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REVIEW PAPER

Silica -magnetic inorganic hybrid nanomaterials as versatile sensing platform

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ABSTRACT

Several hybrid sensing materials, which are organized by interaction of organic molecules onto inorganic supports, have been developed as a novel and hopeful class of hybrid sensing probes. The hybrid silica-magnetic based sensors provide perfect properties for production of various devices in sensing technology. The hybridization of silica and magnetic NPs as biocompatible, biodegradable and superparamagnetic structures provides the opportunity to produce capable sensing materials. The fluorescence, electrochemical and calorimetric sensors based on silica-magnetic materials can be applied in quantitative detection of various analytes. This review touches upon a subject of the design and synthesis of different sensors based on magnetic-silica hybrid nanomaterials and discusses their applications for improved detection of analytes in environmental and biological fields.

Keywords: *Hybrid, Magnetic, Nanomaterial, Silica, Sensor*

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INTRODUCTION

Fe_3O_4 nanoparticles with biodegradable, biocompatible, high saturation, superparamagnetic features that are non –cytotoxic to humans and other animals [1, 2] have attracted great attention in various applications in magnetic separation, sensing environmental contamination and biomedicine [3-5]. Fe_3O_4 MNPs can move following applying an external magnetic field which then it could be applied to purify proteins, nucleic acids, metabolites, and even intact cells [6, 7]. However, superparamagnetic iron oxide nanoparticles are instable in physiological conditions and represent several disadvantages comprising easily oxidized in air, fast biodegradation and loss of magnetism properties [8]. In addition, Fe_3O_4 MNPs are prone to aggregation because of their chemical activity. To overcome these obstacles, the surface of the Fe_3O_4 nanoparticles must be modified with inorganic layers or polymers. Silica is one of the best materials for Fe_3O_4 functionalization with a wide range of applications. Silica with several suitable characteristics such as quick uptake and release of loading molecules, mechanical and chemical stability and approachability for surface modification is appropriate inorganic material [9]. In addition, the surface of mesoporous silica could be used for high concentrations of affinity immobilization (such as aptamer) to adsorb target molecules and has large volumes

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and pore sizes which could be modified with functional molecules [10]. Silica coating is an appropriate modification because it stabilizes the magnetite NPs, prevent aggregation and forms interlayer for functionalization. Immunomagnetic nanostructures should have a rational design to facilitate the capture efficiency and binding capacity [7].

Magnetic silica hybrid rather than other hybrid materials such as polymer, titania, and self-assembled monolayers [11-14] shows low toxicity, simple separation *via* external magnetic field, stability, biocompatibility and thermally stable advantages [15-17]. Moreover, this hybrid material has been applied for isolation and magnetic resonance imaging (MRI) by its instant aggregation in the presence of external magnetic field [18]. The magnetic properties of MNPs could be defected when encountering complex biological systems. Biosensors were used for the detection of biological substances through thermal, electrical or optical signals. Some examples of various applications of biosensors can be mentioned as forensic science [19-21], environmental monitoring [22], defense and the military [23], water characteristic testing [24], biomedicine, food industry and medical diagnosis [25]. Two parts of biosensor devices include transducer and bioreceptor [26]. In this review, magnetic silica hybrids as fluorescent, colorimetric, electrochemical and SERS sensors have been listed.

Fluorescence sensor

Magnetic silica core-shell $Fe_3O_4@SiO_2$ nanoparticles (NPs) have crucial role in separation and sensing technology, because of large surface area for binding with small molecule fluorescent probes, their low toxicity, simple separation *via* external magnetic field and high biocompatibility. Magnetic nanoparticle attached to a fluorescence probe have the tendency to capture target cells and to provide sensitive detection [27]. In fluorescence approaches, suitable indicators (sensitive to analyte concentrations) are applied as molecular recognition materials [28]. For this approach, Fluorescence labeling is time consuming method. In addition, chemical modification is accomplished by multiple handling procedures.

In a study, Jiang and coworkers designed Off-On-Off type fluorescence screening nanoparticles for quantitative detection of Cu^{2+} and S^{2-}. In this study, magnetic core-shell $Fe_3O_4@SiO_2$ which was coated with naphthalimide derivative platform (NPE) was applied as two-photon fluorescent probe. In the presence of Cu^{2+}, the probe reacted with Cu^{2+} selectively and thus fluorescence increased. Eventually, copper ions were efficiently separated with external magnetic field. The production NPE-$Fe_3O_4@SiO_2$-Cu acted as sensor for removing S^{2-}, so the fluorescence of the probe was recovered and decreased. The quantitative detection limit of this probe for S^{2-} and Cu^{2+} in living cells was 0.12 and 0.28 μM μM, respectively[29].

Breast cancer with a high mortality rate and asymptomatic lesion feature is one of the most life-threatening diseases in women [30]. Thus, early diagnosis of this cancer in the initial stage is pivotal for improving patient survival rate. Circulating tumor cells (CTCs) are the most essential factor for detection of the of tumor metastasis progression. Therefore, identification and detection of CTCs released in peripheral blood could decrease mortality rate of breast cancer in early stage [31]. Due to the difficult detection of low CTC concentration, unique overexpressed biomarkers such as mucin1 protein (MUC1) and folate receptor (FR) on the surface of CTC provide more perfect cancer-cell recognition opportunity [29, 32]. Wang and coworkers designed a novel dual-target detection sandwich system based on core-shell magnetic mesoporous silica (Fe_3O_4@ $nSiO_2$@$mSiO_2$@Apt) nanoparticles and FR-targeted fluorescent probes to receive circulating MCF-7 cells as target. In order to achieve this goal, they applied anti-MUC1 aptamer, attached on the exterior of $Fe_3O_4@nSiO_2@mSiO_2$ and a folate receptor (FR)-targeted fluorescent probe (FA-BSA-FITC), coated on the surface of BSA for isolation and identification of circulating target MCF-7 cells in human plasma and whole blood with high improvement. $Fe_3O_4@nSiO_2@mSiO_2$@anti-MUC1-Apt interacted with MUC1 marker which was -highly expressed on the surface of the breast cancer cells. In addition, FR-targeted fluorescent probe coated on the surface of BSA binds to FR over-expressed on MCF-7 cell surface. This sandwich fluorescent system enhanced the target breast cancer cells selectively with detection limit of 100 cells/ml [33].

Bacteria play an important role in the development of foodborne diseases [34]. Thus, for providing a safe food supply, rapid detection and isolation approaches are essential for prevention of bacterial growth [35].

Table 1. Electrochemiluminescence (ECL) sensor based on silica-magnetic NPs

Detection method	Nanoparticle	Detection samples	LOD (CFU/mL)	Ref.
Fluorescent aptamer-based sensor	M-MSNs-EpCAM	CTCs	-	[39]
Fluorescence sensor	M-MSNs –Ab1 and SiO_2-Ab2	CEA antigen	10 µL	[40]
Fluorescence sensor	Rho-MCM@Core RSho-MCM@Core	Nitrite ion	0.4 µM	[41]
Fluorescent aptamer-based sensor	FITC@Fe_3O_4@SiNPs-SA	Human breast carcinoma MCF-7 cells	-	[42]
Fluorescence sensor	Fe_3O_4@SiO_2@UiO-67	Glyphosate	0.093 mg L^{-1}	[43]
Fluorescence sensor	Fe_3O_4@SiO_2-NH_2-fluorescein	Ni^{+2}	0.83 nM	[44]

Chang et al. applied Janus fluorescent-magnetic mesoporous silica nanoparticles (Janus M-MSNs) conjugated to antibody for the identification of foodborne bacterial from milk sample. Janus M-MSNs were comprised of Fe_3O_4 heads with a strong paramagnetic property for bacterial separation while mesoporous SiO_2 bodies with mesoporous features were coated with antibodies specific for *Escherichia coli* targeting and recognition. The Janus M-MSNs-Ab with strong fluorescence and fast magnetic reaction with the magnetic heads together with bacterial-targeting features of the silica-antibodies could be applied for selective isolation and fluorescence identification of *E. coli* in milk samples. Eventually, *Escherichia coli* identified through MALDI-TOFMS analysis [36].

In the work of Zhao et al., a highly sensitive and specific immunosensor prepared using hemoglobin core-shell nanoparticle as label for detection of PSA. Then the CdTe@SiO_2 nanoparticles decorated with PSA detection antibody (Ab2) to form CdTe@SiO_2-Ab2. On the other hand, PSA capture antibody (Ab1) covered magnetic Fe_3O_4 nanoparticles (Fe_3O_4-Ab1) were used to grab and enrich PSA antigen. The captured PSA antigen was then detected by CdTe@SiO_2-Ab2 by forming the sandwich complex. Finally, the easy magnetic separation of the sandwich complex is provided due to magnetic Fe_3O_4 nanoparticles.. A linear concentration range and detection limit for PSA were 0.01 ng/mL to 5 ng/mL and 0.003 ng/mL respectively. When the sensor used with human serum samples, the results proved a good restoration in the range of 95.6%-104.2%, demonstrating an acceptable reliability. Furthermore, CdTe@SiO_2 nanoparticles have greater fluorescence quantum yield compared to pure CdTe QDs since the SiO_2 as a passive layer could suppress the decline of the optical properties, which usually occurred in pure QDs due to photo-oxidation and surface defects [37].

Salmonella enterica is a common cause of inflammation of digestive disease in human through contaminated poultry, eggs, milk, and meat products [9]. In another study, the fluorescent sensor based on aptamer affinity was designed for *Salmonella* separation. This sensor

included two parts, the oligonucleotide sequence with specific affinity for catching *S. enterica* immobilized on Fe_3O_4@SiO_2@pGMA and MCM-41 which was loaded with fluorescein solution and capped with *Salmonella* specific aptamer through glutaraldehyde linkages. In the presence of *S. enterica*, aptamer-target interaction based on affinity binding occurred leading to the release of fluorescein cargo. Thus, fluorescent signal increased. The detection limit of the sensor for *S. enterica* determination was 2336 cells [38]. Other fluorescein sensors were summarized in Table 1.

Surface-enhanced raman spectroscopy (SERS) sensor

Metal nanoshells with important advantages such as auto-fluorescence and a deeper tissue penetration capability, can be excited by a near infrared (NIR) light source [45, 46]. Raman reporter molecules located in the nano-gaps between the bumps on the surface as opposed to a smooth one produce much stronger signals [45]. Moreover, mSiO_2 with biocompatible and optically transparent properties allows light to easily penetrate and thus excite internal analyte molecules entrapped inside mesopores. Thus, combining of mSiO_2 and Fe_3O_4 produces strong SERS activity and the target analyte could be separated easily with an external magnet [47-49]. This approach has some limitations such as low sensitivity and bulky instrumentation.

Leptin and adiponectin belong to adipokine hormones family [50], can be considered as biomarkers which detection is of importance in fatness [51]. Wang and coworkers designed an effective SERS immunosensor for rapid diagnosis of adipokines. Structure of this immunosensor is based on a sandwich form consisted of Fe_3O_4@SiO_2@Ag triple core-shell (TCSMPs) magnetic MPs and 4-mercaptobenzoic acid (4MBA)-modified immune AgNPs. Fe_3O_4 core was used for magnetic responsivity of the system, SiO_2 shell increased the system stability and Ag assigned as producing high SERS activity for TCSMPs in the complex. When the thickness of AgNPs covered the Fe_3O_4@SiO_2 was 40 nm, intensity of normalized E-field was maximum. 4MBA-Ag complex showed excellent SERS activity. Actually, Ab1 and Ab2 are situated in Fe_3O_4@SiO_2@Ag and 4MBA-Ag parts, respectively. Thus, in the presence of target, sandwich structure was formed (Fig 1).

The detection limits of the aforementioned immunosensor for adiponectin and leptin in PBS solution were 25 and 20 pg mL^{-1}, respectively [52].

An exosome with the size of 30–100 nm is a group of extracellular vesicle derived from normal and tumor cells which has a crucial role in intercellular signaling and provides communication and substance transportation between cells. Usually, exosomes of tumor cells with specific biomarkers are more abundant than normal cells [53].

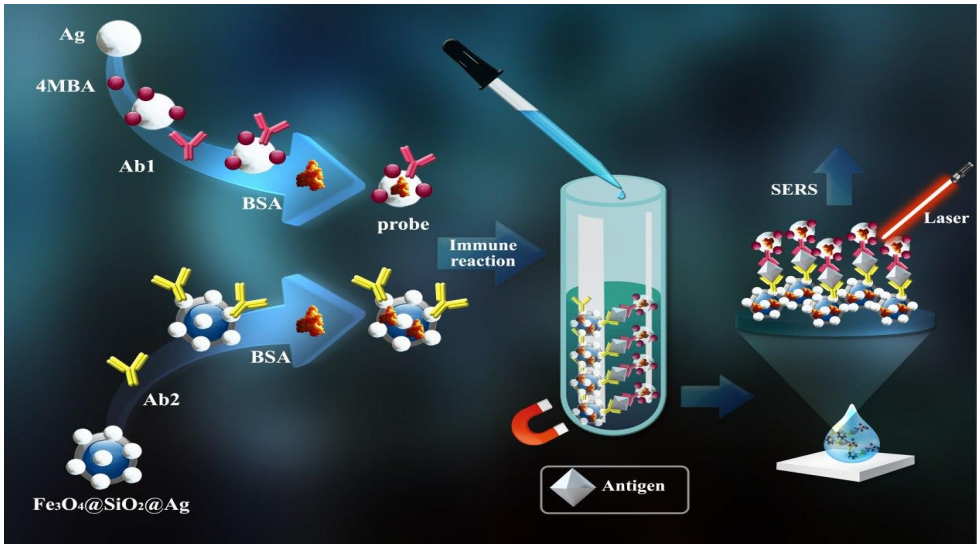

Fig 1. The sandwich structure sensor was consisted of Fe3O4@SiO2@Ag triple core-shell (TCSMPs) and 4MBA-coated AgNPs. Ab1 and Ab2 are located on the Fe3O4@SiO2@Ag and 4MBA-Ag parts, respectively. In the presence of adipokines, sandwich structure is formed. Reproduced with modification from [52]

Implementation of tumor-derived exosomes has a vital role for cancer detection in early stages [54].In this regard, Zong and coworkers applied a surface-enhanced Raman scattering (SERS)-based method for qualitative and quantitative detection of cancer exosomes. This detection method included SERS nanoprobes and magnetic nanobeads. SERS nanoprobes are consisted of active core (gold core–silver shell nanorods (Au@AgNRs), reporter (Raman molecules) and a silica layer. Beside, magnetic nanobeads are comprised of silica shell-coated Fe_3O_4 nanoparticles (NPs). Both of SERS nanoprobes and magnetic nanobeads were conjugated with two kinds of specific antibodies against different proteins on the surface of the exosomes. The SERS nanoprobes and the magnetic nanobeads decorated with anti HER2 and CD63 antibodies respectively could interact with CD63 and HER2 on the surface of the exosomes *via* immune reaction. Prior to sandwich-type immunocomplex formation, the immunocomplex could be separated by a magnetic field and SERS signals were produced immediately after complex deformation. The LOD of this immunocomplex method for the number of the exosomes was 1200 [55].

Electrochemical sensor

Inorganic mesoporous material is one of the best materials as molecular catalysts due to its thermal stability, easy production and modification. Thus, it used in the fields of biomedicine, physicochemistry, and electronics. Silica-coated Fe_3O_4 nanoparticle (Fe_3O_4@SiO_2 NPs), have good biocompatibility, separation ability, excellent conductivity, catalytic activity, low toxicity and electrochemical transducers properties to produce "electronic wires" to increase the electron transfer between electrode surfaces and redox centers in proteins [56].

The difficulties in large-scale production of this platform have limited its industrial application.

5-Hydroxymethylcytosines (5hmC) is one of the epigenetic changes involved in switching of genes to become on and off and thus is implicated in the development of variety of diseases [57].

Jiang and coworkers designed an ultrasensitive-sandwiched immunosensor based on electrochemiluminescence (ECL) sensor for 5hmC recognition in genomic DNA of tumor tissue. The two parts of this sensor were consisted of 1) anti-5hmC antibody immobilized on core–shell structure of Fe_3O_4@SiO_2 by amide linkage and 2) a signal amplification unit, which was conjugated to Ru-PAMAM-avidin.

In this system, perylene-3,4,9,10-tetracarboxylic acid/graphene oxide (PTCA/GO) which was assembled on bare glass carbon electrode provided specific surface area to hold plenty of Fe_3O_4@SiO_2-Ab. When anti-5hmC antibody and 5hmC interacts with each other, 5hmC binds to Phos-tag-biotin.

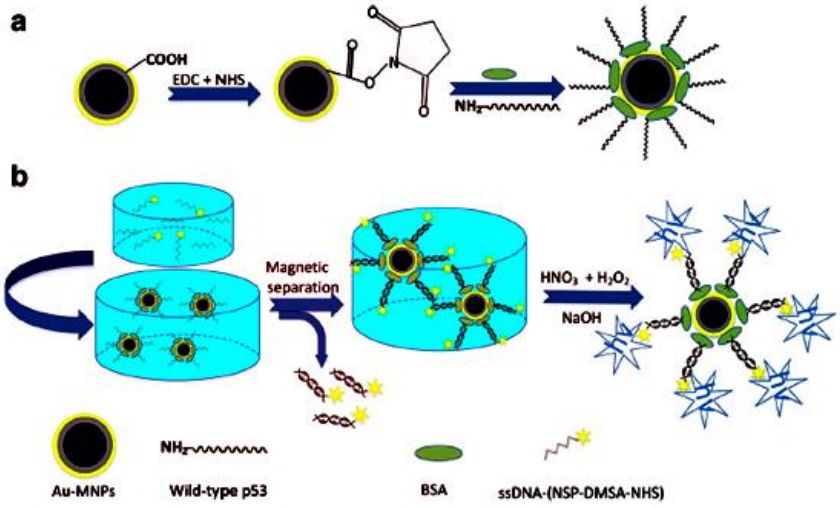

Fig 2. a) Fe3O4@SiO2@Au-functionalized magnetic nanoparticles (Au-MNPs) was prepared for measurement of the p53 gene. The wild-type p53 (wtp53) was attached on the surface of Au-MNPs (wtp53-Au-MNPs). b) NSP-DMAE-NHS as an efficient luminescence reagent was integrated with wtp53-Au-MNPs, Au-MNPs were isolated magnetically and a luminescent measurement system was measured. Adopted with permission from [62]

Thus the ECL signal was amplified through Ru-PAMAM-avidin interactions with of Fe_3O_4@SiO_2-Ab-5hmC-biotin. The detection limit of this ECL sensor was as low as 0.047 nM for 5hmC detection [58].

Epirubicin (EPI) derived from *Streptomyces bacterium* has been widely applied for treatment of cancers such as leukemia, lymphoma and various types of other cancers. Clinical application of EPI is limited. It should be noted that dose-related side effects might lead to cardiotoxicity and bone marrow suppression. In a study, electrochemically detective amplifiers, Fe_3O_4@SiO_2/DABCO was used as a unique label-free electrochemical aptasensor. The functionalized groups immobilized on the surface of Fe_3O_4@SiO_2/DABCO were used for AuNPs deposition which prevented AuNPs aggregation. Thiolated aptamer was attached to thiol groups of AuNPs. Interaction of EPI with the aptamer was determined with linear sweep voltammetry (LSV). In the presence of EPI, the conformation of aptamer was switched and folded. Thus, aptamer-epirubicin complex becomes closer to the electrode surface and the peak current of epirubicin was enhanced. The detection limit of this aptasensor was 0.04 µM [59].

Proline dehydrogenase (PRODH) plays an important role in cancer development. Studies showed that biological activity of the enzymes was improved, when the enzymes were immobilized on the appropriate solid supports [60]. Hasanzadeh and coworkers increased proline dehydrogenase activity by its immobilization on the magnetic mesoporous silica networks. The magnetic mesoporous silica nanomaterial with a high surface area enhanced catalytic activity of enzyme under the harsh environments, since solid support prevented the enzyme conformational changes.

The captured proline dehydrogenase was deposited on the polycysteine-altered glassy carbon electrode. Thus, these networks were applied for electro-oxidation and detection of L-proline in phosphate buffer solution. The detection limit of this electrochemical biosensor was 0.006 µM [61].

In another study, chemiluminescence DNA sensor which was consisted of Fe_3O_4@SiO_2@Au-functionalized magnetic nanoparticles (Au-MNPs) was applied as p53 gene detection The wild-type p53 (wtp53) was anchored on the surface of Au-MNPs (wtp53-Au-MNPs). NSP-DMAE-NHS acted as well regulated luminescence reagent was immobilized on the complementary sequence of the wtp53 to form ssDNA-NSP-DMAE-NHS conjugates. In the first step, the different standard samples with different concentrations of the wild-type p53 were prepared and mixed with the optimal concentration of ssDNA-NSP-DMAE-NHS conjugates. Then, the mixture reacted with wtp53-Au-MNPs conjugates to carry on the competitive reaction. Finally, Au-MNPs were separated magnetically and determined by a luminescent measurement system. The chemiluminescence intensities were linearly decreased by increase of wild-type p53 concentrations due to the competitive binding of the analyte to the ssDNA-NSP-DMAE-NHS conjugates. This approach represented high sensitivity with a detection limit of 0.001 ng mL^{-1} (0.16 pM) and a wide linear range from 0.001-100 ng mL^{-1}. Therefore, this technique is expected to extend to the early diagnosis of cancer and monitoring of patient therapy [62].

For the first time, Hemoglobin (Hb)-enzyme-like biosensor was developed for direct detection of 3-chloro-1, 2-propandiol (3-MCPD). Hb was imprinted on the surface of Fe_3O_4@SiO_2 NPs as magnetic molecularly imprinted polymers nanoparticles (MMIPs NPs). MMIPs NPs were anchored on the surface of a magnetic electrode to fabricate the Hb enzyme-like sensor for bioelectrocatalytic reduction of 3-MCPD. In fact, the coupling of the paramagnetic Fe_3O_4@SiO_2 with an external magnetic field had synergistic effect on catalytic activity of Hb owing to Hb paramagnetism. Furthermore, the electrostatic interaction between negatively charged SiO_2 and positively charged Hb also make Hb as an electroactive center. As a consequence, the electron transfer between Hb and the surface of the electrode is accelerated. The peak current decreased linearly with 3-MCPD concentration ranging from 1.0 mgL^{-1} to 160 mgL^{-1} with a detection limit of 0.25 mgL^{-1}. The biosensor applied successfully for detection in soy sauce samples with recoveries between 97.4% and 99.6% [63].

Colorimetric sensor

Colorimetric biosensors have been attracted much attention due to their simplicity and high selectivity [64]. SiO_2-Fe_3O_4 hybrid nanocomposites displayed cooperative demonstration for colorimetric recognition [65].

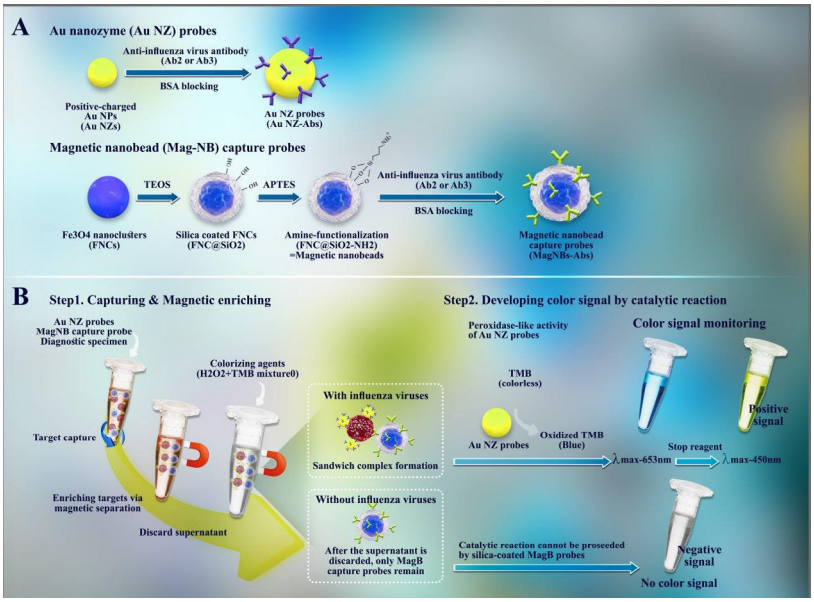

Fig 3. (A) Process for the provision of the MagLISA nanoprobes. (B) MagLISA-based colorimetric diagnostics kit was applied for the quantification of influenza viruses. Reproduced with modification from [67]

In the traditional colorimetric approaches, organic dye probes interacted with target analytes. However, low extinction coefficients of organic dyes limit their utilization.

Implementation of sensitive and rapid method for influenza virus detection is essential for reduction of infection incidence. In a study, by using a magnetic nanozyme-linked immunosorbent assay (MagLISA), one of the ultra-sensitive colorimetric method was applied for influenza virus detection [66]. MagLISA is consisted of three parts: 1) silica-shelled magnetic nanobeads (MagNBs) for separation of target virus, 2) gold nanozymes (AuNZs) for signal amplification by the peroxidase-like artificial activity, and 3) anti-hemagglutinin (HA) monoclonal antibody (mAb) for specific identification. The monoclonal antibody (mAb) immobilized on MagNBs acted as a capture probe by specific antigen-antibody interaction and polyclonal antibody (pAb) coated on positive charged AuNZ, through electrostatic interactions, formed a sandwich-like immunocomplex with MagNBs and facilitated the oxidation reaction of TMB by H_2O_2. This immunocomplex sensor could detect influenza virus with colorimetric signal generation by oxidation of TMB in one-step. The generation of colorimetric signals had direct relationship with the concentration of influenza virus (Fig 3). The limit of detection of this colorimetric sensor in human serum samples was 2.6 PFU_mL^{-1} [67].

Contamination with *Salmonella pullover* (*S. pullover*) and *Salmonella gllinarum* (*S. gallium*) is involved in the development of Pullover and Fowl typhoid diseases in poultry flocks, which threatened the poultry industry in developing countries [68]. Need for rapid detection methods for isolation of pathogenic microorganism including *S. pullorum* and *S. gallinarum* have attracted great attention. Zhu and coworkers designed sandwich complexes for *Salmonella pullorum* sand *Salmonella gallinarum* recognition. This sandwich complex was based on colorimetric sandwich immunoassay and comprised of capture and detection probes. Capture probe consisted of magnetic nanoparticles was covered by silica (MNP) and modified with polyclonal antibody against aforementioned bacteria. Additionally, detection probe was composed of silica nanoparticles modified with Horseradish peroxidase (HRP) and secondary antibodies against *S. pullorum* and *S. gallinarum* (HRP-IgG-SiNP). It was applied to catalytically oxidize the chromogenic substrate. Target bacteria were conjugated with polyclonal antibody and secondary antibodies. Thus, sandwich structures were formed and the chromogenic substrate 3,3′,5,5′- tetramethylbenzidine (TMB) was oxidized by HRP cause an observable color change by the bare eye. This method provides the fast recognition process (less than 1.5 h) with the limit

of detection of 1.7×10^3 $CFUmL^{-1}$ for *Salmonella pullorum* sand *Salmonella gallinarum* [69].

In another study, Jeong and coworkers applied magnetics core–shell $Fe@SiO_2$ NPs functionalized with the (3-aminopropyl) triethoxysilane (APTES) as the amine group *via* a sol–gel reaction for specific separation of heavy metal ions. Metal ions (Co^{2+}, Cu^{2+}, Fe^{2+}, and Hg^{2+}) interacted with amine groups on the surface of silica shell. The interaction *via* metal–APTES–$Fe@SiO_2$ NPs formed aggregates resulting in color change from blue to yellow. The detection limit for the heavy ions was 0.08 mM [70].

Deng et al. established a novel, rapid, low cost, simple, and accurate colorimetric system for the detection of caffeine in beverages using the AgNPs sensors and magnetic MIPs (MMIPs) (Fig 4). In this method, magnetic Fe_3O_4 nanoparticles as core, $mSiO_2$ microspheres as shell, α-methylacrylic acid as functional monomer and caffeine as template were used. Firstly, Coca-Cola and tea beverages were pretreated with MMIPs and caffeine was isolated and enriched. Then the samples were analysed with AgNPs sensors.This colorimetric method quantifies caffeine ranging 0.1–5 mg/L by UV-vis spectroscopy at 393 nm. Moreover, this analytical method can also be used for detection of other substances in foods, such as pesticides and certain additives [71].

CONCLUSION

Magnetic sensory platforms composed of magneto-resistive materials have attracted great attention. In fact, the combination of magnetic-responsive materials and magnetic field provides new features and opportunities for various analyte sensing applications.

In this regard, magnetic-based sensors show promising capability to address challenging issues of modern sensing technology.

This review provides insights into the silica-magnetic based hybrid sensing platforms and their application in static and dynamic sensing. As a derivative of the magnetic-responsive materials, silica-magnetic hybrid systems span large development.

Excellent properties of silica as a mesoporous inorganic material result in better characteristics of silica-based sensory platforms such as good charge transport and improved electrochemical signal.

Hybridization of magnetic and silica NPs introduces ideal opportunity for preparation of sensors with high sensitivity. Research in this field has developed different types of sensors for the detection of various analytes.

In order to bring this technology to practical real-world applications, the selectivity and sensitivity of the prepared sensors should be high enough with a consensus to reduce environmental interference with ligand-target association.

Future development toward magneto-responsive silica-based sensory systems may need expansion of the existing library of specific high affinity ligands against biomarkers or various analytes, optimization of biochemistry, and fabrication of versatile magnetic labels, as well as construction of sensitive magnetic field sensors implementing nanotechnology to overcome the obstacles of molecular diagnostics.

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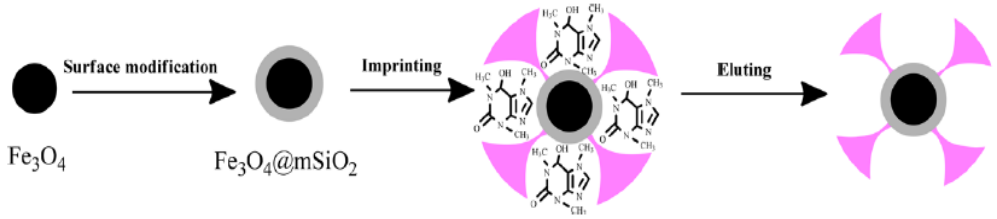

Fig 4. The principle process of MMIPs synthesis. In this system magnetic Fe3O4 nanoparticles as core, mSiO2 microspheres as shell, α-methylacrylic acid as functional monomer and caffeine as template were used. Caffeine was isolated and enriched implementing this system. Adopted with permission form [71]

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