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Review

# Magnetic separation techniques in sample preparation for biological analysis: A review

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ABSTRACT

Sample preparation is a fundamental and essential step in almost all the analytical procedures, especially for the analysis of complex samples like biological and environmental samples. In past decades, with advantages of superparamagnetic property, good biocompatibility and high binding capacity, functionalized magnetic materials have been widely applied in various processes of sample preparation for biological analysis. In this paper, the recent advancements of magnetic separation techniques based on magnetic materials in the field of sample preparation for biological analysis were reviewed. The strategy of magnetic separation techniques was summarized. The synthesis, stabilization and bio-functionalization of magnetic nanoparticles were reviewed in detail. Characterization of magnetic materials was also summarized. Moreover, the applications of magnetic separation techniques for the enrichment of protein, nucleic acid, cell, bioactive compound and immobilization of enzyme were described. Finally, the existed problems and possible trends of magnetic separation techniques for biological analysis in the future were proposed.



**Contents**



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## 1. Introduction

With the great development of analytical instruments, interesting analytes can be directly detected [1]. However, it still remains a great challenge for the detection and quantification of those analytes with low-abundance due to the restriction of instrumental detection limit and interferences of complicated matrix [2]. Thus, it is essential to introduce suitable sample preparation techniques prior to an analytical process in order to improve the detection limit. Sample preparation techniques generally involve isolation of analytes from sample matrix, removal of interfering species and enrichment of analytes [3].

Biological samples are particularly complicated samples with matrix interference. Therefore, prior to the analysis of trace biological targets, it is imperative for the isolation, separation and purification of raw samples [4,5]. Commonly used sample preparation techniques for biological analysis include various extraction techniques [2,6], electrophoresis [7–9], ultrafiltration [10,11], precipitation [12,13], etc. Although electrophoresis is low cost and simple to manipulate, it usually takes relatively long time and has poor repeatability [14]. Ultrafiltration has high separation efficiency, but it fails to obtain dry powder of target analytes and the membrane of ultrafiltration may exhibit adsorption toward biological macromolecules [10]. Precipitation is easy to operate, however, it may lead to the inactivation of biological macromolecules. Among these techniques, solid-phase extraction (SPE) is one of the most important and powerful techniques because of its outstanding selectivity and recovery [15]. Although traditional SPE techniques where the adsorbents are packed into columns have been applied in many successful cases, but it is not suitable for coping with samples containing suspended solid or fouling components [16]. Batch separation technique, during which the adsorbents are incubated directly with the samples, can solve the above problems. Many new materials such as nano-materials and mesoporous materials have been employed in this mode [17,18]. However, when using these materials as affinity adsorbents for the enrichment of biological target analytes, nonreversible adsorption and high-speed centrifugation are often unavoidable, which may result in sample loss and co-precipitation of unwanted interferents despite of their ability to remove salts and other contaminants [19]. Consequently, the application of these advanced materials as adsorbents is restricted to a great extent. Therefore, a rapid, convenient, gentle and efficient sample preparation is urgently needed for biological analysis. In this case, with the use of magnetic materials, magnetic separation techniques have shown their usefulness.

Magnetic separation technique is a batch-scale technique based on functionalized magnetic materials [16,20]. Magnetic materials are adsorbents particularly suitable for biological macromolecules due to their large surface area, good biocompatibility, easy functionalization and convenient manipulation. In a typical process of magnetic separation, magnetic materials, which exhibit affinity toward the isolated structure, are mixed with a sample containing target compounds. Within a period of incubation, target compounds bind to the magnetic particles. The whole magnetic complex is subsequently separated from the sample using an extra magnetic field. After washing out the contaminants, the isolated target compounds can be eluted and used for further work [20,21].

Magnetic separation techniques have several advantages in comparison with standard separation techniques used in various areas of biosciences [22]. Magnetic separation is usually gentle and nondestructive to biological analytes such as proteins or peptides, and even large protein complexes which tend to be broken up in process of traditional column chromatography may remain active. Besides, magnetic separation can be easily and directly used for raw biological samples with several simple steps. Target analytes captured to magnetic materials can be easily and selectively removed from the sample [23]. What is more, the magnetic separation procedures are powerful and efficient, especially for large scale operations. In all, magnetic separation technique is able to facilitate or accelerate many separation and purification procedures and efficiently combine with the majority of other procedures used in biological analysis [24].

The properties of magnetic materials were identified as early as the sixth century BC, but magnetic materials were not applied for separation until 1792 when a patent was filed by William Fullarton describing the separation of iron minerals with a magnet [25]. And even since 1970s, with the application for separation and analysis of various biologically active compounds and cells using magnetic materials, magnetic separation has become a common approach for sample preparation. Since that, an increasing number of researches have been explored focusing on magnetic separation and analysis of biological samples using magnetic materials. Fig. 1 shows the statistics of published articles on magnetic separation of protein/peptide, nucleic acid, cell, bioactive compound and immobilization of enzyme from 2003 to 2013.