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Review

Approaches for the assembly of molecularly imprinted electrospun nanofibre membranes and consequent use in selected target recognition

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ABSTRACT

Molecular recognition plays an indispensable role in nature for the recognition of antibodies, enzymes and nucleic acids. Biomimetic fibrous non-woven materials are being developed to act as highly sensitive and selective artificial receptors based on molecular recognition sites in the constituent fibres. Molecular imprinting technologies (MITs) with specific recognition abilities are currently being developed to produce versatile materials for the recognition of diverse species in various applications, but specifically in membrane separation to express permselectivity. Conventionally, the production of molecularly imprinted polymers (MIPs) involves introducing binding sites where highly cross-linked copolymers are formed around the analyte molecules that act as cavity-creating templates. Subsequent removal of the template molecule provides recognition sites in the polymer that ideally resemble the template in terms of shape, size and functionality. Rebinding of the target molecule within these pre-formed sites can occur when the polymer is incubated in the presence of the template molecule. However, removing of template after polymerization is difficult because cross-linked polymer materials tend to be insoluble. This review paper describes work on new non-covalent molecular imprinting technologies applied to fibrous materials and electrospun fibres that are suitable for selected target recognition. This method has the potential of becoming a tool for producing truly simple, rapid and robust receptors on membranes of the type in regular use in the food industry, making the in-process simultaneous removal of undesirable co-product chemicals and microbial toxins a commercial possibility.

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1. Introduction

Increasing globalization of the food supply means an increase in uncertainty about the provenance of our foodstuffs, and so consumers are

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increasingly concerned about the safety, quality and authenticity of their purchases (Cifuentes, 2012). The need for methods both to monitor and verify food safety standards and quality is evidenced by the ever growing list of food product recalls due to contamination with, for example, *Salmonella*, *Escherichia coli* and *Listeria*, and incidents such as melamine, antibiotic and dioxin contamination (Cifuentes, 2012). Food fraud (e.g. the replacement of beef with horse meat), the introduction of new technologies with potential food safety implications (e.g. nanotechnology) and environmental factors (e.g. climate change) further highlight the importance of the continued refinement, development and innovation in food control measures (Cifuentes, 2012; Song, Xu, Chen, Wei, & Xiong, 2014). Effective techniques are necessary to help assess and manage risks and to protect the consumer (Regal, Díaz-Bao, Barreiro, Cepeda, & Fente, 2012; Song et al., 2014). Acceptable levels of quality and safety must be achieved without compromising the fundamental sensory qualities which add value to the product. Filtration technology has long been perceived as an effective method of extracting unwanted co-products such as dregs or sediment. These residues may contain strongly flavoured micro-flora or fauna that adversely affect product quality for example in terms of shelf life. However, if the aim is to make the food product more attractive, it is important that the process does not remove an excess of flavour or texture (Tragardh, 1991). Filtration techniques were originally considered as a purely physical process, but there is ongoing development of new applications based on the biochemical techniques (Tragardh, 1991). For commercial applications, the development of membranes with high selectivity and long service life is clearly important. So, the incorporation of a given target or analyte molecule into the membrane is critical to the practical expression of permselectivity. Molecular imprinting technologies (MITs) are potential techniques to introduce molecular recognition sites for given target molecules (Yoshikawa, Tanioka, & Matsumoto, 2011).

It is now possible to design and synthesize materials possessing specific binding or catalytic behaviour and hence produce polymers exhibiting molecular recognition or template polymerization properties (Alexander et al., 2006). Molecular recognition is a fundamental process in the natural world for the rapid recognition of antibodies, enzymes and nucleic acids (Alexander et al., 2006; Kondo, Yoshikawa, & Okushita, 2000; Park, Yoon, Bang, Rogers, & Chough, 2005). Molecular imprinting technologies, as processes for the preparation of synthetic polymers with binding sites for specific molecules, are the next development phase in the practical application of molecular recognition.

The main purpose of molecularly imprinted polymer (MIP) synthesis is to achieve high selectivity from the imprinted material. Molecular imprinting may be conveniently classified into two categories: covalent molecular imprinting and non-covalent molecular imprinting (Locatelli, Gamez, & Lemaire, 1997; Park et al., 2005). One of the main drawbacks of covalent molecular imprinting is that removing of template after polymerization is difficult (Yoshikawa, Ooi, & Izumi, 1999). This is because highly cross-linked polymers have an intrinsic resistance to being dissolved. Non-covalent imprinting (hydrogen bonding, electrostatic interaction, and coordination–bond-formation) does not have this problem and is hence much easier to achieve. This method is applicable to a wider range of templates than the covalent one (Dauwe & Sellergren, 1996; Sellergren, 1989; Sellergren & Shea, 1993).

For a given MIP material, the binding capacity, reaction kinetics and site accessibility are significantly affected by the physical format of presentation (Ye, 2013). Current best practice is to prepare molecularly imprinted polymers (MIPs) as porous monoliths: these are mechanically ground to form irregular particles with a wide size distribution, say from 5 to 100 μm (Ye, 2013). Recently research has been directed toward reducing the size of MIP substrates to sub-micron and even nanometre diameters (Acton, 2013; Cai et al., 2010). Reducing the particle size of these molecularly imprinted microspheres and nanoparticles gives demonstrably faster binding kinetics and higher binding capacities. Limiting the physical size of MIP beads means that specific binding sites can be specifically positioned close to copolymerized receptor molecules. This gives the advantage that the occurrence of molecular binding can be directly monitored by measuring changes in the optical properties of the beads (Ye, 2013). In addition, higher affinity, increased sensitivity to target analytes and higher binding capacity, are observed simply because there are more recognition sites available on the reaction surface (Acton, 2013; Ye, 2013). This ready accessibility of binding sites to the target molecules coupled with the homogenous distribution of recognition sites leads to an increase in the rate of binding (Umpleby Ii, Bode, & Shimizu, 2000). So, it is appropriate to review the current state of the art in developing highly sensitive and selective artificial receptors based on constructing molecular recognition sites on micro- and nano-scale electrospun membranes.

2. Molecular imprinting technologies (MITs)

Conventionally, the production of molecularly imprinted polymers involves introducing binding sites where highly cross-linked copolymers are formed around analyte molecules that act as cavity-creating templates. Subsequent removal of the template molecule provides recognition sites in the polymer that ideally resemble the template in terms of shape, size and functionality. Rebinding of the target molecule within these pre-formed sites can occur when the polymer is incubated in the presence of the template molecule (Nicholls & Rosengren, 2001; Whitcombe & Vulfson, 2001). Interaction between the dissolved target molecule and the functional monomer localizes the chemically active moieties of the target molecules during copolymerization obtained by covalent, non-covalent, or metal coordination. Consequently, molecular imprinting according to the type of interaction between the template–crosslink–functional monomer building blocks may be classified into covalent imprinting and non-covalent imprinting (Fig. 1) (Moreno-Bondi, Navarro-Villoslada, Benito-Pena, & Urraca, 2008).

To form molecular recognition sites in polymeric materials, the template, and functional monomer and cross-linker are mixed in a solvent. During this step, the template and monomer complex is polymerized with an excess of cross-linker to form covalent or non-covalent bonds (hydrogen bonding, ionic interactions, π–π interactions, or van der Waals forces) with the template in solution. The template is then removed, usually by methods based on solvation, to generate molecular recognition sites retaining the spatial arrangement of the target molecule and the alignment of the functional moieties optimally set for recognition to occur (Moreno-Bondi et al., 2008; Zhang, Ye, & Mosbach, 2006).

Removal of the template leaves a cavity, matching the physical and chemical characteristics of the template species. Any variation from the structure of the desired species to a structurally similar but non-identical entity may result in loss of selectivity (Lorenzo, Carro, Alvarez-Lorenzo, & Concheiro, 2011). It is not always possible to imprint using the desired template due to factors such as high material cost or scarcity of the template, which may mean that a structural analogue of the target analyte must be substituted as the template during the imprinting process — a so-called "dummy template" (Tabassi, Hashemi, & Mohajeri, 2013). Dummy templates are also used if the target species demonstrates sensitivity to the condition of polymerization (Tabassi et al., 2013).

There are three main approaches available for template removal: extraction with common solvents, physically-assisted solvent extraction, and extraction with sub-critical or supercritical fluids (Lorenzo et al., 2011). Each extraction technique has its own merits and the choice of a particular method is not simple because the nature and the stability of both the template and the MIP must be considered. The aim is to specify a process that is simple, quick, environmentally friendly, uses a minimum amount of solvent, and has consequent low economic cost and general suitability for use at the industrial scale (Kronholm, Hartonen, & Riekkola, 2007).

An advantage of covalent imprinting is the ability to clearly define the template–functional monomer complex, thus obtaining