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Molecularly imprinted polymers in clinical diagnostics—Future potential and existing problems

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Abstract

The last five years have witnessed a fast progress in the area of molecularly imprinted polymers (MIPs). These have included the development of rational protocols for polymer design (combinatorial and computational), the development of MIPs compatible for use in aqueous environment and the development of various procedures for the integration of MIPs with sensors. The substantial improvements in the performance of imprinted polymers have also been accompanied by a growing number of MIP publications related to solving practical problems associated with their use, e.g. in environmental and clinical analysis. This paper furnishes a detailed analysis of recent achievements in MIPs design and applications related to healthcare, made by our group as well as others worldwide.

Keywords: Molecularly imprinted polymers; Diagnostics; Clinical analysis; Sensors

1. Introduction

Modern healthcare relies extensively on a range of chemical and biochemical analytical tests on tissue samples and a variety of body fluids to enable early recognition, diagnosis and management of disease. The market for *in vitro* diagnostics, which includes laboratory equipment, instruments, sample containers, reagents and self-test kits, was approximately $23 billion in 2002 [1].

Major sectors within this market include:

- Clinical chemistry, which includes blood gas testing, urine analysis and other chemistry related products.
- Immunoassays, for example, for therapeutic drug monitoring, drugs of abuse screening, pregnancy and ovulation detection and the testing for and diagnosis of infectious diseases and allergies.
- Haematology/coagulation.
- Diabetes testing.
- Emerging DNA and molecular testing.

Clinical laboratories (hospital and commercial) are by far the largest end users of *in vitro* diagnostics and account for about 76% of the market revenue. Patient self-testing, predominately related to blood glucose measurement systems and strips for diabetes patients, accounts for about 16% of sales.

Medical and technological advances have considerably expanded our diagnostic abilities over the past few decades. In the near future, the human genome project, our increasing understanding of the molecular interactions in the human body, and the emergence of novel technologies, such as microsystems and nanotechnology, will revolutionise diagnostic technology. Experts believe that *in vitro* diagnostics will experience a dramatic boom over the next years, growing to about $37 billion in 2010. This rapid growth will be brought about by molecular diagnostic advances, for example in the fields of infectious diseases, oncology and cardiovascular diseases, and an increasing trend towards decentralised and miniaturised diagnostic procedures.

There will be also a proliferation of point-of-care (PoC) testing in order to address situations, where speed of response is a prime consideration and where therapeutic decisions are

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required quickly. This will facilitate the dialogue between doctor and patient [2].

Despite the recent advances in PoC testing, several compelling needs remain un-addressed. They include increased speed and frequency of test procedures and the simultaneous monitoring of an ever-growing range of analytes. Other functionalities required for success in this market relate to ease of sample preparation and of result interpretation. Increased speed and frequency of diagnostic testing will greatly improve the chances of successfully detecting and analysing the patient's condition and, thus, accelerate decisions on effective, and potentially life-saving, treatment. Moreover, regular monitoring with a measurement frequency that matches the needs of the patient and the characteristics and nature of the treatment will enable more effective monitoring and guidance of therapy as well as ensure compliance with therapy, therefore helping to provide optimal treatment at all times.

Many of the current and future diagnostic tests rely almost exclusively on the use of sophisticated biological receptors, such as enzymes, antibodies and DNA, as chemical or biochemical recognition elements. Due to their biological derivation, these biomolecules may suffer from limitations when used in diagnostic applications, for example, poor reproducibility, instability during manufacture and problems associated with the sterilisation process.

A promising route to overcome these issues is offered by molecularly imprinted polymers. Molecular imprinting is a generic and cost-effective technique for preparing synthetic receptors, which combine high affinity and specificity with robustness and low manufacturing costs. MIP receptor materials have already been demonstrated for a wide range of clinically relevant compounds and diagnostic markers. The goal of this review is to analyse the current progress in MIP area specifically in relations with healthcare, and to highlight the future potential of MIPs for use in clinical diagnostics applications and in a new generation of diagnostic devices. This paper is a continuation of a review on electrochemical sensors [3].

2. MIPs—basic principles and recent progress

Molecular imprinting can be defined as the process of template-induced formation of specific recognition sites (binding or catalytic) in a material, where the template directs the positioning and orientation of the material's structural components by a self-assembling mechanism (Fig. 1). The material itself could be oligomeric (a typical example is the DNA replication process), polymeric (organic MIPs and inorganic imprinted silica gels) or two-dimensional surface assemblies (grafted monolayers). MIPs have a range of advantages when compared with natural biomolecules (Table 1).

Three particular features have made MIPs the target of intense investigation:

- Their high affinity and selectivity, which are similar to those of natural receptors [4].
- Their unique stability, which is superior to that of natural biomolecules.
- The simplicity of their preparation and the ease of adaptation to different practical applications.

A wide range of chemical compounds have been imprinted successfully, ranging from small molecules, such as drugs, to large proteins and cells. The best results have been obtained for molecules with molecular weights in the range of 200–1200 Da. The resulting polymers are robust, inexpensive and, in many cases, possess affinity and specificity that is suitable for industrial applications. The high specificity and stability of MIPs render them promising alternatives to enzymes, antibodies, and natural receptors for use in sensor technology.

However, there are limitations associated with the development of MIP assays and sensors, in particular:

(i) absence of a general procedure for MIP preparation;
(ii) difficulties in integrating them with transducers;
(iii) difficulties in transforming the binding event into an electric signal;

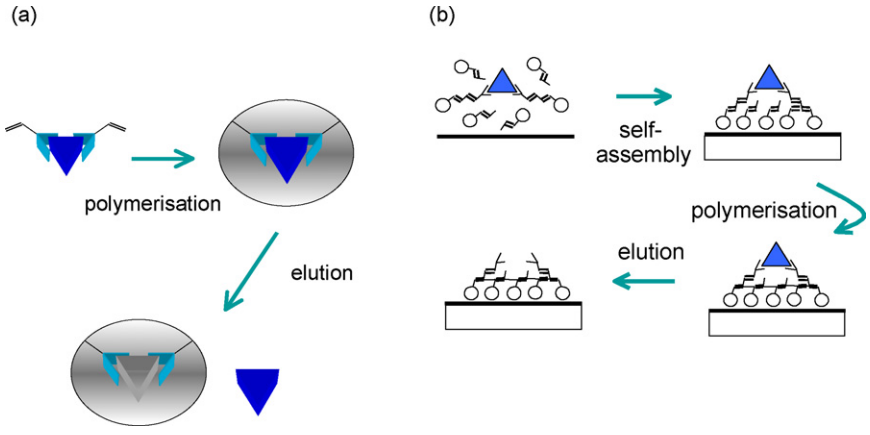

Fig. 1. Scheme of: (a) three-dimensional and (b) two-dimensional imprinting polymerisation (courtesy of VTT, Finland).