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ORIGINAL ARTICLE

Synthesis and evaluation of cyclodextrin-based polymers for patulin extraction from aqueous solutions

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Abstract Patulin is a mycotoxin produced by fungi that contaminate fruits, juices, and other agricultural commodities. Sorption properties of polyurethane-beta-cyclodextrin polymers were evaluated for the ability to remove patulin from solutions, including apple juice. Freundlich isotherm analysis determined the polymers possess a degree of heterogeneity. Evaluation of the polymers by solid phase extraction analysis indicated patulin sorption is enhanced in aqueous environments. Polymers crosslinked with tolylene 2,4-diisocyanate were suitable for extraction of patulin from apple juice. Quantum chemical studies of the interactions of patulin and beta-cylcodextrin using the PM3 semi-empirical method infer patulin is capable of binding to the polymer in multiple modes. Certain of these bound complexes possess intermolecular hydrogen bond interactions between the primary hydroxyls of beta-cyclodextrin and patulin. These nanoporous cyclodextrin polymers exhibit favorable properties to assist the detection of patulin in aqueous solutions.

United States Department of Agriculture—Names are necessary to report factually on available data; however, the USDA neither guarantees nor warrants the standard of the product, and the use of the name by USDA implies no approval of the product to the exclusion of others that may also be suitable.

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Introduction

Patulin is a toxic, secondary metabolite most commonly associated with apple spoilage; however its occurrence has been reported in a variety of fruits and agricultural products [1, 2] (see Fig. 1). This mycotoxin is produced by several fungal species that occasionally contaminate agricultural commodities, including those of the *Penicillium*, *Aspergillus*, and *Byssochlamys* species. Patulin contamination is a health risk to humans and reduces commodity values. Exposure to this mycotoxin is associated with a broad range of adverse effects, including gastrointestinal diseases and potential for carcinogenicity, and genotoxicity, immunotoxicity and neurotoxicity have been observed [3, 4]. Patulin levels are regulated in the United States and many other countries, with levels currently set at 50 μg/L for certain apple based products. A variety of methods ranging in accuracy and rapidity have been developed to monitor levels of patulin, including an array of hyphenated techniques, such as HPLC coupled with UV detection [5–7]. Development of rapid methods to detect patulin using traditional selective molecular recognition materials is complicated by several inherent properties of this mycotoxin. Patulin is reactive under basic conditions and forms adducts through nucleophilic conjugation with thiol containing species, such as proteins and glutathione [8]. Furthermore, patulin naturally occurs as a racemic mixture and is capable of adopting multiple stable conformations which may complicate selective recognition through certain types of binding interactions [9, 10].

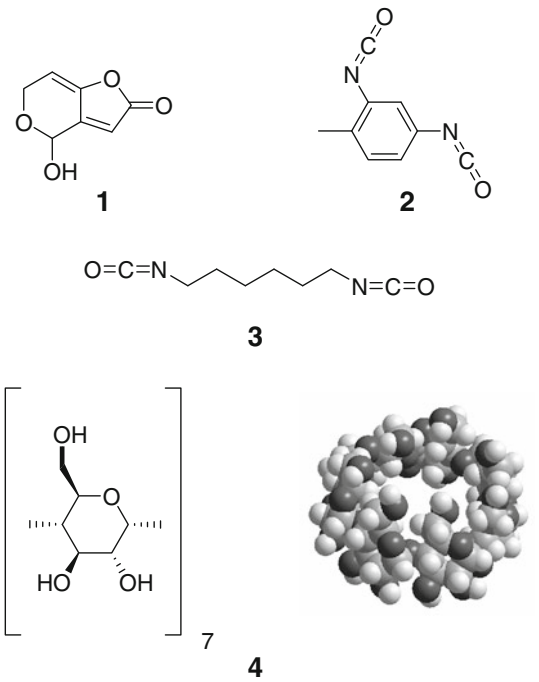

Fig. 1 Patulin and reagents used in polymer synthesis

There is increasing interest for robust sorbents to remove toxins from complex matrices. Polymers based on cyclodextrin components have demonstrated useful properties as sorbents for a variety of contaminants, including toxic phenols, natural organics, dyes, and trace metals [11–15]. Incorporation of cyclodextrins as components of crosslinked polymers provides a nanoporous material with cavities capable of acting as generic binding sites with recognition properties modulated by solvent and other factors [16, 17]. The internal cavities of cycloamylose of six, seven and eight glucopyranose units possess physical properties favorable to forming complexes with small organic molecules. The popular β-cyclodextrin, **4**, with its seven α(1–4) linked glucopyranose units, has seen extensive use for guest–host complexes. It should be noted that previous applications of cyclodextrins for mycotoxin analysis have focused on utilizing the cavities of free cyclodextrins and cyclodextrin deriviatives as selective recognition components to enhance separation and spectroscopic properties [18–20]. Herein, we expand the use of cyclodextrins for mycotoxin analysis to the development of insoluble cyclodextrin-based polymers to extract and clean-up the mycotoxin patulin from apple juice.

In this study, we utilize the favorable binding properties of cyclodextrins to develop a polymer to bind patulin under aqueous conditions. The influence of solvent on the recognition properties of the cyclodextrin polymer is exploited for the concentration and elution of patulin. The efficacy of the polymer is evaluated to assist the detection of patulin in apple juice. Finally, semi-empirical studies are performed to investigate the binding modes of patulin with the β-cyclodextrin components of the polymer.

Experimental methods

Reagents and materials

β-cyclodextrin (**4**), tolylene 2,4-diisocyanate (**2**), 1,6-diisocyanatohexane (**3**), anhydrous dimethylformamide (DMF), methanol, ethanol, acetone (HPLC grade), acetonitrile (HPLC grade), hexane, anhydrous diethyl ether, sodium bicarbonate, sodium acetate, acetic acid, trifluoroacetic acid, and patulin were obtained from Sigma-Aldrich, Inc. (St. Louis, MO, USA). Unless otherwise noted, all reagents were used as provided. β-cyclodextrin was dried at 70° C under vacuum for 24 h prior to use.

Polymer synthesis

Synthesis of polymer **5a**: β-cyclodextrin (2.27 g, 2.0 mmol) was dissolved in 20 mL of anhydrous dimethyl formamide in a 40 mL glass vial using sonication (15 min). The solution was flushed with nitrogen, and 20 mmol (3.48 g) of tolylene 2,4-diisocyanate was added dropwise with gentle mixing. Following the mixing, the vials were sealed, vortexed and placed in a 70° C water bath for 24 h. Resulting polymer monoliths were washed with acetonitrile, water, ethanol, and acetone and dried under vacuum. Dry polymers were ground using a coffee grinder, and mortar and pestle. Polymer particles were sieved and fractions between 38 and 75 μm were collected for analysis. Fine particles were removed by suspension in acetone (3 × 50 mL). Polymer **5b** was synthesized following the same procedure, substituting 10 mmol (1.74 g) tolylene 2,4-diisocyanate and 10 mmol (1.68 g) of 1,6-diisocyanatohexane for 20 mmol of tolylene 2,4-diisocyanate.

Surface area analysis

Surface area analyses were performed on a Quantachrome Autosorb-1 (Quantachrome Instruments, Boynton Beach, FL). Surface areas were determined at 77 K with nitrogen as the adsorptive and areas calculated using the single point BET method at $P/P_0 = 0.2$.

LC-analysis

Patulin levels were determined by LC-analysis. The HPLC system consisted of a Shimadzu LC-20AT pump, SIL-20A autosampler, SPD-M20A diode array detector, a CBM-20A

communications bus module, and a Phenomenex Luna 5 μ C18 100A column (250 × 4.6 mm). Unless otherwise noted, the LC-mobile phase consisted of 10% acetonitrile in water, and the sample injection volume was 20 μL. Patulin concentrations were calculated based on a standard curve using peak areas recorded at 270 nm ($r^2 = 0.997$).

Rebinding experiments

Cyclodextrin polymers were evaluated by measuring their ability to bind patulin by equilibrium binding assays. Assays were conducted in 1.5 mL screw cap vials. Polymers (10 mg) in 1 mL solutions of patulin (0.5, 1, 2, 5, 10, 15, 20, 30, 40, and 50 μg/mL) in buffer pH 5.5 (10 mM sodium acetate) were shaken for one hour on a Lab-line Multiwrist shaker at room temperature with the shaker speed set at eight. The vials were centrifuged and the supernatant was filtered through a Millex Syringe driven PTFE filter (0.2 μm). Patulin concentrations were analyzed by LC-analysis.

Solid phase extraction analysis

The loading capacity of the β-cyclodextrin polymers were determined by solid phase extraction (SPE) columns. β-Cyclodextrin polymer (30 mg) was packed between two frits in 1.5 mL solid phase extraction reservoirs from Alltech (Deerfield, IL, USA). Columns were washed with 5 mL acetonitrile, water, and, ethanol prior to use. Columns were loaded with patulin (1 mL of 50 μg/mL in the appropriate solvent). Solvents investigated are 10 mM sodium acetate buffer, pH 5.5, ethanol, and acetonitrile. Patulin concentrations were analyzed by LC-analysis.

Evaluation of the polymers ability to determine patulin levels in apple juice was carried out with a column packed with 50 mg of polymer **5a**, packed as previously described. Prior to use, columns were washed with 5 mL acetonitrile, water, and ethanol. Spiked apple juice (1 mL; 0.1, 0.5, 1, 5, 10, and 15 μg/mL) was loaded on column. The column was not allowed to go dry, and was washed with 0.5 mL of an aqueous solution of sodium bicarbonate (1% w/v), 0.5 mL of an aqueous solution of acetic acid (1%, w/v), and 0.5 mL of hexane. Finally, patulin was eluted with 1.0 mL of diethyl ether/acetonitrile (4:1). The solvent was removed from the final eluate under a gentle stream of nitrogen, and the residue was resuspended in 1 mL of mobile phase. Patulin concentrations were analyzed by LC-analysis with a sample injection volume of 50 μL using a mobile phase of water:acetonitrile:trifluoroacetic acid (980:20:0.5).

Computational chemistry

Semi-empirical calculations were carried out using the PM3 method with Parallel Quantum Solutions (Fayetteville, AR, U.S.A.) hardware and software v3.2 [21, 22]. Convergence criteria set at 1×10^{-6} Hartree and a gradient of less than 3×10^{-4} a.u. The initial structures were built using the Amber force field with the HyperChem 7.52 program (Gainesville, FL, U.S.A.) [23, 24]. Carbon atoms are displayed in grey, oxygen atoms in black, and hydrogen atoms in white.

Results and discussion

The inherent hydrophobic properties associated with cyclodextrin cavities were a key consideration in selecting the components for polymers synthesis in this study to isolate patulin from apple juice using a water insoluble sorbent. The rationale in polymer design was to use β-cyclodextrin to develop a nanoporous material, for which binding is driven by the hydrophobic effects present under aqueous conditions. Alternatively, an appropriate non-aqueous solvent offers a means to release patulin from the polymer for LC-analysis. Polymer composition, properties and initial solid phase extraction analysis are shown in Table 1. Polymer **5a** (30 mg) was capable of binding 29.2 μg of patulin under aqueous conditions (capacity of 0.97 μg/mg). However, capacity is significantly reduced in the polar, organic solvents acetonitrile and ethanol. Polymer **5b** exhibited ease of flow and less sorption in the solid phase column format.

The surface area of the crosslinked β-cyclodextrin polymers **5a** and **5b** can be compared to the surface areas of common adsorbents found in literature (see Table 2) [25–28]. The surface area of crosslinked β-cyclodextrin is very low compared to more broadly studied adsorbents. The surface area of polymers **5a** and **5b** are similar to previously reported cyclodextrin polymers shown suitable for binding phenol from waste water [28]. The elemental analysis results for polymers **5a** and **5b** indicate lower percentages of carbon and nitrogen, and a higher percentage of hydrogen

Table 1 Composition and patulin binding properties of polymers evaluated in the solid phase extraction format

Polymer	**5a**	**5b**
(β-CD:TDI:HDI)	1:10:0	1:5:5
Capacity (μg patulin/mg polymer)		
Buffer	29.2 ± 3.1	17.6 ± 4.7
Ethanol	7.3 ± 3.0	4.1 ± 0.8
Acetonitrile	6.7 ± 0.2	4.9 ± 2.2
Composition (%)		
Carbon	48.43	47.23
Hydrogen	5.37	6.06
Nitrogen	8.60	8.56

Table 2 Comparison of the surface areas of adsorbents with polymers **5a** and **5b**

Adsorbent	Adsorbate	Surface Area, m^2/g	Reference
SBA-15	Pharmaceuticals	737	[22]
Activated carbon	Amoxicillin	1092	[23]
Bentonite clay	Amoxicillin	92	[23]
Alumina	Phenol	900	[21]
β-CD-polymer	Phenol	0.75	[24]
5a	Patulin	0.92	This study
5b	Patulin	0.56	This study

than the theoretical composition. The experimental results may be influenced by residual solvent and the formation of hydrate complexes. Hydrate complexes of β-cyclodextrin have been observed by X-ray crystallography [29].

Polymers were evaluated by equilibrium binding assays with a set amount of polymer (10 mg) at various concentrations of patulin in sodium acetate buffer. The sorption isotherms for polymers **5a** and **5b** are shown in Fig. 2. Both polymers are suitable for Freundlich isotherm analysis, defined by the following equation [30]:

$B = aF^m$ where a and m are fitting parameters.

Parameter a is a measure of binding capacity for the analyte and average affinity of the population of binding sites. The parameter m is the heterogeneity index (0–1 with 1 being homogenous). B is the amount of bound patulin per gram of polymer, and F is the concentration of free patulin. Polymer **5a** possess slightly better affinity for patulin over polymer **5b**, with $a = 3400$ (μmol g^{-1})(l mol^{-1})^m compared to polymer **5b** $a = 2790$ (μmol g^{-1})(l mol^{-1})^m. Furthermore, Freundlich isotherm analysis indicates the affinity of the population of binding sites of polymers **5a** and **5b** exhibit a degree of heterogeneity (**5a** $m = 0.74$; **5b** $m = 0.76$). It should be noted that the range of affinity indicated in the heterogeneity index may be associated with binding sites formed by the crosslinking agents, **2** and **3**, during polymer synthesis.

Existing methods for solid phase extraction of patulin from juices require several clean-up steps, and use larger columns [31, 32]. Polymer **5a** demonstrated favorable properties as a solid phase sorbent for patulin, and was evaluated for the ability to clean up and detect patulin in apple juice. For comparison, we used spiked levels of apple juice (1 mL, of 0.1–15 μg/mL) which were loaded onto 50 mg columns of **5a**. Columns were washed with 0.5 mL of a sodium bicarbonate solution, 0.5 mL of a solution of acetic acid, and 0.5 mL of hexane. Finally, patulin was eluted with 1.0 mL of diethyl ether/acetonitrile (4:1). The relationships between peak area and recoveries are given in Fig. 3. Both peak area and peak height are suitable for determination of patulin in apple juice for the range of 0.1–15 μg/mL $\left(r^2_{area} = 0.986; r^2_{height} = 0.983\right)$. The cyclodextrin polymers show promise for the solid phase extraction clean up of patulin in apple juice, and potential for other toxins and analytes in aqueous matrices.

The patulin:cyclodextrin interactions were investigated using the PM3 semi-empirical method, and the results are shown in Fig. 4 and Table 3. A molecular representation of patulin bound to the crosslinked polymer built with the AMBER99 molecular mechanics force field is shown in Fig. 5. The accuracy of PM3 semi-empirical calculations to study certain types of hydrogen bond interactions is limited compared to computationally expensive density functional and ab initio calculations [33]. However, the large size of the patulin:cyclodextrin system complicates use of more computationally expensive methods. PM3 methods have been effective in the study of supramolecular inclusion complexes [34–37]. The interaction energies given in

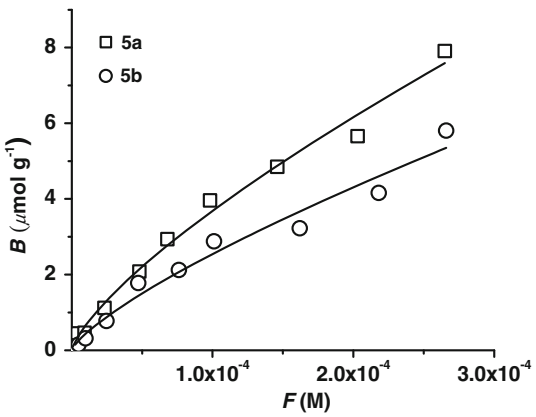

Fig. 2 Sorption isotherms for polymers **5a** and **5b** binding patulin in buffer (10 mM sodium acetate, pH 5.5). **5a** $a = 3400 \pm 90$ (μmol g^{-1}) (l mol^{-1})^m, heterogeneity index $= 0.74 \pm 0.1$, $r^2 = 0.989$. **5b** $a = 2790 \pm 20$ (μmol g^{-1})(l mol^{-1})^m, heterogeneity index $= 0.76 \pm 0.1$, $r^2 = 0.974$

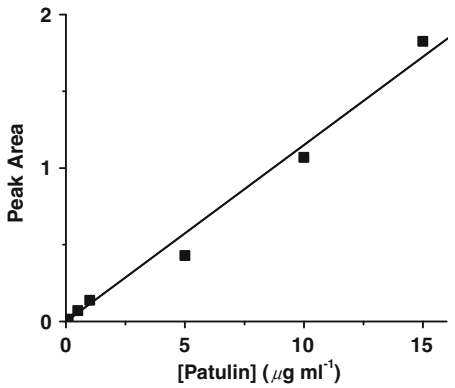

Fig. 3 Correlation between peak areas of patulin isolated by polymer **5a** and patulin concentrations of spiked apple juice ($r^2 = 0.986$)

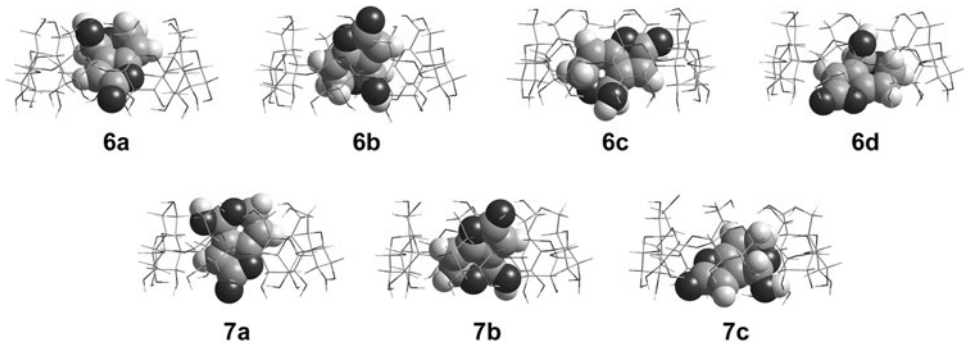

Fig. 4 Molecular models representing patulin binding to β-cyclodextrin in multiple binding modes

Table 3 Calculated parameters for patulin:cyclodextrin interactions

Patulin:cyclodextrin complex	ΔE (kcal. mol^{-1})	μ (Debye)
6a	−13.02	1.68
6b	−10.73	3.14
6c	−7.04	3.93
6d	−12.58	1.32
7a	−11.68	1.86
7b	−13.41	3.98
7c	−9.98	2.54

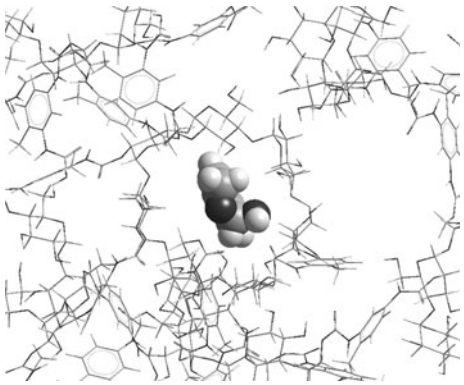

Fig. 5 Molecular representation of patulin bound to polymer **5a**

Table 3 are associated with the heat of formation, and are calculated by:

$$\Delta E = E_{Complex} - \left(E_{Patulin} + E_{Cyclodextrin}\right)$$

where $E_{Complex}$ is the heat of formation energy of the patulin:cyclodextrin complex, $E_{Patulin}$ and $E_{Cyclodextrin}$ are the energies for the free molecules, and ΔE is the stabilization energy. The value μ is the dipole moment of the patulin:cyclodextrin bound complex.

Structures **6a–d** are four complexes of patulin:β-cyclodextrin with the hydroxyl of the patulin in the axial position. Complexes **7a–c** includes conformers of patulin with the hydroxyl in the equatorial position. It has been shown by density functional calculations at the B3LYP/6-311++G** level that the axial conformer is preferred by 1.20 kcal mol^{-1} [9]. Patulin forms several favorable complexes with β-cyclodextrin in the range of 7–13 kcal mol^{-1}. Stable complexes are formed with varying degrees and orientation of dipole moment, indicating the orientation of patulin in the bound complex has a significant influence over the electrostatic properties. Complexes **6a**, **6b**, **6d**, **7a** and **7b** involve favorable intermolecular hydrogen bond interactions between the primary hydroxyls of β-cyclodextrin and patulin. It should be noted that similar types of hydrogen bond schemes have been observed experimentally in patulin-patulin dimers [9, 10]. Furthermore, molecular mechanics studies have found hydrogen bonding and van der Waals interactions contribute to the formation of bound complexes of patulin with β-**D**-glucans [38]. Complexes **6a**, **6d**, and **7a** exhibit interactions between the hydroxyl of the hemiacetal moiety of patulin and the primary hydroxyls of β-cyclodextrin. Complexes **6b**, **6c**, and **7b** possess interactions between the primary hydroxyls of β-cyclodextrin and the carbonyl of the lactone of patulin. Both types of interactions provide favorable patulin:cyclodextrin complexes.

Summary and conclusion

This paper reports the synthesis and evaluation of water insoluble cyclodextrin polymers to clean-up the mycotoxin patulin from aqueous solutions. Polyurethane-β-cyclodextrin polymers were synthesized and possessed very small surface areas by BET analysis. Polymers were suitable for Freundlich isotherm analysis, and possessed populations of binding sites. A polymer crosslinked with tolylene 2,4-diisocyanate was capable of extraction and analysis of patulin from apple juice. These materials show promise for more broad use in mycotoxin detection.

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