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EDITORIAL

ABC Spotlight on magnetic composite nanoparticles in analysis: increased sensitivity at decreased analysis time

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Analytical chemistry continuously pushes toward decreasing detection limits to meet the requirements in such diverse fields as, e.g., diagnostics, environmental analysis, and process control. This leads to fundamental consequences both for instrumental, laboratory-based analytics, and sensors/assays:

- Virtually, any protocol in instrumental analysis requires sample preparation for multiple purposes: These include pre-concentrating target species, separating them from their matrix, and transferring them into solvent systems that are compatible with further analysis steps.
- Sensors and arrays face a slightly different challenge: Even if they are inherently highly sensitive, one has to make sure that sufficient numbers of target molecules meet the sensitive area within a realistic time frame.

Solid phase (micro) extraction SP(M)E has successfully tackled these issues and fundamentally improved the analytical process. Nonetheless, rapid progress in synthesizing tailor-made nanoparticles has opened up unprecedented opportunities for improving it. Among these, functionalized magnetic nanoparticles (MNP) have attracted special interest and made way for a range of novel application scenarios. This has been driven by their ferromagnetism, which allows for separating them from sample solutions by applying external magnetic fields. The beauty of the approach lies in the fact that magnetic fields usually do not affect any species present in the sample and thus are also compatible with biological matrices.

Such advantages seem less obvious when utilizing modified nanoparticles to pre-concentrate samples prior to separation and analysis. Nonetheless, the last 2 years saw several approaches published in *Analytical and Bioanalytical Chemistry*, such as a system for pre-concentrating endocrine-disrupting compounds from water [1], or estrogenic compounds from milk [2], extracting Bisphenol A from human serum [3], or a MNP-based method for determining di(2-ethylhexyl)phthalate in aqueous solutions [4]. Figure 1 shows the general approach: First, suitably functionalized Fe_3O_4 (magnetite) nanoparticles are added to samples. After stirring/agitating, those particles are collected by an external magnet followed by washing steps and re-solubilization of the respective analyte(s) prior to analysis. Compared to "classical" SPME that uses (functionalized) cartridges, MNPs allow for much faster analysis: Distributing them in the sample matrix and agitating them there substantially increases the probability that a particle meets its target analyte. The idea therefore is bringing the analytical "device"—the nanoparticle extraction medium—to the sample analyte, rather than the other way round: Whereas two of the papers exposed the samples (around 100 ml) to the particles for a few hours [3, 4], the other two report incubation times of 0.5–2 min for sample sizes of 1.5 and 20 ml, respectively.

These examples also highlight the use of a variety of functionalization strategies to achieve selectivity, namely modification with sodium oleate [1], coating with polydopamine [2], with molecularly imprinted polymers (MIP) [4], and aptamers [3], respectively. They cover the entire range from broad-band affinity to high selectivity during extraction. Among selective functionalization methods, molecular imprinting has attracted considerable attention (see for instance [4–6]), because it allows for generically designing polymer matrices with tailor-made selectivity. Kong et al. [7] even succeeded in generating a multi-selective matrix: Instead of utilizing their target analyte for imprinting—which would be the "standard" way of doing MIP—2,4-diamino-6-methyl-1,3,5-triazine served as a so-called pseudo-template. This allowed them to synthesize multi-selective particles for enriching melamine (MEL), cyromazine (CYR), triamterene (TAT), diaveridine (DVD), and trimethoprim (TME) with the same particles to analyze them by HPLC-MS.

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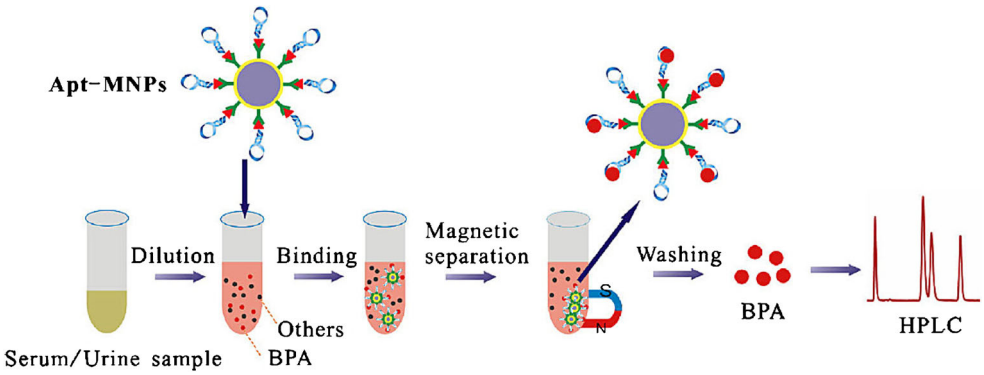

Fig. 1 General approach for utilizing MNPs in sample preparation [3]. Reprinted with permission, © Springer Nature, 2018

As previously mentioned, MNPs have also played an important role in developing sensors and assays. In these cases, MNPs are usually fully integrated into the sensing protocols. For instance, Che et al. [8] published an assay utilizing MNPs for magnetically enriching pathogenic bacteria prior to fluorescence analysis. They modified SiO_2@Fe_3O_4 MNPs with aminopropyl triethoxysilane (APTES), a well-established strategy to functionalize particle surfaces with $–NH_2$ groups. The resulting particles were 90–105 nm in diameter and inherently affine to the outer shell of, e.g., *E.coli*. Due to the difference in sizes between MNPs and bacteria, several MNPs bound to each bacterium, which made it possible to separate them from unreacted particles by PEG-based magnetophoretic chromatography followed by labelling with a fluorescence marker and analysis. This lead to detection limits of 100 cfu, which is close to current LoDs obtained by PCR-based DNA analysis.

Of course, selectivity of MNPs can be substantially increased: Lai et al. [9] reported a nanoparticle-based sandwich immunoassay for detecting a cytokine (TNFα) in biological samples. They report antibody-coated MNPs to capture the target analyte and incubate the solution with SERS-active gold NPs functionalized with the secondary antibody. Figure 2 clearly shows that TNFα links the two types of nanoparticles to each other, which strongly increases SERS signals. In a similar way, Ding et al. [10] combined antibody-coated MNPs with antibody-coated ZnS nanocrystals and achieved a LoD for human IgG of LoD = 0.5 fmol/L. In both cases, the role of the particles is to locally increase concentration of the target analyte on their respective surfaces to increase the respective analytical signal. This is of course of special interest for developing assay formats to detect biomarkers: Those are usually present at very low concentrations in the body. Some recent examples include pro-inflammatory cytokines [11] or a specific tumor marker [12], both of which were accessible in their physiological concentrations.

In a sensor setting, using MNPs makes most sense when combining them with highly sensitive detection. Aside from electrochemical techniques, fluorescence obviously plays an important role there, usually in sandwich immunoassay formats. A very recent paper on the detection of alpha-fetoprotein [13] beautifully exemplifies the benefits of the approach: Again, MNPs are coated with a capture antibody and fluorescent nanoparticles (Rhodamine 6G@SiO_2) with a secondary antibody. The main advantage of this approach is to mix the MNPs with the sample followed by shaking/stirring and magnetic separation. This leads to lower detection limits and wider linear range than ELISA: The latter requires reactions on the substrate surface, rather than in the

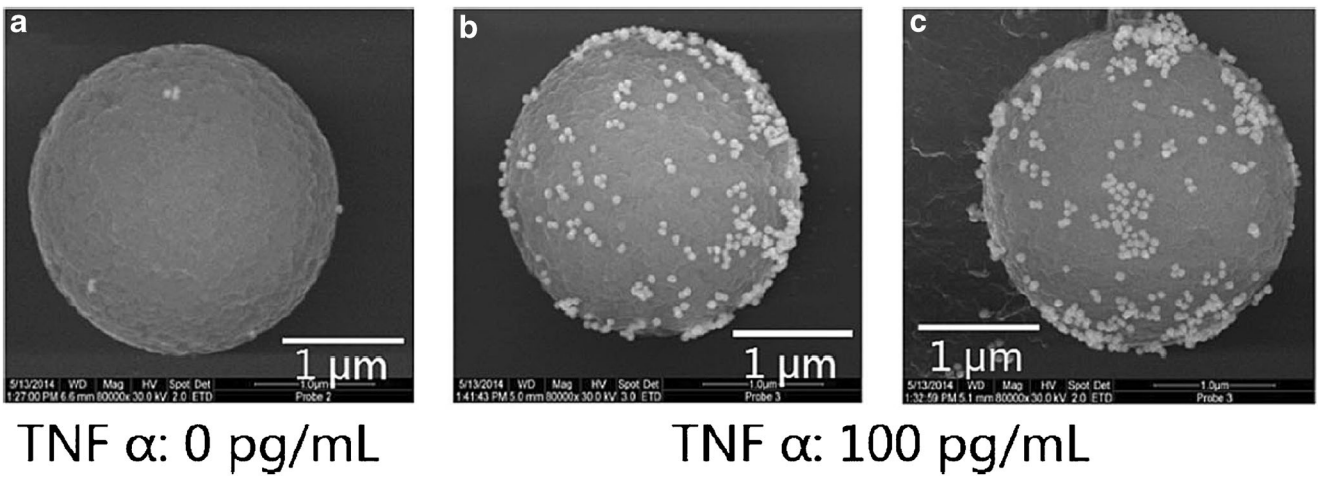

Fig. 2 Linking of MNP and SERS-active indicator nanoparticles depending on the concentration of TNFα [9]. Reprinted with permission, © Springer Nature, 2018

bulk volume of the sample. For the same reason, the MNP assay reduces analysis time to one-third of that required by ELISA. All these approaches pre-concentrate the target analyte by the means of MNPs. However, there are also reports for removing the matrix [14]: There, authors succeeded in detecting folic acid in food samples by removing most of the unwanted background by C6-modified MNPs and thus replacing a stationary SPME cartridge.

Overall, MNPs hence are a powerful tool to improve sample preparation and assay strategies, because they help analysts to "bring receptors to the samples" rather than the other way round. This either means that larger sample volumes can be extracted in shorter time, than through cartridges, or that sensing processes can make use of the entire sample volume rather than only the sensor surface. This also means that they are highly useful tools in overcoming a fundamental problem in sensing at low concentration: MNPs make it possible that there is realistic chance of a target analyte meeting a nanoparticle in the agitated sample within a reasonable amount of time. In that sense, ABC will continue to cover this important aspect of analysis and sample preparation.

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