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Review

Monodispersed, molecularly imprinted polymers as affinity-based chromatography media☆

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Abstract

This review article deals with preparation methods for spherical and monodispersed molecularly imprinted polymers (MIPs) in micrometer sizes. Those methods include suspension polymerization in water, liquid perfluorocarbon and mineral oil, seed polymerization and dispersion/precipitation polymerization. The other methods are the use of beaded materials such as a spherical silica or organic polymer for grafting MIP phases onto the surfaces of porous materials or filling the pores of silica with MIPs followed by dissolution of the silica. Furthermore, applications of MIP microspheres as affinity-based chromatography media, HPLC stationary phases and solid-phase extraction media, will be discussed for pharmaceutical, biomedical and environmental analysis.

Keywords: Molecularly imprinted polymer; Monodispersed MIP; MIP microsphere; Affinity-based media; Pharmaceutical analysis; Environmental analysis; Bioanalysis

Contents

1. Introduction

Molecular imprinting techniques are very attractive because specific recognition sites for a target molecule could be easily molded in synthetic polymer networks [1–10]. The prepared molecularly imprinted polymers (MIPs) have been utilized as chromatographic media, sensors, artificial antibodies and

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catalysts [1,2]. Typically, MIPs were prepared by a bulk polymerization method, where the resultant monoliths had to be crushed, ground and sieved to produce microparticles for their applications [1]. When MIPs could be used as affinity-based chromatography media, HPLC stationary phases or solid-phase extraction (SPE) media, it is desirable to prepare the spherical and monodispersed beads.

To prepare spherical and monodispersed MIPs, several new polymerization methods have emerged. Typically, spherical MIPs were prepared by conventional suspension polymerization, where water is used as a continuous phase to suspend a droplet of pre-polymerization mixtures (template molecule, functional monomer, crosslinker and initiator) in the presence of a stabilizer or surfactant [1,4]. However, the size of the droplet formed is different depending on the conditions used. Therefore, the MIPs prepared by suspension polymerization are different in sizes (a few to a few hundred micrometers) and are always polydispersed [4]. It is thought that water is to weaken the non-covalent interactions such as hydrogen bonding and electrostatic interactions between a template molecule and functional monomer [4,11,12]. Water soluble template molecules and monomers would also be lost due to partitioning into the aqueous phase. Furthermore, a stabilizer or surfactant, which is required for the formation and stabilization of droplets, could interfere with interactions between a template molecule and functional monomer. Attempts to make MIP microspheres by suspension polymerization in water have led to only very poor recognition [4,11,12].

Recently, two new suspension polymerization techniques based on droplets of pre-polymerization mixtures formed in liquid perfluorocarbon [11] or mineral oil (liquid paraffin) [12] have been developed. These liquids were used as a continuous phase instead of water. The advantages of the former method are that liquid perfluorocarbons are immiscible with almost all organic solvents, and that many combinations of monomers and crosslinkers and a wide range of solvents, employed for bulk polymerization, could be utilized [11]. However, it is required to synthesize perfluoro polymeric surfactants. On the other hand, a suspension polymerization technique using mineral oil as a continuous phase comprises the formation of droplets of pre-polymerization mixtures directly in mineral oil by vigorous mixing followed by transformation of the droplets into solid spherical beads by photo polymerization [12]. It is interesting that no stabilizers or surfactants were required for the droplet formation. However, neither chloroform, nor dichloromethane, nor toluene, which is generally used as a porogen in molecular imprinting, could be used with mineral oil because these solvents are miscible with mineral oil. Both methods give polydispersed beads as well as suspension polymerization in water.

The second method for the preparation of MIP microspheres is seed polymerization, typically multi-step swelling and polymerization [13], as shown in Fig. 1. Uniformly-sized polystyrene seed particles were utilized as the shape template. The seed particles were swollen by microemulsion droplets containing an activating solvent (i.e., dibutylphthalate) and further swollen by pre-polymerization mixtures. After completion of swelling, monodispersed MIPs could be prepared by photo or thermal polymerization. The advantages of the method are as follows: it is easy to prepare monodispersed MIPs and to perform in situ modification. However, interactions between a template molecule and functional monomer could be interfered since water is used as a continuous phase.

The third method is dispersion/precipitation polymerization. In dispersion polymerization, primary particles swell in a polymerization medium and the polymerization proceeds in the particles, resulting in the formation of spherical beads, while in precipitation polymerization, primary particles do not swell in a polymerization medium and the polymerization takes place in the medium, leading to irregularly shaped and polydispersed particles [14]. However, a sharp distinction between dispersion and precipitation polymerization does not exist [10,14]. A crucial difference between the bulk polymerization and dispersion/precipitation polymerization techniques is the volume of a polymerization medium used. The latter requires larger volumes of the medium than the former. The excess of a polymerization medium may hamper interactions between a template molecule and functional monomer.

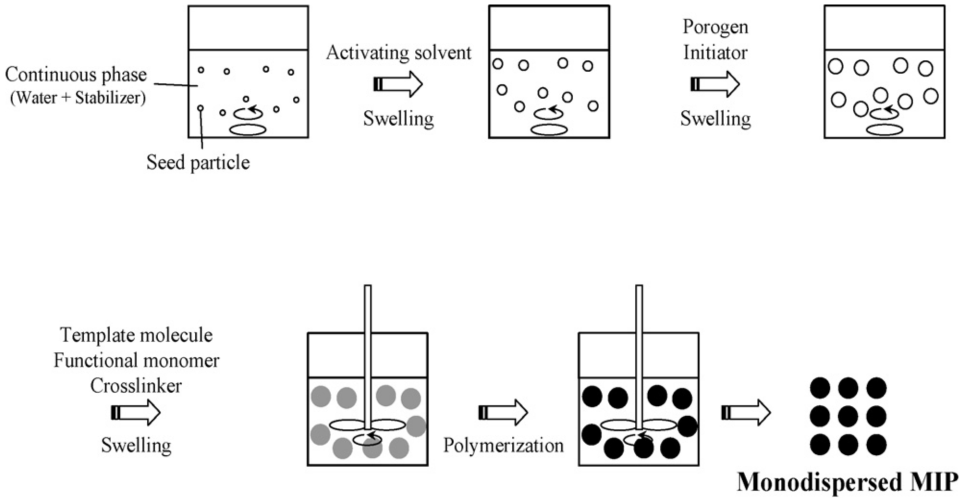

Fig. 1. Preparation method of monodispersed MIP by multi-step swelling and polymerization.