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Computational Design and Synthesis of Molecular Imprinted Polymers for solid-phase Extraction of Acyclovir

Gholamali Haghdoost*

Department of Chemistry, Kazerun Branch, Islamic Azad University, Kazerun, Iran

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ABSTRACT

Highly selective molecularly imprinted polymers (MIPs) for solid-phase extraction of acyclovir have been designed and prepared. In order to study the intermolecular interactions in the pre-polymerization mixture and to find a suitable functional monomer in MIP preparation, a computational approach was developed. It was based on the comparison of the binding energy of the complexes between the template and functional monomers. The effect of the polymerization solvent was included using the polarizable continuum model. According to the theoretical calculation results, the MIP with acyclovir as template was prepared by precipitation polymerization method using acrylamide (AAM) as functional monomer and ethylene glycol dimethacrylate (EGDMA), as cross-linker in acetone. Having confirmed the results of computational method, three MIPs were synthesized with different functional monomers, i.e. acrylamide (AAM), allylamine (AA) and acrylonitrile (ACN), and then evaluated using Langmuir–Freundlich (LF) isotherm. The results of this study have indicated the possibility of using computer aided design for rational selection of functional monomers and solvents capable of removal of acyclovir from contaminated fluids.

Keywords: Molecularly imprinted polymer; acyclovir; Molecular modeling Ab initio calculation; bonding energy; Continuum Model (PCM).

INTRODUCTION

Molecularly imprinted polymers (MIPs) are synthetic materials able to selectively recognize a guest molecule or related compounds and were introduced by Wulff (covalent approach) [1] and Mosbach (non-covalent approach) [2]. Basically, MIPs are prepared by the polymerization of a suitable monomer and a cross-linker agent in the presence of a template molecule. After polymerization, the template is removed from the polymeric matrix leaving cavities complementary in

* Corresponding author: haghdoost1352@yahoo.com

size and shape to the template, and thus the resulting MIP is able to specifically rebind this molecule or related compounds from a complex mixture. Therefore, MIPs have been employed in those fields where a certain degree of selectivity is required such as catalysis [3], solid-phase extraction [4], sensors [5] and chromatography [6, 7].

In order to improve the properties of MIP, computer-aided study of MIP has been suggested as a rational and fast method to search for optimal imprinting conditions. Piletsky group [8–12] used a virtual library of functional monomers to assign and screen against the target template molecule, and with the computer simulation the selectivity of MIP was greatly improved. Pavel group [12-14] applied computational tools to achieve an understanding of intermolecular interactions in molecular imprinting of theophylline and chemical warfare agents into complex polymeric and monomeric systems. Tunˇ o´ n-Blanco group [15, 16] developed a methodology based on density functional theory calculations for the rational design of MIP. The method was based on the comparison of the stabilization energies of the pre-polymerization adducts between the template and different functional monomers, and the effect of the polymerization solvent was included using the polarizable continuum model. In this paper, we try to develop a computational approach for the rational design of MIP by combination of functional monomer and polymerization solvent rending the most favourable interaction energy is supposed to give the polymer with the highest removal efficiency and selectivity.

RESULT AND DISCUSSION

Theoretical Selection of the Functional Monomers

Formation of a complex between the template molecule and functional monomers is the first step in the preparation of MIPs. The monomer that can interact with the template most intensively will give the complex with the highest stability, so the selection of the suitable functional monomers is a crucial factor in the preparation of MIPs.

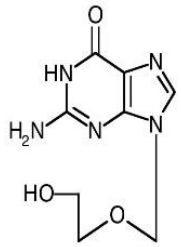
In this work, five functional monomers, i.e. acrylamide (AAM), allylamine (AA), acrylonitrile (ACN), methacrylic acid (MAA) and methacrylamide (MAAM) were theoretically selected as possible functional monomers. The conformation of template, functional monomers and template–monomer complexes were optimized to the lowest energy using Hartree-Fock (HF) method with 6-31G (d) basis set. The investigation of possible interactions was done to obtain optimized geometries for template–monomer complexes in the molar ratio of 1:1, 1:2, 1:3 and 1:4. As an example, Fig. 1 shows the optimized geometries of complexes between acyclovir (Scheme 1) and acrylamide (AAM). In theory, the monomer interacting with the given template with the highest binding energy would be more suitable for being used to prepare MIP.

In the calculation of electronic energies, the highest stability was obtained for 1:4 mole ratio of template-monomer - complexes. Table 1 summarizes the calculated interaction energies after BSSE correction for 1:4 complexes in different solvents.

Results of Table 1 make sense since salvation of a species also involves intermolecular interactions of the same nature as monomer–template and so the solvent acts as a competitor.

From the data listed in Table 1, it is concluded that type of solvent has a significant influence on the complex stability. However, because of the good solubility of acyclovir (Scheme 1) in acetone and also results concluded Form

Table 1 that the stability order in acetone is ΔE (AAM >ΔE (MAA) >ΔE (AA) >ΔE (MAAM) >ΔE (ACN) acetone was selected as polymerization solvent. These results indicate that acyclovir interacts most strongly with AAM and most weakly with ACN in acetone, so the MIP synthesized with AAM in the solvent is expected to give the highest removal efficiency to acyclovir. To examine the accuracy of the theoretical calculations, several polymers acyclovir were prepared by precipitation polymerization using AAM (MIP1), MAAM (MIP2) and ACN (MIP3) as functional monomers with low, medium and high interaction energy respectively. EGDMA and acetone were used as cross-linker and polymerization solvent.



Scheme1. Acyclovir

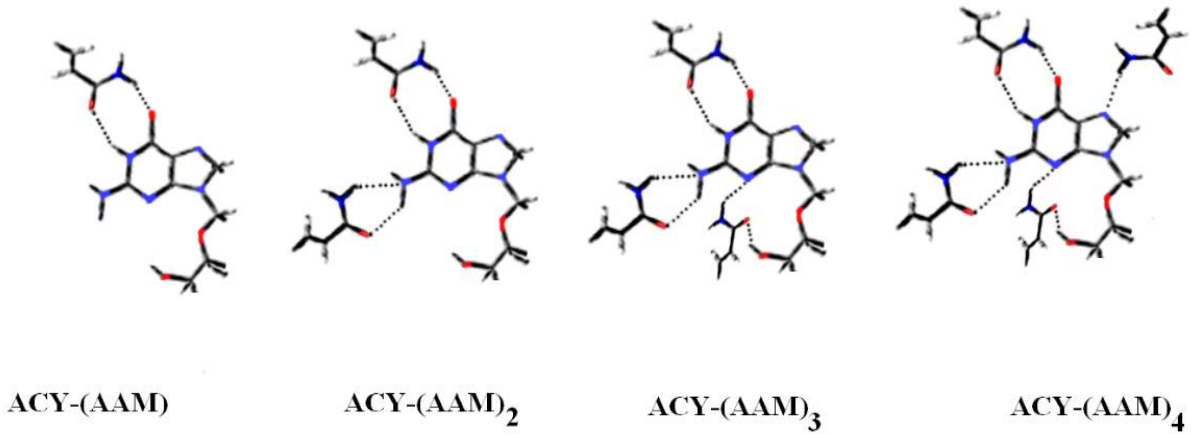


Fig. 1. Optimized conformations of the most stable 1:1, 1:2, 1:3 and 1:4 complexes of acyclovir with acrylamide (AAM)derived by Hortree- Fock (HF) method with 6-31G(d) basis set.

Table 1. Interaction energies (ΔE, $KJmol^{-1}$) of 1:4 template–monomer complexes in different solvents

Complexes	Acetone	MeCN	MeOH	DMSO
$FL(AAM)_4$	-62.261	-52.679	-58.654	-49.259
$FL(MAAM)_4$	-41.933	-40.915	-42.498	-37.569
$FL(AA)_4$	-50.897	-51.698	-48.325	-42.987
$FL(ACN)_4$	-7.986	-12.598	-8.478	-8.025
$FL(MAA)_4$	-52.915	-57.326	-48.029	-43.289

Binding Experiments

In this section, the heterogeneous Langmuir–Freundlich (LF) isotherm was considered for evaluation of binding characteristics of the synthetic MIPs [17]. The LF isotherm (Eq. (1)) is an hybrid model of Langmuir and Freundlich isotherms which describes a specific relationship between the equilibrium concentration of bound (B)and free guest (F) with three fitting coefficients: N_t, a and m. N_t is the total number of binding sites, a is related to the average binding affinity (K_0) towards $K_0 = a^{1/m}$, and m is the heterogeneity index which will be equal to 1 for a homogeneous material, or will take values within 0 and 1 if the material is heterogeneous**.**

$$B = \frac{N_t a F^m}{1 + a F^m} \quad (1)$$

The experimental isotherm data (F and B) were successfully fitted to the LF isotherm in order to evaluate the N_t, K_0, and m values (Fig. 2 is shown as an example for MIP1).

The resulted fitting coefficients at the desired concentration window are listed in Table 2. As seen, the value of m demonstrates the heterogeneity of all MIPs. However, MIP1 shows the highest degree of binding site homogeneity with the highest heterogeneity index (m= 0.86).

The comparison of other binding parameters reveals that MIP1 has the highest concentration of binding sites per gram of polymer (N_t = 117µmol g^{-1}) and median binding affinity (K_0 = 92.33mM^{-1}).

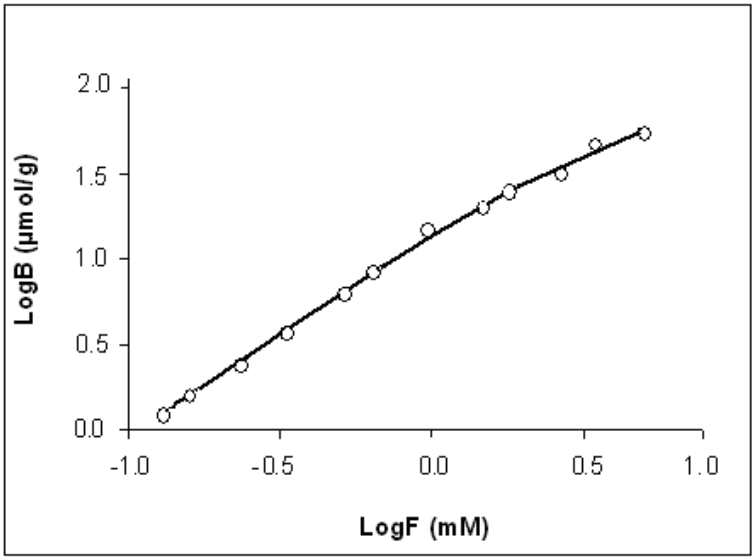


Fig. 2. Experimental isotherm (dot) and LF fit (line) for MIP1.

Table 2. Binding parameters obtained for LF fit to the experimental adsorption isotherms of acyclovir in acyclovir - imprinted polymers obtained in various mole ratios

polymer	N_t (µmolg^{-1})	a(mM^{-1})	m	K_0(mM^{-1})	R^2
MIP1	117	49	0.86	92.33	0.997
MIP2	85	27	0.81	58.49	0.999
MIP3	56	15	0.75	36.99	0.998

The Specific Affinity of the Polymers for the Template

In general MIP theory, two factors are important for the ef--fective recognition of the template by MIP: the strength and quantity of the interactions between the monomers in the polymer network and the template. The MIP cavities created after removal of the template are complementary to the imprint molecule in size and coordination geometries that leads to much greater affinity for the template molecule in comparison with non-imprinted sorbent. In several batch experiments, 20mg amount of each MIP and corresponding NIP particles were incubated in 10.0ml solution of acyclovir (50µg.ml^{-1}) for 12 h. The distribution ratio (K_d) was calculated using the equation:

$$K_d = \frac{(C_i - C_f)V}{C_f m} \qquad (2)$$

Where V, C_i, C_f and m represent the volume of the solution (ml), drug concentration before and after adsorption (µg.ml^{-1}) and mass of the polymer, respectively. The imprinting effect of a certain MIP is often evaluated by the imprinting factor, which is defined as follows [18]:

$$IF = \frac{K_d(impr\,\text{int}\,ed)}{K_d(non-impr\,\text{int}\,ed)} \qquad (3)$$

The obtained results are shown in Table 3. As it is seen, all synthesized MIPs show an imprinting effect and they are able to rebind more template than the corresponding NIP, confirming the presence of the imprinted cavities in their structure. As well as, results in Table 3 lead that MIP1 demonstrates high tendency and selectivity to acyclovir rather than other MIPs.

The MIP using AAM as functional monomer gives the maximum IF while the MIP using ACN gives the minimum IF. This is consistent with the theoretical calculations. From the theoretical molecular modeling studies and binding experiments, the MIP1that is manufactured by AAM was identified as the favored imprinted material.

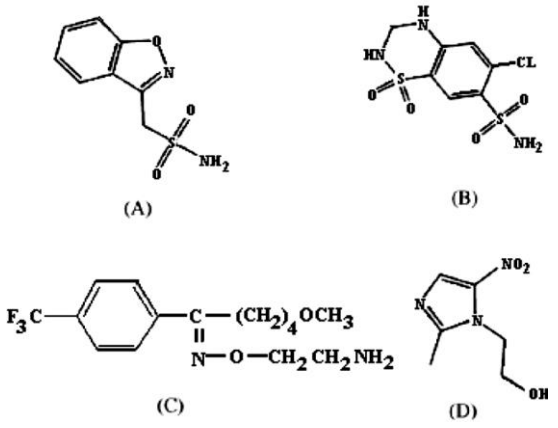
Table 3. Distribution ratios (K_d) and imprinting factors (IF) of acyclovir for imprinted and corresponding non-imprinted polymers

polymer	K_D		IF
	MIP	NIP	
MIP1	60.4	25.1	2.4
MIP2	36.9	18.8	2.0
MIP3	23.5	16.4	1.4

The Selectivity Test

In order to evaluate the overall selectivity of the synthesized MIP, several substrates with H-bonding ability such as, zonisamide, hydrochlorothiazide, fluvoxamine and metronidazole in present of acyclovir were tested (Scheme 2).

In several batch experiments, the distribution ratios (K_d) and selectivity coefficients (α) were calculated and are listed in Table 4. These results clearly suggest that the unique shape of the template molecule plays an important role in its selective binding to the polymer and the MIP is capable for recognition of acyclovir in various complex metrics such as biological fluids.



Scheme 2. Chemical structures of: (A) zonisamide, (B) hydrochlorothiazide, C) fluvoxamine (D) metronidazole.

Table 4. Distribution ratio (K_d) and selectivity coefficient (α^1) values for imprinted and nonimprinted polymers

Compound	MIP		NIP	
	K_D	α	K_D	α
acyclovir	63.5		20.4	
zonisamide	26.5	4.8	18.9	1.7
hydrochlorothiazide	15.1	4.3	17.5	1.5
fluvoxamine	16.4	4.1	15.6	1.2
metronidazole	17.9	3.8	14.2	1.9

[1] K_d (acyclovir)/K_d (Foreign compound).

CONCLUSION

The results of this study showed that the computer aided design could be used as an effective evaluation tool for MIP syntheses. The computational method was applied to study the intermolecular interactions in the pre-polymerization mixture and to find a suitable functional monomer in MIP preparation. It was found that acyclovir interacts more strongly with AAM in comparison with other functional monomers. The MIP demonstrated high efficiency and selectivity to the acyclovir rather than other tested substances which is suitable to use in biological fluids.

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طراحی محاسباتی و سنتز پلیمر قالبگیری شده مولکولی با انتخابگری بالا به منظور استخراج آسیکلوویر

غلامعلی حق دوست *

گروه شیمی، واحد کازرون، دانشگاه آزاد اسلامی، کازرون، ایران

چکیده

پلیمرهای منقوش مولکولی بسیار انتخابی (MIPs) برای استخراج فاز جامد آسیکلوویر طراحی و آماده شده است. به منظور مطالعه برهمکنش‌های بین مولکولی در مخلوط پیش‌پلیمریزاسیون و یافتن یک مونومر عملکردی مناسب در تهیه MIP، یک رویکرد محاسباتی توسعه داده شد. این بر اساس مقایسه انرژی اتصال کمپلکس‌ها بین الگو و مونومرهای عملکردی بود. اثر حلال پلیمریزاسیون با استفاده از مدل پیوسته قطبش‌پذیر گنجانده شد. با توجه به نتایج محاسبات نظری، MIP با آسیکلوویر به عنوان الگو با روش پلیمریزاسیون رسوبی با استفاده از آکریل آمید (AAM) به عنوان مونومر عملکردی و اتیلن گلیکول دی متاکریلات (EGDMA)، به عنوان پیوند متقابل در استون تهیه شد. پس از تایید نتایج روش محاسباتی، سه MIP با مونومرهای عملکردی مختلف، یعنی آکریل آمید (AAM)، آلیلامین (AA) و اکریلونیتریل (ACN) سنتز شدند و سپس با استفاده از ایزوترم لانگمویر–فروندلیچ (LF) ارزیابی شدند. نتایج این مطالعه امکان استفاده از طراحی به کمک کامپیوتر را برای انتخاب منطقی مونومرها و حلال‌های کاربردی با قابلیت حذف آسیکلوویر از مایعات آلوده نشان می‌دهد.

کلید واژه‌ها: پلیمر حک شده مولکولی؛ آسیکلوویر؛ مدل‌سازی مولکولی؛ محاسبه اولیه؛ انرژی پیوند؛ مدل پیوسته (PCM)

* مسئول مکاتبات: haghdoost1352@yahoo.com