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Research Review Article

Computational modeling for rational designing of imprinted polymers for herbicides: a review

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ABSTRACT

Herbicides, the most widely used agrochemicals, have high solubility in water which poses threat to aquatic life and human health along with different sources of water. Therefore, selective, simple and reliable methods for detection as well as removal of these contaminants from different matrices are required. Amongst different available techniques, molecular imprinting is being used for selective detection of the target molecule amongst various analytes with the advantages of high sensitivity and low cost of production. To understand the interaction between the reactants and implement the technique on large scale, computational modeling has played a significant role. Molecularly imprinted polymers can be designed for specific detection of an individual or a class of herbicides by simulating and understanding the complex behavior of the system. In this review, the current status of different in silico strategies being used to design molecular imprinted polymers of different herbicides has been presented.

Key words: Computational modeling, Herbicides, Molecular imprinting, Monomer

Since ages there is a constant competition between insect- pests and human civilization for crop yield. Crops are attacked by insect-pests and disease at different stages and lead to crop losses. To increase the crop production by minimizing insect- pests and diseases infestation, modern agriculture largely uses agrochemicals of different classes.

According to the study (Agrochemicals Knowledge Report, 2016), the pesticide consumption is lowest (0.6 kg/ha) in India as compared to other countries. There are different classes of pesticides for controlling particular infestation and their usage depends upon the severity of the problem along with the crop on which infestation is occurring.

On the basis of usage pattern of pesticides in the country, insecticides constitute the major proportion of crop protection market with major application in rice and cotton crops. It is followed by fungicides and herbicides with the contribution of 18% and 16%, respectively.

Amongst different agrochemicals, herbicides have attained a significant position as they play an important role in eliminating weeds of economic importance in different agriculturalcrops. Nowadays, usage of herbicides in India is gaining popularity because of better weed control, affordability and reduced dependence on manual labor (Information Bulletin 2016). According to Hossain (2015), herbicide market grew by 39% worldwide from 2002 to 2011 and will growto 11% by 2016.

Though the usage of herbicides is very low in India' their prolonged use involves not only the risk of their retention in crops and soils but also pose threat to surface and ground water as theyreachthrough different processes. Due to their potential impact on aquatic life and human health even at low concentration, it becomes imperative to develop selective, simple and reliable method for their detection as well as removal from different matrices.

Though various sensitive methods are available to detect the presence of theirquantity in differentmatricesviz. LC-MS/MS, HPLC, GC, CE (Pateiro-Moure *et al.* 2013, Rojano and Castro 2014) but these methods are not only time consuming and cumbersome but costly also. So there is a need to develop a method which is easy, cost effective and faster as compared to the existing ones.

Molecular recognition has played crucial role in almost every biochemical process vital to living organisms due to their natural control over complex interactions at molecular level. It has also prompted scientists to apply this knowledge for designing the artificial receptors with the capability of mimicking these processes (Meier and Mizaikoff 2010). Consequently, numerous efforts have been made to design and synthesize artificial receptorswith bio-mimetic properties. Amongst them, molecular imprinting offers a facile and straight forward strategy towards the development of such artificial receptors (Ansell *et al.*z 1996). Molecularly Imprinted Polymers (MIPs) are the synthetic polymeric materials obtained by the polymerization of

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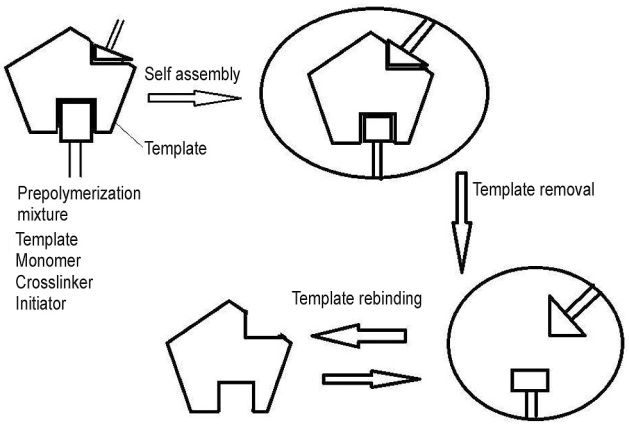

Fig 1. Molecular Imprinting Process

functional monomer and cross linker in suitable porogenwith the template molecule. Subsequent removal of imprinting molecule (template) leaves behind the cavities which are complementary in size and shape to the template. These cavities help in the selective recognition of the target analyte amongst different analytes (Fig.1). The imprinted polymers have the ability to selectively recognize and bind with the template molecule amongst the closely related chemical species. Along with the low cost of production, these materials are stable to extreme variation in pH, temperature and organic solvents as compared to their biological counterparts (Vlatakis *et al.* 1993).

The efficiency and performance of MIPs is based on three factors that includes binding affinity (BA), the imprinting factor (IF) and separation factor (SF). Though the method of preparation of MIPs is relatively simple but the optimization of the compositional variables (monomers, cross-linkers, porogenic solvents, template to monomer ratios) and operational variables (temperature, pressure, time etc.) is cumbersome task. So, there is need to develop a method which can help to establish an optimal monomer system for MIP preparation in a short time with better precision and minimum error. Computational modeling based approach utilizes the computers to simulate and study the complex system behavior with the help of different principles of mathematics, physics and computer science. The techniques ranging from statistical treatment to quantum mechanical simulations are being used to study different aspects of molecular imprinting (Nicholls *et al.* 2011). In this review, we will cover the use of computational tools for studying electronic structure and molecular dynamics (MD), and brief presentation of their application for the preparation of MIPs for herbicides in particular.

Electronic structure methods/Quantum chemical calculations

These methods include semi empirical, ab initio and density functional theory (DFT) which describe different aspects of MIPs with high degree of accuracy at reasonable computational cost. As compared to theoretical approaches, these methods describe electronic structures of the system to give better picture of non-covalent interactions in the complex. Generally these methods are used to explore the possible interactions between the template molecule and functional monomers in the pre-polymerization mixtures. Pietrzyk *et al.* (2009) used the method along with DFT to model a complex between melamine and the functional monomer molecules. The B3LYP theory level was also used with 6-31G (d,p) basis set for modeling template: monomer complexes of GA with polarizable continuum model (Pardeshi *et al.* 2014).

Electronic structure techniques can also be applied for optimization of MIP performance by selection of suitable functional monomer. The strategy utilizes binding energies as a guide for selecting an optimal functional monomer obtained from calculations on complexes modeled for template molecule and different functional monomers. This strategy was followed to design MIP for recognition of N,O-dibenzylcarbamate by using AM1 level of theory (Baggiani *et al.* 2005). Luliński *et al.* (2007) used PM3 theory level to design dopamine imprinted polymer following the same strategy. Dong *et al.* (2005) used more sophisticated B3LYP/ 6-31G**// B3LYP/ 3-21G level of theory to design MIP for theophylline. Gholivand *et al.* (2010) used the same strategy to design furosemide-imprinted polymer using HF/6-31 G(d) level of theory. Different density functional methods and MP2 combined with different basis sets were used for designing nicotinamide imprinted polymers (Del Sole *et al.* 2009).

If a template differs from the target structure of MIP, the electronic structure methods can be used for assisting the choice of template itself. This strategy was employed by Rathbone *et al.* (2005) to design MIP based binding mimic of cytochrome CYP2D6. On the basis of superposition studies on known CYP2D6 substrates with selected templates, the templates to be imprinted were chosen. Based on PM3 calculations, electronic structure methods have also been used to design an ester hydrolysis-catalyzing polymer (Sagawa *et al.* 2004). These calculations strengthened the hypothesis that the template used in MIP synthesis is a mimic of the transition state of the reaction to be catalyzed. Rahangdale *et al.* (2016) also utilized the same strategy for the design of 4- hydroxybenzoic acid, which served as dummy template of SA, using B3LYP/ 6-31 G(d) theorylevel.

Quantum mechanics methods can also be used for evaluation of a given MIP. Wang *et al.*(2005) suggested a recognition mechanism which explained the selectivity of an N-(4-isopropylphenyl)-N'-butyleneurea imprinted polymer towards a series of substrates whose geometries were optimized and Mulliken charges were calculated using B3LYP/ 6-311 G**. Using a series of B3LYP and MP2 calculations along with electron spin echo envelope modulation (ESEEM) spectroscopy, Christoforidis *et al.* (2008) investigated the mode of interaction of semiquinone radicals with an imprinted polymer.

Recent years have seen rise in exploring different aspects related to MIP science by utilizing quantum

chemical calculations. Though these strategies are being used primarily to study pre polymerization mixture interactions but with the development and improvement in computational techniques, impact of these techniques is expected to rise.

Molecular dynamics simulation

Though quantum and semi empirical methods have helped to determine the absolute energies of monomer-template interactions but are unable to explicitly simulate solvent and/or account for dimerization of mixture components along with the effect of temperature or pressure on stoichiometry of polymer components (Piletsky *et al.* 2001, 2005).

Keeping in mind all the complexities involved in optimizing the conditions for MIP preparation, a strategy is required to handle different variables along with keeping costs and time to the minimum. One such strategy for handling the task is Molecular Dynamics (MD) which force field based and allows simulation and prediction of nature of ensemble of non-covalent complexes formed in MIP pre polymerization mixture. Though there are number of force fields being used for study of biomolecules and small organic molecules but due to high accuracy and degree of information provided through MD simulations, this technique is being preferred and used successfully for simulating various biomolecular systems (Garrison and Delcorte 2000; Hsu, Wu and Fang 2005).

According to current concept of molecular imprinting, the nature and extent of functional monomer template complexation is correlated to the origin of the predetermined recognition in MIPs in the pre-polymerization mixture (Karim *et al.* 2005; Alexander and Andersson 2006). In order to select best binding functional monomer/s MD-based protocol was first reported byPiletsky *et al.* (2001) for the enantiomer of template ephedrine in which they created and screened virtual library of 20 different functional monomers. On the basis of this MD based screening method, the group further prepared MIPs for other pharmaceutically important compounds which included simazine (Piletska *et al.* 2005), creatinine (Subrahmanyam *et al.* 2001), biotin(Piletska *et al.*, 2004) and the cyanobacterial toxin microcystin- LR (Chianella *et al.* 2002, 2003). This technique was also utilized by Pavel and Langowski (2005a, 2005b) to study the effect of the growing polymeric chain on the functional monomer-template complexation during polymerization of theophylline and its derivatives. The strategy was further developed by Monti *et al.* (2006) to obtain the best functional monomer for template theophylline by using a combination of MD, molecular mechanics (MM), docking and site mapping.Yoshida *et al.* (2000) used MD simulation to represent the functional monomer template complex stability studies for MIPs prepared by methods other than bulk polymerization.

As there are large numbers of atoms in a MIP pre-polymerization mixture, the time required for computation of binding energies of monomer-template by QM takes large share of time. This can be simplified by combination of MM and QM for virtual library screening for choosing best functional monomer to be used for template imprinting. This strategy has been successfully applied for imprinting of rhodamine B (Liu *et al.* 2009) and sulfadimine (Li *et al.* 2009).

For successful predictions ofMIP template recognition characteristics, it is necessary to account for all non-covalent interactions formed between functional monomer and the template. Using MD approach, various studies have been carried out by differentinvestigators on this aspect also (Svenson *et al.* 2004; Olsson *et al.* 2012; O'Mahony *et al.* 2013).

MD simulations can also be used to study the role of the solvent during template rebinding along with the simulation of dynamics of final MIP. This concept was utilized to study the dynamics of polymeric hydrogel in the presence of cholesterol as a template (Zhao *et al.* 2008). Furtherstudies suggested that the recognition process is solely governed by the mesh size of the network (Luo *et al.* 2014).

In summary, MD-based studies cannot only be utilized to provide insight into the pre-polymerization system but can also be used to investigate physical characteristics of the final MIP- matrix.

Prepolymerization complex studies of herbicides based on computational approaches

Computational modeling is becoming a reliable tool for identification of suitable functional monomer on the basis of binding energies. On the basis of the results obtained through programming and their successful validation through different experiments, the techniques were also implied for herbicides. As these chemicals can pose a threat of leaching and environmental contamination, it becomes utmost necessary to identify and quantify them. Zhu *et al.* (2002) used combinatorial protocol withWeblab Viewer Pro 4.0 to optimize the polymer in terms of the kind and relative amounts of functional and cross-linking monomers using metsulfuron methyl urea as template molecule. The monomer and cross linker used for the purpose were 2-(trifluoromethyl) acrylic acid (TFMAA) and divinylbenzene (DVB), respectively with dichloromethane as porogen.

Chapuis *et al.* (2003) optimized the imprinting of terbutylazine on methacrylic acid (MAA) for selective solid phase extraction of triazines and their polar degradation products from aqueous samples using Hyper-Chem Pro 6.0 combined with ab-initiomechanics. The effects of the electric charge distribution and the size of the molecules on the retention mechanism of polymers prepared for terbutylazine and ametryn as template molecules were studied by using Hyper-Chem Pro 6.0 software. The value of capacity for terbutylazine MIP was also measured. The polymers, so prepared, showed high selectivity when used for clean-up of grape juice and soil extracts(Chapuis *et al.* 2003).

Piletska *et al.* (2005) used Leapfrog algorithm with SYBL 6.9 for screening against a library of 20 polymerisable functional monomers. The results helped to

Table 1 Computational procedure for the design of MIPs for herbicides

Process	Template	Monomer	Matrix/ Purpose	Reference
Weblab Viewer Pro 4.0	Metsulfuron methyl	TFMAA	Optimization of MIP synthesis	(Zhu *et al.* 2002)
HyperChem Pro 6.0 combined with ab-initio mechanics	Terbutylazine	MAA	Selective solid phase extraction of triazines from aqueous samples	(Chapuis *et al.* 2003)
HyperChem Pro 6.0	Terbutylazine Ametryn	MAA	Grape juice Soil	(Chapuis *et al.* 2004)
Leapfrog algorithm (SYBL 6.9)	Siamzine	MAA HEM	Control release in water	(E. V. Piletska *et al.* 2005)
1-ns MD simulations	2,4-D	4-VP	To study recognition mechanism of MIPs	(Molinelli *et al.* 2005)
Leapfrog algorithm (SYBL 6.9)	Atrazine	MAA ITA AM	Optimization of composition of *in situ*-polymerized MIPMs	(Sergeyeva *et al.* 2008)
Gaussian 03 pbe1pbe/6-311 G (d,p)	2-MPA MCPA 4-CPA	4-VP	To study recognition mechanism of imprinted polymers	(Zhang *et al.* 2008)
GROMOS-96 and B3LYP/ 6-31 G(d)	Acetochlor	MBAAM	Rational design of MIP	(Dong *et al.* 2009)
Gaussian 03 B3LYP/ 6-31 G*	Simetryne	Allobarbital	Corn Soil samples	(Wu *et al.* 2011)
Gaussian 03 B3LYP/ 6-31 G(d)	Cyanazine	Acrylamide	Food samples	(Gholivand *et al.* 2012)
Gaussian 03 B3LYP/ 6-31 G(d)	Propazine	MAA AAM 4-VP	Food samples	(Gholivand and Malekzadeh 2012)
Leapfrog algorithm (SYBL 6.92)	Monosulfuron Monosulfuron-ester	MAA	Selective binding of monosubstituted sulfonyl urea	(Wang *et al.* 2012)
Leapfrog algorithm (SYBL 7.3)	Atrazine	MBAAM MAA NPEDMA	Rapid screening and optimization of MIPs	(Lakshmi *et al.*. 2013)
Gaussian 09 B3LYP/ 6-311 G	Sulfadiazine	MAA 4-VP NIPAM	Selective recognition ability of TMIPs	(Ma *et al.* 2014)
HyperChem 8.0.5	Diuron	MAA	Electrochemical sensor	(Wong *et al.* 2015)
HyperChem v.8.5	Hexazinone	2-VP, MAA, AAM	Biomimetic sensor	(Toro, Marestoni and Del Pilar Taboada Sotomayor, 2015)
Gaussian 09 B3LYP/ 6-31 G (d,p)	Atrazine	o-phenylenedi-amine	Electrochemical sensor	(X Li *et al.* 2015)

prepare simazine-specific molecularly imprinted polymer for its controlled release into water to control algae. The speed of release of herbicide also correlated with the calculated binding characteristics. The stability of the complex formed between the template 2,4-dichlorophenoxyacetic acid (2,4-D) and the functional monomer 4-vinylpyridine (4-VP) solvated in chloroform or water was studied using 1-ns MD simulations. Hydrogen bond interaction in chloroform and π-π stacking interaction in water was suggested for explaining nature of interactions during pre-polymerization stage as well as during MIP rebinding in aqueous solution (Molinelli *et al.* 2005). Sergeyeva *et al.* (2008) used computational modeling (SYBL 6.9) to optimize composition of *in situ* polymerized atrazine-imprinted polymer membrane with MAA as optimal functional monomer. The studies also showed correlation between the estimated binding energy, the number of functional groups taking part information of the complex with the template molecule and the abilityof functional monomers to form selective sites in the MIP membranes. The computational *in situ* polymerized porous MIPmembranes were characterized by high adsorption capability towards template molecules (12.5 mg/g membrane), high selectivity as foratrazine close structural analogues, as well as with high storagestability (up to 18 month). Zhang *et al.* (2008) investigated cross selectivity of molecularly imprinted polymers prepared for 2-methylphenoxyacetic acid (2-MPA), 2-methyl-4-chlorophenxyacetic acid (MCPA) and 4-chlorophenoxyacetic

acid (4-CPA) and showed that it depends on the binding energies of complexes. Computational modeling was carried out to study the ion-pair interactions between template molecules and functional monomer 4-vinylpyridine with pbe1pbe level of theory and 6-311G (d,p) as basis set. The studies suggested that 2-MPA can be used as a dummy template for imprinting the polymers to retain phenoxyacetic herbicides. Combination of molecular dynamics simulations and quantum mechanics calculation was used to prepare MIP for acetochlor by Dong *et al.* (2009). Mulliken charge distribution and 1H NMR spectroscopy of the synthesized MIP also helped to probe governing interactions for selective binding site formation at a molecular level. Wu *et al.* (2011) prepared molecularly imprinted microspheres (MIMs) with homogeneous binding for triazines with allobarbital as novel functional monomer and divinyl benzene as cross linker. Molecular simulations were carried out to know the host-guest binding characteristics by using Gaussian 03 software with B3LYP/ 6-31G* level. These MIMs were used further as specific sorbent for selective extraction of simazine from corn and soil samples. Molecularly imprinted polymers have also been used for developing the electrochemical sensor for cyanazine determination in food samples (Gholivand *et al.* 2012). DFT based calculations [B3LYP/6-31G(d)] were used to screen to screen functional monomer and polymerization solvent. On comparison of binding energies of different monomer: template complex, acrylamide (AAM) and toluene were chosen for MIP synthesis. The polymer prepared, which was embedded in the carbon paste electrode (CPE), served both as recognition element and preconcentrator agent for cyanazine in cathodic stripping voltammetric method. The MIP-CP electrode showed high recognition ability with the detection limit of 3.2 nM.Gholivand *et al.* (2012) extended their work in designing highly selective voltammetric sensor for propazine detection in food samples. Acrylamide was selected as the best monomer for the purpose on the basis of computational data obtained for intermolecular interactionsin the pre-polymerization mixture. The detection limit of the sensor, so developed, was calculated as 0.001 μmol^{-1}. MIPs have also been used for selective binding mono-substituted sulfonylurea herbicides (Wang *et al.* 2012). Computational modeling (SYBL6.9) was used to understand the recognition mechanism which showed that monosulfuroncan form multiple hydrogen bonds with methacrylic acid and acrylamide to form stable complexes that was not possible with monosulfuron-ester using the same monomers. The studies were further validated by the experimental data which showed that monosulfuron-imprinted polymers had better selectivity than the commercial C18 HPLC stationary phase material for monosulfuron-ester. Lakshmi *et al.* (2013) prepared MIPs for atrazine detection on conjugated polymer coated microtiter plate. The optimized composition for the synthesis of MIPs was based on molecular dynamics simulations which used leapfrog algorithm (SYBL 7.3) for screening the virtual library of monomers. Ma *et al.* (2014) used molecular simulation with the help of Gaussian 09 software (B3LYP/ 6-311 G level of theory) to prepare temperature-responsive molecularly imprinted polymers (TMIPs). In the experiment, methacrylic acid (MAA) and 4-vinylpyridine (4-VP) served the purpose of cofunctional monomers on the basis of N-isopropyl acrylamide (NIPAM) as a temperature-responsive monomer. The TMIPs having optimal performance were used with SPE to determine sulfadiazine in real water samples. An electrochemical sensor, for the selective and sensitive detection of diuron in water, has also been developed using molecularly imprinted polymer (MIP) and carboxyl- functionalized multiwalled carbon nanotubes (MWCNT-COOH) (Wong *et al.* 2015). The group used HyperChem 8.0.5 software to select the most suitable monomer amongst the library of twenty monomers with diuron as the template molecule. On the basis of binding energies, methacrylic acid (MAA) was chosen as the best monomer which was further validated in the laboratory. In comparison to the plain carbon paste electrode (CPE), MWCNT-COOH-MIP/CPE showed enhanced electrochemical response with 7.9 times higher sensitivity. The sensor so developed has the ability to detect diuronup to 5.2×10^{-8} in comparison to HPLC method which can detect only up to $2.1 \times 10^{-5} mol\ L^{-1}$. For the determination of hexazinone in environmental samples, Toro (2015) designed a biomimetic sensor based on molecularly imprinted polymer. To select the best functional monomer out of the library of 20 monomers, computer simulation studies were carried out with the help of HyperChem v 8.0.5 software. To ensure accuracy in the interaction energy calculations between the analyte and monomer conformations, three different conformers were used. On the basis of simulation studies and experimental validation, 2-vinyl pyridine was used as functional monomer for the development of the sensor. The sensor so developed was found to be highly selective and sensitive for hexazinonewhich enabled its detection up to $10^{-10}\ molL^{-1}$.

Using the density functional theory method, Li *et al.* (2015) have recently developed an electrochemical sensor for atrazine detection using o-phenylenediamine (o-PD) as functional monomer without using the cross-linker. They optimized the ratio of atrazine and o-PD on the basis of interaction energies for preparation of MIP film by electro-polymerization of the monomer. The developed sensor showed specific recognition towards atrazine with low detection limit of 1.0×10^{-9} M.

Though molecular imprinting technique has been used for long time but the studies based on computational and theoretical techniques for describing, predicting and analyzing the molecularly imprinting systems have seen a big surge in recent years only. The potential is still untapped for different classes of herbicides (except atrazine) though they play a significant role in increasing world food production along with other agrochemicals. With the continued development of computer hardware and software technologies, it is expected that important aspects related to molecular imprinting like functional site heterogeneity, template aggregation and restructuring of imprinted pores

will be addressed which will help to design the polymers with improved performance in a better way in near future.

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