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Latest developments in the detection and separation of bovine serum albumin using molecularly imprinted polymers

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ABSTRACT

Recently, enormous attention has been focused on the development of protein-molecularly imprinted polymers (MIPs). In this sense, bovine serum albumin (BSA) is well regarded as a favorite template in various MIPs-based biochemical/analytical assays mainly due to its low price, easy availability, and high structural homology to human serum albumin (HSA). Equally, the implications of BSA in the pathology of different human-related disorders necessitate the development of methods for its precise detection in biological samples. Accordingly, the current review seeks to provide an update on the design, synthesis, and characterization of the developed MIPs which have used BSA as template protein. Also, the recognition and quantification of BSA in different real samples using the prepared MIPs are discussed. Additionally, main strategies, such as surface imprinting, epitope-MIPs, microcontact imprinting and other methods to overcome the problems associated with the molecular printing of BSA are discussed here. The final discussion provides a comparative exploration of different approaches developed, emphasizing their relative advantages and disadvantages and underlining developments and possible future directions.

1. Introduction

Albumin is a significant blood plasma protein playing critical functions in the maintenance of plasma pressure, nutrition balance, binding, and the transportation of different chemicals. The concentration of albumin in the blood plasma or other biological fluids in the body is also closely associated with the health status [1,2]. Also, its presence in the urine may indicate certain forms of liver or renal disorders. In many instances, serum albumins are used as model proteins. Among different types of serum albumins, HSA, and BSA have been widely used in the research, food, and pharmaceutical industries [3–5].

BSA is the main protein present in the serum of bovine blood. Human beings are exposed to BSA because of the consumption of bovine meat and milk. It can also be consumed as a dietary protein. The development of some infections and diseases such as insulin-dependent diabetes mellitus, membranous nephropathy as a rare renal disease, mad cow disease, Crutchfield-Jacob disease (CJD) and bovine spongiform encephalopathy (BSE) maybe is due to the exposure of the anticipated BSA to human. It is hypothesized that prions composed of the prion protein (PrP) are the cause of BSE and CJD. Furthermore, the significant reduction of blood BSA can lead to numerous diseases in the cattle of cows [6]. BSA is a central component of the fetal bovine serum (FBS) which is commonly used in the production of vaccines as a culture medium. The World Health Organization (WHO) has set guidelines for a vaccine dose of 50 ng or less residual BSA because it may cause allergic reactions in the human body. Thus, it seems that the development of sensitive assays for residual BSA detection in vaccine companies is critical. The quantitative analysis of BSA is, therefore, extremely important for clinical, pharmaceutical and laboratory purposes [7]. BSA detection has consequently led to extensive immunological and bioanalytical research. Thus, it has been attracted increasing attention for the recognition of this bio-macromolecule. For those critical reasons,

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Abbreviations

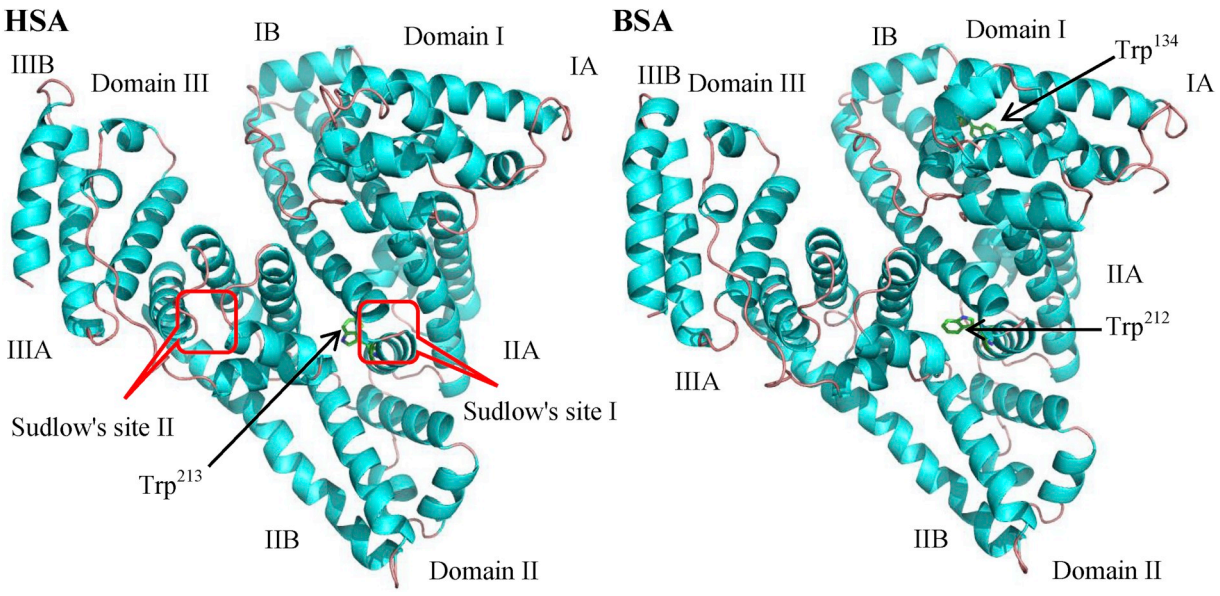
2-VP	2-Vinyl pyridine
3-APBA	3-Aminophenylboronic acid
3D	Three-dimensional
AA	Acrylic acid
AAM	Acrylamide
AAs	Amino acids
ADH	Alcohol dehydrogenase
Ag_2SNPs	Silver sulphide nanoparticles
AgNPs	Silver nanoparticles
AgNSs	Silver nanostructures
AIBN	2, 2′-Azobisisobutyronitrile
AMPS	2-Acrylamido-2-methylpropanosulfonic acid
AO	Acridine orange
APBA	*m*-Aminophenyl boronic acid
APS	Ammonium persulfate
APTES	3-Aminopropyl triethoxysilane
AQ	9, 10-Anthraquinone
ATRP	Atomic transfer radical polymerization
AuNPs	Gold nanoparticles
AuNRs	Gold nanorods
AVIMBF4	3-(3-Aminopropyl)-1- vinylimidazolium tetrafluoroborate
BCA	Bicinchoninic acid
BCG	Bromocresol green dye
BHb	Bovine haemoglobin
Bio	Biotin
BMIMPF6	1-Butyl-3-methyl imidazolium hexafluorophosphate
BSA	Bovine serum albumin
BSE	Bovine spongiform encephalopathy
CaA	Calcium alginate
CaA/PAAM MIPs	CaA/PAAM molecularly imprinted polymers
CCG	Chemically converted graphene
CdTe QDs	Cadmium telluride quantum dots
CE	Capillary electrophoresis
CeE	Ceramic electrode
CGNPs	Citrate capped gold nanoparticles
CIHARP	4-Chloro-(2′-hydroxylophenylazo) rhodanine
CJD	Crutchfield–Jacob disease
CL	Chemiluminescence
CS	Chitosan
CV	Cyclic voltammetry
Cyt C	Cytochrome C
CZE	Capillary zone electrophoresis
DAA	Diallylamine
dBSA	Denatured BSA
DISA	2,4-Dihydroxyl-3-iodo salicylaldehyde azine
DMAEMA	2-(Dimethylamino) ethyl methacrylate
DMAPMA	3-Dimethylaminopropyl methacrylamide-acrylate
DNA	Deoxy ribonucleic acid
DPP	Diketopyrrolopyrrole pyrrole
DPV	Differential pulse voltammetry
EGDMA	Ethylene glycol dimethacrylate
EIS	Electrochemical impedance spectroscopy
ELISA	Enzyme-linked immunosorbent assay
EMIPs	Epitope-based molecular imprinting polymers
FBS	Fetal bovine serum
FDA	Food and drug administration
FET	Field effect transistors
FI-CL	Flow injection chemiluminescence
FPLC	Fast protein liquid chromatography
FRET	Fluorescence resonance energy transfer
FT-IR	Fourier-transform infrared
GCE	Glassy carbon electrode
GE	Gold electrode
GO	Graphene oxide
GOX	Glucose oxidase
Gr	Graphene
GrCE	Graphene modified carbon electrode
H-bonding	Hydrogen bonding
HCNTs	Helical carbon nanotubes
HCPT	10-Hydroxy camptothecin
HPIR	Hydrophilic protein imprinted resin
HPLC	High performance liquid chromatography
HRP	Horseradish peroxidase
HSA	Human serum albumin
IEC	Ion exchange chromatography
IF	Imprinting factor
ILs	Ionic liquids
KH-550	γ-Amidopropyl triethyoxysilane
KH-570	β-Methoxyethylene triethyoxysilane
L-Cys	L-cysteine
LOD	Limit of detection
LSPR	Localized surface plasmon resonance
Lys	Lysozyme
MAA	Methacrylic acid
MIECS	Molecularly imprinted electrochemical sensor
MIPMs	Molecular imprinting polymeric microspheres
MIPs	Molecularly imprinted polymers
MIT	Molecular imprinting technology
MMA	Methyl methacrylate
MMIPs	Magnetic molecularly imprinted polymers
MNPs	Magnetic nanoparticles
MNPs/CS-MWCNTs	CS-coated MNPs modified MWCNTs
MOFs	Metal-organic frameworks
MoS_2	Molybdenum disulphide
MTMS	Methyltrimethoxysilane
MW	Molecular weight
MWCNTs	Multi-walled carbon nanotubes
NaA	Sodium alginate
NIPAAM	*N*-Isopropylacrylamide
NIPs	Non-imprinted polymers
NIR	Near-infrared
NIRDRS	Near-infrared diffuse reflectance spectroscopy
NNMBA	*N,N′*-Methylenebisacrylamide
NPs	Nanoparticles
NR	Neutral red
OTMOS	Octyltrimethoxysilane
Ova	Ovalbumin
PAAM	Polyacrylamide
PCR	Polymerase chain reaction
PDA	Polydopamine
PDDA	Poly (diallyldimethylammonium chloride)
PEG400DMA	polyethylene glycol 400 dimethacrylate
PEGDMA	Poly-ethylene glycol dimethacrylate
pI	Isoelectric point
PMIMs	Protein molecularly imprinted membranes
PMMA	Polymethyl methacrylate
pNIPAAM	poly-(*N*-isopropylacrylamide)
PP	Polypropylene
PP-g-PAAM MIPs	PP fiber-grafted PAAM molecularly imprinted polymers
PP-s-CaA/PAAM MIPs	PP fiber supported CaA/PAAM molecularly imprinted polymers
PrP	Prion protein
PS	Polysiloxane
PtNFs	Platinum nanofibers
QCI	Quartz crystal impedance
QDs	Quantum dots
R6G	Rhodamine-6G

RFM	Resorcinol-formaldehyde-melamine
RLS	Resonance light scattering
SA	Streptavidin
SEM	Scanning electron microscopy
SERS	Surface-enhanced Raman scattering
Si NWs	Silicon nanowires
SIPTCFs	Surface imprinted tubular carbon nanofibers
SMIT	Surface molecular imprinting technology
SPE	Solid phase extraction
SPR	Surface plasmon resonance
TAgNPs	Triangular silver nanoplates
TDSN	Two dimensional silica network
TEGMPA	Tetraethylene glycol-3- morpholine propionate acrylate
TEMED	N, N, N′, *N*′-Tetramethylethylenediamine
TEOS	Tetraethoxysilane
Ti	Titanium
TMB	3,3′,5,5′-Tetramethylbenzidine
U.S.	United States
UV–vis	Ultraviolet–visible
WHO	World Health Organization
γ-MAPS	γ-Methacryloxypropyltrimethoxysilane

exploring new methods for BSA detection is particularly essential [8]. Recently, MIPs as artificial receptors have been received increasing interest for the detection of proteins. MIPs technology is a simulation of Fischer's lock and key theory. Pauling initially recommended it for the preparation of an antibody with an antigen as a template [9]. Four specific valuable properties of MIPs make them as advantageous materials [10,11]: (i) high selectivity and affinity which is similar to natural receptors; (ii) exceptional mechanical, thermal, and physicochemical stability; (iii) easily adaptation for practical uses; and (iv) the simplicity of preparation methods. As a state of the art technology, the development of MIPs as mimics for biological molecules is now possible using molecular imprinting technology (MIT) [12]. In this paper, the progress made in relation to optical and electrochemical MIPs using albumin as a template protein is discussed. Subsequently, the use of MIPs prepared for analysis and determination of bovine albumin is highlighted. The use of MIPs for the extraction or detection of BSA, reported in different studies using various considered strategies to overcome the present problems, is discussed here. The advantages/disadvantages of the proposed methods, as well as the analysis of real samples, have also been described.

2. Protein detection

Proteins in all organisms are the fundamental elements of life playing essential roles in physiological processes [13]. In general, the quantification of proteins appears to be problematic because their three-dimensional (3D) structure is susceptible to severe conditions such as temperature, high salt concentration, and low/high pH [14]. Besides, among different biomolecules of interest, the detection of proteins is a more challenging issue than other biomolecules such as nucleic acids. The problem is due to two main reasons: (i) requiring the minimal concentrations of protein detection because of the lack in the



	HSA	BSA
Shape	Globular	Globular
Number of AAs	583	586
MW (kDa)	66.4	66.5
Number of domains	3(I,II,III)	3(I,II,III)
Number of subdomains	6	6
Number of Trp residues	1	2
pI	4.7	4.7

Fig. 1. The cartoon illustration of BSA and HSA structures along with some biochemical properties. Both of them are categorized as globular proteins and mainly composed of three main domains, and each domain contains two subdomains. There are two main binding sites on albumin, namely as sites I and II, which are located in the subdomains IIA and IIIA, respectively.

amplification methods for the proteins like polymerase chain reaction (PCR) for deoxyribonucleic acid (DNA), (ii) tightly controlled environmental conditions, e.g., pH, contamination, and the temperature are challenging in the successful sensing of proteins. On the other hand, protein detection is a critical feature in different biomedical applications and clinical diagnoses. The demand for a simple, label-free, and highly sensitive technology for the detection, separation, and analysis of proteins is of great interest among scientists especially in the past two decades [10,15–18]. As a result, protein analysts or biochemists are looking for different tools to quantitatively and qualitatively detection of proteins [19]. Today, enormous research is underway to develop an environmentally friendly, non-toxic, and easy protein detection system with the lowest possible detection limit. Nano- and micrometer- scale sensing devices can provide new tools for investigating the physical parameters of a wide range of molecules. Research has already focused on producing sensors capable of detecting the low amounts of the analyte, which are especially important in the context of biosensing. In this area, there is a high demand for the detection of the analyte of interest at low concentration levels with high specificity. The recognition of any biophysical and biochemical signal at the level of a single cell or even a molecule is the ultimate goal of nano- and microscale-based biosensors which are associated with a specific disease [20]. The development of a system with high precision measurement, detection at low concentrations, must, therefore, be an essential point in the successful sensing of proteins [21].

3. Serum albumins

HSA and BSA are researched as the major serum proteins. The main biochemical properties and the structures of both proteins are compared in Fig. 1. HSA is the main serum protein (~60%) present abundantly in the blood circulatory system of human. This multifunctional bio-macromolecule plays vital roles in the bloodstream because it acts as a transporter for a broad spectrum of endogenous and exogenous substances, including fatty acids, amino acids (AAs), some metal ions, or other small molecules and pharmaceuticals. Different bioactive chemicals bind to albumin and distribute in the body and it improves the solubility of low soluble compounds [1]. Therefore, weak and strong interactions between chemicals and albumin determine their fate and effects in the body. HSA in structure is a heart-shaped globular protein with a molecular weight (MW) of 66.4 kDa and consists of 583 AAs. It's structure comprises three main homologous domains I, II and III, and each of them includes two A and B subdomains [22]. There are two main binding sites on serum albumins, namely as Sudlow's sites I and II positioned in the subdomains IIA and IIIA, respectively. Most of the molecules and chemicals bind to these sites of albumin. Recently, the binding of some compounds to other regions on albumin has been reported [23]. Serum albumins have been extensively used in the preparation of albumin nanoparticles (NPs) over the past several decades [24]. Abraxane is a well-known albumin-based NPs approved for the treatment of metastatic breast cancer by the United States (U.S.) Food and Drug Administration (FDA) in 2005. It contains the paclitaxel anticancer agent with 130 nm mean particle size [25].

BSA as another serum protein has many applications in biological and medical fields., It is a globular protein with a single polypeptide chain consisting of 586 AAs and 17 disulfide bridges stabilize the heart-shaped structure [23]. In the water medium with a neutral pH, BSA is well characterized as an acidic protein since the isoelectric point (pI) of protein is about 4.7. Thus, it will have a negative charge, and subsequently, the hydrophobic cavities are placed inside the molecule. Because of high structural homology to HSA, BSA is comprehensively investigated as a model protein [26]. Similar to HSA, BSA is structurally composed of three homologous domains I, II, and III with two A and B subdomains in each domain.

4. BSA detection and quantification

For BSA analysis and quantification, different traditional colorimetric assays such as Ultraviolet–visible (UV–vis) absorption measurement, Bicinchoninic acid (BCA), Bradford and Lowry assays are now available. Traditional methods in BSA detection are frequently based on spectrometric and colorimetric techniques. The principles and other important points along with the advantages/disadvantages regarding each assay are summarized in Table 1. Specific techniques such as enzyme-linked immunosorbent assay (ELISA) and Western blot analysis as individual protein quantitation methods can be considered for BSA determination. These types of immunological assays as useful diagnostic methods for the biomolecules analysis, for example, BSA are commonly based on antibodies, but, high costs and some problems during the preparation of antibodies with specific biological properties restrict the wide application of such approaches [27]. Chromatographic techniques such as fast protein liquid chromatography (FPLC), gel

Table 1
The main properties of spectroscopic and colorimetric assays considered in the determination of protein concentrations such as BSA.

Assay	Absorption	Mechanism	Advantages	Disadvantages
UV	280 nm	Tyr and Trp residues absorption	Small sample volume Rapid Low cost Directly measurements High sensitivity Ease of performance Nondestructive method	Incompatible with detergents and denaturating agents High variability UV spectrophotometers and quartz cuvettes requirement
BCA	562 nm	Cu^{2+} reduction to Cu^{1+} BCA reaction with Cu^{1+}	Compatible with detergents and denaturating agents Low variability High sensitivity (100 times higher than the Biuret) commercially availability of simple two-solution reagent Ease of procedure	Low or no compatibility with reducing agents
Biuret	540 nm	Complex formation between cupric ions and peptide bonds of proteins	Applicable Reasonably accurate Short color development time Constant color intensity	Lack of sensitivity Buffer and or other compounds interfering with color development
Bradford	470 nm	Complex formation between Coomassie brilliant blue dye and proteins	Compatible with reducing agents Rapid Sensitive Easy to perform	Incompatible with detergents
Lowry	750 nm	Cu reduction by proteins Folin-Ciocalteu reduction by the Cu-protein complex	High sensitivity (100-fold more sensitive than the Biuret) High precision	Incompatible with detergents and reducing agents Long procedure

Table 2
Historical overview in the extraction, analysis, and determination of BSA.

Year	Employed methods	Used materials	Concentration range	LOD	Real sample analysis	Ref.
1992	CE	–	25–1000 μg mL^{-1}	–	BSA assay	[96]
	CE	–	–	2 × 10^{-10} mol L^{-1}	BSA assay	[97]
1997	Fluorescence	AQ-labeled BSA	0–1.8 × 10^{-7} mol L^{-1}	1.2 × 10^{-10} mol L^{-1}	BSA detection	[98]
	CZE	Carbon fiber microdisk	1 × 10 $^{-6}$ - 5 × 10 $^{-5}$ mol L^{-1}	4 × l0^{-7} mol L^{-1} (0.7 fmol)	Serum	[99]
	Optical	Antibody	–	–	BSA determination	[100]
2001	QCI	$CuSO_4$	4 × 10^{-3} – 4 × 10^{-1}g L^{-1}	1.9 × 10^{-4}g L^{-1}	BSA detection	[29]
2003	Fluorescence	Nile Blue and Triton X 100	0.5–12.0 μg mL^{-1}	0.2 μg mL^{-1}	BSA determination	[101]
2005	CV	Si NWs	1.08 μM	–	BSA detection	[102]
	UV	BCG dye	–	–	Milk	[103]
2007	RLS	Aminopolycarboxyl-modified Ag2S NPs	0.01–0.7 μg mL^{-1}	8.6–112.6 ng mL^{-1}	Milk	[104]
	Fluorescence	CdTe/CdS QDs	0–1.2 × 10^{-6} mol dm^{-3}	5.4 × 10^{-8} mol dm^{-3}	BSA determination	[105]
2008	Electrochemical	Diamond electrode	5–3000 mg dl^{-1}	5 mg dL^{-1}	BSA detection	[106]
	Fluorescence	ClHARP–Ti(IV) probe	0–12 μg mL^{-1}	0.182 μg mL^{-1}	Milk	[107]
	HPLC	MMA	–	–	BSA recognition	[43]
	UV	Calcium phosphate/alginate MIPs	–	–	BSA detection	[75]
2009	HPLC	–	1–100 μg mL^{-1}	0.5 μg mL^{-1}	Vaccine	[108]
	HPLC	CS and APBA	–	–	BSA recognition	[52]
	UV	OTMOS, APTES, and TEOS	–	–	BSA separation	[57]
	HPLC	MTMS	–	–	Used as template	[59]
	Electrical	Electrolyte-gated Gr FET	–	–	BSA detection	[109]
2010	Fluorescence	DISA	0.3–50 μg mL^{-1}	50 ng mL^{-1}	Serum	[110]
	CL	MAA	1.0 × 10^{-8}–5.0 × 10^{-6} g mL^{-1}	1.5 × 10^{-9} g mL^{-1}	Milk	[92]
	UV	AAM and APS	–	–	BSA as template	[55]
	Electrochemical	CdSe/ZnS QDs	0.5–500 ng mL^{-1}	0.5 ng mL^{-1}	Phosphorylated BSA detection	[111]
2011	Fluorescence (FRET)	NR and CdTe QDs	0.4 × 10^{-3} - 11.00 × 10^{-3} g L^{-1}	0.13 g L^{-1}	BSA detection	[112]
	HPLC	NIPAAM and DMAPMA	–	–	BSA rapid separation and purification	[45]
	Fluorescence	CCG and squaraine	–	–	BSA detection	[113]
2012	Fluorescence	InGaP QDs	0.1–0.5 mg mL^{-1}	–	BSA analysis	[114]
	Fluorescence	CdTe QDs	–	–	dBSA as template	[49]
	Electrochemiluminescence	CdTe QDs	1.0 × 10^{-9}–1.0 × 10^{-6} g mL^{-1} 1.0 × 10^{-6}–1.0 × 10^{-5} g mL^{-1}	5.48 × 10^{-10} g mL^{-1}	Milk	[115]
	Voltammetry	AgNSs	10^{4}–10^{11} g mL^{-1}	50 pg mL^{-1}	BSA determination	[116]
	DPV and EIS	MNPs/CS-MWCNTs	1.0 × 10^{-4}–1.0 × 10^{-10} g mL^{-1}	2.8 × 10^{-11} g mL^{-1}	BSA detection	[42]
	UV	AMPS, NIPAM and AAM	–	–	BSA recognition	[70]
	UV	AAM and MAA	–	–	BSA as template	[90]
	UV–Vis	DMAEMA	–	–	BSA recognition	[64]
	UV–Vis	2-VP and AIBN	20–200 mg L^{-1}	0.67 mg L^{-1}	Whey, milk, urine, serum	[89]
2013	NIRDRS	–	0.61–8.10 mg mL^{-1}	–	BSA determination	[117]
	Fluorescence	Fluorescein derivatives	–	–	BSA detection	[28]
	SPR	3-APBA	0.02–0.8 mg mL^{-1}	0.02 mg mL^{-1}	BSA recognition	[95]
	CV and DPV	TEGMPA, MWCNTs-CE	1.99–30.91 ng mL^{-1}	0.42 ng mL^{-1}	Milk, serum, vaccine	[54]
	Fluorescence	GO and HCPT	0.00–52.67 μg mL^{-1}	2.25 μg mL^{-1}	BSA detection	[118]
	Fluorescence	CCG and Cy3 dye	0–8 × 10^{-6} mol L^{-1}	5 × 10^{-8} mol L^{-1}	BSA determination	[119]
2014	Fluorescence	CdTe QDs	5.0 × 10^{-7} - 1.0 × 10^{-5} mol L^{-1}	1.1 × 10^{-7} mol L^{-1}	Blood	[14]
	CV	MAA	1.0 10^{-20}–1.0 10^{-8} mol L^{-1}	1.0 × 10^{-19} mol L^{-1}	BSA detection	[63]
	CE-based Western	–	5.2–420 ng mL^{-1}	5.2 ng mL^{-1}	Vaccine	[7]
	Fluorescence (NIR)	DPPAM	0–3.5 μM	180 nM	BSA detection	[120]
	Fluorescence	Ruthenium complexes	–	–	BSA detection	[121]
	UV	PP-g-PAAM MIPs	–	–	BSA detection	[69]
	UV	PP-s-CaA/PAAM MIPs	–	–	BSA recognition	[79]
2015	Electrical conductance	ZnO nanospheres	0–40 pM	10 pM	BSA detection	[122]
	CV	AVIMBF4 ILs	1.50 × 10^{-9} - 1.50 × 10^{-6} mol L^{-1}	3.91 × 10^{-10} mol L^{-1}	Milk	[67]
	Fluorescence	Au NRs@SiO_2-AO	0.75–33.86 μmol L^{-1}	0.25 μmol L^{-1}	Serum	[123]
	Fluorescence	Flavone dyes	0–1 μL mL^{-1}	0.09 μg mL^{-1}	Serum	[124]
	Electrochemical (EIS)	GE–TDSN–CGNPs–PDDA	9.9 × 10^{-12}–1.6 × 10^{-10} mol L^{-1}	8.4 × 10^{-13} mol L^{-1}	Milk, serum, urine	[125]
	Fluorescence	DPP-anthracenone conjugates	0–5.0 μM	680 nM	BSA sensing	[126]
	SPR	Anti-bovine BSA antibodies	10–1000 ng mL^{-1}	0.02 mg g^{-1}	Milk	[30]
	UV	CaA/PAAM MIPs	–	–	BSA detection	[76]
2016	Electrochemical	ZnO microwires	–	–	BSA detection	[21]
	LSPR	TAg NPs	1.0–100.0 ng mL^{-1}	0.5 ng mL^{-1}	BSA determination	[127]
	Electrical conductance, SPR, and SERS	AgNPs	–	10^{-8} mol L^{-1}	BSA determination	[128]
	CV	MoS_2 nanosheets	0.01–10 ng mL^{-1}	0.006 ng mL^{-1}	Serum	[129]
	CV, DPV, and EIS	CS/IL–Gr/GCE	1.0 × 10^{-10} to 1.0 × $^{10-4}$ g L^{-1}	2 × 10^{-11} g L^{-1}	Plasma	[66]
2017	Optical	Fiber	0.2–2 mg mL^{-1}	2.57 × 10^{-4} mg mL^{-1}	BSA detection	[130]
	UV	Polydiacetylene/triblock copolymer	–	0.05 mM	Milk	[131]

(*continued on next page*)

Table 2 (*continued*)

Year	Employed methods	Used materials	Concentration range	LOD	Real sample analysis	Ref.
2018	Fluorescence	Enoxacin-Al (III) probe	0.13–10 ng mL^{-1}	0.03 ng mL^{-1}	Serum	[132]
	HPLC	Resorcinol and melamine	–	–	Urine	[87]
	Fluorescence (FRET)	R6G and AuNPs	0.8–5.6 × 10^{-11} mol L^{-1}	4.58 × 10^{-11} mol L^{-1}	Urine, blood and serum	[133]
	CV, DPV and EIS	AuNPs@NH_2-MIL-125(Ti) composites	10^{-18} - 10^{-12} g mL^{-1}	4.147 × 10^{-19} g mL^{-1}	Milk	[84]
	Fluorescence	Amino acid-derived 1,2,3-triazoles	–	–	BSA as model	[134]
	UV	Polysiloxane MIPs	–	–	BSA as template	[80]
2019	Fluorescence	Aniline oligomer derivatives	1.68–23.5 mg mL^{-1}	3.56 μg L^{-1}	BSA detection	[135]
	ELISA	dopamine and MNPs	5–1000 μg mL^{-1}	–	Serum	[47]
	Electrochemical	AAM, NNMBA, AA and DAA	1.5 × 10^{-16}–10^{-12} mol L^{-1}	7.2 × 10^{-18} mol L^{-1}	Serum	[93]
	UV	NIPAAM, MAA, NNMBA and pNIPAM	–	–	BSA recognition	[81]
	UV	SIPTCFs	–	–	BSA separation	[56]
	Electochemical	CaA hydrogel membrane	–	–	BSA recognition	[77]
	Electochemical	Pt NFs/HCNTs	0.25–2.50 μM	1.7 nM	BSA quantification	[136]

electrophoresis, ion-exchange chromatography (IEC) and capillary electrophoresis (CE), fluorescence resonance energy transfer (FRET), fluorescence emission spectroscopy [28], or other spectroscopic methods such as piezoelectric quartz crystal impedance (QCI) technique [29], Raman or surface plasmon resonance (SPR) [30] are employed in recent decades for the recognition and quantification of BSA. The majority of such protein detection systems are generally time-consuming and expensive equipment. These methods, additionally, suffer from some other limitations such as complicated steps, a narrow linear range, and limited sensitivity, and are often required to shorten the time of detection [31]. Thus, the development of alternative techniques to sense the low concentrations of BSA is of great interest.

The overview of various researches shows that there is a growing attention regarding BSA detection and its quantification. The historical development in bovine albumin sensing along with the employed detection methods, the used materials, and also further details have been summarized in Table 2. In recent years, the use of various nanoscale materials has enabled scientists to detect the low levels of bovine albumin. Different types of NPs, nanowires, MIPs, and quantum dots (QDs) prepared from different materials in combination with powerful spectroscopic methods are employed in the development of novel techniques for the quantitative analysis of BSA.

5. MIPs

In the last decades, MIT has been widely considered as an advantageous technique for the development of artificial receptors with acceptable selectively for sensing of different molecules of interest. The main sensing aspect of MIPs involves selective recognition of the target molecule due to the specific cavity structure constructed in the polymer matrix. These cavities are created in three steps (see Fig. 2 for further details): (i) functional monomer molecules are prearranged around the template molecule in solution; (ii) the formed complex is polymerized in the presence of cross-linker monomers; and finally (iii) template molecules are removed from the prepared MIPs. To generate extremely selective molecular cavities, the first step is essential. This prearrangement can be achieved either through the formation of covalent bonds or through the self-assembly of noncovalent bonds [17].

Accordingly, two types of MIT strategies have generally been developed which are based on covalent bonds or non-covalent interactions between the template molecules and the functional monomers. During the polymerization procedure, template molecules are imprinted into and on the polymer. After the removal of templates by appropriate chemicals, the prepared polymer contains shallow and pits holes. If the templates come into contact with the polymer, they return to the imprinted sites with high specificity [32]. Covalent imprinting procedure was firstly introduced by Wulff [33]. Functional monomers are bound to template molecules with covalent bonds in covalent imprinting. After polymerization, templates will be removed by cleaving these bonds from the resulting polymer. The analyte is detected through similar covalent bonds being formed. The primary benefit of this technique is that the cavities are well designed in the polymer architecture. Nevertheless, MIPs development using this method is difficult, time-consuming and costly. Moreover, for the removal of the template from MIPs, harsh conditions are needed. Furthermore, the applied functional monomers must react with the template easily. The choice of these monomers is therefore mostly restricted to the derivatives of boronic acid. As suggested by Sellergren et al. [34] in 1988, another approach entails noncovalent imprinting. In this procedure, template molecules and functional monomers are preorganized completely by noncovalent interactions in solution, such as chelation, hydrogen bonding (H-bonding), and van der Waals forces or hydrophobic interactions. Template molecules are detected by the same noncovalent interactions after preparing of MIPs. These MIPs are readily prepared and, under mild conditions, templates are easily removed. The significant disadvantage of noncovalent imprinting is the reversibility of prepolymerization complex formation. In fact, the imprinted molecular cavities may not be homogeneous and the portion of the functional monomers may not be situated inside the cavities but spread randomly in the polymer matrix, thus reducing the imprinting factor and therefore the analyte selectivity of the MIPs. To overcome these shortcomings, Sellergren launched a semi-covalent imprinting approach in 1990 [35]. Covalent binding of a template with functional monomers is involved in this approach. The template is removed after subsequent polymerization by cleaving the covalent bonds created. The analyte then binds to its binding sites just in a noncovalent mode to the recognition regions of the imprinted cavity. The semi-covalent imprinting approach combines covalent imprinting benefits with non-covalent imprinting flexibility. An approach using a 'sacrificial spacer' established by Whitcombe et al., in 1995 is an effective modification of semi-covalent imprinting [36]. In this approach, a short linker such as a carbonate connects functional monomer and a template and then polymerized. Then, two bonds are cleaved and the linker and template are released. Thus, the distance is effectively controlled between the functional monomer molecule and the template.

6. BSA-MIPs

While significant development has been made in the molecular imprinting field, many challenges, particularly for biological macromolecules, remain to be overcome. The synthesis of imprinting artificial materials for the detection of macrobiomolecules such as BSA is very problematic because of the instability of such macromolecules [37]. The developed MIPs for small molecules have high affinity, strong

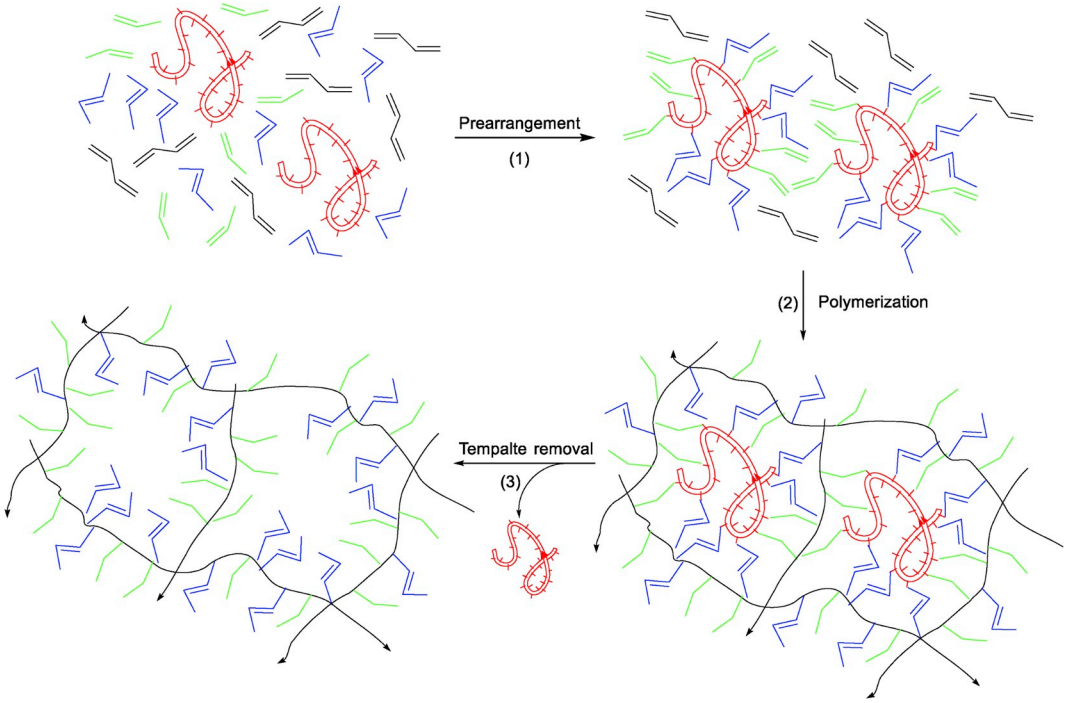


Fig. 2. Schematic illustration of MIPs preparation. The procedure can be mainly outlined in three main steps: (1) prearrangement of functional monomers around template molecules; (2) polymerization of the formed complex by cross-linker monomers; (3) template molecules removal from the MIPs [10].

stability, and excellent specificity enabling their applications in different fields such as drug delivery, the prevention of viral infections, selective separation, and sensor preparation [38]. However, due to molecular instability, relatively conformational flexibility, sizeable molecular structure, and functional groups with high diversity in proteins, that lead to low mass transfer, template removal difficulty from inside binding sites, non-specific interactions, and the mild conditions required for imprinting process, the fabrication of MIPs for bio-macromolecules such as BSA remains a challenging issue [39]. The fabrication process of MIPs requires to be undertaken in non-aqueous conditions that are not compatible with the stability of proteins. Thus, MIPs should have reasonable water compatibility properties for any further applications because many identified macromolecules like BSA or other proteins as biomarkers must be determined in an aqueous biological matrix such as urine and blood. Consequently, the aqueous condition is needed for both the imprinting process and protein detection [16]. To overcome such difficulties, some approaches such as surface molecular imprinting technology (SMIT), epitope-mediated imprinting, micro-contact imprinting, imprinted ionic liquids (ILs) and imprinted hydrogels have been developed for selective detection of BSA, and established to be effective strategies for improving the efficiency of the prepared MIPs.

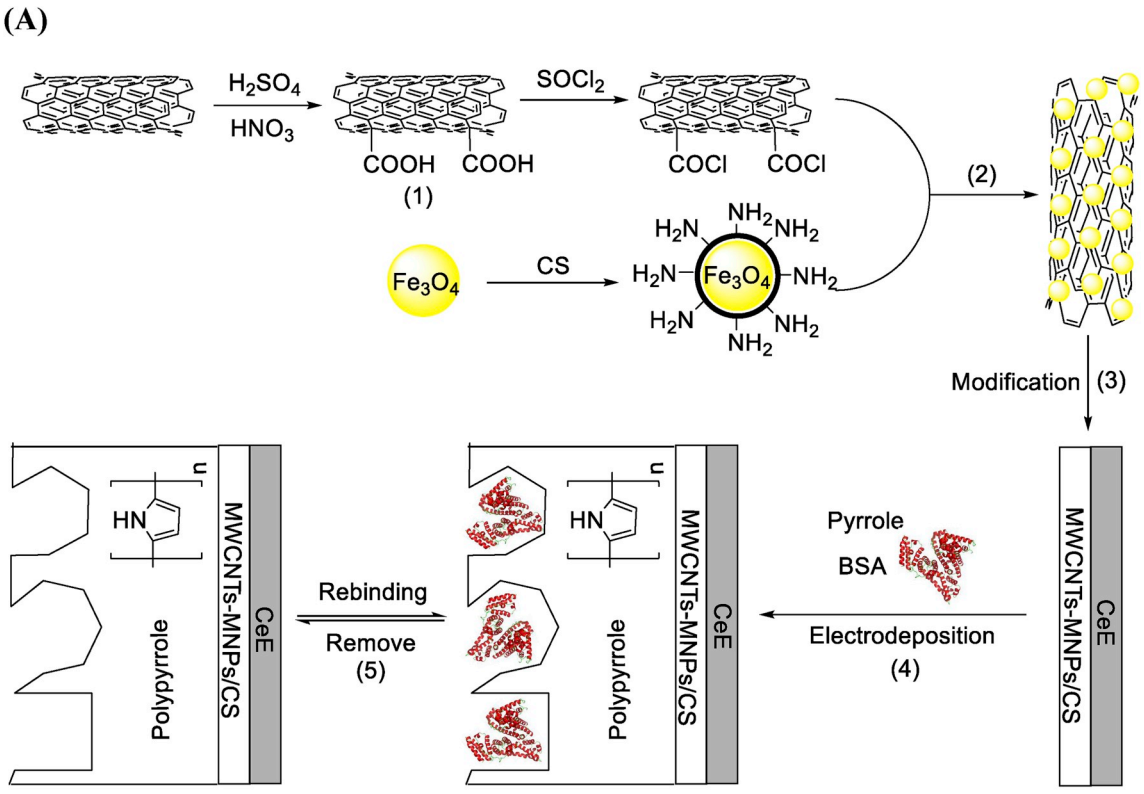
6.1. Developed BSA-MIPs based on SMIT

The SMIT which has been used in the preparation of MIPs has many advantages, involving homogeneous distribution of binding sites, high binding capacities, mass transfer improvement, diffusion barrier reduction with the creation of molecular recognition sites on the support substrate surface and increase the adsorption dependency [40]. In this approach, the cavities and pits are exposed on the surface of the prepared MIPs matrices. Thus, the created cavities and pits on the polymer matrix are readily available to the protein molecules. Different materials have been recently considered for the surface imprinting of bovine albumin which is discussed in the following with further details.

6.1.1. Magnetic NPs (MNPs)

When MIPs are combined with the magnetic materials, the resulting magnetic molecularly imprinted polymers (MMIPs) will have both magnetic and high target protein selectivity properties, making the process of separation more efficient, more accessible and faster [41]. MNPs in combination with chitosan (CS) and multi-walled carbon nanotubes (MWCNTs) have been considered by Chen et al. [42] in the development of a surface-imprinted CS-coated MNPs modified MWCNTs (MNPs/CS-MWCNTs) biosensor for the detection of BSA. The composites of CS/MWCNTs have been used in the preparation of electrochemical biosensor because of the excellent mechanical, electronic, and chemical properties of MWCNTs. Step by step, the fabrication of the biosensor is presented in Fig. 3A. Fourier-transform infrared (FT-IR) spectroscopy and scanning electron microscopy (SEM) were used for the characterization of the MNPs/CS-MWCNTs structural configurations properties. The prepared molecular imprinting biosensor was tested using differential pulse voltammetry (DPV) for investigating the relationship between the current response and the concentration of BSA. According to the obtained results, authors reported a wide linear detection range (1.0×10^{-4}–1.0×10^{-10} g mL^{-1}) for the detected BSA. The low limit of detection (LOD) was obtained to be 2.8×10^{-11} g mL^{-1}. The surface imprinted biosensor displayed high sensitivity, good reproducibility, and excellent selectivity. Rapid response time of 30 s was also shown by the recommended biosensor, which was suitable for the quick detection of protein in samples. The imprinted biosensor's advantages recommended an attractive and extensively appropriate way of developing such biosensors. Additionally, long-term stability, excellent reproducibility, and high sensitivity have been described for the prepared imprinted biosensor.

In another investigation, using SMIT, the covalent immobilization of BSA as a template has been adopted for the imprinting of this protein [43]. In this work, the monomers of methyl methacrylate (MMA) and ethylene glycol dimethacrylate (EGDMA) were used as functional and cross-linker agents, respectively. A two-stage core-shell mini-emulsion polymerization system was used for the preparation of surface-imprinted sub-micrometer particles with the size of 500–600 nm (for more details, see Fig. 3B). The developed particles with magnetic



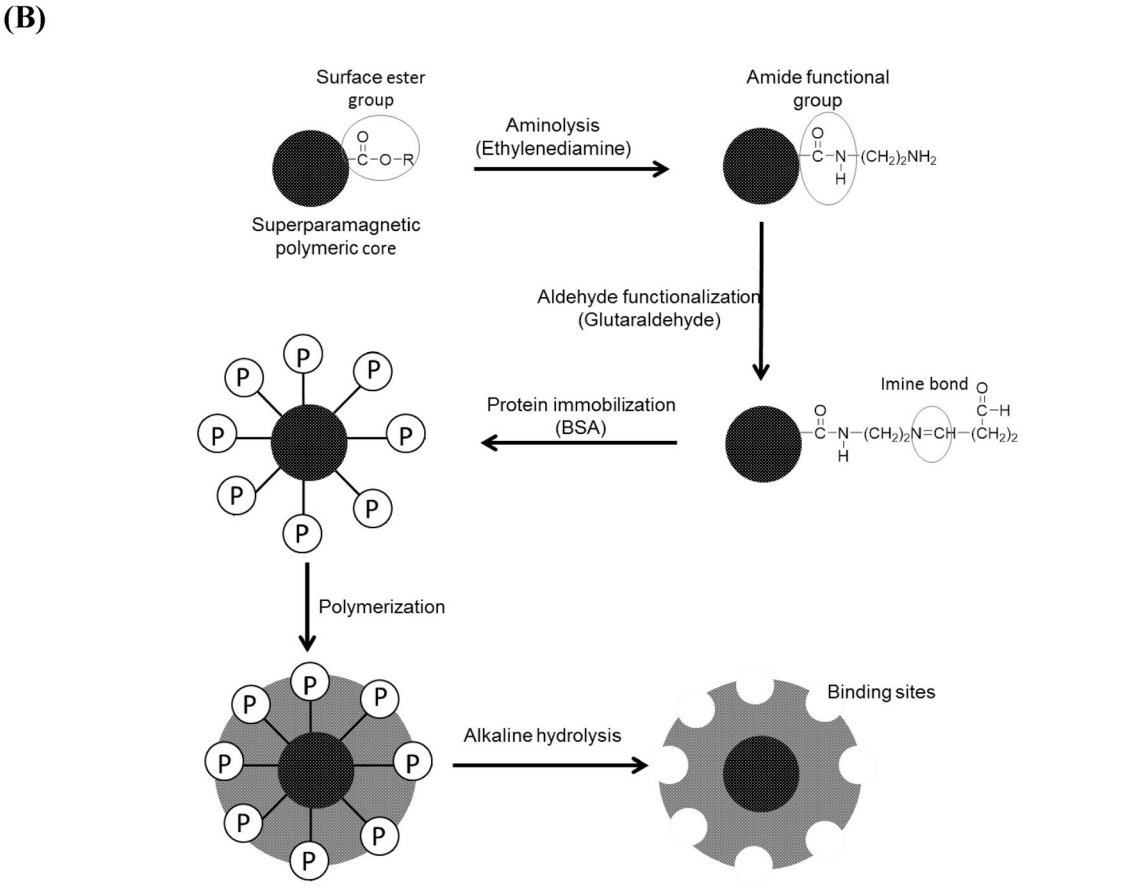


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Fig. 3. Schematic diagrams for the fabrication of MIPs/MNPs/CS-MWCNTs/CE biosensor. The preparation procedure can be summarized as (1) the modification of MWCNTs using H_2SO_4, HNO_3, and $SOCl_2$; (2) the stabilization of CS-coated MNPs with NH_2 groups on the modified MWCNTs; (3) CeE modification by MNPs/CS-MWCNTs; (4) synthesis and polymerization process using pyrrole and BSA as monomer and template molecules, respectively; (5) removal of template BSA and its rebinding recognition (A) [42]. The proposed reactions for the surface functionalization of the support particles and the immobilization of the BSA template molecules in the two-stage imprinting process of mini-emulsion polymerization (B) [43]. Schematic representation for the synthesis of the superparamagnetic BSA surface-imprinted polymers. The main steps of fabrication procedure are (1) the creation of amine groups on the surface of MNPs using APTES; (2) preparation of MIPs in the presence of monomers and BSA template protein via ATRP method (C) [45]. The illustrative diagram of biomimetic ELISA assay for BSA determination. The main steps of this method can be summarized as MIPs immobilization on the surface of MNPs; competitively bounding of Bio-BSA and BSA on the recognition sites of the MIPs; removal of the unbound compounds; the addition of HRP-SA solution and its specifically binding to biotin; the addition of TMB reagent; measurement the absorbance intensity at 450 nm (D) [47].

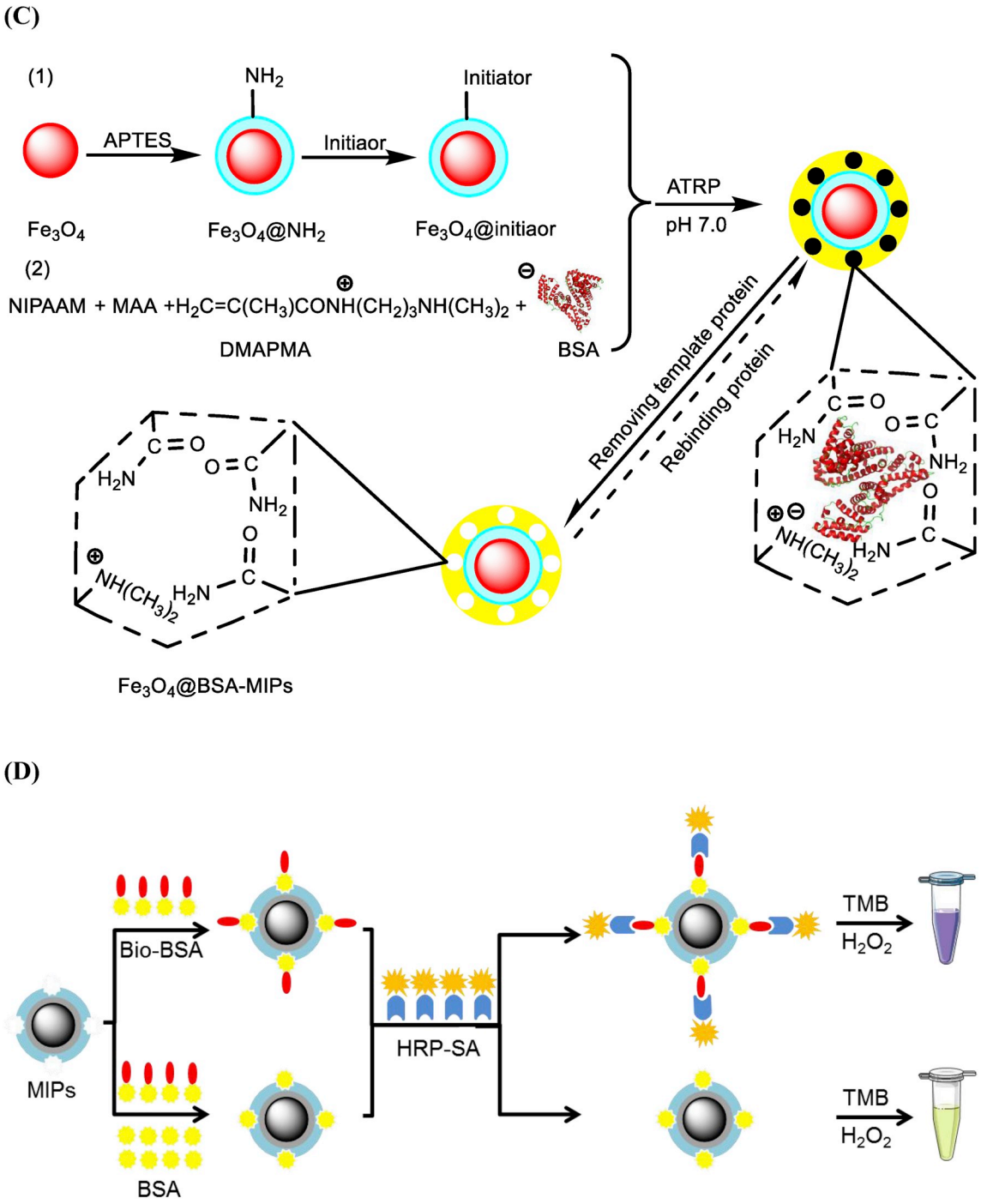

Fig. 3. (*continued*)

susceptibility showed the structure of a red blood cell and excellent property in recognition of BSA was obtained. Compared to non-template proteins in a two protein system, the particles showed high recognition property and were very specific for the template protein detection. The successfully encapsulated Fe_3O_4 NPs has imparted the magnetic sensitivity and the super-paramagnetic features make the possible applications in the cell labeling, bioimaging, and magnetic bioseparation fields. Authors also demonstrated the importance of template immobilization in successfully imprinting of proteins and clarified the potential of the methodology for protein imprinting as a common approach.

Atomic transfer radical polymerization (ATRP) method is a radical polymerization process for controlled radical polymerization. It is one of the most widely used methods that has great potential to develop new materials because of the capacity to control polymer architecture and MW [44]. BSA molecular size is large, and the conformational transitions are more flexible during the imprinting process; thus the formed H-bonding between *N*-isopropylacrylamide (NIPAAM) as functional monomer and BSA as a template are very weak, causing the formation of unstable imprinting complexes between BSA and the used monomers. In an attempt reported by Gai et al. [45], they tried to imprint BSA protein under mild reaction conditions using the ATRP technique. In this investigation, they successfully synthesized BSA surface-imprinted magnetic polymer in the presence of NIPAAM as a standard monomer with the primary assist of functional monomers namely as *N*-[3-(dimethylamino) propyl]-methacrylamide (DMAPMA) and acrylamide (AAM). The surface of MNPs was modified by the introduced amine functional groups using 3-aminopropyl triethoxysilane (APTES), and due to strong H-bonding and electrostatic interactions between template BSA and DMAPMA, the basic functional monomer enabled the successful fabrication of BSA surface-imprinting polymer. Fig. 3C schematically represents the synthesis procedure of the superparamagnetic BSA surface-imprinted polymers. The authors combined magnetic separation with a polymer prepared by MIT because the fabricated imprinting polymer with magnetic properties can selectively detect the protein in the mixed medium and thus their collection and separation are comfortable in an external magnetic field. It has been observed higher selectivity and adsorption capacity to BSA for the imprinted polymer compared to the non-imprinted polymers (NIPs). It was indicated that the imprinted polymer in competitive adsorption experiments had better recognition properties and selective adsorption in the mixture for BSA. The specific selectivity was also obtained for BSA imprinted polymer in bovine serum. Finally, some advantages such as the easy fabrication, magnetic properties, and high selectivity of the imprinted polymers have been proposed demonstrating their potential use in rapid separation, purification, and quantification of BSA.

In the field of analysis, the immunoassay is extensively applied as a primary analytical tool. Antibodies adsorption method is widely used for the detection of different molecules because of specific binding and a high affinity. However, some typical problems in the use of biological antibodies remain unresolved such as time-consuming preparation, reproducible immobilization on the crystal surface, low stability, batch-to-batch variation and high cost in the standard immunoassay tests [12]. MIPs can be considered an alternative to antibodies in current immune-affinity-based analytical techniques [46]. In a recently published paper, a biomimetic ELISA method was developed using MIPs as an alternative to antibodies [47]. The MIPs were fabricated by dopamine polymerization using BSA as a template, ammonium persulfate (APS) as an initiator, Fe_3O_4 NPs as a magnetic core, and dopamine as a functional monomer. Fig. 3D shows the principle and procedure of the reported biomimetic assay based on Biotin (Bio)-avidin ELISA test. In the first step, the immobilization of MIPs was performed on the surface of MNPs using an external magnet. In the solution, BSA and Bio-BSA bound competitively on the recognition sites of the MIPs. In the next step, the unbound compounds were removed, and the horseradish peroxidase-labeled streptavidin (HRP-SA) solution was added, which bound explicitly to Bio. After the addition of 3, 3′, 5, 5′-tetramethylbenzidine (TMB) reagent, the substrate coloration reaction in the solution was catalyzed by the attached HRP-SA to MIPs. Finally, the enzymatic reaction was stopped, and the absorbance intensities were obtained at 450 nm. The absorption value was closely linked to the BSA and Bio-BSA competition in the solution. The detection range of the developed biomimetic ELISA technique was reported to be 5–1000 $\mu g\,mL^{-1}$, which demonstrated high sensitivity for BSA compared to other proteins. It has been found that the method could be applied for the quick detection of BSA with high accuracy and selectivity in bovine serum. Moreover, it was suggested that high-potential affinity synthetic biomaterials for the detection of proteins could be obtained by preparing MIPs using the dopamine polymerization method to replace antibodies in biomimetic ELISA.

6.1.2. QDs

Due to quantum confinement effects, QDs as colloidal nanocrystalline semiconductors have distinctive spectral properties. Some properties such as tunable emission frequencies, sharp emission spectra, high emission quantum yield, photostability and broad absorption spectra make them a suitable material for developing QD-based biosensors [48]. It has been shown that the anchored MIPs on the surface of denatured BSA (dBSA)-modified cadmium telluride quantum dots (CdTe QDs) can be considered as a new type of MIPs-based artificial fluorescent receptor and a selective tool for the target protein recognition [49]. The combination of MIT and the fluorescent properties of CdTe QDs is the main advantage of the method. As it has been depicted in Fig. 4, MIPs-coated CdTe QDs were obtained using the SMIT procedure. The used dBSA not only modified the defects on the surface of the CdTe QDs but also as a secondary monomer, it created specific cavities for effective recognition. The tested molecules as templates in this study were methylated BSA, lysozyme (Lyz), and cytochrome C (Cyt C). It has been indicated that the artificial fluorescent receptor can serve as a starting point for the development of a particular synthetic fluorescent receptor for target protein sensing.

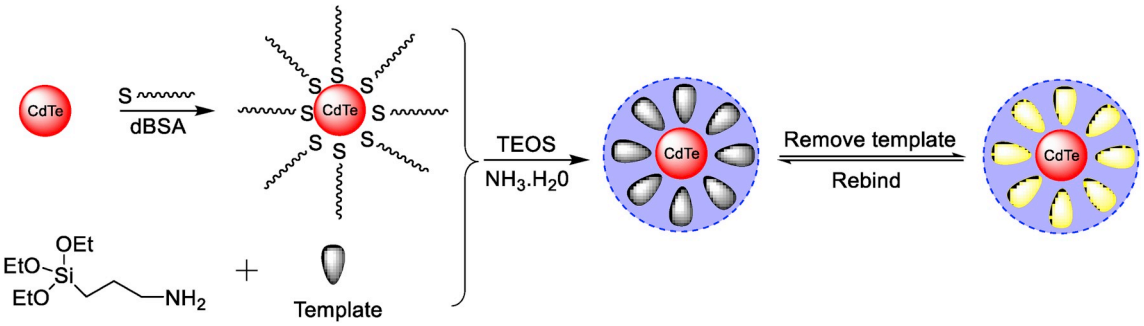

Fig. 4. Illustration of the fabrication procedure for the preparation of MIPs-coated CdTe QDs as an artificial fluorescent receptor [49].

6.1.3. CS

In recent years, CS is widely used in the manufacture of biosensors for the immobilization of various enzymes. CS is a natural poly-aminosaccharide obtained by the chitin deacetylation process. Principally, it is a polysaccharide composed of the unbranched chains of β-(1 → 4)-2-acetoamido-2-deoxy-D-glucose [50]. Usually, CS is mostly used in electrochemical biosensing platforms in combination with MWCNTs, conducting polymers, metal NPs, or redox mediators [51]. CS is also used as a supporting matrix or functional monomer in MIPs sensors because of its low cost and high contents of amino and hydroxyl

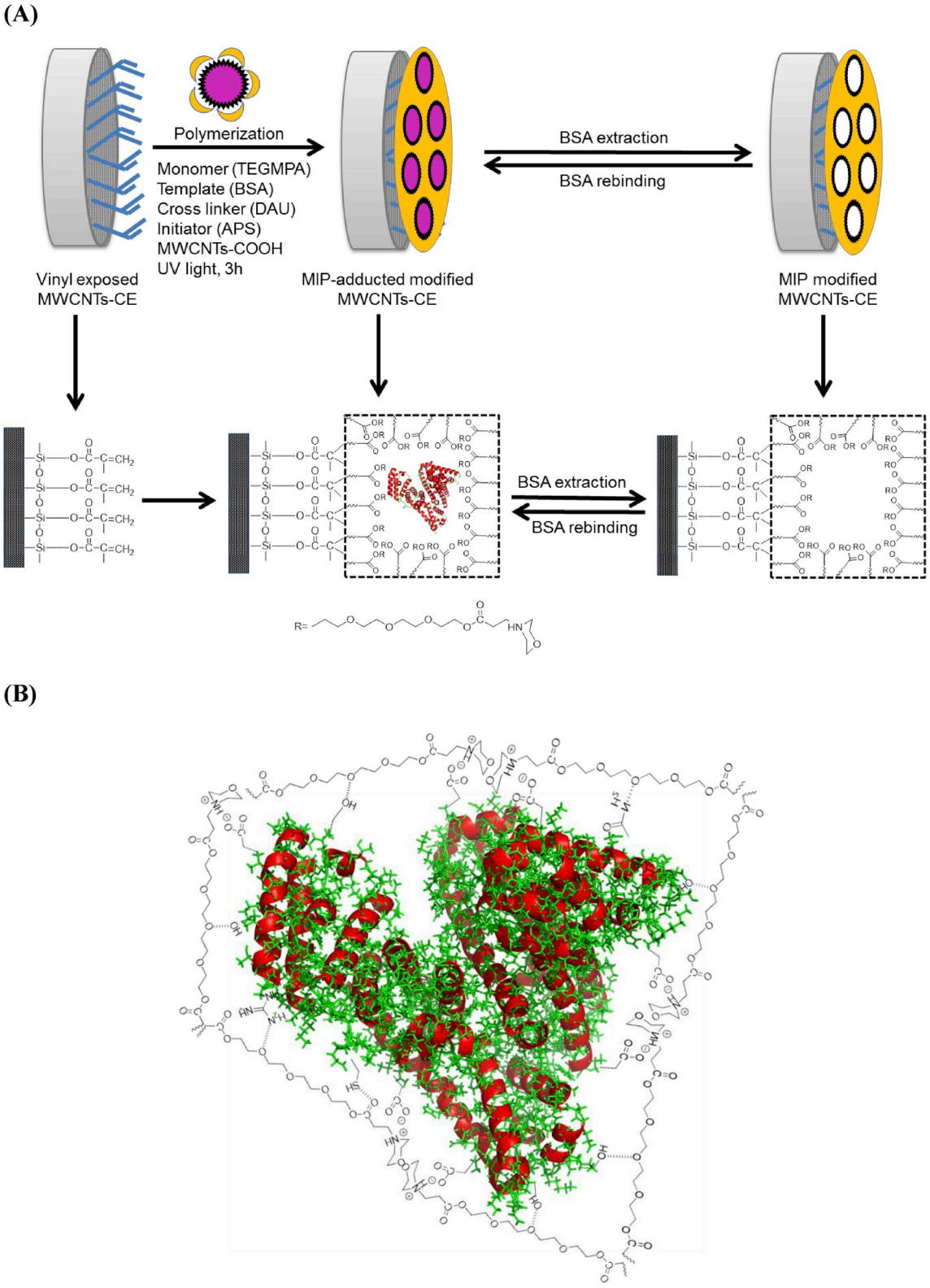

Fig. 5. Schematic representation of MIPs-modified MWCNTs-CE fabrication (A) and the proposed binding mechanism of BSA via multiple points electrostatic and H-bonding interactions (BSA: monomer molar ratio 1:20; for the sake of brevity, only a few monomeric units are shown) with the MIPs motif (B) [54].

functional groups. Using *m*-aminophenyl boronic acid (APBA) as a functional monomer, a new method was established for the protein-responsive imprints fabrication on a homemade CS substrate [52]. High performance liquid chromatography (HPLC) and equilibrium adsorption assays were employed for the characterization of the produced polymers properties. Compared to Lyz and bovine haemoglobin (BHb) as control proteins, it was revealed that the manufactured BSA-MIPs had a strong affinity to their template. The synthesized BSA-MIPs were mainly characterized by their acceptable reversible adsorption properties, especially in competitive binding tests, which have great biological importance in separations. In a competitive experiment for evaluation of BSA/BHb binding properties, non-specific binding was decreased by about zero, and a unique HPLC template recognition profile was found for BSA-MIPs even under harsh mobile phase conditions. It has been indicated that using the trapped template release process, BSA could be recovered. This approach of developing a synthetic receptor for proteins with a high degree of adsorption reversibility and affinity promised to separate target protein from complicated biological samples online.

6.1.4. MWCNTs

Harsh chemical conditions, which is mainly due to the incompatibility between the organic solvents and template causes protein unfolding or denaturation. Thus, the imprinting of the proteins under biologically benign status, while keeping the protein in its physiological conditions, is relatively problematic [32]. MIPs for proteins at neutral and aqueous solutions may be an alternative that has, but, gained limited consideration to date, mainly due to water competition for the formation of H-bonding. Nevertheless, combined effects of hydrophobically driven electrostatic interactions and H-bonding could rescue the condition, and in the aqueous medium, the establishment of a stable adduct of MIPs-template could be possible without the denaturation of

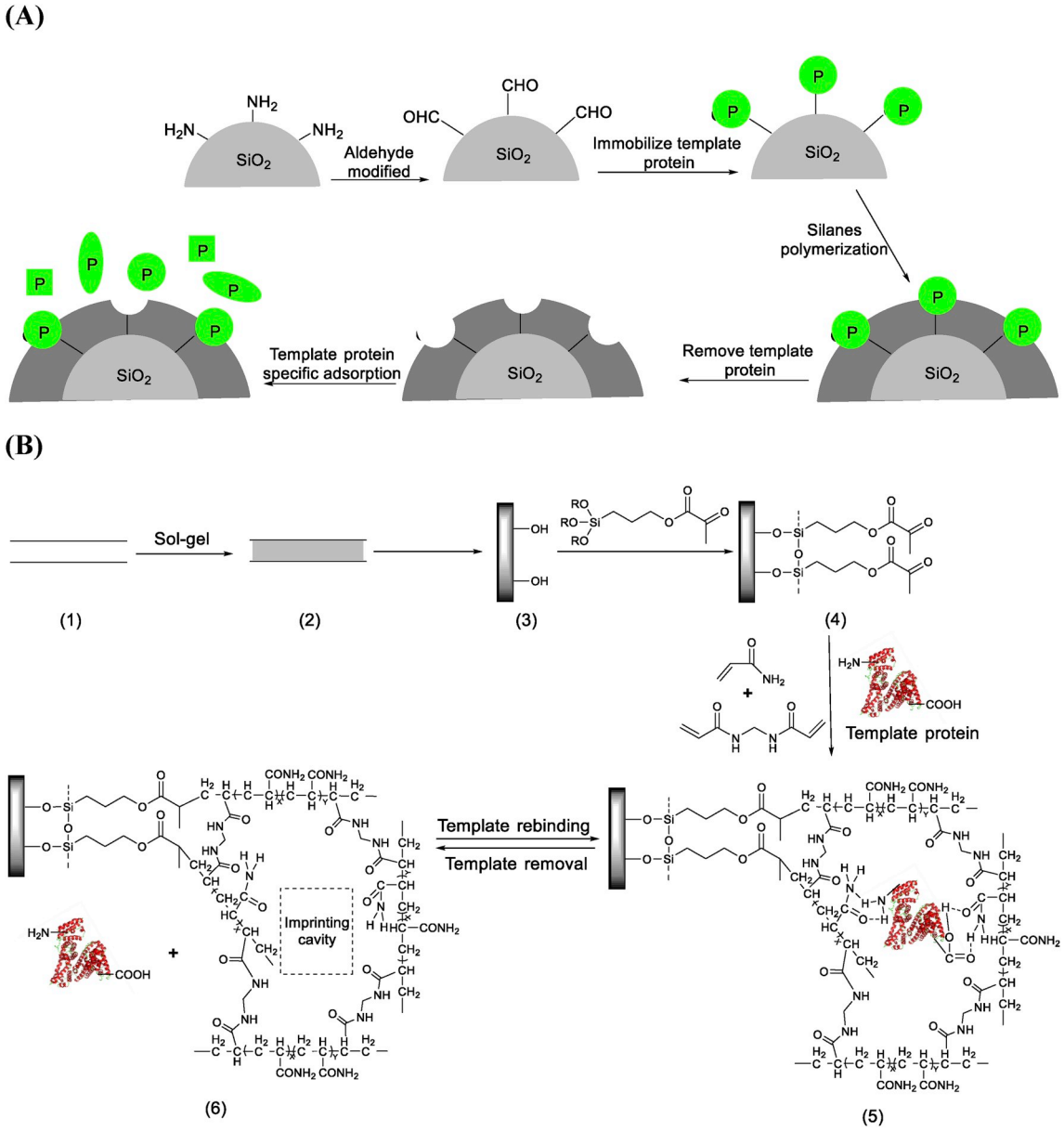

Fig. 6. Schematic representation of the construction of MIPs based on the sol-gel process. The main steps of preparation procedure can be recognized as the surface modification of silica beads; BSA template immobilization; removal of template protein; the MIPs specific adsorption in the presence of various proteins (A) [57]. Schematic representation of preparation procedures of hybrid silica-based MIPs monolithic column which can be summarized as: (1) bare stainless steel column; (2) naked silica skeleton prepared by sol-gel process; (3) silanols on the surface of silica monolith; (4) vinylation on the surface of silica monolith; (5) formation of MIPs coating on the surface of silica monolith; (6) removal of template protein (B) [59].

the whole protein template during the synthesis of protein-imprinting polymers [53]. This method was first adopted for imprinting of BSA, where impressed chains were directly grown through free radical polymerization on the surface of exposed vinyl groups of MWCNTs ceramic electrode (CeE) [54]. In this study, the fabrication of a different type of MIPs with the substrate-selective property has been described. Tetraethylene glycol 3-morpholine propionate acrylate (TEGMPA) and BSA were employed as functional monomer and template, respectively. Polymerization was directly performed using "surface grafting-from" method in aqueous solution on the exposed vinyl functional groups of MWCNTs modified CeE electrode (Fig. 5A). Simultaneously, in aqueous condition at pH 6.8, the recognition of BSA involved the formation of hydrophobically ionic interactions and H-bonding between BSA molecules bearing negative charge and the fabricated MIPs nanofilm with a positive charge (Fig. 5B). The obtained LOD (0.42 ng mL^{-1}) was free from any matrix complications and cross-reactivity in the tested samples, including aqueous, liquid milk, pharmaceutical, and serum. Finally, it has been recommended the practical use of the proposed sensor for the ultra-detection of BSA in clinical assays.

For the recognition of BSA, protein molecularly imprinted membranes (PMIMs) were used as a novel approach for the preparation of MIPs. For possible detection of BSA molecules by this methodology, it has been considered the synthesis of PMIMs on the MWCNTs surface via SMIT process. BSA as the template, AAM as the functional monomer, *N*,*N*′-methylenebisacrylamide (NNMBA) as the cross-linker and APS as the initiator were used in this study [55]. The optimum amounts of raw materials in this work were obtained to be 0.1 g of MWCNTs, 0.02 g of BSA, 0.24 g of AAM, 0.1 g of NNMBA and 0.025 mg of APS in 5 mL phosphate buffer solution. The ability of the developed PMIMs/MWCNTs for selective recognition was evaluated using adsorption experiments. At a BSA concentration of 0.2 mg mL^{-1}, the maximum adsorption capacity was obtained while a saturation value of 5.53 mg g^{-1} was achieved for the PMIMs/MWCNTs. Higher adsorption capacities of the PMIMs/MWCNTs in the selectivity adsorption experiments for BSA compared to other template molecules, such as HSA, BHb, pepsin, and HRP was also reported. The affinity to BSA was found to be 2.6-fold higher for the PMIMs/MWCNTs compared to the non-PMIMs/MWCNTs. On the other hand, the synthesized PMIMs/MWCNTs affinity against other template molecules did not show significant changes compared to non-PMIM/MWCNTs.

6.1.5. Surface imprinted tubular carbon nanofibers (SIPTCFs)

It has been shown that SIPTCFs can be considered as promising materials for protein separation and purification because of the excellent separation ability and reusability for actual samples. SIPTCFs with the self-driven property were first developed by Yang et al. [56] in order to promote protein purification procedures. Tubular carbon nanofiber carrier was obtained by hypercrosslinking, carbonization, and carboxyl functionalization reactions. During the adsorption process, the cavity and porous tube wall of the prepared materials were the cause of the difference in the osmotic pressure between outside and inside of SIPTCFs providing self-driven specific adsorption performance. BSA was used as a template and polydopamine (PDA) as an imprinted polymer layer. It was reported reasonable pore structure, high specific surface area, and self-driven properties for the SIPTCFs. The amount of adsorption of SIPTCFs to BSA could reach 541,99 mg g^{-1} in 60 min. In the presence of the mixed proteins including HSA, Lyz, Cyt C, BHb and FBS, SIPTCFs recognized the target protein BSA with high selectivity.

6.1.6. Silica beads

One of the specific interests of different MIPs is the use of these materials as a stationary phase in HPLC and other solid phase extraction (SPE) applications for the separation of the protein of interest because of their unique predetermination and selectivity. Fig. 6A illustrates the fabricated sol-gel MIPs for the recognition of BSA, which were synthesized through the polymerization on aminopropyl silica beads surface by the immobilization of BSA as template [57]. On the surface of aminopropyl silica beads, BSA as template was modified and then, the organic silanes were added and polymerized. For the creation of imprinting cavity, BSA molecules were removed. The reaction of medium with glutaraldehyde was considered for the introduction of aldehyde groups on the surface of beads. For imine-bond formation, they

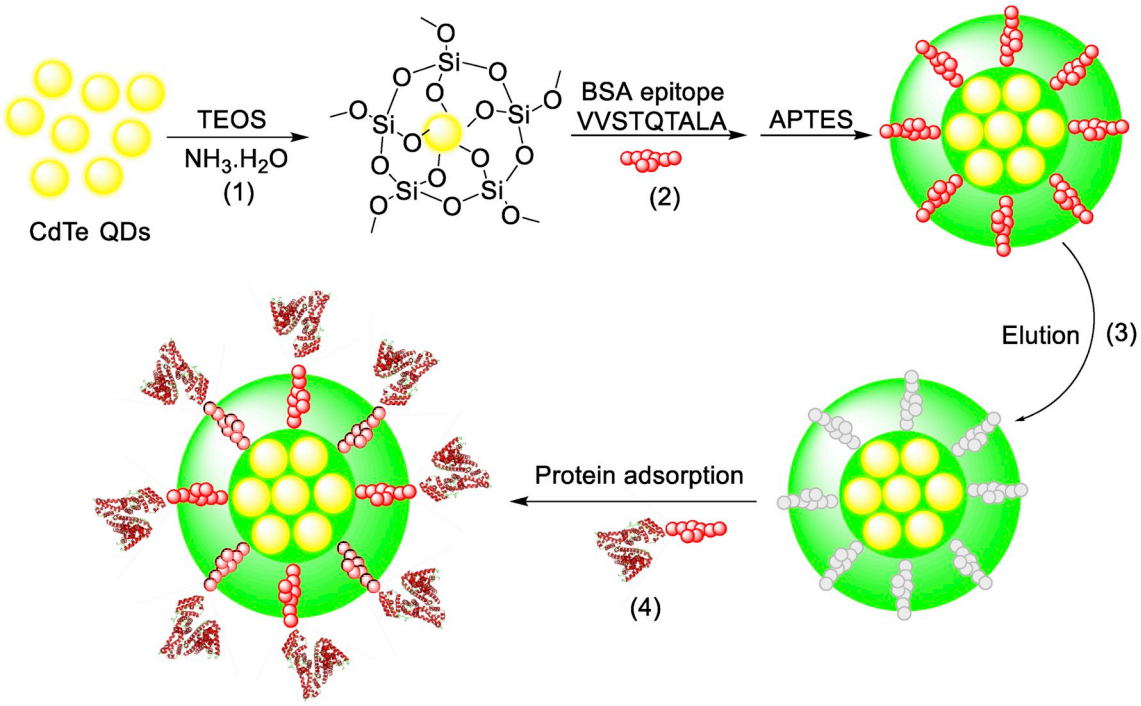

Fig. 7. Scheme for the preparation of EMIPs-coated CdTe QDs. The main steps of the fabrication process are included as (1) modification of CdTe QDs with silica shell; (2) the development of EMIPs-coated QDs in the presence of the synthetic peptide as a template molecule obtained from the C-terminus of BSA; (3) removal of template peptide; (4) the adsorption of BSA molecules on the surface of EMIPs-coated QDs [14].

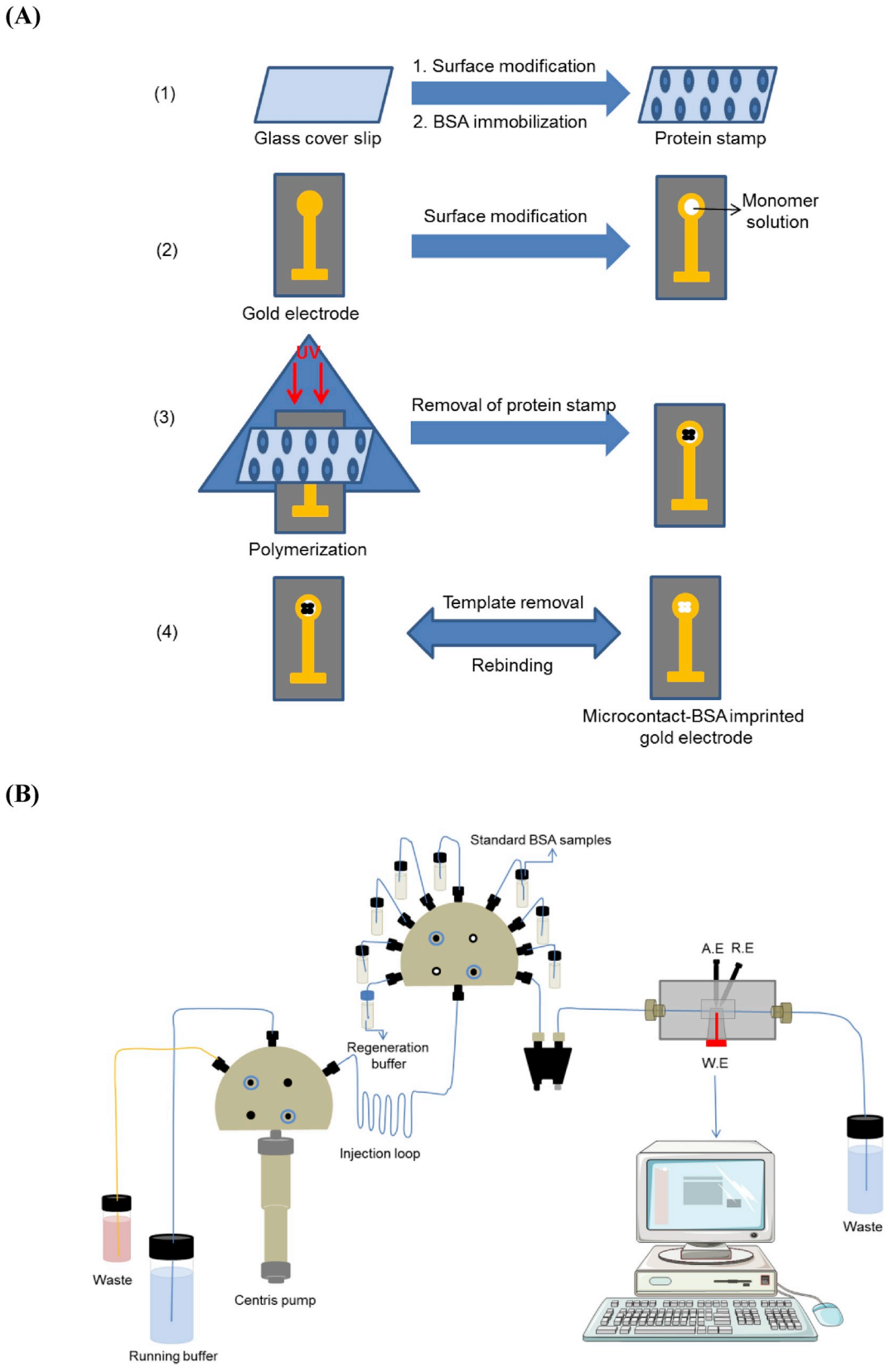

Fig. 8. Schematic representation of the microcontact-BSA imprinted capacitive biosensor. (1) The main preparation steps include the glass coverslips (protein stamps); (2) preparation of the capacitive gold electrodes; (3) microcontact imprinting of BSA onto the gold electrode surface via UV-polymerization, and (4) the removal of template protein (BSA) from the electrode surface (A). Schematic diagram showing the capacitive immunosensor with an automated flow injection system (B) [63]. General schematic procedure for the preparation of microcontact thin surface imprinted polymers (C) [64]. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

immobilized BSA on the surface of the silica beads by covalent interaction between the amino group of BSA and the aldehyde group. The relationship between fundamental parameters of MIPs preparation and their effect on the selectivity of separation was studied based on the above system. Before the removal of template protein, a mixture of octyltrimethoxysilane (OTMOS), APTES, and tetraethoxysilane (TEOS) at a ratio of 42.5:42.5:5:15 was used for the polymerization. The best separation selectivity obtained for the fabricated MIPs can be explained by the prolongation of the carbon chains, the formation of stronger hydrophobic interactions and the template separation with high selectivity. In another research, a novel type of column packed with macroporous hybrid silica monolithic fabricated by the MIT method for the first time was used for the evaluation of recognition property by imprinting BSA and Lyz as templates. In this investigation, the authors synthesized the macroporous silica skeleton based on monolithic in a stainless steel column by a mild sol-gel method using methyltrimethoxysilane (MTMS) as a sole precursor, and vinyl groups were then introduced by chemical modification of γ-methacryloxypropyltrimethoxysilane (γ-MAPS) on the surface of the silica skeleton. Then, the copolymerized MIPs were anchored on the surface of silica monolith (see Fig. 6B for further details). Lyz and BSA with different pIs, charges, and molecular size as the imprinted templates were selected to evaluate the protein sensing capability of hybrid silica MIPs. The obtained hybrid silica-based MIPs monolith exhibited a higher binding affinity for the templates under optimum conditions than its corresponding non-imprinted monolith. Keeping in mind that the measurement of the interaction strength between the template molecule and the imprinted polymer is defined as imprinting factor (IF) [58], the IF values for BSA and Lyz were obtained to be 9.07 and 6.52, respectively. Moreover, their results indicated that the hybrid silica-based MIPs monoliths have excellent recognition ability for both template proteins. Finally, for the prepared hybrid silica MIPs monolith, higher durability and proper recognition compared to the stationary phase imprinted silica beads and in situ organic polymer-based monoliths MIPs were reported [59].

6.2. BSA-epitope-based MIPs (EMIPs)

The large molecular size is another challenge in the development of MIPs for the recognition of the BSA molecule. To overcome this obstacle, "epitope approach" as an alternative template for the use of complete protein was firstly recommended by Rachkov and Minoura [60], which uses only a small part of the protein as a substitute for the complete protein and the resulting imprinted polymers are capable of determining the complete protein. Nishino et al. [61] reported the development of an imprinting technique based on the epitopes derived from BSA,Cyt C, and alcohol dehydrogenase (ADH) C-terminus domains as peptides for the imprinting on silica surfaces or clean glass. BSA-EMIPs displayed reasonable affinity when a mutant peptide with only one mutated amino acid was used as a template at the same conditions. The resulting film for the prepared EMIPs of Cyt C exhibited approximately seven times higher affinity and target capacity. A new EMIPs for the recognition of BSA as the target protein with high specificity and direct measurement of fluorescence intensity was reported [14]. The polymerization was done on the silica nanospheres surface surrounded CdTe QDs. In this research, the CdTe QDs were directly modified by the sol-gel reaction using $NH_3.H_2O$ as a catalyst which accelerates the reaction with a silica shell. The preparation steps of EMIPs-coated QDs are illustrated in Fig. 7. As a template molecule, the synthetic peptide

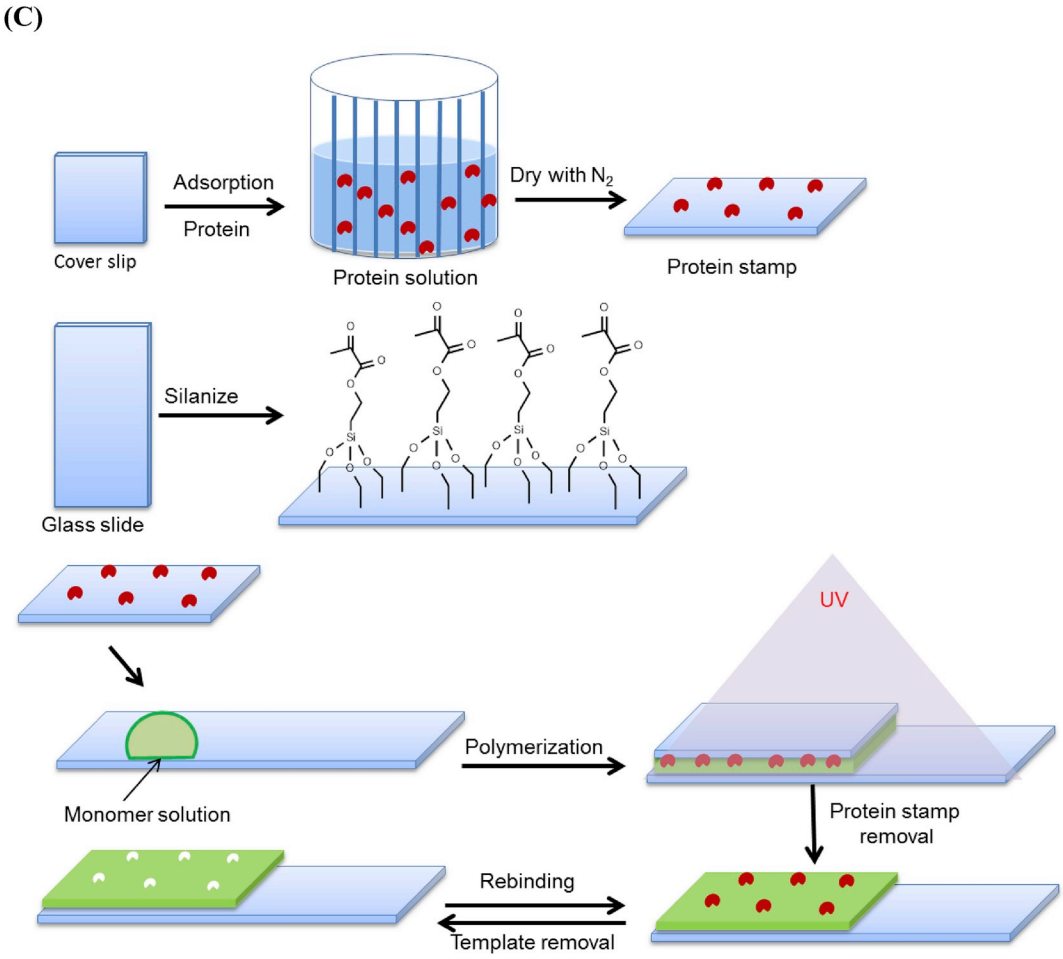

Fig. 8. (*continued*)

was obtained from the C-terminus positioned on the surface of BSA molecules (599–607 residues). The resulting recognition cavities enabled the fabricated EMIPs film to capture the template peptide and BSA protein selectively. Compared with MIPs-coated CdTe QDs and BSA as the template, the direct fluorescence quantification of BSA for the MIPs-coated CdTe QDs nanospheres and the used epitope as the template was successful. The adsorption capacity and the IF of EMIPs-coated QDs were significantly improved. The fabricated EMIPs-coated QDs can also distinguish even one incorrect sequence from the selected epitope of the BSA original sequences. By evaluating BSA detection in the bovine sample of calf serum, satisfactory results were reported for the analytical performance and useful application of the EMIPs-coated QDs. Moreover, the obtained nanospheres of EMIPs-coated QDs were also effectively used for BSA separation from the bovine blood samples.

6.3. BSA-MIPs based on microcontact imprinting technology

Due to some problems in the fabrication of MIPs for the recognition of proteins with large molecular size as templates, many scientists have motivated to imprint directly the template protein on a substrate, and thus, the target protein recognizes the created surface of the substrate. Microcontact imprinting is well-known as a powerful technique for surface coating; therefore, it is suitable for the recognition of macromolecules. Generally speaking, the method procedure depends on the polymerization between the protein stamp and the polymer support. In the first step, the protein stamp is formed by adsorbing the template protein to a pre-cleaned glass surface. On the second surface, the protein stamp will then come into contact with the monomer-coated substrate. The thin polymer film is thus formed through UV polymerization on the support. Finally, specific recognition sites for protein on the imprinted support surface are produced by the removal of template protein [62]. The simultaneous use of microcontact imprinting method and applications of biosensor technology can provide promising tools for future purposes. In this way, it has been reported the combination of capacitive biosensor technology and microcontact imprinting technique for the analytical detection of BSA [63]. As it has been shown in Fig. 8A, protein stamps were prepared using the glass coverslips, and the capacitive experiments were measured by using an automated flow-injection system (Fig. 8B). The microcontact-BSA imprinting gold electrodes (GE) were manufactured in the presence of polyethylene glycol dimethacrylate (PEGDMA) as a cross-linking agent and methacrylic acid (MAA) by contacting the protein stamp and GE during the polymerization under UV light. The cross-reactivity of 5 and 3% was found towards BSA and IgG, respectively. For two months, the electrodes were used for more than 70 tests and retained the binding properties during this period.

Thin surface imprinted polymers films of cognitive networks based on 2-(dimethylamino) ethyl methacrylate (DMAEMA) as the functional

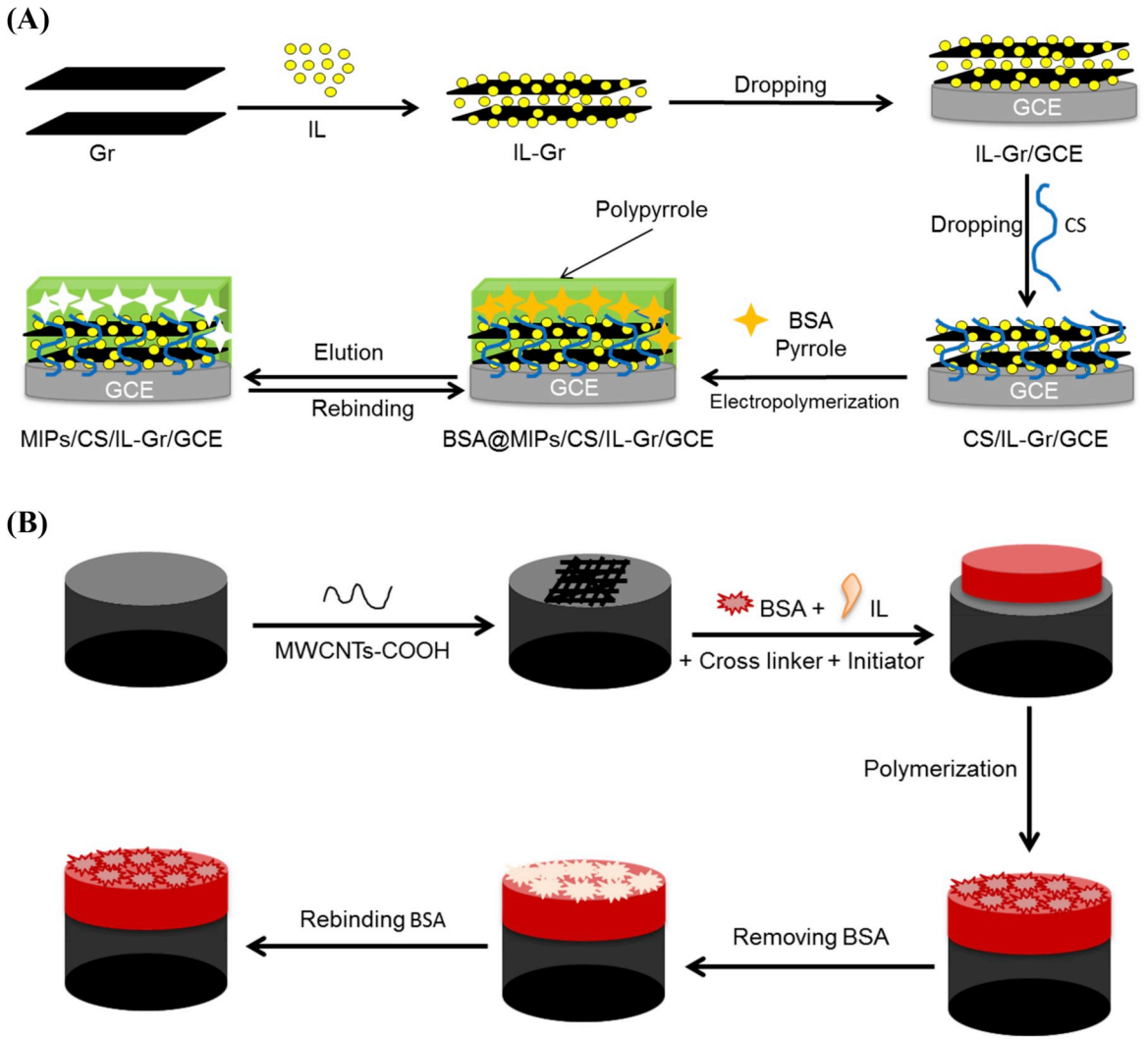

Fig. 9. Schematic illustration procedure for the preparation of electrochemical sensor based on CS/IL-Gr modified GCE (A) [66]. Schematic representation for the fabrication of the BSA imprinted sensor using IL and the specific recognition of BSA (B) [67].

monomer and different amounts of NNMBA or polyethylene glycol 400 dimethacrylate (PEG400DMA) as the crosslinking agent was manufactured using UV free radical polymerization as a novel technique and characterized for the BSA specific recognition (more details are given in Fig. 8C). For these systems, a precise and reproducible increase in the template recognition was shown at 1.6–2.5 times more BSA than control polymers recognized by the MIPs sample. These polymers also showed selective template recognition relative to competing proteins with up to 2.9 times more adsorbed BSA than either glucose oxidase (GOX) or BHb. As the next generation of robust recognition elements in a wide range of bioassay and biosensor applications, these synthetic antibody mimics are claimed to be promising [64].

6.4. BSA-MIPs based on ILs

ILs are known as the preserved stable salts present in the liquid form, which have been gained increasing attention in the development of electrochemical sensors because they have some benefits such as high chemical stability, electrochemically large windows and good ionic conductivity [65]. They can be used as a supporting electrolyte or a modifier in an electrochemical sensor based on graphene (Gr). For the selectively and sensitively detection of BSA, a novel and straightforward MIPs electrochemical sensor based on CS/IL–Gr modified glassy carbon electrode (GCE) was electrochemically prepared. 1-butyl-3-methyl imidazolium hexafluorophosphate (BMIMPF6) as a room temperature IL was employed in this work. The use of Gr nanocomposites, ILs, and CS, had the synergistic effects and improved the electrochemical response and sensitivity of the developed sensor. The details of CS/IL–Gr/GCE preparation procedure are illustrated in Fig. 9A. The described MIPs/CS/IL–Gr/GCE revealed a linear relationship between the logarithms of BSA concentration and the change of current response in the range of 1.0×10^{-10}–$1.0 \times 10^{-4}\,g\,L^{-1}$ with a LOD of $2 \times 10^{-11}\,g\,L^{-1}$. Besides, the manufactured sensor was good reproducibility, high selectively, acceptable recovery, and excellent stability, indicating its clinically potential uses [66].

Using another IL 3-(3-aminopropyl)-1-vinyl imidazolium tetrafluoroborate (AVIMBF4) as the functional monomer, the MIPs film was in situ polymerized at room temperature on a carboxyl functionalized MWCNTs modified on the GCE surface in an aqueous solution [67]. In this investigation, APS and N, N, N′, *N*′-tetramethylethylenediamine (TEMED) were used as initiators, and NNMBA and BSA were considered as the crosslinker, and template molecules, respectively. Fig. 9B illustrates the representation for the manufacture of BSA imprinted sensor and its specific quantification. High sensitivity, enhanced accessibility, and reasonable specificity towards bovine albumin were reported for the MIPs film based on the used ILs. A linear relation for the current change of BSA recognition and its concentration was obtained (1.5×10^{-9}-$1.5 \times 10^{-6}\,mol\,L^{-1}$) in optimal conditions, and the LOD was $3.91 \times 10^{-10}\,mol\,L^{-1}$. The produced imprinting sensor was practically applied in liquid milk samples for the determination of BSA.

6.5. BSA-MIPs based on imprinted hydrogels

The intelligent hydrogel is a type of matrix that can correspond to a small environmental stimulation such as temperature, pH, ionic strength or various chemicals with the specific size and structure [53]. It contains a monomer component which is sensitive to stimulation causing the matrix to swell or shrink and a functional monomer constituent with small size act as a holder for the target molecules at multiple points via electrostatic interactions. Unlike traditional imprinting polymers with a rigid matrix, it is possible to control the relative position of the functional groups in this type of smart hydrogel through the hydrogel matrix stimulus response. The flexibility in structure allows the intelligent hydrogel to control the absorption and release of template molecules while overcoming the problem of elution and mass transfer [68]. The use of hydrogels with macroporous and soft structure in the fabrication of BSA-MIPs is considered as another approch, which helps diffuse and elute the template easily. Since the preparation conditions are useful for keeping the natural protein conformation, either synthetic or natural hydrogel polymers are often chosen as the matrix for hydrogel-based MIPs [69]. As shown in Fig. 10, a new method based on temperature-sensitive molecular imprinted hydrogel which is composed of 2-acrylamido-2-methylpropanosulfonic acid (AMPS), NIPAAM, NNMBA, and AAM monomers was prepared using free-radical crosslinking copolymerization under two different temperatures (−20 and 25 °C) in aqueous solution. The effects of external temperature stimuli on the hydrogel affinity have been investigated, and the optimal binding conditions have been tested while BSA was used as template. Compared to the non-imprinted hydrogels, the adsorption capacity for BSA in the frozen imprinted hydrogels was found to be higher. The plots of Langmuir isotherm were used for determining the association constant and adsorption capability for the template protein and the hydrogel specific interactions. Several protein types as references, different in MW and pI, were examined to investigate the hydrogel selectivity. It was shown that for the recognition of BSA, the charge effect and the shape memory were the significant factors. This imprinted hydrogel was used to adsorb BSA from a protein mixture and actual samples, which showed its potential selectivity [70].

Sodium alginate (NaA) is a naturally occurring polysaccharide found in brown algae. It comprises mannuronic and guluronic acid units, in which the latter can complex with calcium ions in aqueous solution to create the insoluble calcium alginate (CaA) like egg box junctions [71]. To obtain MIPs for macrobiomolecules, the use of alginate as the matrix has been considered in some investigations [72–74]. By using an inverse suspension method, polymeric microspheres of calcium phosphate/alginate hybrid embedded and coated

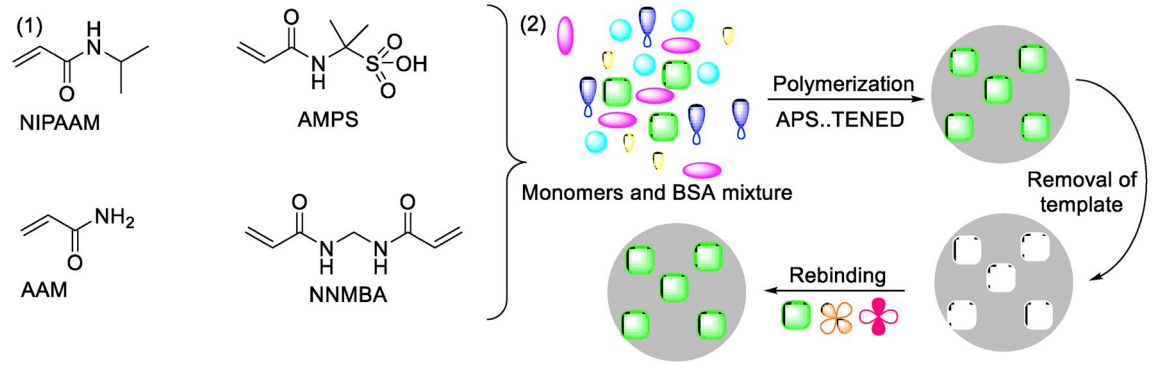

Fig. 10. Schematic representation for the preparation of the imprinted hydrogels. (1) The chemical structures of the used monomers; (2) the synthesis of hydrogels in imprinting process utilizing the mixture of different monomers and BSA protein along with the removal of template molecules and rebinding capability of prepared hydrogels in recognition of BSA among different proteins [70].

with BSA on the surface have been developed with NaA and $(NH_4)_2HPO_4$ and the gelling agent $CaCl_2$. All the results showed that the imprinted microspheres showed better imprinting efficiency and higher re-binding capacity. Selectivity studies showed excellent recognition characteristics for the template protein versus others in the imprinted beads [75]. The reusability of alginate is restricted by its bad mechanical stability. To resolve this obstacle, a method based on UV radiation-reduced polymerization for the preparation of a high toughness protein molecularly imprinted CaA/polyacrylamide (PAAM) hydrogel film (CA/PAAM MIPs) in the presence of BSA as template, and using NaA and AAM as functional monomers, NNMBA as the covalent cross-linker and $CaCl_2$ as the ionic cross-linker was reported [76]. MIP's adsorption capability for BSA was 22.49 mg g^{-1}, 2.7 times greater than NIPs, and CaA/PAAM MIP's imprinting efficiency retained 77.95% of the original value after five repetitions.

Very thick CaA hydrogel membrane and the larger microcapsule are thought to be the reasons of slow adsorption rate and the low adsorption capacity of BSA by the prepared MIPs. To overcome this problem, Qi, et al. [77] prepared BSA-imprinted CaA hydrogel membrane using BSA, NaA and $CaCl_2$ as a template, functional monomer, and cross-linker, respectively. A glass rod enlaced with brass wires with 0.1, 0.2, 0.3, 0.4, and 0.5 mm diameter was used for controlling the thickness of the CaA membrane. It was indicated that during the process of preparation and elution, the conformation of BSA did not change. The higher imprinting efficiency and larger adsorption capacity were reported for thinner CaA hydrogel membrane. The maximum adsorption capacity of MIPs and CaA hydrogel membrane NIPs was 38.6 mg g^{-1} and 9.2 mg g^{-1}, respectively, with an imprinting efficiency of 4.2.

PAAM as a biocompatible hydrogel has a soft and wet macroporous framework that can allow large proteins to be diffused. The formation of strong interactions between the amide functional groups of PAAM and peptide bonds in the protein even in polar solvents is the main advantage described for PAAM [78]. Nearly all protein-imprinted PAAM hydrogels are particles or microspheres whose shapes are difficult to control in aqueous solution during recycling. An organic solvent is frequently employed as a dispersion medium in the preparation of microspheres, which inescapably leads to protein denaturation. In several applications, film materials have more benefits than microspheres or granules. Using non-woven polypropylene (PP) fiber as the matrix, BSA as template, AAM as functional monomer and NNMBA as cross-linker, BSA imprinted PP fiber-grafted PAAM hydrogel membrane (PP-g-PAAM MIPs) was prepared via UV radiation-reduced polymerization in aqueous solution [69]. The evaluation of adsorption and recognition properties showed that the PP-g-PAAM MIPs had a significant improvement in terms of adsorption capacity for BSA compared to non-imprinted ones. Using Lys, ovalbumin (Ova), BHb, and GOX as control proteins, PP-g-PAAM MIPs could recognize the template protein, and the selectivity factor (β) was above 2. The imprinting efficiency of PP-g-PAAM MIPs tended to be stable after three cycles and maintained 76% of the initial value of the IF even after five times use. It has also been reported the preparation of BSA imprinted nonwoven PP fibre supported CaA/PAAM hydrogel film (PP-s-CaA/PAAM MIPs) using nonwoven PP as matrix, BSA as template molecule, NaA and AAM as functional monomers, NNMBA as covalent cross-linker, and $CaCl_2$ as ionic cross-linker by UV radiation-reduced polymerization in an aqueous phase. In this research, authors obtained the adsorption capacity of 27.02 mg g^{-1} for BSA- MIPs with the adsorption time of 900 min and 2.8 times higher than of the NIPs [79]. The use of polysiloxane (PS) has been proposed as an alternative to resolving the thermostability and mechanical strength problems of PAAM-based hydrogels. BSA-MIPs membrane using PS was prepared by sol-gel technology. β-methoxyethylene triethyoxysilane (KH-570) and γ-amidopropyl triethyoxysilane (KH-550) silanes as the functional monomers, BSA as the template and CaA hydrogel film as the matrix have been used in this work. The adsorption capacity of BSA-imprinted PS for BSA was 28.83 mg g^{-1} and it was reported to be 2.18 times the NIPs membrane. Among different control proteins such as BHb, Ova and bovine γ-globulin, BSA-imprinted membrane based on PS could identify BSA molecules [80].

The combination of thermo-sensitive polymers with hollow Fe_3O_4 microspheres has also been reported in the preparation of surface-imprinted materials for the practical and specific recognition of BSA indicating its great potential in bioseparation and biosensor development

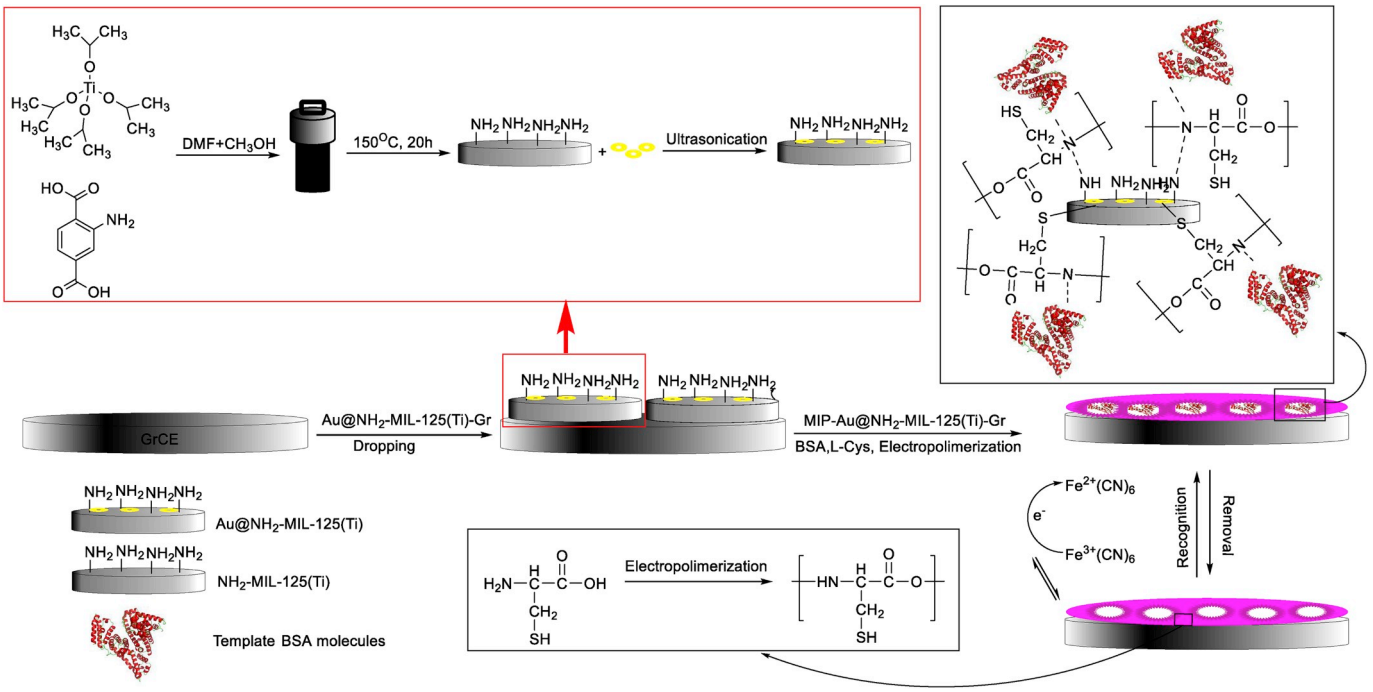

Fig. 11. The specific fabrication process of MIPs-Au@NH_2-MIL-125(Ti)-Gr/GCE. The process can be summarized in three main steps: (1) the Au@NH_2-MIL-125(Ti)-Gr functional materials were dropped on the surface of GCE to fabricate a 3D versatile imprinting sensitive platform; (2) electropolymerization of L-Cys and BSA on the above modified electrode; (3) removal of the template BSA molecules by HCl solution to form a specific BSA sensor [84].

[81]. In this study, the optimal adsorption capacity and IF for BSA at 32 °C were reported to be 430.67 mg g^{-1} and 2.01, respectively. NIPAAM, MAA and NNMBA were used for the synthesis of thermo-sensitive imprinted microspheres. In the presence of hollow Fe_3O_4 microspheres as substrates, the imprinted microspheres were prepared using MIT and grafting copolymerization technique. Hollow Fe_3O_4 microspheres have been used in the imprinting system because of their unique properties such as high specific surface area, excellent water dispersibility, and lightweight. The existence of poly-(*N*-isopropylacrylamide) (pNIPAAM) in the fabricated MIPs played a significant role in the efficient recognition of BSA and the high sensitivity in the ambient temperature.

6.6. Other considered approaches

6.6.1. BSA-MIPs based on metal-organic frameworks (MOFs)

MOFs with a crystalline porous structure and 3D stereoscopic network are a new type of organic-inorganic composite materials which have been examined to solve the water competition problem during the preparation of BSA-MIPs. MOFs can be prepared by connecting metal ions to organic linkers and the modification of functional groups for altering their physical and chemical properties [82]. The structures of MOFs are mainly microporous, which exhibit tunable pore size, high surface area, and high absorption capability. Thus, they could be considered as useful multifunctional solid materials for the recognition of different molecules, including proteins, metal ions, and metal oxide NPs [83]. For the possible ultra-trace detection of BSA, the construction of a new 3D molecularly imprinted electrochemical sensor (MIECS) based on materials with 3D porous electrocatalytic structures and Gr modified carbon electrode (GrCE) has been tired by Duan et al. [84]. In this study, they used a rapid and straightforward ultrasonic technique for the preparation of gold nanoparticles (AuNPs) supported amino-functionalized Titanium (Ti)-benzenedicarboxylate porous MOFs [AuNPs@ NH_2-MIL-125 (Ti) composites] and the stable MIPs films were made using BSA as templates and L-cysteine (L-Cys) as functional monomers by electropolymerization. The details of the preparation procedure are illustrated in Fig. 11. The constructed Au/NH_2-MIL-125(Ti) in combination with the electrocatalytic AuNPs provided a conductive 3D porous framework material for high electron transferring. Excellent porous structure with a large surface area enabled the sensor for more specific binding sites and fast electrolyte diffusion. NH_2-MIL-125(Ti) has been chosen as a useful 3D matrix since it had higher catalytic activity and large pore due to the presence of amine functional groups. In 3D structures, AuNPs interacted with L-Cys functional monomers via Au–S links. H-bonding and electrostatic forces are the main interactions formed the stable protein-MIPs complex between L-Cys and BSA. For the interaction between MIPs and BSA via H-bonding or electrostatic forces and weakening the water competition, L-Cys acted as the functional monomer. Besides, L-Cys functional monomers were electrocatalytically oxidized by the Au/NH_2-MIL-125(Ti) and thus, the sensitivity of MIECS for the detection of BSA molecules was enhanced. Under the optimal conditions, it has been shown that the MIECS with 3D frameworks presented a wide linear range of 10^{-18} to 10^{-12} g mL^{-1} and a low LOD of 4.147×10^{-19} g mL^{-1}. Authors found that the manufactured 3D MIECS could be used with satisfactory results for BSA quantification in the liquid milk samples.

6.6.2. Resorcinol-formaldehyde-melamine (RFM) hydrophilic resins

The presence of polar groups on the hydrophilic resins makes such materials extremely water-compatible [85]. RFM as a hydrophilic resin has dual monomers, resorcinol, and melamine, as well as various hydrophilic groups such as ether and amino, hydroxyl and imino groups [86]. RFM, therefore, combines the merits of melamine-formaldehyde resins with resorcinol-formaldehyde, such as high rigidity and good hydrophobicity. The specific recognition and high selectivity of MIPs in combination with the high stiffness and hydrophobicity of RFM can provide a practical approach to the interaction of abundantly present functional groups on RFM with proteins through different types of weak interactions including π–π or electrostatic interactions and H-bonding. The synthesis process is simple (no nitrogen atmosphere and initiator

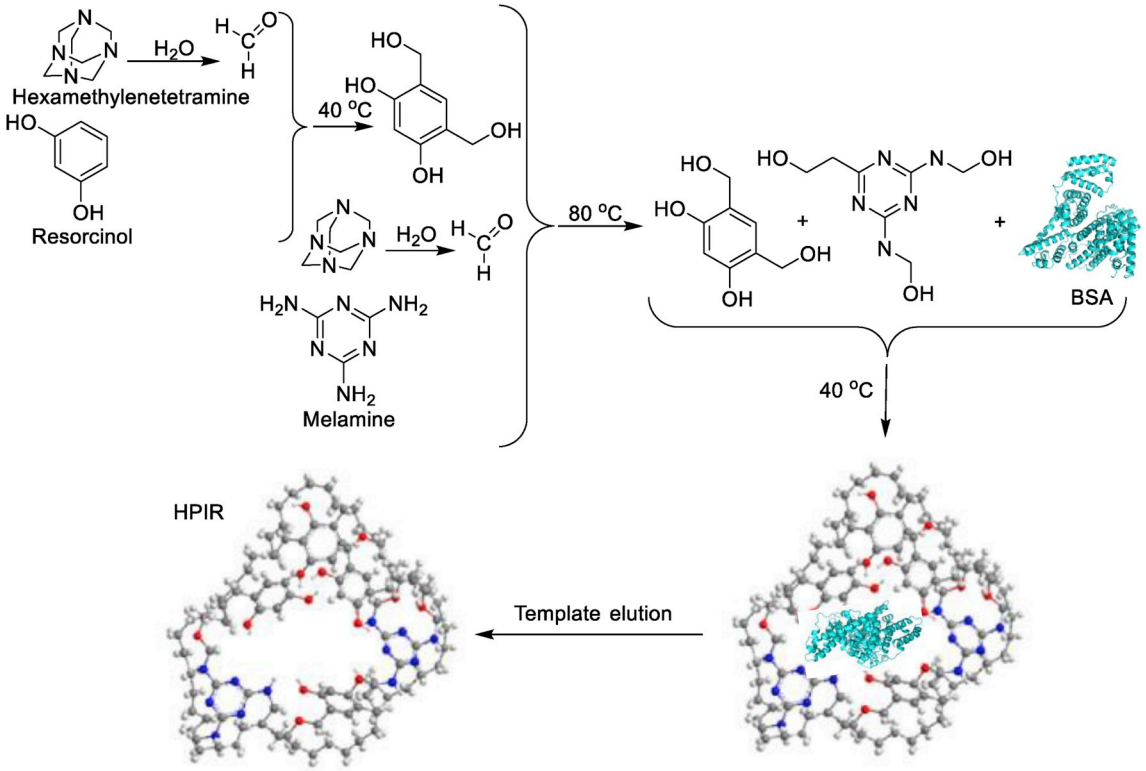

Fig. 12. Principle and procedure of HPIR synthesis [87].

required), time-saving, and the used solvent is only water. For the above reasons, an environmentally friendly green synthesis method for the preparation of hydrophilic protein imprinted resin (HPIR) using hexamethylenetetramine instead of cross-linker formaldehyde, melamine and resorcinol as dual-functional monomers, solvent water, and BSA as a dual function template have been newly developed [87]. The preparation of HPIR procedure is illustrated in Fig. 12. It has been observed that BSA plays a central function as both imprinting and porogenic template in the development of HPIR. The kinetics of BSA adsorption on HPIR followed pseudo-second-order kinetics, and the obtained data for equilibrium were well fitted with the Langmuir isotherm. At a temperature of 25 °C, IF for BSA binding was reported to be 5.78, and the adsorption capability was 44.3459 mg g^{-1}. In an aqueous solvent, HPIR exhibited high specific selectivity, rapid mass transfer rate, and high adsorption capacity for BSA. It has been recommended that HPIR can be used to adsorb BSA protein with high selectively in urine without the biological matrix interference. HPIR is, hence, promising to be applied to pharmaceutics, diagnostics, and proteomics.

6.6.3. BSA-MIPs beads

Generally, SPE is a useful technology in the pre-concentration and clean-up of environmental and biological samples analysis because of its some benefits such as high speed, the low consumption of organic solvents and simplicity. Despite the excellent properties, the separation of analytes using C8 or C18 as classical sorbents in SPE procedure is based on non-selective hydrophobic reactions leading to partial extraction of other interfering molecules. Thus, for the removal of co-extractants, additional purification steps are still required. Therefore, novel sorbents such as MIPs and immune sorbents are extensively prepared to meet the requirement of high selectivity [88]. The study performed by Soleimani et al. [89] describes the synthesis of MIPs by radical polymerization using bovine albumin, 2-vinyl pyridine (2-VP), EGDMA and 2, 2′-azobisisobutyronitrile (AIBN) as a template, functional monomer, cross-linker, and initiator, respectively. In the absence of bovine albumin, NIPs with the same method were prepared and treated. In this study, for the separation of BSA by the developed MIPs and NIPs, an adsorption process based on SPE under various conditions was employed by the authors. The competitive experiment implied that the adsorbents based on MIPs had the highest selectivity enrichment and retention compared to NIPs for bovine albumin. The highest adsorption for BSA by the prepared MIPs was 24 mg g^{-1}, and in the range of 20–200 mg L^{-1} of BSA, calibration curves were obtained to be linear.

The reverse suspension polymerization phase has been found to be as another practical and simple technique to solve the challenge of water compatibility in the imprinting of macromolecules such as albumin. BSA-MIPs beads, which had narrow recognition capability and reasonably good adsorption properties, were obtained with a combination of MAA and AAM as two functional monomers and NNMBA as a crosslinking agent [90]. The obtained polymer beads physical properties and selectivity were investigated, and when the ratio of MAA and the degree of crosslinking in the total monomers was chosen at 40% and 30%, respectively the resultant polymer beads had excellent physical properties and selectivity.

6.6.4. Molecular imprinting polymeric microspheres (MIPMs)

Because of rapid determination, high accuracy, and available procedure, flow injection chemiluminescence (FI-CL) has recently been considered extensively [91]. MIPMs as a detection tool was reported in the preparation of an FI-CL sensor for BSA determination [92]. In the presence of BSA as a template,MAA as functional monomer andEGDMA as cross-linker, BSA-MIPMs were synthesized in toluene using suspension polymerization method. As presented in Fig. 13, a novel FI-CL flow path was designed and to achieve a Y-shaped flow path, a module of polymethyl methacrylate (PMMA) was drilled, by which two reactants were injected simultaneously. The BSA solution was initially delivered to the MIPMs column by pump 1(the switching valve was connected to b) while the second pump was off. During this process, BSA was adsorbed selectively on the polymer. Pump 1 delivered water (connected to a switch valve) to clean the MIPMs. Pump 2 delivered potassium permanganate and hydrochloric acid through the column of MIPMs to react with the adsorbed BSA and produce strong chemiluminescence (CL) after adequate cleaning time (80 s). At this time, the binding affinity between MIPMs and BSA destroyed and unoccupied the binding sites. The pump 2 was switched off after the stabilization of the CL signal for blank and the MIPMs column was cleaned by water and ready for the next test. For the preparation of FI-CL sensor, they packed the synthesized BSA-MIPMs into the flow cell. In the range of 1.0×10^{-8} to 5.0×10^{-6} g mL^{-1}, the registered CL intensity was linearly correlated with the BSA concentration, and the LOD was obtained to be 1.5×10^{-9} g mL^{-1}. It was indicated that the developed sensor can be reused, and the selectivity and sensitivity for CL analysis were significantly enhanced. Additionally, MIPMs-CL sensor was efficiently used to determine BSA in milk samples.

6.6.5. BSA-MIPs cryogen

Cryogels with protein imprinting amphoteric PAAM are materials with high potential for detecting charged biomaterials such as macro-biomolecules, microorganisms, cells, or other elements of interest. A protein-imprinting cryogen has been reported in the recent study that shows high affinity and selectivity, such as an antibody against BSA as template [93]. The synthesized MIPs were obtained from AAM, diallyl amine (DAA), NNMBA, and acrylic acid (AA) copolymerization. Due to the involvement of AA and DAA as ionizable monomers, BSA was recognized by the imprinted cavities with private clung groups on the surface. Each pit, therefore, appears as a molecular condenser charged with amino and carboxyl groups (for further details, see Fig. 14). A MIPs membrane contains a wide range of molecular transducers due to the molecular size volume of all cavities. When the sorption/desorption of template occurred on the sensor, it produced a synergistic effect and amplified the impedance signal variations considerably. Superior sensitivity and selectivity were simultaneously achieved when the MIPs were used as an artificial antibody to create an electrochemical sensor. BSA determination was in a linear range of 1.5×10^{-16}-10^{-12} mol L^{-1}. Moreover, a low LOD was also reported at 7.2×10^{-18} mol L^{-1}.

6.6.6. BSA-MIPs sensor chip based on SPR

The simple yet sensitive recognition of biomolecules by optical

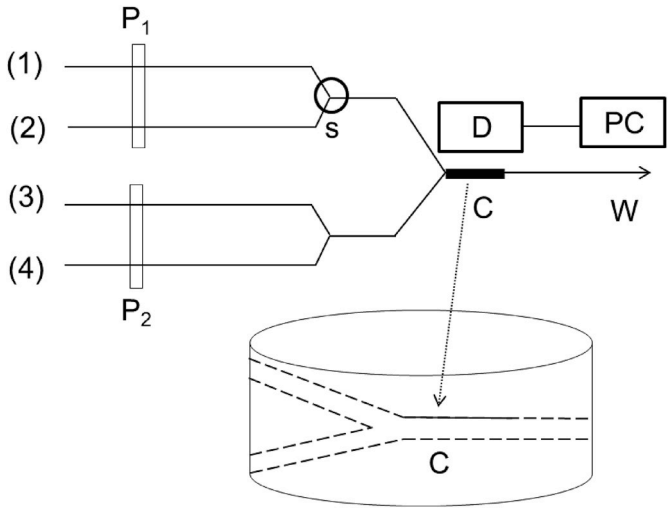

Fig. 13. Schematic diagram of the experiment pathway for FI-CL sensor used for BSA determination. (1) water; (2) sample solution; (3) hydrochloric acid; (4) potassium permanganate solution; (P_1, P_2) peristaltic pump; (S) switch valve; (C) MIPMs column; (D) detector; (PC) computer; (W) waste solution [92].

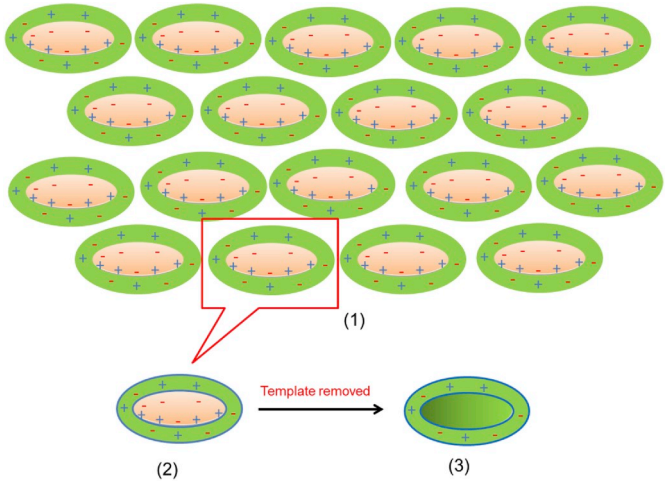

Fig. 14. Schematics of (1) bulk MIPs, (2) imprinted cavity with and (3) without protein template for a constructed protein-imprinting cryogen [93].

transducers has been utilized in the design format of various analytical methods, among others. Optical transduction in SPR renders this approach as an indirect means of mass measurement. That SPR is a powerful technique based on the fluctuations in the refractive index of reaction medium upon the molecular interactions of receptor and ligand on the surface of a metal in real-time and without any labeling of the analyte [94]. As proof of concept, an SPR sensor chip for BSA detection was fabricated by 3-aminophenyl boronic acid (3-APBA) electropolymerization technique [95]. The SEM images displayed the homogeneous formation of cavities at nano size on the surface of the prepared MIPs film due to the removal of template BSA molecule, which played an essential function in recognition of BSA. Consequently, MIPs films showed better adsorption to the bovine albumin. The obtained MIPs films showed good adsorption against BSA (0.02–0.8 mg mL^{-1}) with the LOD of 0.02 mg mL^{-1}.

7. Conclusions

In this review, some MIPs preparation methods using bovine albumin as a template molecule and their applications as useful and highly selective tools for BSA determination and analysis in biological samples has been comprehensively summarized. For the electrochemically developed BSA-MIPs biosensors, the process of analysis in these approaches was reported to be reproducible, more stable, highly sensitive, and selective when the unique properties of the used materials such as ILs, CS, MWCNTs, MOFs, QDs, MNPs, Au NPs, Gr, GO and other methodological concepts and applications are combined together. It is observed that since the last 2–5 years, many studies have been reported based on these approaches. According to the numerous reports reviewed here, surface imprinting method has been considered as an effective strategy among different approaches for imprinting a challenging template such as BSA. However, careful control of pH and salt concentration may be necessary to maintain the native conformational structure and control the charge state for the successfully imprinting of whole protein. However, such accurate control may not be essential in the epitope imprinting method, depending on the functionality of the AAs and whether aqueous or non-aqueous polymerization conditions are used. The most effective approach for imprinting macrobiomolecules like BSA, in our perspective, includes the use of short to intermediate peptides as the template, providing an epitope of the target protein. To date, few studies have been conducted using this strategy. Nevertheless, the imprinting of epitopes seems to be a promising strategy and should be studied accordingly. The entrapment and covalent immobilization difficulties of the entire BSA indicate that almost all approaches directed at surface imprinting, or stamping/printing methods are capable of competing with those based on epitope imprinting.

MIPs' recognition properties depend significantly on the quality of the binding sites created in the matrix, and this applies perfectly to protein-imprinted MIPs. The selection of monomers and cross-linkers as well as their quantities are key considerations determining the performance of the imprinted cavities. Monomer selection is essential, and it can assist with computational and combinatorial approaches. Optionally, it is possible to make a reasonable selection either with a combinatorial (experimental) technique, a chemometric experimental design or computational models. However, most of the functional monomer should be neutral, with AAM and its derivatives being the obvious favorite for BSA imprinting. To maintain the integrity of the imprint sites, the washing conditions used to remove the template must be carefully selected while eliminating as much template as achievable. The microcontact imprinting technique can simplify the removal of templates, as most of them are taken off with the substrate used to introduce the templates to the polymerization mixture.

8. Future perspectives

Undoubtedly, the development of protein-MIPs has been increasing rapidly in recent years. In this regard, the reported studies that were reviewed here concerning bovine albumin confirm the increasing concentration in this area. The importance of determining albumin in this respect is crucial because it can pave the way for the use of MIPs in the analysis of other proteins. It seems that MIPs-based studies and developments not only for BSA but also for other proteins may further focus on the following areas:

(i) Improving the performance of the proposed approaches that can assist in the extraction, separation, and analysis of albumin in analytical laboratories, clinical and nutritional applications.
(ii) Considering new synthesis methods for the preparation of high selectivity MIPs to expand their applications in analyzing other favorite macromolecules of interest in addition to bovine albumin.
(iii) Finding appropriate and practical solutions to problems with the detection of albumin or other proteins in the aquatic medium will be an essential pathway to research.
(iv) The introduction of new polymerization techniques and the exploitation of new high-performance monomers that will lead to the development of new MIPs.

Conflicts of interest

The authors declare no conflicts of interest.

CRediT authorship contribution statement

Ali Jahanban-Esfahlan: Writing - original draft, Supervision. **Leila Roufegarinejad:** Writing - review & editing. **Rana Jahanban-Esfahlan:** Writing - original draft. **Mahnaz Tabibiazar:** Writing - original draft. **Ryszard Amarowicz:** Writing - review & editing.

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