Molecular Imprinting Technology: A New Approach for Antibacterial Materials

E. Kweinor Tetteh, S. Rathilal, M. Amankwa Opoku, I. D. Amoah, and M. N. Chollom

Abstract This chapter presents Molecular Imprinting Technology (MIT) as a biomimetic technique suitable as binding sites for synthetic receptor molecules and functional monomers owing to their definite interest of selectivity, sensitivity, recognition, and applications. MIT has been used extensively for the detection of pharmaceutical compounds like antibiotics which have become a global challenge due to their occurrence in the environment. Also, their detection and recognition in various industrial sample matrices are time-consuming, laborious, expensive, and very intricate. Additionally, MIT has shown great potential in producing antibacterial coatings, which could play a critical role in the fight against antibiotic-resistant bacteria especially in biomedical devices.

In this chapter, recently advanced materials used for biorecognition in terms of their morphological, physiological, and chemical properties together with their preparation techniques, are highlighted. Among the types of MITs, the sol–gel imprinting route based materials derived from polymers, ceramics, and glass which seems very promising are presented here. Additionally, the chapter investigates the strength and limitations of the sol–gel imprinting route to design antibacterial agents or receptors from pharmaceutical compounds, biomaterials, chitosan, nanomaterials, and cell implanting for biomedical applications. It was found to be economically viable with benefits good for both healthcare and environment sustainability. Therefore, MIT development presents economical application for antibacterial detection, recognition, and quantification, due to the high

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selectivity, rapid response, excellent stability, simplicity, and robustness of their materials when integrated with sensor detection technology.

Keywords Antibacterial · Antibiotics · Biosensors · Nanomaterials · Magnetized nanomaterials polymers · Pharmaceuticals · Sol–gel synthesis · Virus (COVID-19)

1 Introduction

Molecular imprinting technology (MIT) is a binding phenomenon for creating ligand selective recognition sites. This involves the binding of a high order structural element or template (ion, atom, molecule, molecular or complex macromolecular or ionic assembly, as well as microorganisms) with a natural molecular species such as receptors (e.g. Antibodies, enzymes, nucleic acids, peptides) (Alexander et al. 2006; Lofgreen and Ozin 2014; Whitcombe et al. 2014; Chen et al. 2016). MIT is mostly used as a molecular lock to mimic designs lock to match a molecular key (Chen et al. 2016). For instance, MIT is employed to facilitate recognition sites of biopolymer during natural interaction occurring in a covalent assembly of a bulk phase through a polycondensation or polymerization process, following the removal of the targeted template species (Alexander et al. 2006; Chen et al. 2016). According to Chen et al. (2011), MITs present unique features, including recognition specificity, structure predictability, and application universality. Since its promulgation by Polyakov in 1931, using silica matrices has received great attention as a practical synthetic method in designing durable molecular identification materials (Polyakov 1931).

In recent years, the concept of the MIT has been built upon by various scholars, which have progressively evolved to be economical and effective in providing versatile receptors with a broader interest in designing, preparations, and characterization (Fu et al. 2015). These include chromatographic sorbents, sewage treatment, purification, separation, receptor systems, biosensors, artificial antibodies, drug delivery, polymers, catalysis, and photocatalytic degradation (Castell et al. 2011; Fu et al. 2015; Chen et al. 2016). The versatile application of MIT is attributed to their significant strength, high physical stability, low cost of operating, and upfront preparation (Nicholls et al. 2013; Qiu et al. 2013; Fu et al. 2015; Chen et al. 2016). However, MIT's biological related research information is limited compared to advanced technologies such as nanomaterial synthesis (Chen et al. 2016). Also, some of the imprinting functional monomers are usually neglected to a certain degree with a restriction on their selectivity for specific applications. Meanwhile, antibodies or antigens have been utilized for the quantification and identification of microorganisms and other complex emerging sample matrices. Of public concern, imprinting bioentity materials like a virus, microbes, bacterial and mammalian cells with tolerable toxic side effects for bioanalytical recognition and biomedical applications must be of importance to stimulate MIT development (Fig. 1).

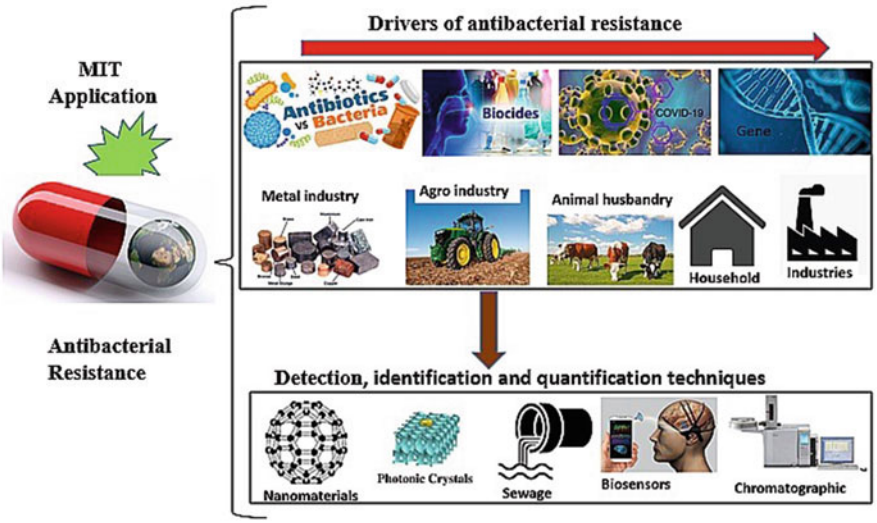

Fig. 1 Schematic account on current emerging antibacterial resistances route and molecular imprinting technology

Since the discovery of antibiotics like Penicillin by Alexander Fleming in 1928, its application has improved healthcare to curb various forms of infections caused by bacteria, viruses, fungi, and parasites (Chollom et al. 2020; Levy and Marshall 2004; Zhang et al. 2020). Of interest, most of these antibiotics are amphipathic (having both hydrophilic and hydrophobic properties), amphoteric, or ionizable organic compounds (Mühlen et al. 2020; Chollom et al. 2019). However, their physiological properties and structural chemistries (size, shape, solubility, and hydrophobicity) can undergo series of phase transformations processes such as biodegradation, dilution, and photolysis (Mühlen et al. 2020; Chollom et al. 2020; Levy and Marshall 2004; Zhang et al. 2020). This usually affects their mobility, persistence, and bioavailability as well as their behaviour in the environment either in a solid or liquid state (Mühlen et al. 2020; Chollom et al. 2020). Despite this, the overuse and misuse of antibiotics in humans, animals, and plants are estimated to rise with an increase in the human population projected to be 9–10 billion by 2050 (Chollom et al. 2020; Zhang et al. 2020). Although there is a remarkable interest in antibiotics (Table 2), some of these biorecognition components like biomarkers of cancer or pathogens used in biomedical applications are becoming infections and resistance, owing to their technical complexity and extraction procedure (Chen et al. 2020; Levy and Marshall 2004; Zhang et al. 2020). For example, the recent coronavirus (COVID-19), antibacterial resistance, and medical implantable device infections are difficult issues to handle (Chen et al. 2020; Levy and Marshall 2004; Zhang et al. 2020) because most of the microbes or bacterial species are no longer susceptible to some of the produced antibiotic compounds (Zhang et al. 2020). In addition to these drawbacks, biomolecules are suggestible, denature easily, and hard-wearing for reuse

(Alexander et al. 2006; Chen et al. 2016). Today, antibacterial resistance is a primary health concern globally, which is caused by a genetic mutation of bacteria in human, animals, and plants or exposure to antibiotic or heavy metal selective pressure in the environment (Levy and Marshall 2004; Zhang et al. 2020). These selective pressures could be from the agricultural, hospitals, pharmaceutical, nanomaterials, sewage, water, and wastewater treatment settings (Fig. 1) (Levy and Marshall 2004; Chollom et al. 2019; Zhang et al. 2020).

Recently, this has prompted many efforts to put forth in designing and synthesizing of artificial materials with antibody-like functions for analytical detection, quantification, and identification of bacteria species as well as monitoring of their growth (Zhang et al. 2020). This has hastened the high demand for MIT based nanomaterials (Sharma and Kandasubramanian 2020; Pandey et al. 2020). Conventionally, some of these include the use of silica nanoparticles, carbon nanotubes homogenized with sensor technology, titanium dioxide (TiO2), zinc oxide, zeolite, silver oxide, liquid crystals, and microfluidics. Whereas TiO_2 nanoparticles have been widely used due to their superior-excellent biological compatibility and photocatalytic properties (Chollom et al. 2020; Tetteh et al. 2020). For instance, composite materials which incorporate silver nanoparticles (AgNPs) have been developed and tried out for antimicrobial purposes (Chen et al. 2009; Castell et al. 2011). Herein, antimicrobial efficiency of Ag–TiO_2 composite as reported can be improved under light irradiation (Chen et al. 2009; Komiyama et al. 2018).

Today, biological imprinting as a kind of nonantibiotic and the antimicrobial agent has received little attention as compared to fluorescent probe techniques and nanomaterial synthesis. Meanwhile, MIT's seems very promising as an alternative to synthesis bioreceptors for biomedical applications (Sharma and Kandasubramanian 2020). Therefore, with a desktop approach, the principles of MIT based on direct and indirect imprinting of materials with antibody-like functions are presented in this chapter. Compared to other recognition systems, techniques relating to the preparation of biorecognition molecule for detection, quantification, and identification of antibiotics and bacteria species are highlighted. Also, the recent development of MIT with nanomaterials, polymer, and other natural based materials to exhibit the antibody like selectivity and binding affinity via size, shape, and functional groups matching is discussed. Furthermore, materials that possess remarkable characteristics for MIT reusability, including easy availability, low cost, and high stability to withstand severe physical and chemical ambience are also reported.

2 History and Types of MIT's

Generally, in the presence of imprinted molecules, MIT which is a part of molecular imprinting polymers (MIPs) is prepared from functional monomers by way of copolymerization and cross-linkers serving as target analytes (Chen et al. 2011).

The historical background of molecule imprinting can be traced as far back as 1931 (Chen et al. 2011). Polyakov (1931) hypothesized the concept as "unusual adsorption properties of silica particles prepared using a novel synthesis procedure". Based on the "adsorption properties" having displayed countless polymers during the experimentation, the concept of MIP has now been adopted by many researchers (Alexander et al. 2006; Fu et al. 2015). Patrikeev (1960) also employed bacteria templates in the 1960s. In the 1970s, Wulff and colleagues went further to develop the techniques being used for polymer imprinting (Wulff et al. 1972; Takagishi and Klotz 1972; Wulff 1995). Fu et al. (2015) further proposed two broad techniques for MIPs, which include covalent and non-covalent imprinting polymerization. Liu et al. (2019) also affirmed the two types of MIPs in their study of using MIP fluorescent sensors in food and environmental analysis. Huang et al. (2015) and Ren and Chen (2015) further built upon the existing technologies and categorize them into five types including non-covalent, semi-covalent, covalent, ionic/electrostatic, and metal centre-coordination.

Further development setbacks reported include incompatibility in aqueous media, irregular material shape, template leakage, and low binding capacity (Fu et al. 2015; Liu et al. 2019). Based on smart preparation technology, Chen et al. (2016) proposed three principal MIT types, which include ingenious technologies, special imprinting strategies, and stimuli-responsive imprinting technologies. Subsequent ingenious imprinting technologies (IITs) involve nanoimprinting (Fig. 2), porous polymer synthesis, microfluidic on-line synthesis, surface imprinting, solid-phase synthesis, click chemistry cycloaddition reaction, and living or controlled radical polymerization (Chen et al. 2011; Pandey et al. 2020). Researchers base the principle of IIT on the template and receptors molecule efficiency to rebind the imprinted sites, which are usually termed as an angiotensin-converting enzyme. A recent claim by Chinese scientists shows that nanoimprinting materials is a possible receptor to absorb and deactivate the COVID-19 virus in humans with an accuracy of 96.5–99.9% (Chen et al. 2020).

The development of nanostructured MIPs (N-MIPs) research interest has significantly improved their characteristics in contrast to bulk MIPs (Fig. 2). Also, surface imprinting, segment imprinting, nanoimprinting, dummy imprinting, multiple-template imprinting strategies are some of the special imprinting strategies that have recently been popularized (Komiyama et al. 2018). For instance, surface imprinting methods are used in the extraction of pentamidine from solid-phase extraction (urine) (Chen et al. 2011), Ethynylestradiol from river water (Bravo et al. 2009), estrone from well water (Xu et al. 2009), Oxytetracycline from tissue (Chen et al. 2009), and Diosgenin from herb (Sun and Qiao 2008). These various outcomes indicated that the suggested surface imprinting would be possibly applicable for clinical screening of other biomarkers. From the above-mentioned types of MITs, the novel stimuli-responsive technology has gained very attractive attention as being superior for imprinting of receptors and is considered and explained in detail.

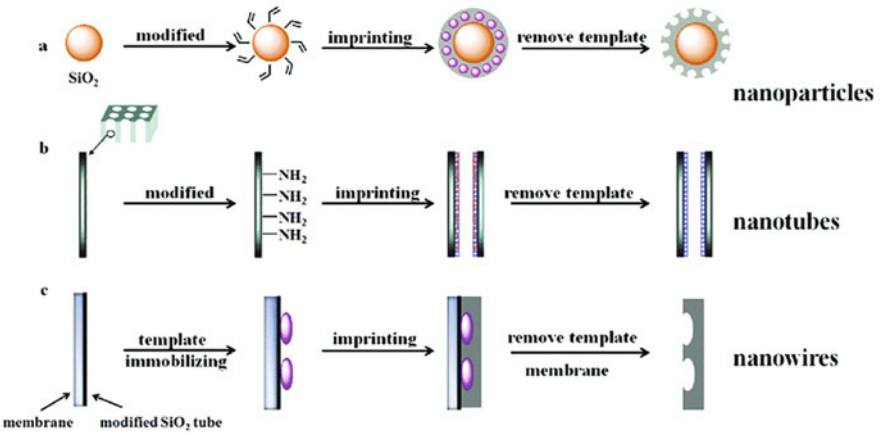

Fig. 2 Schematic portrayal of a nanoimprinting procedure for various types of N-MIPs (**a**) Imprinting on the SiO2 support for the development of centre shell nanoparticles imprinting, (**b**) Imprinting on silica nanotubes for the arrangement of nanotubes imprinting, and (**c**) Imprinting on a conciliatory layer bolster. Source adapted Chen et al. (2016)

2.1 Stimuli-Responsive Imprinting Technologies

Stimuli-responsive MIPs (SR-MIPs) use SR technology for imprinting molecules by mimicking the natural receptors' characteristics to achieve intelligent materials (Chen et al. 2016). Chen et al. (2011) stated that SR-MITs, including magnetic response technology, thermos-responsive technology, photo-responsive technology, pH-responsive technology, and other responsive technologies could occur either through single responses or multiple responses. However, most of these imprinting technologies use nanomaterials like magnetite, silver nitrate, and titanium dioxide as their principal imprinting template (Chen et al. 2016). These technologies have a smart application in fields like bio/chemosensing, biotechnology, separation of science, cell encapsulation, and drug delivery in biochemistry (Ren and Chen 2015; Schirhagl 2014).

Unfortunately, some conventional MIT which have highly cross-linked polymers have relatively rigid structures, thereby, limiting their availability to bind with a targeted molecule (Yan and Row 2006). Such that polymer gels with lightly cross-linked structures can be subjected to a degree of temperature change in response to either reversible swelling or shrinking (Yan and Row 2006; Zhang et al. 2014). This type of imprinting technologies is usually known as "thermo-responsive" and is used as smart materials in cell encapsulation, tissue engineering, and drug delivery in biochemistry (Yan and Row 2006; Wulff 1995). They also have the potency for the design and application of protein-imprinted polymer matrices. For instance, a temperature-responsive polymer like Poly (N-isopropyl acrylamide) (PNIPAAm) is subjected to temperatures of 32.1 °C greater than its lower critical solution

temperature (LCST) during the phase separation stage (Venkatesh et al. 2014; Whitcombe et al. 2014). However, at high LCST, the hydrophilicity/hydrophobicity equilibrium becomes relatively inactive due to the high thermodynamic transition. Also below the LCST, water can be emitted from the interior of the polymer, which can lead to a massive reduction in the volume of the polymer.

2.1.1 Magnetic Responsive Technology

Molecular imprinting together with nanotechnology has improved both selectivity and sensitivity for recognizing diverse analytes, going from little particles to huge proteins and macromolecules (Wang and Zhang 2008; Li et al. 2014a, b; Whitcombe et al. 2014; Liu et al. 2019; Sharma and Kandasubramanian 2020). The imprinted nanostructures present a large surface area, which exposes more of their binding sites in order to trap the targeted analyte (Schirhagl 2014). Hence, integrating magnetite with MIPs has an extraordinary driving potential for some promising applications. These applications include drug delivery, sewage pretreatment, enzyme immobilization, catalysis, and magnetic bioseparation, which are among few to be mentioned (Sharma and Kandasubramanian 2020; Singh 2017). Due to their rapid, more accessible, cheap, high magnetic susceptibility, recoverability, and practical separation ability from a medium, it makes them essential to use (Singh 2017; Chen et al. 2009).

Herein, by magnetic imprinting technology, an artificial antibody-microbial was imprinted with silver materials as known—antibiotic or antimicrobial agents for microbial inactivation. Silver materials have hefty bacterial and inhibitory effects as well as a wide spectrum of antimicrobial activity (Chen et al. 2009; Sharma and Kandasubramanian 2020; Sun and Qiao 2008; Komiyama et al. 2018). However, there are reports of microbes developing resistance to silver, thus considered as silver-resistant (Singh 2017; Zhang et al. 2020; Chen et al. 2016). Singh (2017) reported on ways to reduce the risk of developing silver-resistant strains by imprinting composite materials with silver nanoparticles (AgNPs). A composite of Ag–TiO_2 made by synthesizing AgNPs with TiO_2 for antimicrobial activity showed dramatic efficiency as reported by Sharma and Kandasubramanian (2020), suggested the need to improve the efficiency by light irradiation.

Furthermore, incorporation of magnetic components like Fe_3O_4 nanoparticles into MIPs is in good direction upon application of an external magnetic field for separation of adsorbed analytes without additional centrifugation or filtration process (Li et al. 2014a, b; Zhang et al. 2020; Yan and Row 2006). Some of the standard techniques used in preparing M-MIPs including suspension, grafting, emulsion, and precipitation polymerization, offer better shape and size than bulk polymerization processes (Ren and Chen 2015; Liu et al. 2019). There have also been several reports that to obtain Fe_3O_4–MIP nanoparticles (Fig. 2), a well-regulated protocol MIPs has to be coated on the surface of superparamagnetic (Fe_3O_4) nanoparticles for rapid

Table 1 Diverse imprinting methods and preparation procedures of MIPs

Method	Benefits	Drawbacks
Bulk polymerization	Purity in the produced MIPs; simplicity and rapidity in preparation; no requirement for expensive and sophisticated instrumentation	Low-affinity sites; irregular particles in size and shape; time-consuming for sieving and grinding
Suspension	Spherical particles; one step and simple polymerization process	Poor recognition; big particle size (a few to a few hundred micrometers)
Precipitation polymerization	Uniform; high-quality; one single preparative step	High dilution factor; a substantial amount of template
Emulsion polymerization	Water-soluble polymers; monodispersed polymeric particles; High yield	Low imprinting capacity; suffers from the presence of remnants of surfactants
Sol–gel process	Eco-friendly reaction solvent; ease of fabrication at room temperature	Lack of polymerization; high cost of raw materials
Seed polymerization	Controllable, regularly spherical particles; monodispersity; suitable for HPLC	Laborious process; time-consuming

enrichment and separation (Lofgreen and Ozin 2014; Chen et al. 2009). In Table 1, the sol–gel process comes in handy and is useful for preparing M-MIPs due to its free radicals for polymerization (Lofgreen and Ozin 2014). Therefore, the steps in preparing of Fe_3O_4–MIP nanoparticles are as follows:

1. By synthesizing the Fe_3O_4 magnetic nanoparticles by solvothermal reduction approach or coprecipitation approach.
2. By functionalizing or surface modifying Fe_3O_4 magnetic nanoparticles.
3. By imprinting molecules on Fe_3O_4 magnetic particles in order to prepare M-MIPs via a free radical polymerization or sol–gel process.

2.1.2 Photo-Responsive Technology MIPs (P-MIPs)

Recent interest in producing P-MIPs has resulted in the integration of a photoreactive moiety in a polymeric system. Thus dimerization and isomerization are a product of converted chemical signals from photo-irradiation via photoreactions (Komiyama et al. 2018; Chen et al. 2011; Huang et al. 2015). Due to their photoreactive moieties, photoisomerization is seen to be faster, reversible, and reliable (Fu et al. 2015), for examples include, azobenzene and spiropyran used in functionalizing MIPs (Chen et al. 2009, 2016; Castell et al. 2011). Photo-responsive functional monomers are generally grouped into three categories; (1) the polymerizable group, (2) the recognition group, and (3) the photo-responsive group (Chen et al. 2009, 2011). This acts as a stimulus or kind of "clean energy" in various molecular devices and smart materials, which are due to their adjustable parameters such as intensity, duration, and wavelength (Chen et al. 2016; Castell

et al. 2011). Ideally, P-MIPs are generated by imprinting MIP with uniform nanoparticles, including zinc oxide or titanium dioxide (Chen et al. 2009, 2016; Fu et al. 2015). For instance, Komiyama et al. (2018) were able to synthesize a photo-responsive functional monomer with azobenzene moieties and siloxane polymerizable group via a sol–gel route, which was able to release and selectively bind a template molecule upon irradiation at 440 and 360 nm, respectively.

2.1.3 Other Responsive Imprinting Technologies

1. *Salt ion and biomolecule responsive*: The influence of salt ions on penicillin and propranolol as a targeted template for binding MIPs in water–acetonitrile mixtures has been reported (Mosbach and Ramström 1996; Parry and Humphreys 2009). Following the Hofmeister series with kosmotropic ions, studies show that 3M salt solutions in 100% aqueous solution augment the binding of templates to a substantial increment (Mosbach and Ramström 1996; Parry and Humphreys 2009). This supposed that the hydration of kosmotropic particles diminished the water movement in water-poor media, giving a balancing impact on the MIP-template of water-sensitive reactions (Bravo et al. 2009; Chen et al. 2016).
2. *Multi-stimuli responsive MIPs*: These are receptive to at least two stimuli being emerged. Double responsive polymers essentially incorporate salt/thermo, pH/thermo, photo/thermo, photo/magnetic, thermos/magnetic dual responsive MIPs (DR-MIPs) (Chen et al. 2016, 2011; Lofgreen and Ozin 2014).
3. *PH-responsive technology*: pH-responsive polymers are polymers containing an amino-functional group or a carboxylic acid, sensitive to changes in pH (Chen et al. 2009, 2011; Bravo et al. 2009). Such a polymeric network contains ionizable groups and can accept or donate protons at a specific pH (Chen et al. 2009; Bravo et al. 2009). The pH-responsive MIP hydrogel/nanospheres composite is a covering sensor with implantable glucose. By using a template molecule of dexamethasone-phosphate disodium (DXP) via a process of precipitation polymerization within the pH range tested (6.0–7.4), H-sensitive nanospheres also exhibited a faster DXP discharge rate at a lesser pH value.

2.2 The Components of MIT's

MIPs are prepared (Fig. 3) from functional monomers by way of polymerization and cross-linkers in the presence of the imprinted molecules serving as target analytes (Chen et al. 2011). As mentioned above, imprinting technologies (Table 1) have a distinct template and corresponding functional monomers for a constellation of template–monomer complexes. These are mostly hinged on the non-covalent and covalent interactions between the functional monomer and the template (Ansell et al. 1996; Whitcombe et al. 2014; Chen et al. 2016). Wang and Zhang (2008) assert that since the rate of chain propagation is not subject to control, preparing regular MIPs is

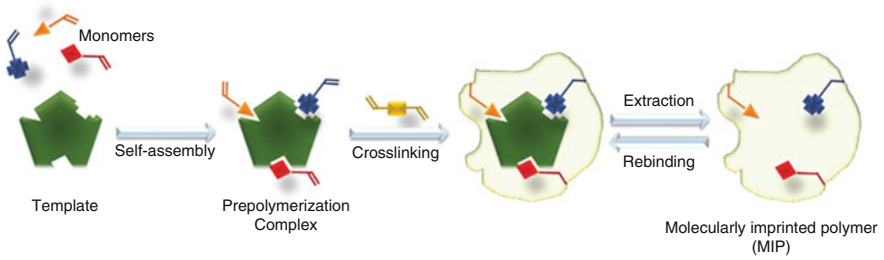

Fig. 3 Schematic portrayal of the process of molecular imprinting (Chen et al. 2011)

not simple in standard radical polymerization. The reason being that polymers generally have an expansive distributive size due to termination, chain transfer, and side reactions. Meanwhile, covalent imprinting, on the other hand, being stoichiometric, warrants functional monomer residues to exist in the imprinted cavities (Ramström and Ansell 1998; Schirhagl 2014). Also, polymerization reactions (Table 1 and Fig. 3) can be affected by some essential elements of MIT. These include the amount and type of monomers, temperature, cross-linker, time of polymerization reaction, and the initiator and the type of solvent (Ramström and Ansell 1998; Chen et al. 2016). To overcome such problems, there is a need for thermodynamic control of the polymer chain growth with a slower reaction rate and negligible chain termination. This will result in a narrow and homogeneous spread of networks of polymers as opposed to the highly cross-linked monomers (Chen et al. 2016; Whitcombe et al. 2014).

2.2.1 Target Template

According to Chen et al. (2011), potential MIPs must have high affinity and specificity compared to biological receptors, such that the template molecule (Figure 3) must meet the following requirements; (1) functional groups that cannot curtail polymerization, (2) functional groups to form complexes with functional monomers, and (3) excellent chemical stability during polymerization. For instance, in ion-imprinting, ligand complexes and metal ions are used due to their ability to pre-polymerize with functional monomers, contribute to high selectivity and adsorption of metals (Singh 2017). For instance, Zhang et al. (2014) conducted an experiment using a sol–gel route for dithizone chelating agent, with 3 aminopropyltriethoxysilane as a functional monomer and dithizone-Hg^{2+} chelate as a template. The result showed that Hg-IIPs had a perfect selectivity toward Hg^{2+} over its natural states and other metal ions. So far, MIPs have been successfully applied for the recognition and detection of a wide scope of nanoscopic natural molecules.

2.2.2 Functional Monomers

Chen et al. (2016) contend that by providing functional groups with the target template, they form a pre-polymerization complex. As a known fact, there are limited functional monomers for molecular imprinting (Table 1), which restricts their selectivity for further application to some extent (Zhang et al. 2014, 2020; Yan and Row 2006). Figure 4 presents the chemical structure of some of the most common photo-responsive functional monomers. In essence, functional monomers must be able to interact with the target template to form antibody–antigen complexes or specific donor–receptor before polymerization. Moreno-Bondi et al. (2008) noted that it is essential to design and amalgamate new functional monomers due to their ability to form a strong bond with templates. Besides, most functional monomers comprise two units, for example, silicon hydroxyl and a vinyl double bond, for recognition and polymerization, as shown in Fig. 4. For instance, a photopolymerizable diacetylene monomer was imprinted with dinuclear zinc cyclen receptors (Zn_2PCDA, compound 36) amidst a template peptide to simultaneously hobble two receptors of a membrane fluid (Zhang et al. 2020; Xu et al. 2009). In essence, this photo-induced polymerization of polydiacetylene formed shapes on the surface of the vesicle with organized varieties of receptor sites.

2.2.3 Cross-Linkers

As shown in Fig. 3, cross-linkers are used to fix functional monomers around template molecules in the process of polymerization (Xu et al. 2015). In the process, forms a highly cross-linked rigid polymer after removing the template. For instance,

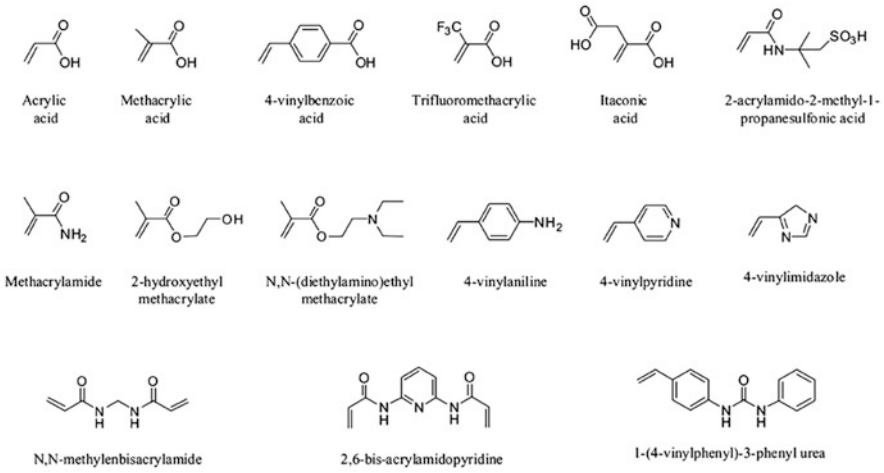

Fig. 4 Chemical structures of photo-responsive functional monomers (adapted from Zhang et al. 2020; Xu et al. 2009; Chen et al. 2016)

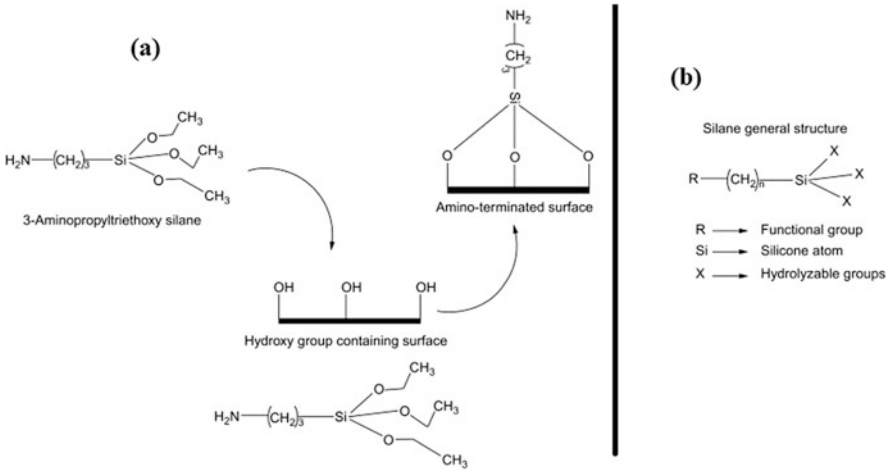

Fig. 5 Cross-linked structure of silicone in (**a**) sol–gel routes and (**b**) free radical polymerization (adapted from Li et al. 2014a, b)

in Chinese medicine, due to the non-toxicity and biodegradability of resin, it is used as a raw material for separating and purifying ingredients of the Chinese herbs (Xu et al. 2015; Li et al. 2014a, b). However, the binding capacity and selectivity of MIPs depend on the amount and type of cross-linker present. Generally, unstable mechanical properties of cross-linkers are due to low cross-linking degrees, whereas an extremely high amount of cross-linker will reduce the number of recognition sites per unit mass of MIPs. According to Li et al. (2014a, b), cross-linkers have three double bonds with excellent rigidity which can participate in polymerization reactions (Fig. 5). Thus the imprinted cavity, even in an organic solvent enhances the degree of cross-linking in a way that is maintained in the template molecule structure. An example of an imprinted cross-linked structure of silicone in sol–gel routes and free radical polymerization is shown in Fig. 5.

2.2.4 Porogens

In the polymerization process, porogens serve as pore-forming agents or dispersion media (Chen et al. 2016). These are solvents that play an important role during MIP synthesis and polymerization; these include N dimethylformamide (DFM), methanol, 2-methoxy ethanol, acetonitrile, toluene, tetrahydrofuran (THF), chloroform, and dichloroethane (Gladis and Rao 2004; Zhang et al. 2020). However, in non-covalent interaction systems, the extremity of porogens can influence the pace of interaction between the functional monomer and the template molecule. Ionic liquids (RTILs) are now used as solvents due to their unique characteristics (Chen et al. 2016). As solvent polarity subsequently affects the adsorption and morphological properties of the polymer, it is, therefore, vital to consider theoretical calculations before MIP selectivity (Yan and Row 2006; Zhang et al. 2020). Since

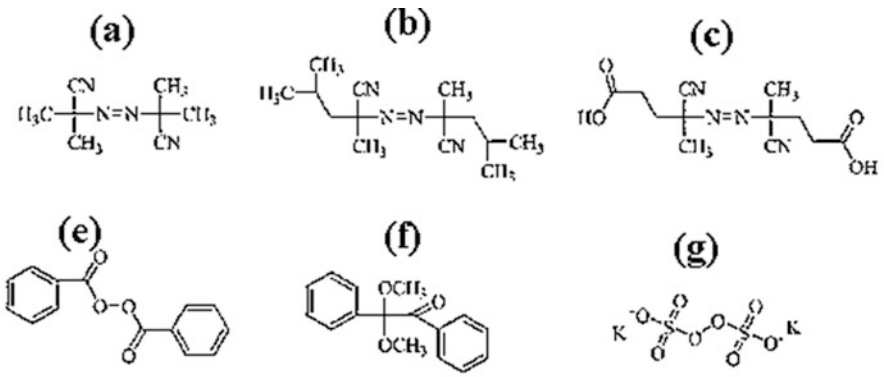

Fig. 6 Chemical structures of known initiators in molecular imprinting. (**a**) Azobisisobutyronitrile (AIBN); (**b**) azobisdimethylvaleronitrile (ADVN); (**c**) 4,40-azo (4-cyanovaleric acid) (ACID); (**d**) benzoyl peroxide (BPO); (**e**) dimethyl acetal of benzyl (BDK); and (**f**) potassium persulfate (KPS) (adapted from Chen et al. 2016)

this will give an insight for monomers and solvent types to be selected. For instance, the effects of acetone, acetonitrile, chloroform, and methanol were studied on monomer–template binding energy by Gladis and Rao (2004), whereby the density functional theory (DFT) was employed to determine their structural, vibrational frequency and selectivity for molecular imprinting.

2.2.5 MIP Initiators

Electropolymerization, free radical polymerization (FRP), or photopolymerization are among the most commonly used initiators for MIPs (Chen et al. 2011, 2016). With a wide range of template structures and functional groups, FRP can be ignited by either thermal or photochemical means during the imprinting process (Yan and Row 2006), wherein Fig. 6, azo-compounds can also be used as initiators apart from peroxy compounds (Chen et al. 2016). Azobisisobutyronitrile (AIBN) is most convenient among them to be utilized at the decomposition temperatures of 50–70 °C (Chen et al. 2016, 2011). Usually, in the polymerization reactions, inert gases, like nitrogen or argon, are used to deoxygenate the dissolved oxygen from polymerization solutions before proliferation.

3 Characterization of MIPs or Biomaterials

The imprinting of monomers to biocompatible and nontoxic materials requires ideal preparation protocols, this is to ascertain the attainability of the desired qualities for industrial production (Yan and Row 2006; Singh 2017; Ren and Chen 2015). The

orientation of monomers is directed based on the template being chemically stable and inert under polymerization (Schirhagl 2014; Ren and Chen 2015). Also, the ratio of functional monomer and template could have an impact on the efficiency of the imprinting polymer. In this instance, some of the preparation mechanisms including the sol–gel processes and the free radical polymerization as mentioned earlier are essential for the production of MIPs (Schirhagl 2014; Singh 2017; Whitcombe et al. 2014).

Ensuring large-scale production, detection, and characterization of MIPs plays a major role including screening of the monomers and obtaining information from template interactions (Chen et al. 2016; Wu and Qiu 2014). Monomer–template interactions, which are the most essential aspect of MIP design, are usually characterized by a UV-Vis and infrared (IR) spectroscopies and nuclear magnetic resonance (NMR) (Chen et al. 2011; Singh 2017). The forms of MIPs can be explored by the transmission electron microscopy (TEM) and scanning electron microscopy (SEM). Furthermore, various fluorescence method and atomic force microscopy (AFM) method have also been employed in characterizing thin-film MIPs (Sun and Qiao 2008; Li et al. 2014a, b). Also, studies on ligand–MIP interactions including the use of X-ray photoelectron spectroscopy (XPS), diffraction, and X-ray absorption fine structures have become very attractive (Sharma and Kandasubramanian 2020; Singh 2017). Also, thermogravimetric analysis (TGA) can be employed when conducting a thermal stability. By nitrogen adsorption experiments via the Brunauer–Emmett–Teller (BET) analysis, the pore sizes and the exact surface areas of the polymers could be measured (Li et al. 2014a, b; Liu et al. 2019). The vibrating sample magnetometer (VSM) is used to measure magnetic properties (Fe_3O_4) during magnetic imprinting technology (Li et al. 2014a, b; Lofgreen and Ozin 2014). Apart from the morphological analysis, MIPs efficacy can also be examined by looking at the molecule's durability, robustness, and endurance for reuse. At equilibrium, the binding capacity (Q_e, mol/g) representing the total of adsorbed template/weight of the polymer could be calculated by using Eq. (1) (Lofgreen and Ozin 2014).

$$Q_e = \frac{(C_i - C_e) \times v}{m} \tag{1}$$

where c_e and C_i (mol/L) are the equilibrium and initial template concentrations, respectively, m (g) is the weight of the polymer and V (L) is the volume of the solution.

4 Application of MIT's

Global interest in polymerization for industrialization has inspired the rapid development and improvement of MITs for diverse applications (Fig. 7). The MIPs, nanoimprinted, and magnetized nanomaterials prepared using the novel sol–gel

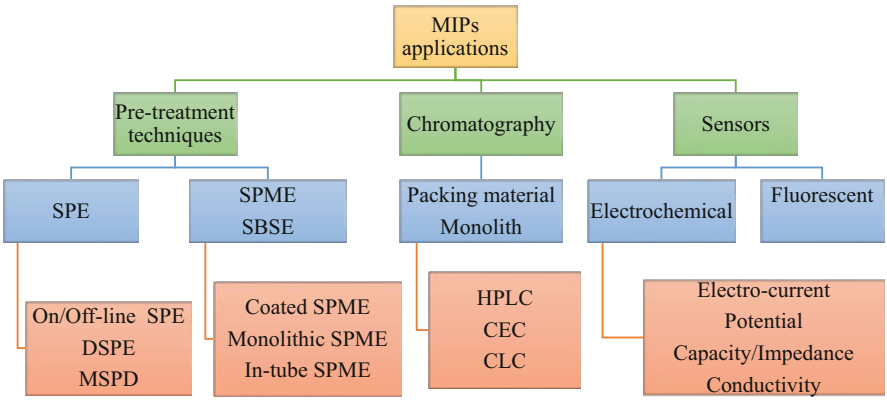

Fig. 7 Structural outline MIPs application in sensors, chromatography, and in pretreatment techniques. Abbreviations: *CLC* capillary liquid chromatography, *CEC* capillary electrochromatography, *HPLC* high-performance liquid chromatography, *SBSE* stir bar sorption extraction, *SPME* solid-phase microextraction, *MSPD* matrix solid-phase dispersion, *DSPE* dispersive SPE, *SPE* solid-phase extraction (Adapted from Chen et al. 2016)

Table 2 Classical types of antibiotics (adapted from Zhang et al. 2020; Wulff 1995; Chollom et al. 2020)

Class	Antibiotics
β-lactams	Penicillin, amoxicillin; ceftiofur
Macrolides and lincosamides	Tylosin; tilmicosin; tulathromycin, lincomycin
Aminoglycosides	Gentamicin; neomycin
Fluoroquinolones	Enrofloxacin, danofloxacin
Tetracyclines	Tetracycline; oxytetracycline, chlortetracycline
Sulphonamides	Sulfamethazine, sulfamethexazole and sulfasalazine
Streptogramins	Virginiamycin
Polypeptides	Bacitracin
Phenicols	Florfenicol
Pleuromutilin	Tiamulin

process (Fig. 2) are known to have an outstanding interface, electrical and optical properties, stability and suitable for chemical/biological sensors (Liu et al. 2019; Chen et al. 2020; Sun and Qiao 2008; Bravo et al. 2009). Subsequently, SIT-MIPs with which makes judicious use of hollow porous polymer synthesis technology for polymerizing precipitation results in high MIPs efficiency, ideal surface properties, uniform size, good morphology, and adsorption capacity (Chollom et al. 2020; Bravo et al. 2009). However, monitoring of pharmaceuticals (Table 2) is essential, because they are made up of different chemical structures and physicochemical properties, which can metabolize into different forms (Chollom et al. 2020; Wu and Qiu 2014; Wulff 1995; Chen et al. 2009). Figure 7 presents MIT techniques for detection and quantification of nanomaterials, pharmaceuticals, and environmental pollutants (Chen et al. 2016).

4.1 Pharmaceuticals (Antibiotics)

Pharmaceutical compounds are drugs that are commonly used to prevent and cure diseases and infections as well as improve health (Chollom et al. 2020; Zhang et al. 2020). They are classified according to the anatomical, therapeutic, and chemical functional groups as in the target anatomical system, therapeutic properties of the drug, or chemical characteristics of the molecule (Chollom et al. 2020; Wulff 1995; Zhang et al. 2020). There are a lot of pharmaceuticals (Table 2) which are widely used including endocrine-disrupting compounds, antibiotics, steroid hormones, antiretroviral drugs, and non-steroidal anti-inflammatory drugs (NSAIDs). These are usually found in the environment via various sources such as households, hospitals, wastewater treatment plants (WWTPs), industrial units, and human excretion as metabolites (Zhang et al. 2020; Xu et al. 2009; Wulff 1995). For instance, NSAIDs like diclofenac, ketoprofen, naproxen, and ibuprofen are rejected from the body of humans with 10, 70, 80, and 100% of unchanged compounds, respectively, which are swept into the WWTPs (Chollom et al. 2020; Wulff 1995; Wu et al. 2019). Most studies have reported that during the treatment of sewage and wastewater, pharmaceuticals and other emerging contaminants are partially removed during the treatment process, this is due to the fact these contaminants are recalcitrant, and therefore still persist even after the treatment process (Chollom et al. 2020; Zhang et al. 2020). Yet still, there is limited data and information on altered pharmaceutical waste streams, which pose a high risk to food security, human health, and the ecosystem sustainability (Zhang et al. 2020; Chen et al. 2016). Hence, integrating MIT (Fig. 7) into robust and effective monitoring and detecting technologies comes in handy for the environmentalist.

4.1.1 Sample Analysis

Comprehensively, assessing emerging environmental contaminants like the pharmaceuticals in a broader range involves the use of high liquid performance chromatography (HPLC) and liquid chromatography (LC). For example, antibiotics in food have been set at a 4–1500 μg/kg for milk and 25–6000 μg/kg for the other foodstuff of animal origin (Parry and Humphreys 2009; Liu et al. 2019; Li et al. 2014a, b). As a known fact, gas chromatography (GC) in the early 1930s was commonly used for the chromatographic separation of diverse compounds (Polyakov 1931; Ramström and Ansell 1998). However, the steps of GC include sample preparation to increase the selectivity and quantification by the analytical unit (Liu et al. 2019; Mühlen et al. 2020; Mosbach and Ramström 1996).

Conventionally, the treatment of pharmaceuticals in wastewater settings using degradation or advanced oxidation processes remains complex (Chollom et al. 2020; Zhang et al. 2020). This has necessitated the development of particular analytical approach for detecting and quantifying pharmaceutical compounds in the environment (Table 3) by applying MIPs as a sorbent in the pre-concentration step of the sample to enhance its sensitivity (Li et al. 2014a, b; Ren and Chen 2015; Liu et al. 2019). Some of the sorbents commonly used during the extraction steps before

Table 3 SPE protocols used in analysing pharmaceuticals (Wulff 1995; Zhang et al. 2020)

Analyte	Amount of sorbent (mg)	Effluent sample loading	Elution	Analytical method and detection limit
Diclofenac	35	1000 mL river water and wastewater	2 mL of methanol	LC-M5/M5
Carbamazepine	200	100 mL wastewater effluent at pH11	5 mL of methanol	LC-UV LOD— 25 μg L^{-1}
Metformin	50	50 mL aqueous samples including wastewater at pH10	1 mL of acetic acid and methanol (1.9)	LC-DAD-ESI/MS LOD— 1.5–3.4 ng L^{-1}
Ketaprofen	14	50 mL wastewater at pH5	1 mL of methanol	LC-UV LOD— 0.23 μg L^{-1}
Indomethacin	200	100 mL river water at pH5	2 mL methanol	LC-UV LOD— 0.03 μg ml^{-1}

filtration include chitosan, biochars, silica, zeolites, graphene, others (Moreno-Bondi et al. 2008; Chen et al. 2009; Li et al. 2014a, b; Wu and Qiu 2014; Xu et al. 2015; Huang et al. 2015). On the other hand, the solid-phase extraction (SPE) technique has proven to be efficient for pre-concentration and extraction of hydrophobic compounds (Chen et al. 2009, 2011; Bravo et al. 2009; Li et al. 2014a, b; Zhang et al. 2020). SPEs have been the drive for the application of MIPs as chromatographic stationary phases. Bravo et al. (2009) reported that this can be executed through slurry packaging of the readied MIPs into the stainless steel chromatographic column. The result is that the MIP attaches the packed material firmly during the application response with a strong retention time (Ren and Chen 2015; Chen et al. 2009).

4.1.2 Preparation of Pharmaceutical Templates

Recalcitrant traces of pharmaceuticals and personal care products are reported to be present in water bodies (Chollom et al. 2020; Ren and Chen 2015). In the environment, their presence poses potential risks with few toxicological pieces of information available to address their negative effects on the ecosystem and human health (Wu and Qiu 2014; Huang et al. 2015). However, most of these pharmaceutical compounds have a molecular structure with a variety of functional groups, which makes them highly selective for the imprinting process (Whitcombe et al. 2014; Wu and Qiu 2014; Wang and Zhang 2008). In the synthetic reaction shown in Fig. 8, the methacrylic acid, ethylene glycol dimethacrylate, and fluconazole are used to represent a template, cross-linker, and functional monomer, respectively, where the functional group's presence makes it easy for the template to undergo molecular

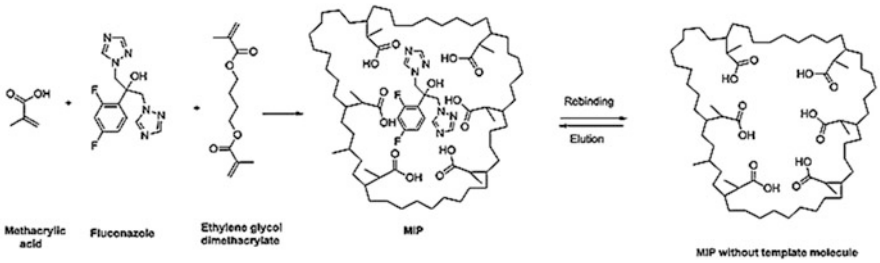

Fig. 8 Scheme of a MIP of fluconazole as a pharmaceutical detection agent (adapted from Wulff et al. 1972)

Table 4 MIPs in hydrolysis reactions for pharmaceutical products

MIP composition	Template	Substrate	Reference
Radical copolymerization of vinyl imidazole with divinylbenzene	*p*-Nitrophenyl phosphate	p-Nitrophenyl acetate	Chen et al. (2016)
Polymerization of N, N-diethyl(4-vinyl phenyl) amidine in the presence of phosphate transition state analog	Cholesteryl 4-nitrophenyl Phosphate	Cholesterol 4-nitrophenyl carbonate	Wulff et al. (1972)
Radical copolymerization of N,N′-diethyl-4-vinylbenzamidine with methyl methacrylate in the presence of the template	(4-carboxybenzyl) triphenylphosphonium bromide Phthalic acid, di(3,5-dimethylphenyl) ester	N-(4Carboxybenzoyl)-i-amino acid (3,5-dimethylphenyl) esters derived from land D-leucine and I- and D-valin	Chen et al. (2016) Chen et al. (2011)
Suspension polymerization of methyl methacrylate in the presence of the template	Diphenyl phosphate	Diphenyl carbonate and diphenyl carbonate	Whitcombe et al. (2014)
Co(coordinated monomers template assemblies of N-methacryloyl-l-serine; N-methacryloyl-l-aspartic acid and N-methacryloyl-histidine with the templates	N-Actyltrosyl-2 amino pyrazinamide and N-nicotinoyltrosyl benzyl ester	N-Acetyl tyrosyl-para nitrophenyl ester and N-benzoyl tyrosyl-para nitrophenyl ester	Xu et al. (2015)
Allyl 1H-imidazole-1-carboxylate	p-Nitrophenyl phosphate	p-Nitrophenyl acetate	Wu and Qiu (2014)

interactions with the hydrogen bonding in the acidic medium (Xu et al. 2015; Wulff 1995; Wulff et al. 1972). This makes it easy for smaller molecules to be able to penetrate the pores. Table 4 also presents pharmaceuticals being used as molecular imprinting templates, where companies like MIP Technologies in Lund (Sweden, Europe), Biotage in Barcelona (Spain, Europe), and Supelco in Bellefonte (PA,

USA) have been able to commercialize MIP sorbents (Wulff et al. 1972; Wulff 1995; Moreno-Bondi et al. 2008; Li et al. 2014a, b).

4.1.3 Chitosan as a Pharmaceutical Template

Chitosan (Fig. 9) is a versatile hydrophilic polysaccharide material which can be derived from chitin, and can be used for antimicrobial activity (Li et al. 2014a, b). The reactive functional groups (amino and hydroxyl groups) present in chitosan can readily be transformed to enlarge its biocompatibility, mechanical and solubility properties (Li et al. 2014a, b; Chen et al. 2009; Liu et al. 2019). These characteristics render chitosan as a right template for MIPs, although the potential exists, chitosan has not been applied for this purpose yet. Subsequently, chitosan and chitin have been investigated as an antimicrobial material in position to a broad spectrum of target organisms such as fungi, yeasts, bacteria, and algae (Moreno-Bondi et al. 2008; Li et al. 2014a, b). Likewise, in the biomedical sector, chitosan films are used as scaffolds for bone and tissue engineering and therapeutic wound dressing (Li et al. 2014a, b). Chitosan, as a biological activity depends extensively on the degree of acetylation (DA) and its molecular weight (MW) (Xu et al. 2015). Even though these parameters independently impact the chitosan antimicrobial activity, the effect of the DA is lesser than the effect of the MW on the antimicrobial activity (Wu and Qiu 2014; Xu et al. 2015). Three mechanisms by which chitosan can be used as an antibacterial agent are being proposed (1) the forming of chelating metals, external barriers and suppressing essential nutrients for the growth of microbial (2) inhibiting protein synthesis and mRNA through the perforation of chitosan microorganism via its nuclei (3) ionic surface interaction resulting in the leakage of the cell wall (Wu and Qiu 2014; Xu et al. 2015; Mühlen et al. 2020). These are likely to be used simultaneously or at different strengths, depending on the targeted product.

4.2 Sol–Gel-Derived Biomaterials

Sol–gel imprinting technology with biochemistry offers a great alternative to produce bioactive surface area for various biomedical applications (Table 1). During

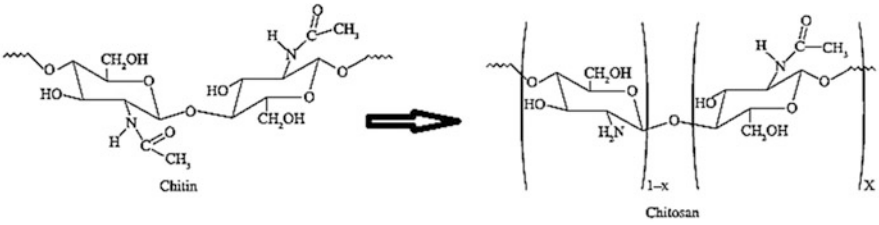

Fig. 9 Schematic scheme of chitosan in MIP (adapted from Xu et al. 2015; Wu and Qiu 2014)

biochemical reactions in constrained matrices, the MIPs enhance the bioactivity for easy controlling, as a result of their high surface area, micro-pores, and residual hydroxyl ions (Sun and Qiao 2008; Chen et al. 2009; Li et al. 2014a, b). In medical device designs, sol–gel imprinting is used to treat the device surfaces by either coating or modifying their characteristics, e.g. biocompatibility, functionality, hydrophobicity, hydrophilicity, and lubricity (Qiu et al. 2013; Mühlen et al. 2020; Nicholls et al. 2013).

Current development in imprinting technology allows for the prevention and treatment of bone infections in the clinical environment, without excluding drug delivery which allows for no extensive bodily reactions during healing responses (Mühlen et al. 2020; Schirhagl 2014). Also, sol–gel films or layers do not only have a high specific surface area as adsorbed drug carriers but also provide biocompatibility with external functional monomers (Xu et al. 2009). However, there remains a significant challenge in the apt use of magnetic nanoparticles in drug delivery vectors, even though no composite material produced can be compared to its magnetic response strength (Takagishi and Klotz 1972; Ren and Chen 2015; Chen et al. 2016). Despite that setback, imprinting magnetic nanoparticles involving inorganic matrices like silica with rich chemistry and useful outer surface makes them an auspicious material to be used as magnetic carriers for imprinting other biomolecules, medical drugs, proteins, and antibodies (Yan and Row 2006; Mühlen et al. 2020). Also, the distribution of pore-size and thickness of the silica nanomaterials are usually controlled by sol–gel dip-coating techniques, which gives an unmediated approach to modify the duration and rate of drug delivery (Nicholls et al. 2013; Lofgreen and Ozin 2014; Mühlen et al. 2020). Furthermore, sol–gel imprinting technology offers numerous merits which include controlling of chemical reactions, precise and ease in fabricating microstructures, and low-temperature processing (Fig. 10).

Other sol–gel applications in MIT include the following;

1. *Mixed-oxide layers*: This involves the tailoring of oxide layers to influence its adsorption ability with elements which are biocompatible like Ta, Zr, Nb, and Ti by using mixed precursors (Li et al. 2014a, b; Moreno-Bondi et al. 2008). The imprinting efficiency usually depends on the surface oxide layer, especially the electronic structure, for example, solid electrolytes for fuel elements, ceramic passive bioimplants, eye and neuro-microsurgery and producing nanocrystalline powders for paediatrics using ZrO_2 (Hanak and Manovic 2018; Fu et al. 2015).
2. *Superparamagnetic nanoparticle*: This involves integrating two useful functional monomers with luminescence and superparamagnetism, alongside an effortlessly conjugated silica surface (Chen et al. 2011; Fu et al. 2015). Silica ends up being a quality material for a defensive lattice by virtue of its stability and biocompatibility and in many biosystems including magnetic resonance imaging (MRI), targeted drug delivery, magnetic separation, as well as in bioanalysis for sensing and detection (Mosbach and Ramström 1996; Moreno-Bondi et al. 2008). Sol–gel methods are used globally in preparing powders made of magnetic iron oxide like Fe_3O_4, γ-Fe_2O_3, and α-Fe_2O_3 of nanometre-size (Moreno-Bondi et al. 2008).

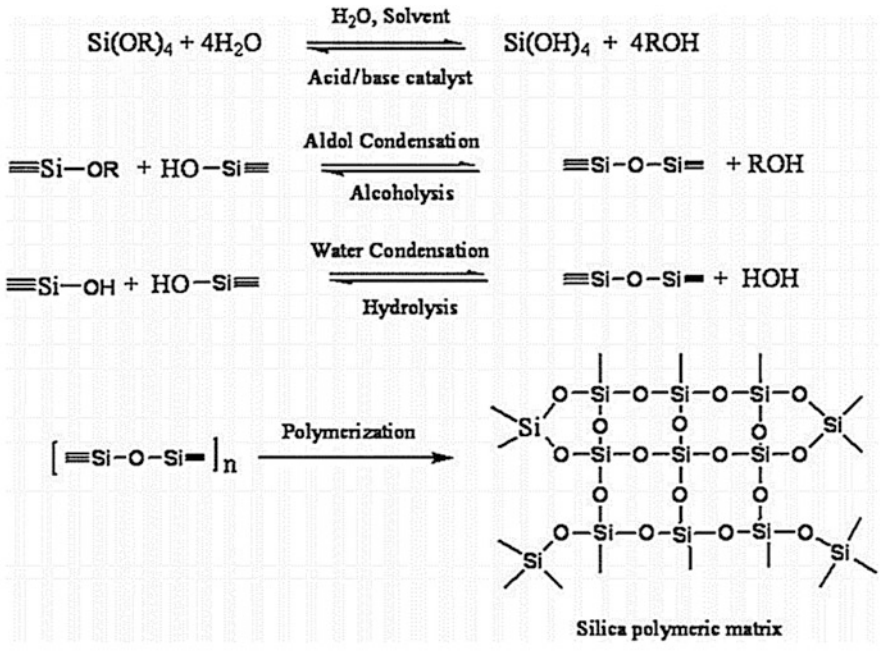

Fig. 10 Chemical reactions of molecularly sol–gel silica (adapted from Lofgreen and Ozin 2014)

These are usually characterized based on their particle size, discrete and superparamagnetic properties for a discrete biomedical application with their chemical reactions in Fig. 10 (Lofgreen and Ozin 2014).

3. *Bioactive hybrids (organic–inorganic):* Living bone is created by the kind of impulsive bond when implanted in a defective bone, makes glass-ceramics and bioactive glasses to be very captivating for numerous biomedical applications (Parry and Humphreys 2009; Tetteh and Rathilal 2019). This is a bond to increase their flexibility by making inorganic–organic hybrid materials by integrating important parts for bioactivity (calcium and Si–O ions) with natural polymers (Lofgreen and Ozin 2014). Also, with plasma spray methods, metal implants (stainless steel alloys and titanium) can be covered with a film of hydroxyapatite to get bioactive materials of high mechanical strength (Fu et al. 2015).
4. *Surface modification with metallic implants*: These are classified as metallic, ceramics, and polymers. The metallic materials have high ductility and strength properties as opposed to ceramics and polymers (Gladis and Rao 2004; Chen et al. 2009, 2016). Likewise, ceramics and polymers are more corrosive as opposed to metallic materials (Chen et al. 2011). This imprinting technology comes in handy, as corrosion can reduce the strength of the implants, which might cause untimely failure and impose harmful effects on its surroundings. In this case, cobalt alloys, titanium alloys, and stainless steels are often utilized for implanted biomaterials (Chen et al. 2016; Fu et al. 2015).

4.3 Antibacterial Coating

The field of antibacterial coating technology (Table 5) as a concept in MIT has entered an energizing phase with innovations constantly evolving (Chen et al. 2016). In the biomedical device industry of the medical community, a strong pull of MIT has gained much popularity in the rapid concern of detecting and recognizing infections (Levy and Marshall 2004; Gladis and Rao 2004; Chen et al. 2020).

Table 5 Application of MIT as antibacterial and antimicrobial agents for characterizations (Levy and Marshall 2004; Gladis and Rao 2004; Chen et al. 2016)

Template	Functional monomer	Imprinting technique	Determination technique
Saccharomyces cerevisiae	*Polyurethane*	Surface printing	QCM
Saccharomyces cerevisiae	*Titanium ethyate*	Surface printing	QCM
Escherichia coli	*Polyurethane*	Surface printing	QCM
Deinococcus radiodurans	*Tetraethoxysilane*	Bulk printing	Fluorescence
Escherichia coli	*Tetraethoxysilane*	Bulk printing	Fluorescence
Bacillus subtilis	*Tetraethoxysilane*	Bulk printing	Fluorescence
Sphaerotilus natans	*Tetraethoxysilane*	Bulk printing	Fluorescence
Pseudomonas aeruginosa	*Pyrrole*	Electro polymerization	Fluorescence
Escherichia coli	*Pyrrole*	Electro polymerization	QCM
Pseudomonas aeruginosa	*Pyrrole*	Electro polymerization	QCM
A. calcoaceticus	*Pyrrole*	Electro polymerization	QCM
S. marcescens	*Pyrrole*	Electro polymerization	QCM
Escherichia coli	*Tetraethoxysilane*	Bulk printing	QCM
Sulfate-reducing bacteria	*Chitosan reduced graphene*	Electro polymerization	EIS
Bacillus subtilis endospore	*Pyrrole*	Electro polymerization	EIS
Escherichia coli	*Silane*	Electro polymerization	Electrochemical sensor
Escherichia coli	*MAH*	Electro polymerization	Captive biosensor
Escherichia coli	*MAH*	Electro polymerization	QCM
Escherichia coli	*MAH*	Electro polymerization	SPR

[a]*CFU* colony-forming unit, *EIS* electrochemical impedance spectroscopy, *QCM* quartz crystal microbalance, *SPR* surface plasmon resonance, *MAH* N-methacryloyl-L-histidine methyl ester

Subsequently, medically implanted devices like central venous and urinary catheters and prosthetic hip implants are risked to bacterial infections with serious complications (Gladis and Rao 2004; Fu et al. 2015; Chen et al. 2016). Classically, these are prone to early removal of implants that might be fatal, very expensive, and stressful to the patient (Levy and Marshall 2004; Chen et al. 2020). Furthermore, immediately after surgery, aggressive bacteria could still be located at the imbedded sites despite preventative measures like sterilization (Chen et al. 2011). For instance, explanted orthopaedic devices which have biofilms on it are formed from species of *Staphylococci,* including *Staphylococcus epidermidis and Staphylococcus aureus* (Wulff 1995; Wu et al. 2019).

The sol–gel dip-coating process has shown to be an effective technique to develop immobilization of an antimicrobial agent using nanoparticles (Huang et al. 2015; Levy and Marshall 2004). Examples of nanoparticles include silver and titanium dioxide, which could be immobilized covalently or electrostatically to films of plasma polymer housing suitable surface functionalities (Gladis and Rao 2004; Komiyama et al. 2018). This becomes very interesting to bind the microbes with the different surfaces of the antimicrobial or antibacterial materials in the matrix (Komiyama et al. 2018). Therefore, imprinting technology comes in handy to control and prevent microbial contamination of medical devices during antibacterial activities.

Recent studies show that silver ions or silver have wide-range antibacterial action as opposed to Gram-negative and Gram-positive bacterial strains, including safe antimicrobial strains (Parry and Humphreys 2009; Pandey et al. 2020). This makes it increasingly hard for microbes to create protection from silver as contrasted with ordinary antimicrobial. Figure 11 presents the multifaceted mechanism of action of silver oxidizes when putting in a physiological medium and discharges silver particles. These ions act by stopping the replication of DNA and bind the cell membrane, enzymes, and proteins, causing interference with the bacterial metabolism (Pandey et al. 2020). This approach takes into account simple control of the silver nanoparticles immobilized on a superficial level and can prompt coatings giving full insurance against bacterial colonization, a favourable combination of mammalian cells and tissue, as well as in the absence of adverse immune responses.

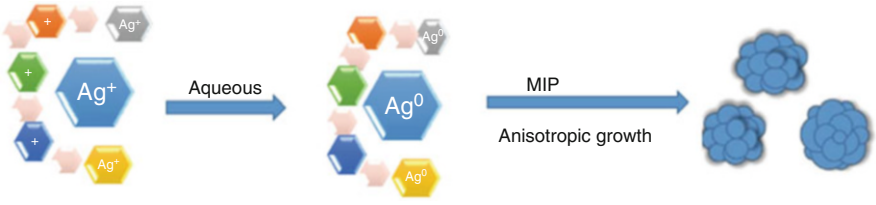

Fig. 11 Dissolving silver nanoparticles in an aqueous condition releases silver ions

4.4 Biomedical Application of MITs

4.4.1 Biomaterial Scaffold

Today imprinting biomaterials have become very useful in developing cell adhesion and proliferation materials in replacing damaged tissue, especially in the wound healing process (Li et al. 2014a, b; Mühlen et al. 2020). For instance, a manufactured extracellular grid and building new bone tissue with cells has been the methodology in the recovery of mineralized tissues contrasted with regular transplantation of bone (Mühlen et al. 2020; Parry and Humphreys 2009). As shown in Fig. 12, scaffold materials based on smart technology are easy to attach, proliferate, and differentiate cells into functional and suitable structures of tissues. Example minerals and proteins like carbonate-apatite, fluorapatite, and hydroxyapatite (HA) [Ca10(PO4)6(OH)2] are mostly considered for cartilage regeneration and engineering bone tissue (Mühlen et al. 2020; Chen et al. 2016). Among these biomaterials, the porosity in HA structures makes them essential for the growth of bones and tissues surrounding a supportive framework by allowing free passage of nutrients (Mühlen et al. 2020; Mosbach and Ramström 1996). HA seems to be a very promising biomaterial, i.e. improving bioactivity. Pandey et al. (2020) reported that by using sol–gel technology in bioactivity and biocompatibility of HA scaffolds, the biomedical application could be improved via its morphology, crystal size, impurity concentration, and controlling composition.

4.4.2 Cell Coating

In the biomedical settings, MIT has become an alternative technique to conventional cell culture developing systems, which incurs cost through the multi-construction steps (Chen et al. 2009). This becomes crucial to develop a distinct pattern of mammalian cell adhesion and monitor their growth (Wulff 1995; Levy and Marshall 2004; Li et al. 2014a, b). In terms of the MIT (Table 5), this involves conjugation of a cell surface to cell-adhesive affinity reagent, which is carried out by using specialized methods like microfluidics, 3D printing, photoablation, and photolithography

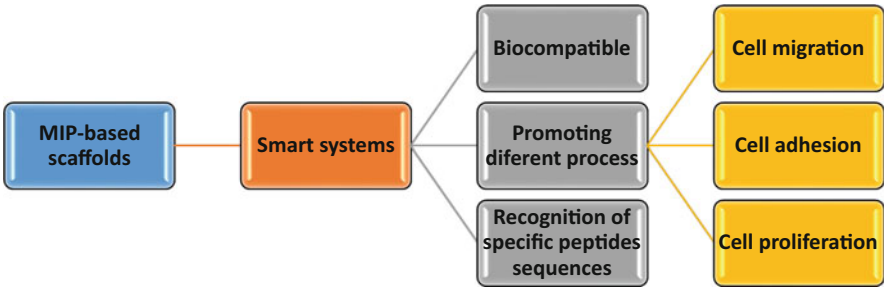

Fig. 12 Schematic of MIT based scaffold applications (Chen et al. 2016)

(Mühlen et al. 2020; Nicholls et al. 2013). A research group of DePorter effectively developed imprinted polyacrylamide hydrogels like MRC-9 (fibroblast-like cells), HEK-293T (epithelial-like cells), and HeLa cells as substrates for mammalian cell growth and adhesion (Wulff et al. 1972; Xu et al. 2015; Wang and Zhang 2008).

4.4.3 Biosensors

In recent years, many biomedical engineers are trying their best possible means to develop implantable glucose sensors, which can give direction on administering an amount of insulin and monitor ambulatory diabetic patients' blood level (Nicholls et al. 2013; Pandey et al. 2020). The biosensors are also employed for clinical diagnostics, drug detection, pollutant monitoring and food analysis (Levy and Marshall 2004; Li et al. 2014a, b; Liu et al. 2019), for example, improvement of MIP for cell recognition in cancer therapy and regenerative medicines (Moreno-Bondi et al. 2008). Therefore, the interest of advancing biological sensors and MIP-based chemical comes in handy. It is very significant to have an ideal interface amid the transducer and the recognition element (Li et al. 2014a, b). Therefore, developing and processing of MIP particles or films for MIP-based sensors becomes essential in biomedical engineering settings. Some of these materials are made up of nanomaterials, electropolymerized thin-film matrices, stimuli-responsive hydrogel, and inorganic materials (Levy and Marshall 2004; Li et al. 2014a, b; Liu et al. 2019). However, high MIP-based throughput exhibit sensors, including multisensory units, have challenging and promising possibilities for simultaneous multi-part analysis (Qiu et al. 2013; Singh 2017; Sun and Qiao 2008). Despite this, imprinting sensors towards enzymes, cells, bacteria, viruses, and gas seem very promising with economic opportunities for explorations (Levy and Marshall 2004; Huang et al. 2015; Hanak and Manovic 2018).

4.5 Social-Economic Interest

MITs have gained attractive attention as a synthetic approach to mimic natural molecular recognition (Mosbach and Ramström 1996; Ansell et al. 1996; Ramström and Ansell 1998). Molecularly imprinted biomaterials reported (Table 5) are physically robust due to their highly desirable selectivity, thermal stability, easy preparation, and low cost. These properties and other derivatives make them very attractive for various industrial applications including pharmaceuticals, breweries, biomedical, health, sewage treatment, and so on (Chen et al. 2011). Wu et al. (2019) also highlighted various forms of MIT applications in nanotechnology.

Currently, world grapples with food and water insecurity (Ghuman and Sharma 2019), health and sanitation crisis (Parry and Humphreys 2009), climate change as well as the destruction of natural resources (Parry 2019). Whereby the United Nations have disseminated 17 sustainable development goals (SDGs) towards the

year 2030, as a way to meet the needs of the world without compromising that of the future generation. Furthermore, to curb this, it is expedient that integrating MITs into the conventional process will be economically viable and possible leeway to improve most systems to sustain the world. For instance, Wu and Qiu (2014) found that the adsorption rate for imprinted polymer in artificial seawater was about 71.57 m^3/s with an adsorption capacity of 2.505 mg/g. This method provides an efficient treatment of water at a low cost as compared to lanthanum nitrate modified chitosan. Many researchers have also used MIPs (imprinted-polymeric organic or inorganic coagulants) in wastewater and water treatment (Venkatesh et al. 2014; Kweinor Tetteh and Rathilal 2020).

Singh (2017) reported on nanoimprinting technology in agricultural and food production, which aided in the crop growth as well as post-harvest preservation. Hanak and Manovic (2018) also demonstrated the application of MIT for carbon dioxide (CO_2) capturing for energy generation. Remarkably, most literature findings on MITs are geared towards higher economic efficiency (Chen et al. 2011), low production cost (Liu et al. 2019; Teixeira et al. 2015), low energy consumption (Hanak and Manovic 2018), equipment improvement, and eco-friendliness (Wu and Qiu 2014), which propels MIT as a promising, smart, and sustainable technology for social-economic growth and development.

5 Conclusion

In this chapter, MIT represents an advanced method for formulating and designing engineered antibacterial and biomaterials valuable for biomedical, nanotechnology, cell adhesion, and environmental applications. Different types of MITs were defined based on structural designs of polymeric materials, by highlighting their applications and definite structural arrays with their corresponding binding sites that allow a specific recognizing of bioreceptor patterns. Among the imprinting technologies, materials derived by the sol–gel route have interesting, stimulating characteristics which have been employed in several hands-on applications, extending from glass materials, ceramics, nanomaterials, medical devices, and biosensors. The expediency of the sol–gel route for formulating super magnetic and bioactive nanomaterials, glasses, hybrids, and coatings for biomedical applications with possibilities of designing more biocompatible or antibacterial agents was further elaborated. Also considering molecularly imprinting polymers (MIPs) hinged on their hydrophobicity and inhomogeneity could be useful to improve the selectivity or sensitivity of devices for different kinds of target molecules. The prospects of MIT are, therefore, foreseen to be a successful venture as commercial MIP sorbents that exist are being utilized. Furthermore, as antibacterial resistance and emerging contaminants like pharmaceuticals are still being recognized in the environment, their future rise can economically be detected by the possible applications of molecularly imprinted materials.

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