maleimide  $\approx$  isolated ene >  $\alpha$ -bromo ester > epoxide  $\approx$  aziridine. Finally, another novel highly efficient functionalization reaction involving the catalysis and heat free grafting of PS chains onto precipitation polymerized porous DVB particles via hetero-Diels-Alder chemistry was developed by Barner-Kowollik and co-workers [367]. The microspheres were functionalized with cyclopentadiene and PS chains were furnished with thiocarbonyl moiety as dienophile. Very high PS couplings were reported for time scales as short as 2h without heat treatment.

#### 4.1.3. Coupling Strategies of Solid Phase Peptide Synthesis

Strategies developed over decades for solid phase peptide synthesis [368] and solid phase organic synthesis [369] are generally very efficient. Coupling of an amino acid on a resin carrying  $-\text{NH}_2$  groups (Scheme 1) can be completed in less than 1h at room temperature [370] thanks to various efficient catalysts [371] developed over decades. This chemistry is certainly as efficient as any well accepted click reaction. In addition to amidation, several highly efficient esterification strategies are also well established [372]. Various other peptide ligation strategies such as native chemical ligation [373] and



Scheme 3. Monitoring the agarose functionalization by the released *p*-nitrophenol group. Reproduced from [356] with permission. Copyright 2005 American Chemical Society.

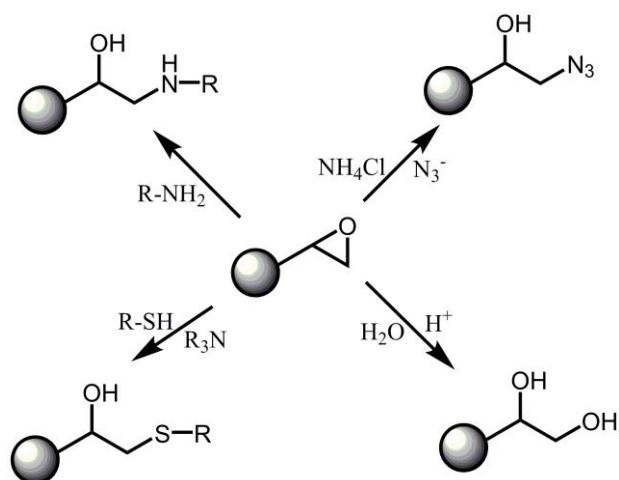
Staudinger ligation [374] are well described in literature [375] but are kept out of the scope of this review.

#### 4.1.4. Epoxy Group as an Electrophile on Particles

Finally, we conclude this functionalization section by mentioning further possibilities offered with epoxy carrier resins. The potential of spring loaded epoxy ring for effective transformations constitutes an important part in the review of Sharpless and co-workers [325] where 'click chemistry' was first defined. Opening the three-membered ring with an azide anion (acid catalyzed) or a thiol (base catalyzed) is already mentioned in this review. Amines (preferably primary) can also open the ring (Scheme 4) without the need of any catalyst or heat. Consequently epoxy groups are good starting points for several modifications. Moreover, the most commonly used epoxy carrying vinyl monomer GMA is stable in (neutral) water based emulsions. It should be noted however that opening of the epoxy ring with a nucleophile results in secondary –OH groups, which may interfere with some chemistries.

## 4. 2. Surface- and Pore-Size-Specific Functionalization

Site-specific functionalization of particles and their usage in novel applications will gain more importance in the near future to our belief since very little work has been done so far, although the first papers appeared in early 90's. Core-shell particles, for which there are well established preparation strategies [49, 376-377], provide an easy medium for site-specific functionalization since core and shell are made of different chemical nature. The difficult task is the site-selective functionalization of a



Scheme 4. Some of the effective modifications of epoxy particles. Only the attack to the less hindered carbon atom is considered

uniform particle. To achieve this via wet methods, diffusion of the reagents to the core or smaller pores should be prevented. Limited reaction times, polymeric reagents and hydrophilic-hydrophobic contrast between particle and reagent/medium may prevent reagent penetration to the core or smaller pores.

In this respect, Landry and co-workers first blocked the pores of mesoporous silica particles with Fmoc protected silanes [378]. Pore blockage was proved by  $N_2$  sorption measurements. In the next step, a short treatment with a base cleaved only the surface Fmoc groups, which could be then labeled with a fluorophore. Location of the fluorophore was followed by confocal analysis. Using polymeric reagents for pore-size-specific functionalization of macroporous particles is developed by Svec and Fréchet [379-381]. When macroporous, epoxy-containing beads were treated with poly(styrenesulfonic acid), only the epoxy groups of the larger pores hydrolyzed, leaving the remaining epoxy groups of the smaller pores to be functionalized with small amines. Epoxy group titration showed that the amount of intact epoxy groups were increasing by the size of hydrolyzing reagent, which was used as a proof for pore-size-specific functionalization. Recently, the same chemistry was applied by Buchmeiser and co-workers to monoliths [382]. After poly(styrenesulfonic acid) treatment, pores smaller than 7 nm remained unchanged, half of the ~80 nm pores were lost and the number of ~40 nm pores increased by 150%. This was followed by inverse size exclusion chromatography as a proof of pore-size-specific functionalization. An interesting extension of this work is the functionalization of large pores by thermoresponsive polymers that act as temperature controlled gates [383-385].

About the utilization of the hydrophobic-hydrophilic contrast, Gooding and co-workers first formed a dense alkyl layer on mesoporous silica, which prevented water diffusion into the material [386]. Aqueous reagent solutions functionalized only the surface, followed by an organic solution that functionalized the pores. Functionalization was followed by reflectance spectra since the silica was engineered with a photonic band gap. The authors also reported that IR is only sensitive to the changes in the bulk of the material but not to the surface.

In addition, there are directional methods that are being used to form chemical patches on surface of particles such as microcontact printing [221, 387], etching [388], laser- [389] or UV-induced deposition [390], projection lithography [391], metal deposition [392-393] and temporary masking one side of particles while modifying the other [394-395]. Most of these methods are waiting to be explored for porous particles.



## 5. Applications

### 5.1. Ion-exchange, Catalysis and Scavenging

Ion-exchange has been the first area where porous resins resulted in commercialization [396]. These resins possess ionic groups such as  $-\text{SO}_3^-$ ,  $-\text{CO}_2^-$  and  $-\text{NH}_3^+$ , together with a complementary anion or cation such as  $\text{H}^+$ ,  $\text{Na}^+$ ,  $\text{Cl}^-$  or  $\text{OH}^-$  [397]. In the classical example, a PS-sulphonic acid based ion-exchange column can soften water by exchanging  $\text{Ca}^{++}$  and  $\text{Mg}^{++}$  with  $\text{Na}^+$ . Toxic heavy metals can also be removed from water thanks to their high affinity to polar groups such as carboxylates. Later, it has been discovered that this metal complexing ability of ion-exchange resins can be used in heterogeneous catalysis [398]. Once the resin is loaded with the desired metal, the organic transformation can be realized either in batch [399] or in a continuous process. Moreover,  $\text{H}^+$  carrying cation-exchange resins can be used for acid catalyzed organic reactions [400-401]. On the other hand, non-ionic porous resins are also used in catalysis [402-403]. The catalyst is either a covalently attached organic molecule [404] or a metal that is chelated to the resin thanks to the electron donating ligands [405-409]. Simple precipitation of the metal to the pores is also reported [410-411].

Physical absorption, electrochemical absorption and covalent absorption abilities of porous resins lead to several applications. As discussed in the sub-section on multistage polymerizations, particles can swell to a great extent by absorbing hydrophobic species. This can be used for removing undesired species either from water [412-415] or from organic media [416]. Moreover, gaseous species can also be absorbed by particles [417-419]. Scavenging is another field for which porous polymers are effectively used [420-423]. Scavenger resins ideally possess chemical groups that selectively react and therefore remove undesired compounds from a mixture.

The size, polydispersity and even the shape are not the most important issues for the applications mentioned so far; on the other hand the surface area is a crucial parameter. In this respect, for ion-exchange, catalysis, absorption and scavenging applications, suspension polymerization can be the first technique to be considered for particle preparation. Sieving can be utilized if particles are going to be packed into a column.

### 5.2. SPE and Chromatography

Another absorption based application area is solid phase extraction (SPE) [424]. Small particles packed in a cartridge absorb (generally hydrophobic) solutes from an analyte. Solute are removed from the sorbent by washing with an organic liquid in the second stage. In this way, solutes are enriched and ready for analysis. Since the interaction time is relatively short, a high performance of absorption is requested from particles (=sorbent). In that respect, hypercrosslinked particles are suitable due to their extremely high surface area. Seed preparation accompanied by hypercrosslinking in the second stage seems to be a suitable approach to produce such sorbents.

Chromatography [2, 270] is perhaps the most delicate of all the mainstream applications of porous polymer particles. In the range of 2-5  $\mu\text{m}$ , highly spherical and narrowly monodisperse beads are necessary to obtain reproducible results from a packed chromatographic column. Whereas silica packed columns are preferred over polymer packed columns in HPLC, polymer particles are mainly used in size exclusion chromatography (SEC) due to their 'configurable' pore size and pore size distribution. In SEC, smaller polymer chains spend more time in pores of packed beads compared to the larger chains, which is the basis for the separation [425]. For a batch of higher MW polymer to be analyzed, beads with a higher pore size are necessary for better separation. On the other hand, a lower average pore size is needed for the separation of a lower MW polymer. Seeded polymerizations seem to be suitable for production of SEC beads [426] since the pore size and pore size distribution can be easily controlled in the second swelling step. For HPLC columns, aerosol and precipitation [51, 281] polymerizations are also available, together with seeded polymerizations [12, 68-69, 427-428].

### 5.3. Solid Supported Synthesis

A final mainstream application area of porous particles is solid phase peptide (SPPS) and organic (SPOS) syntheses [429-430]. Porous particles are used to some extent for SPPS and SPOS [431-432], however gel-type nonporous particles are preferred over porous ones. Thanks to their very lightly crosslinked nature (1% in general) nonporous gels can swell to a great extent when immersed in a good solvent, such as toluene for styrene-DVB based resins. However, if a nonsolvent is necessary for transformation, especially in the case of SPOS, permanently porous resins

can perform better. It is also worth to mention that by the growth of the desired molecule (such as peptide), space restrictions become more prominent. Porous (especially macroporous) resins can offer room to accommodate such large molecules and prevent 'saturation of resin'. Too small resins are not easy to handle as supports for solid phase synthesis due to clogging of the filters and loss of visibility by naked eye. Therefore beads with sizes ranging from 100 to 500  $\mu\text{m}$  are used for this purpose. In addition, shape and monodispersity are not the highest priorities. Suspension polymerization [433] accompanied by sieving, multistage polymerizations, microfluidics and also membrane/microchannel emulsification methods are all appropriate.

## 5.4 Future Applications

The previously described applications in this chapter are already known for decades. In the close future, novel applications of porous particles are expected to emerge, providing solutions to the current problems of our society such as energy, health-care, microreactors and sensing. In the field of energy,  $\text{H}_2$  is believed to replace fossil fuels as a greener alternative soon [434]. An enormous amount of research is currently being devoted to metal-organic frameworks as  $\text{H}_2$  storage materials [435]. Microporous polymer particles may also play a role in this field [436]. Carbon capture and sequestration is also one of the energy related applications for which porous polymer particles can be useful. There are suggestions to capture  $\text{CO}_2$  from air by using base immobilized particles [437-438].

Porous hydrogel particles are already being utilized as tissue engineering scaffolds and drug delivery systems in the field of biology and medicine [439]. Advances in the life sciences will require novel polymer particles. Porous particles will also likely to play an increasing role in microsensors [440-442]. Finally, microreactors are receiving increasing attention because of the ability to reduce costs and environmental effects by reaction miniaturization [443-445]. It is well-known that polymer particles can absorb organic species. This ability can be used to capture toxic chemicals (i.e. from wastewater) and transform them into harmless substances via immobilized catalysts or enzymes.

We believe that more interesting applications may emerge if porous particles are designed with stimuli-responsive characteristics in the future [446]. A trigger can be a temperature increase [447], pH change [448], added chemicals [191], external electric [449] and

magnetic [223] fields, microwave radiation [450] or light [451]. The response of these smart materials can be controlled in an automated way to obtain novel devices.

## 6. Conclusions and Outlook

This review is intended to be written in such a way that any researcher who has little knowledge about polymer particles can design the path to synthesize, characterize and also functionalize custom made porous particles according to the targeted applications. We believe that researchers planning to prepare nonporous particles will benefit as well from this manuscript since this is the first one to compare classical heterophase polymerizations (suspension, precipitation, dispersion and multistage) with the newest ones (membrane/microchannel and microfluidics) in detail. Size, size dispersity, functionality, porous nature and also shape of the particles have been addressed for each synthetic method and compared in a summary table. Characterization and functionalization strategies of particles have been covered too, including site-specific functionalization. The functionalization section includes a discussion about effective strategies including well accepted click chemistries. Finally, the applications section not only put the accent on bringing interests towards the development of new technologies, but also aims at building a correlation between the choice of synthetic method and the type of application.

For the future, complexity and simplicity will continue to be the two driving forces. On one hand, novelties are generally connected with complex structures. On the other hand, simplicity makes it easily reachable, which is very important for industrialization. Breakthroughs come out when the two are combined: complex in nature but simple in design. Microfluidics was revolutionary for paving the way to unprecedented control over size dispersity, shape anisotropy and structure complexity of particles. A novel or improved technique [452-454] inheriting abilities of microfluidics but overcoming its problems such as tedious device preparation and scalability would be another renaissance for particle production. Finally, unique mechanical, packing and assembly properties of nonspherical particles are already drawing attention [6, 85, 161, 452-453, 455-467] but the effect of porosity on such regular nonspherical particles is still waiting to be further exploited.

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