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Selective Removal of Silver Impurity from Oxaliplatin by Sorption on Functionalized Polymer

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ABSTRACT: This report relates to synthesis of functionalized polymeric adsorbents for selective removal of silver ion in the presence of platinum(II) from crude oxaliplatin, thus providing an effective method for its purification with a desired impurity profile for silver. Two chelating ligands, thiourea and thiosemicarbazide, were grafted on styrene backbone cross-linked with 2% divinyl benzene (DVB) and tested by batch adsorption studies for the uptake of silver and platinum. The maximum sorption capacity values for both the adsorbents for Ag⁺ were 101.58 and 67.75 (mg/g), respectively, with an exceptionally high value of separation factor ($\alpha = 1155$ and 231) over platinum. The experimental sorption data were fitted well with the Langmuir model. Desorption of silver from the polymer can be achieved by using 0.3 M Na₂S solution for regeneration.

INTRODUCTION

Oxaliplatin is an antineoplastic chemotherapy drug frequently used against metastatic colon and rectal cancer.^{1,2} The pharmaceutical properties of this platinum based drug which functions by forming both *inter*- and *intra*strand cross-links with DNA, was first reported by Kidani et al.^{3–6} The product, oxaliplatin, prepared following the Scheme 1 is, however, usually contaminated by various impurities like, its optical isomer (1*S*,2*S*-form), *cis*-diaquadiamine platinum(II) complex (II), bridged dimeric platinum(II) complex (VI), oxalic acid, residual Ag⁺, and other heavy metal ions.^{7–9} The major concern is having silver ion as one of the impurities, since unlike other organic and organometallic impurities, it cannot be completely removed by repeated crystallization processes. The US and EP Pharmacopeia demands that the silver content in the drug should be less than 5 ppm.^{7,10} It becomes, therefore, imperative that the silver content is reduced to the minimum acceptable level as it creates intense adverse effects in the therapeutic uses of oxaliplatin. Conventionally, sodium or potassium iodides are added for the removal of silver ion in the form of silver iodide but these salts also react with the intermediate product (II) producing *cis*-monoiodo (III) and *cis*-di-iodo (IV) complexes as side products, creating additional impurities and thus effectively further reducing the yield of the desired product.^{11,12} The formation of these new iodo impurities also lead to the yellow coloration of oxaliplatin which is unacceptable as per the specifications. Again, the low solubility of oxaliplatin in water makes its crystallization process possible only at higher temperatures, which further leads to the degradation of oxaliplatin to *cis*-diaquadiamine complex (II), dihydroxo complex (V), and the bridged dimer complex (VI). Repeated recrystallization processes are required to remove these degradation products, which decrease the yield of oxaliplatin to a significantly low value (40–50%).

Thus the need exists to remove silver ions in a more effective way without generation of the side products and making the synthetic process more cost-effective at the industrial scale.

We report in this paper, synthesis of two polymeric adsorbents having silver specific functional groups on a polystyrene backbone for selective removal of silver ions in

the presence of platinum(II) from the crude oxaliplatin product. The application of polymeric adsorbents for extraction and preconcentration of heavy metal ions is widespread.^{13–15} The use of ligand functionalized styrene-divinyl benzene copolymer for recovery or removal of heavy metal ions from aqueous solutions^{16–18} and purification of natural products^{19,20} has been extensively investigated in recent years. Surface modification of the polymer by grafting specific functional groups changes the surface adsorption properties keeping the mechanical strength of the adsorbent beads intact. The chemical grafting of the functional groups on the polymer provides, apart from an improved selectivity, the unique advantage of resistance to leaching as the ligand is covalently linked to the polymeric support. These functionalized polymers also provide a greater specificity over conventional ion exchange resins when the ionic system under consideration consists of multiple elements.

Various functional groups like thiourea,²¹ thiosemicarbazide,²² dithiocarbamate,²³ bithiourea,²⁴ thiol-amine,²⁵ polythiazalkane,²⁶ 2-mercapto-benzothiazole,²⁷ and thiophene²⁸ are reported as silver selective ligands for the extraction and preconcentration of silver alone. In this work, we have used thiourea and thiosemicarbazide as chelating groups to prepare functionally modified poly(styrene-DVB) for selective removal of silver even when present at extremely low concentration in the crude oxaliplatin solution that too in the presence of a large excess of platinum. Conventional ion exchange resins are adversely affected here because of higher concentration of platinum(II) that interferes in the uptake of silver ion.

EXPERIMENTAL SECTION

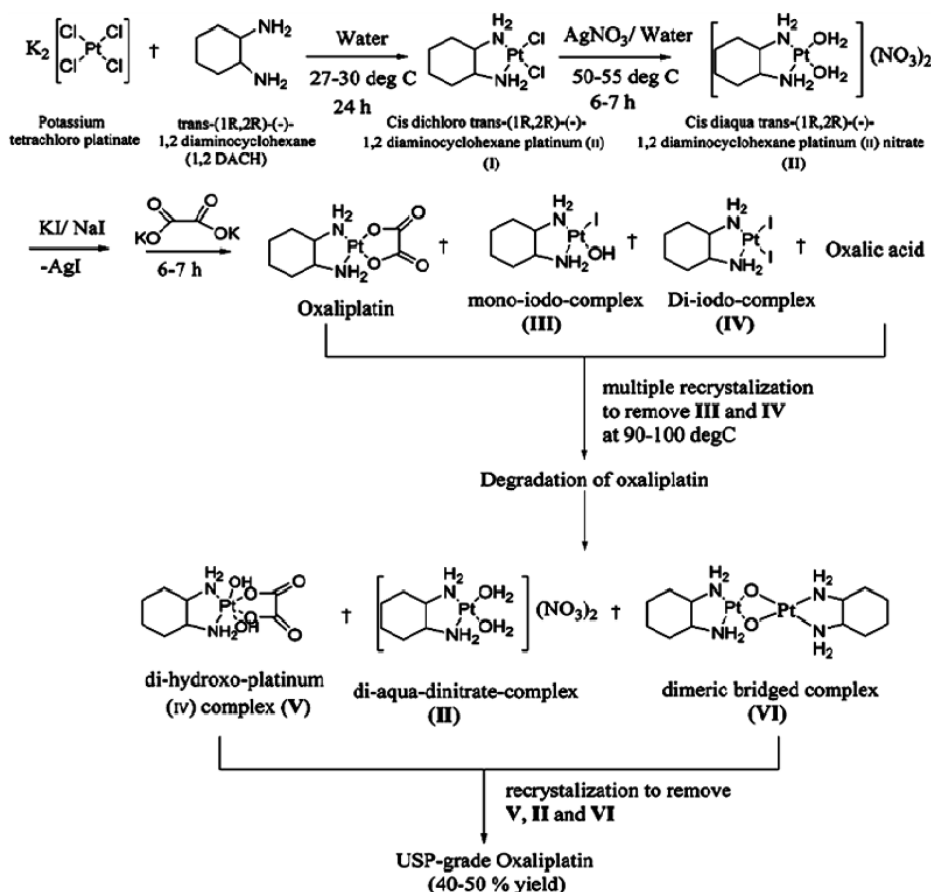
Materials. Potassium tetrachloroplatinate (K₂PtCl₄) was purchased from Hindustan Platinum Pvt. Ltd., Mumbai. Thiourea, thiosemicarbazide, Na₂S·xH₂O (55–58%) and

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Scheme 1. Synthesis of Oxaliplatin with Process Impurities⁶

K_2CO_3 (all LR grade) were used as received from s.d. Fine Chemicals. Standard solutions of silver and platinum (1000 mg/L) for ICP-AES were obtained from s.d. Fine Chemicals. AR grade AgNO_3 was purchased from Merck Ind. Ltd. Aq. 0.1 M HNO_3 solution was prepared using spectroscopic grade HNO_3 from Spectrochem Pvt. Ltd. and was used to maintain the pH during ICP-AES analysis. Chloromethylated polystyrene (CMPS) cross-linked with 2% divinyl benzene in bead form was obtained from Auctel Pvt. Ltd. Mumbai, having the chloride ion content of 3.5 mequiv/g. $\text{K}_2\text{C}_2\text{O}_4 \cdot \text{H}_2\text{O}$ was synthesized in the lab using a normal acid–base reaction process between $\text{C}_2\text{O}_4\text{H}_2 \cdot 2\text{H}_2\text{O}$ (LR grade, s.d. Fine Chemical) and KOH (LR grade, Himedia).

Synthesis of Thiourea Modified (PS-DVB-1) and Thiosemicarbazide Modified (PS-DVB-2) Polymers. CMPS (5.0 g, 0.017 mol) beads were swollen in water (20 cm^3) at 90 °C for 10–12 h. The swollen beads were then added to a clear solution of 0.05 mol of thiourea (or thiosemicarbazide) in water (40 cm^3), and then, the reaction mixture was stirred under reflux conditions for 24 h. The reaction mass was cooled to 60 °C, to which then a solution of potassium carbonate (4.83 g, 0.035 mol) in water (20 cm^3) was added and stirred for 2–3 h at the same temperature. The polymer beads were then filtered, thoroughly washed with water till neutral pH, followed by methanol (30 cm^3), and then oven-dried at 90 °C under atmospheric pressure. The surface modified polystyrene beads were characterized through FTIR and elemental analysis.

Methods. Chloromethylated polystyrene (CMPS) and surface modified PS-DVB beads were analyzed for their carbon,

hydrogen, nitrogen, oxygen, and sulfur contents using Perkin-Elmer 240B Elemental Analyzer. Micro Meritics ASAP-2020 was used for surface characterization of the polymer beads, before and after, the functionalization. The polymer beads were oven-dried at 90 °C for 1 h before the BET surface analysis. The Fourier transform infrared (FTIR) spectra of grafted polymers were recorded with KBr pellets using a Bruker-VERTEX 80 V vacuum FT-IR spectrophotometer aligned with Ultra-Scan interferometer (peak resolution of 0.03 cm^{-1}). The metal ion concentrations were measured on ICP-AES (ARCOS from M/s. Spectro, Germany). ICP-AES is one of the most accurate techniques for determination of silver and platinum contents in the solution at the parts per billion level. In the operating conditions, a charge-coupled device (CCD) detector was used along with a radio frequency (RF) generator power of 1400 W, and the frequency of the RF generator was 27.12 MHz. Argon was used as auxiliary gas, as nebulizer gas, and for generation of plasma with a flow rate of 1, 0.8, and 12 dm^3/min , respectively. The pump speed was maintained at 30 rpm for injection of samples into the plasma. The most sensitive line for silver is at 328.068 nm and that of platinum is at 265.945 nm with an instrument detection limit (IDL) of 10 ppb each.

Synthesis of Oxaliplatin. *cis*-Dichloro-*trans*-1,2-diaminocyclohexane platinum(II) complex (I) was prepared from K_2PtCl_4 in 96% yield as per the reported method.¹¹ Silver nitrate (1.79 g, 0.01 mol) was added to a suspension of *cis*-dichloro complex (I) (2.0 g, 0.005 mol) in deionized water (100 cm^3), and the reaction mass was stirred in the dark at 50 °C with 600 rpm for 7 h. The precipitated silver chloride was removed by filtration under a Celite bed to get transparent

Scheme 2. Synthetic Scheme for Functionalization of Polystyrene-DVB with Thiourea and Thiosemicarbazide with Possible Complexation with Silver Ion

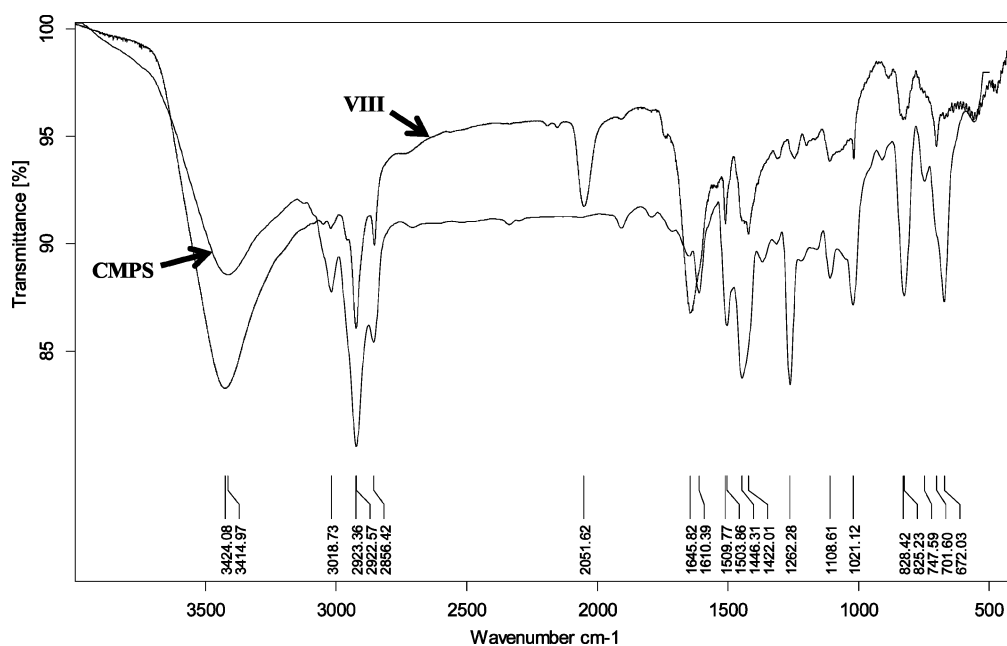
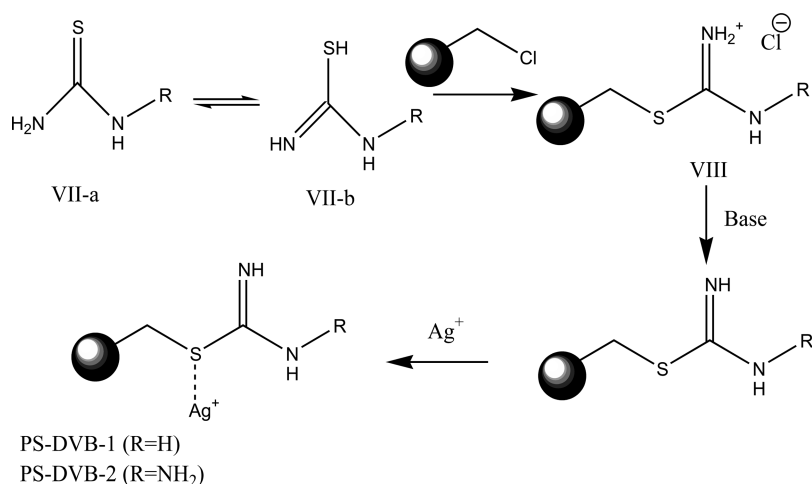


Figure 1. FTIR spectrum comparison between CMPS and isothiuronium salt (VIII).

liquid containing *cis*-diaqua platinum(II) dinitrate complex (II) in soluble form. To the filtrate, dipotassium oxalate monohydrate (0.98 g, 0.005 mol) was added and the reaction mass was stirred at 60 °C for 7 h to prepare the desired crude product. The silver content of this crude solution was estimated to be 141.88 ppm, using ICP-AES. This oxaliplatin crude solution was taken for adsorptive removal of silver ion in the presence of platinum using the functionalized polymer beads, PS-DVB-1 and PS-DVB-2.

Adsorption Studies. In a typical adsorptive separation experiment, 20 mg of the selected adsorbent was added to a stoppered conical flask containing 20 cm³ of the crude oxaliplatin solution. The flask was kept on an orbital shaker with an agitation rate of 100 strokes/min at the ambient temperature of 298 ± 2 K, for 24 h. The suspension was filtered and residual metal ion concentration was analyzed by ICP-AES. All studies were carried out in duplicate. The standard deviation observed in repeated experiments was less than 3%. From the initial and residual liquid phase concentrations, the equilibrium

adsorption capacity (Q_{av}) (mg/g), distribution coefficient (K_d) (dm³/g), percent adsorption, and separation factor (α) for both the metal ions were calculated.

In separate experiments, to determine the equilibrium adsorption isotherm, 10 mg of the polymer beads were equilibrated to 10 cm³ of oxaliplatin crude solutions at five different concentrations on an orbital shaker for 24 h. The residual metal concentrations were measured by ICP-AES.

RESULTS AND DISCUSSION

In the synthetic process of oxaliplatin (Scheme 1), the *cis*-dichloro complex (I) reacts with the silver salt to produce *cis*-diaqua product (II). The reaction was known to be carried out at room temperature for 3 days because of the extremely low solubility of the reactant (I) in water.¹¹ Also the precipitated silver chloride may hinder the reaction progress by creating a barrier between the two reactants located in two different phases.¹² However, the long reaction time can be reduced to

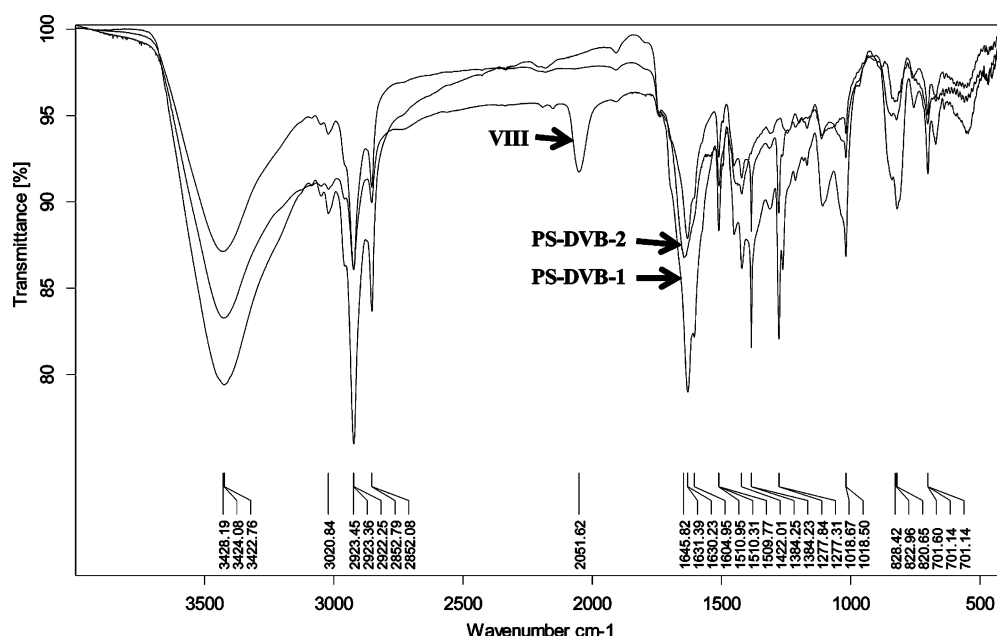


Figure 2. FTIR spectrum comparison between PS-DVB-1, PS-DVB-2, and isothiuronium salt (VIII).

Table 1. Elemental Composition and Physical Properties of Resins

resins	carbon (%)	hydrogen (%)	nitrogen (%)	oxygen (%)	sulfur (%)	specific BET surface area (m ² /g)	pore size (Å)	pore volume (cm ³ /g)
CMPS	72.38	6.72	not detected	2.44	not detected	29.9	384	0.288
PS-DVB-1	72.39	6.91	2.48	2.64	6.84	31.4	353	0.278
PS-DVB-2	69.12	6.59	5.77	2.56	4.39	29.8	342	0.255

6–7 h by conducting the reaction at 50–55 °C and increasing the water quantity as described in our earlier work.²⁹ The intermediate product (II) when treated with dipotassium oxalate produces the crude oxaliplatin.

The silver content of the crude oxaliplatin solution was determined to be 141.88 ppm. Our objective was to remove this silver impurity from the crude solution and to meet the desire specifications of the product using the newly developed functional polymers. The adsorptive purification technique is advantageous over the previously reported methods as no new side products are formed in the process.^{11,12} Also the silver removal process is carried out at the final stage instead of at the intermediate step, since oxaliplatin is a much more stable product compared to the *cis*-diaqua complex (II) which is highly reactive and easily forms the side products when metal iodides are used.¹² Thus the polymeric adsorbents with sufficient mechanical strength and selectivity toward the silver impurity over platinum are of great interest.

In the chemical modification of the polymers, thiourea (VII) (or thiosemicarbazide) was first treated with CMPS to produce an intermediate product, isothiuronium salt (VIII) as shown in Scheme 2.^{30,31} The formation of VIII was evident from the presence of the characteristic frequency bands at 2051 and 1645 cm⁻¹ for an ammonium salt and C=N of an imine salt, respectively, in the FTIR spectrum (Figure 1).³² The intermediate salt gets converted to its free base form on treatment with a metal carbonate. The grafting of the functional group was confirmed through the disappearance of the characteristics bands for CMPS (CH₂-Cl stretching, 674 cm⁻¹, and CH₂wagging, 1264 cm⁻¹) and appearance of a new band at 1630–1631 cm⁻¹ due to C=N of S-substituted isothioure

group as shown in Figure 2.^{16,17,33} The sulfur content obtained from the elemental analysis further supported the functionalization of the polymer beads (Table 1).

Both, CMPS and modified polymers have a tendency to absorb moisture as shown in their respective FTIR spectra as $\nu(\text{O}-\text{H})$.³⁴ The physical characteristics of the polymer after the chemical modification were measured to observe the changes in its surface characteristics. The surface area for both the adsorbents was measured by a standard BET procedure using nitrogen adsorption–desorption isotherm data whereas pore size distribution of the adsorbents was measured by the Barrett–Joyner–Halenda model as shown in Figures 3 and 4, respectively. The pore volume was calculated at a relative pressure (P/P_0) of 0.98 with pore diameter less than 156 nm. The nitrogen adsorption on the modified polymers falls under a type IV isotherm and initially shows monolayer adsorption with relative pressure P/P_0 up to 0.9 followed by capillary condensation from 0.9 to 0.96 and multilayer adsorption above 0.97. However, the capillary condensation and multilayer adsorption were negligible as compared to monolayer adsorption supporting the Langmuir adsorption model. Both the functional polymers, PS-DVB-1 and PS-DVB-2, showed a small decrease in the pore size with no significant change in the surface area (Table 1). The decrease of pore size could be because of blockage of few pores with the added functional groups.

The adsorption capability of the PS-DVB-1 and PS-DVB-2, for metal ions pick up, was examined in a batch process. The equilibrium time for maximum uptake of the metal ions by the polymers was almost 24 h (Figure 5). Initially, the rate of extraction of silver ion was high and within 3 h, 50% of silver

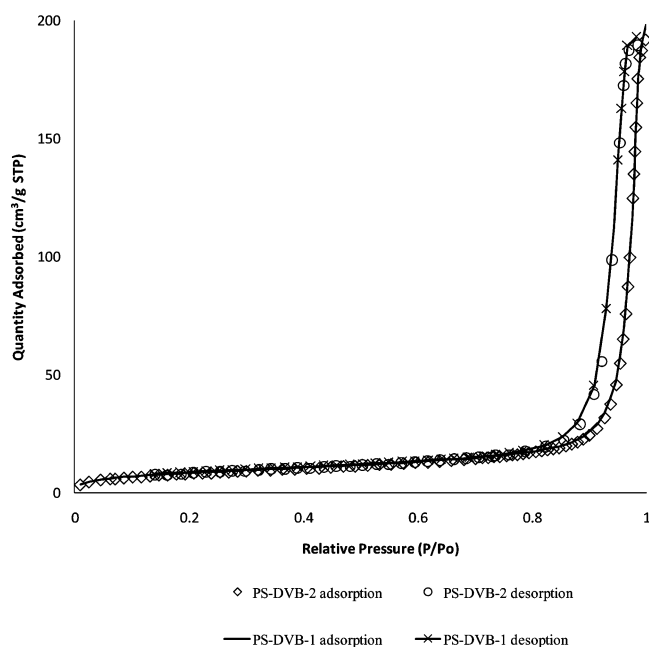


Figure 3. Nitrogen adsorption/desorption isotherm for adsorbents.

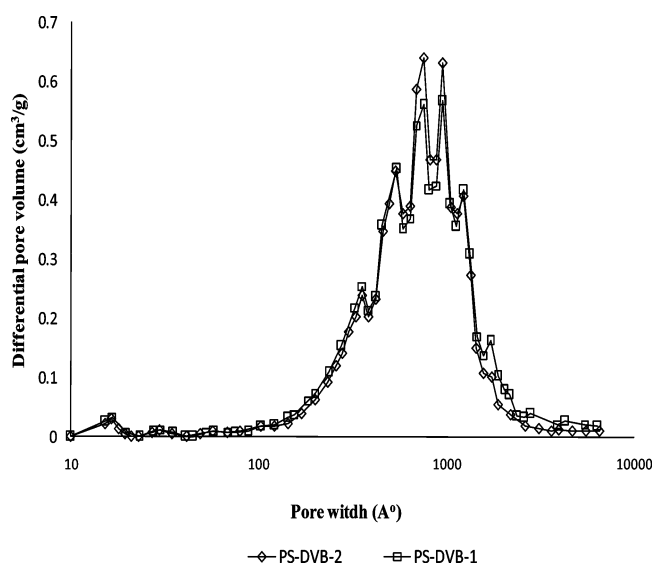


Figure 4. PSD curve for adsorbents.

uptake was complete. Later on, the uptake rate slowly decreased and the time required for 98% of the silver extraction was close to 24 h.

The amount of the metal ions uptake by the adsorbent was estimated from the residual metal ion concentrations in the aqueous solutions after the adsorption. The equilibrium adsorption capacity Q_{av} and the distribution coefficient K_d for both the metal ions were calculated from eqs 1 and 2, respectively,

$$Q_{av} = \frac{C_o - C_e}{W_s} V \quad (1)$$

$$K_d = \frac{C_o - C_e}{C_e W_s} V \quad (2)$$

Where Q_{av} is the average amount of silver (or platinum) ions adsorbed per unit weight of the adsorbent, C_e and C_o are the

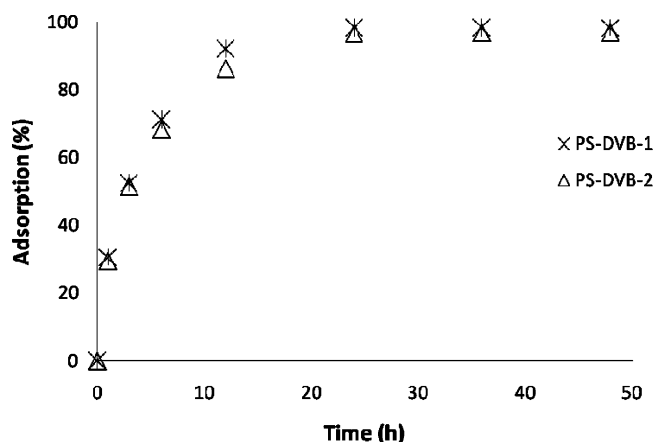


Figure 5. Effect of contact time on adsorption efficiency for PS-DVB-1 and PS-DVB-2.

equilibrium and initial concentrations in milligrams per cubic decimeter, V is the volume of the solution in cubic decimeters, W_s is the weight of the adsorbent in grams, and K_d is distribution coefficient (dm^3/g). Table 2 shows the concentrations of both the metal ions, before and after the adsorption, along with the percentage of adsorption, Q_{av} , respective K_d values, and the separation factor (α) indicating separation efficiency of the polymers. The maximum adsorption capacity of PS-DVB-1 for silver was 101.58 mg/g, which is much higher compared to that of PS-DVB-2 (67.75 mg/g). The strong adsorption of silver on PS-DVB-1 over PS-DVB-2 was further supported by its distribution coefficient (K_d) value. Table 2 also shows the platinum coadsorption values in the presence of silver on both the adsorbents. Poor adsorption of platinum, despite having very high concentration in the aqueous solutions, shows very high selectivity of the new adsorbents toward silver ion.

The separation factor between the two metal ions which is a measure of selective adsorption on the adsorbent was calculated as the ratio of their distribution coefficients following eq 3

$$\alpha = \frac{K_{\text{dsilver}}}{K_{\text{dplatinum}}} \quad (3)$$

From the equilibrium sorption data, an extremely high value of separation factor i.e. 1155 was obtained for PS-DVB-1 compared to PS-DVB-2 which has a value of α equal to 231. The high value of separation factor for thiourea modified polystyrene reflects selective adsorption of silver with negligible platinum coadsorption. Thus the loss of the platinum during the adsorption process was insignificant.

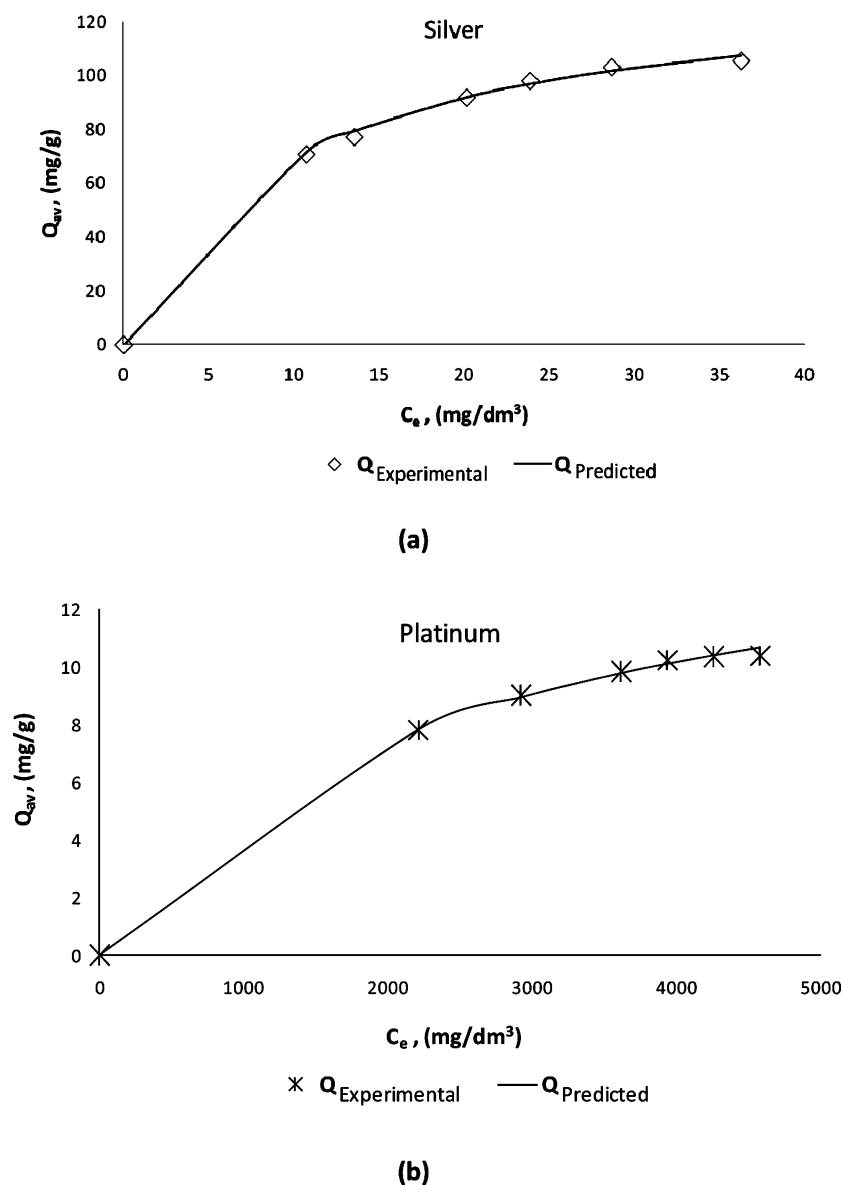
The experimental equilibrium adsorption data for the uptake of silver and platinum ions were further analyzed by Langmuir adsorption model. In its linear form, the model is expressed as eq 4,

$$\frac{C_e}{Q_{av}} = \frac{C_e}{Q_{\max}} + \frac{1}{K_L Q_{\max}} \quad (4)$$

Q_{\max} (mg/g) is the Langmuir constant representing the maximum monolayer adsorption capacity, and K_L (dm^3/mg) is the Langmuir constant related to the energy of adsorption. Figures 6 and 7 show the plots of amount of silver and platinum adsorbed (Q_{av}) vs their respective equilibrium concentrations (C_e) for both the adsorbents. Initially the percent adsorption was more due to presence of a large number of available sites

Table 2. Experimental Results for Adsorption of Silver and Platinum on Functional Polymers

adsorbents	silver					platinum					separation factor (α)
	initial (C_0 ; ppm)	equilibrium (C_e ; ppm)	% of adsorption	Q_{av} (mg/g)	K_d (dm ³ /g)	initial (C_0 ; ppm)	equilibrium (C_e ; ppm)	% of adsorption	Q_{av} (mg/g)	K_d (dm ³ /g)	
PS-DVB-1	141.88	40.3	71.59	101.58	2.52	4588	4578	0.217	10	0.00218	1155
PS-DVB-2	141.88	74.13	47.75	67.75	0.91	4588	4570	0.392	18	0.00393	231

Figure 6. Amount of (a) silver and (b) platinum adsorbed (Q_{av}) vs the equilibrium concentration (C_e) on PS-DVB-1.

on the adsorbents and at higher concentration in the liquid phase, a plateau is observed. These figures also show a good correlation between the experimental (Q_{Exp}) and the Langmuir model (Q_{Fit}) for both the adsorbents, suggesting the monolayer adsorption of silver and platinum on the adsorbent. Table 3 shows the adsorption parameters obtained from the plots for both the metal ions on the polymer supports. The K_L values are higher for silver than platinum with both the adsorbents but a comparison of the data shows, the extent of adsorption of silver on PS-DVB-1 is roughly 250 times higher than platinum while the corresponding value for PS-DVB-2 is 70. Thus on the basis of adsorption capacity and selectivity obtained from the model

expressions, the efficiency of thiourea modified polystyrene was found to be far better than the other adsorbent.

The Langmuir model also helps in validating the suitability (R_L) of the resin for uptake of metal ions through the expression,³⁵

$$R_L = \frac{1}{1 + K_L C_0} \quad (5)$$

Where, K_L is the Langmuir adsorption constant, and C_0 (mg/dm³) is the initial concentration of metal ions. Table 3 shows the R_L values for both the adsorbents against the metal ions and in all cases the values were less than one, suggesting the

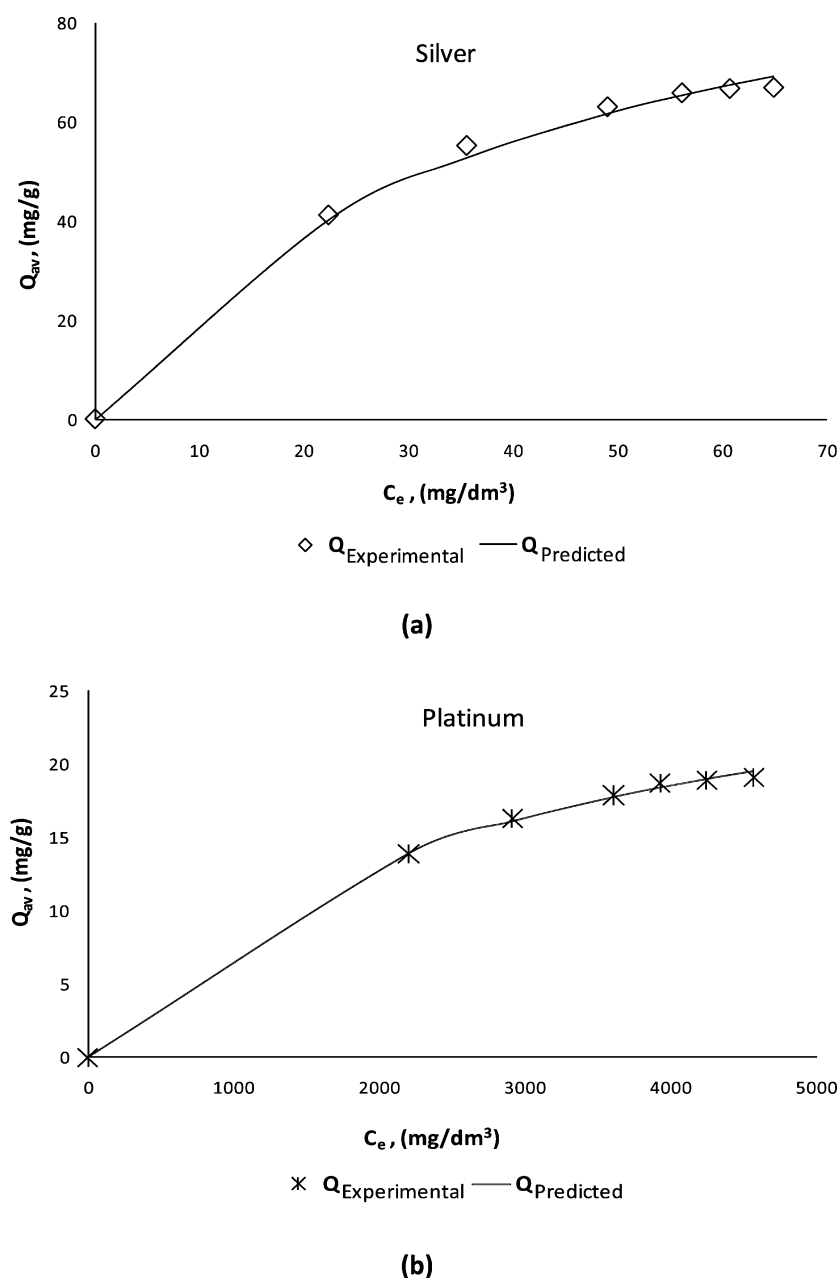


Figure 7. Amount of (a) silver and (b) platinum adsorbed (Q_{av}) vs the equilibrium concentration (C_e) on PS-DVB-2.

Table 3. Adsorption Constant and Degree of Suitability Values for Adsorbents

adsorbents	K_L (dm ³ /mg)		Q_{max} (mg/g)		R_L^a	
	silver	platinum	silver	platinum	silver	platinum
PS-DVB-1	0.103376	0.000424	136.2	16.1	0.06–0.105	0.03–0.51
PS-DVB-2	0.025488	0.000364	111.1	31.2	0.21–0.32	0.37–0.55

^aIf $R_L > 1.0$, the adsorbent is unsuitable; $R_L = 0$, it is irreversible; $R_L = 1$, it is linear; and $0 < R_L < 1$, it is suitable.

synthesized polymers are suitable for adsorption for both the metal ions, silver and platinum.

A process comparison was made for the preparation of oxaliplatin between the conventional method where alkali iodides were used for removal of silver and the current method employing a silver selective functionalized polymer. A block diagram for the entire process is shown in Figure 8, which clearly reflects that although the use of KI reduces the silver content to 5 ppm but 38% loss of the product in the process

was observed in the form of mono/di-iodo platinum(II) complex (as impurities) and oxaliplatin itself (in the mother liquor). The light yellow product obtained due to the presence of a small amount of iodo-impurities had to be further subjected to the recrystallization to meet the specification grade, where loss of another 14% of product was observed making the overall yield only 52%.

The extremely high separation factor makes PS-DVB-1 more selective toward silver over platinum from the drug solution.

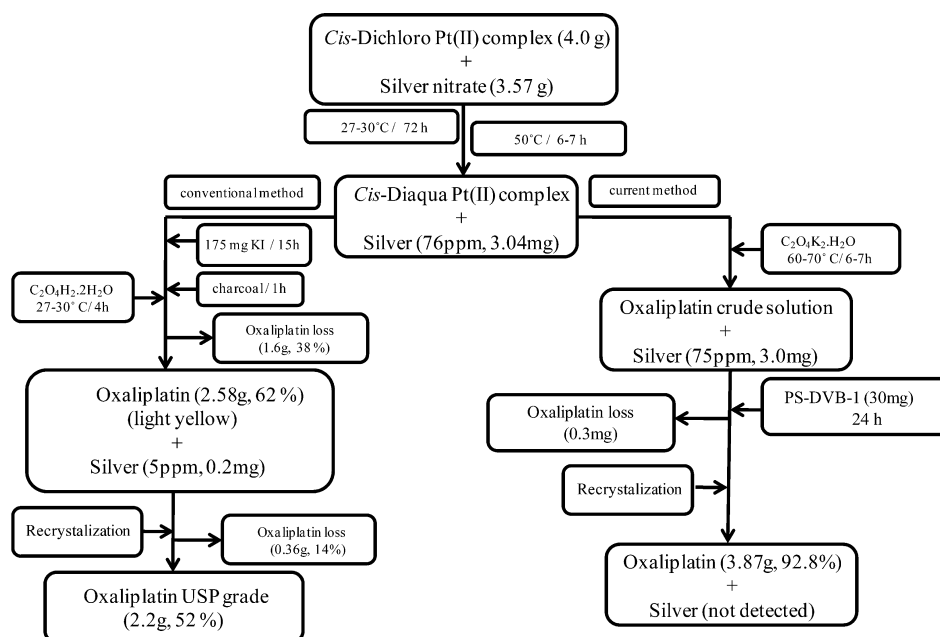


Figure 8. Block diagram showing a process comparison between conventional and proposed method.

Thus unlike alkali iodides, the functionalized polymer PS-DVB-1 removes only silver from the solution without affecting the platinum based drug. It was observed that 30 mg of PS-DVB-1 (Figure 8) was sufficient to remove all silver from the crude solution in the equilibrium period and the loss of oxaliplatin on the basis of platinum coadsorption was just 0.3 mg. Hence, the process not only excludes the formation of any side product in the solution but also avoids the extensive crystallization process responsible for the noticeable yield loss.

The reusability of PS-DVB-1 was tested by allowing the desorption of metal loaded polymer with 0.3 M sodium sulphide solution. Resin was reused for 3 cycles and the efficiency of further silver sorption was found to decrease gradually after each cycle. The adsorption capacity was 92%, 85%, and 70% of its initial Q_{\max} with same selectivity for silver over platinum. These results showed that, even though maximum silver sorption capacity of the adsorbent decreased, the selectivity remained constant hence the resin can be used in repeated runs.

A recent survey revealed the use of some polymeric adsorbents¹¹ like Dowex 50×80 and Sompex 101 for removal of silver in the purification of oxaliplatin. But, their maximum adsorption capacity (Q_{av}) values for silver were 1.84 and 1.89 mg/g, respectively, which are extremely low compared to PS-DVB-1. Further, no study has been reported regarding the selectivity of those adsorbents toward silver and the respective platinum coadsorption values on the surface of the polymer.

CONCLUSION

A thiourea modified polymeric adsorbent having styrene backbone was evaluated as an excellent silver selective adsorbent in presence of platinum. The maximum adsorption capacity of the adsorbent for silver was 101.58 mg/g with a very high separation factor (1155) for silver(I) over platinum(II). The resin was successfully employed for effective removal of silver up to the permissible limit from the crude oxaliplatin solution with insignificant loss of the product. The new process

thus eliminates use of alkali iodides for the removal of silver and thus avoids loss of oxaliplatin during purification.

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Notes

The authors declare no competing financial interest.

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