

New Method of Palladium Metal Trapping through Resins in Antiviral Drug: Valacyclovir HCl

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ABSTRACT

This process describes a novel technique for effective trapping of “Pd” metal through resins during the process development of L-valine, 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl) methoxy] ethyl ester, and mono hydrochloride known as a Valacyclovir hydrochloride (**1**). This technique is suitable for large-scale production of **1** and it is described here Pd metal trapping by using different resins.

Keywords: Valacyclovir Hydrochloride; Antiviral Drug; *N*-Phthalimide-L-Valine Ester; Monomethylamine; Commercially Scalable Process; Less Cycle Time

1. Introduction

Valacyclovir (Valtrex[®]) (**Figure 1**) is an orally active prodrug of the antiviral drug acyclovir [1,2]. Valacyclovir is the L-Valyl ester of the antiviral drug acyclovir which is active against herpes simplex virus types 1 and 2 and varicella zoster virus [3-5]. After oral administration, the prodrug Valacyclovir is rapidly absorbed from the gastrointestinal tract and nearly completely converted to acyclovir and L-valine. Acyclovir is a specific and selective inhibitor of viral herpes replication and is neither highly lipid nor aqueous soluble, with limited and variable oral bioavailability (15% - 21%) that decreases with increasing doses. Conversely, Valacyclovir has an oral bioavailability of 3 to 5 times higher than that of Acyclovir itself [6,7].

Synthesis of **1** involved steglich esterification (**Scheme 1**) between 9-(2-hydroxyethoxy) methyl)-2-amino-1H-purin-6-(9H)-one **4** and *N*-Benzyloxy carbonyl-L-valine **3** in the presence of *N,N*-(dimethylamino) pyridine (DMAP) and a coupling reagent dicyclohexylcarbodiimide (DCC) in dimethylformamide (DMF) medium

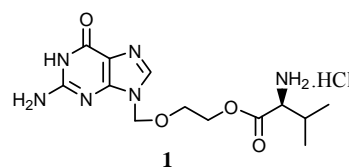


Figure 1. Structural framework of Valacyclovir hydrochloride (1).

obtain *N*-benzyloxy protected ester **2**. This is the further deprotection in the presence of Pd/C catalyst to afford **1** [8].

Reported reference process suffers from a major disadvantage of metal content, which is coming higher level, which is not acceptable by International Conference on Harmonization (ICH) and the metal content should be less than 10 ppm. [Pd] This metal is carried from the Pd/C catalyst which is used for deprotection of **2**, which makes process less viable for commercial production.

Pd Adverse Effects

Metal cations in dental alloys such as mercury and palladium are continuously released and accumulated in the kidneys, liver, thyroid, brain. Mercury and palladium

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have high levels of galvanic current densities when near other metals, with the current densities of Pd alloys approx. It is 10 times higher than for high noble alloys. This causes extensive migration of mercury and palladium to saliva, tooth roots, jaw, gums, and other parts of the body [9,10].

Palladium is cytotoxic and kills or damages cells. Palladium also causes considerable damage and degradation of DNA and exacerbates hydroxyl radical damage [11-13]. Palladium also damages cell mitochondria and inhibits enzyme activity and function [14-16]. Palladium also causes significant numbers of allergic reactions as well as contacts dermatitis, stomatitis, lichenoid reactions, and periodontal gum disease [17-21]. Herein we report a simple and effective resin absorption method for Pd metal and it is consistently showing less than 5 ppm level to produce **1**.

2. Results and Discussion

Our efforts are to develop a robust process for desired product **1** to get metal content below 10 ppm described below in greater level with different resins for effective trapping of "Pd" metal.

During the isolation of **1** an in-depth study was done by treating the reaction mass with different reagents like thiourea, ethylene di amine tetra acetate (EDTA), Zeolites, CH-97 resin, and T-63 resin. The metal trapping was not so effective by using thiourea, EDTA, and Zeolites. Out of all these CH-97 resin & T-63 resin are effectively trapping comparatively T-63 resin more effective and yield loss also less. So decided T-63 resin is suitable commercialization of process. "Pd" metal was selectively trapped by using T-63 resin. It is made up with resin po-

lystyrene co-polymer and macroporoces with high porosity and large surface area.

In our approach process involves (**Scheme 2**) deprotection of **2** by using 10% Pd/C in dimethylformamide medium and during the workup Pd/C catalyst removed by filtration and further concentration of filtrate and followed by pH adjustment up to 4.0 - 4.5 with 36% Aq. HCl. Finally treating with T-63 Resin **5** (**Figure 2**) further solid was isolated by adding anti solvent acetone to the filtrate to afford **1**.

Attempts made by using different resins effective trapping of "Pd" metal during the isolation of **1** described below in greater details in **Table 1**.

Above results of "Pd" content with different resins are mentioned in graphical diagram **Figure 3**.

3. Conclusion

In summary, the present study describes a novel technique for effective trapping of "Pd" metal through resins during the process development of L-valine, 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl) methoxy] ethyl ester, and mono hydrochloride known as a Valacyclovir hydrochloride (**1**). This technique is suitable for large-scale production of **1** and it is described here "Pd" metal trapping by using different resins.

4. Experimental Section

4.1. Reagents & Condition

Warm the **4** & DMF mixture at 60°C, to that add **3** and DMAP & DCC. Maintain for 24 h at 25°C - 35°C. Stir for 48 h at 25°C - 35°C after addition of same quantity of **3** and DMAP & DCC to the above reaction mixture, re-

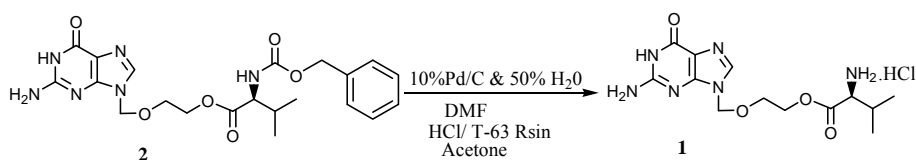
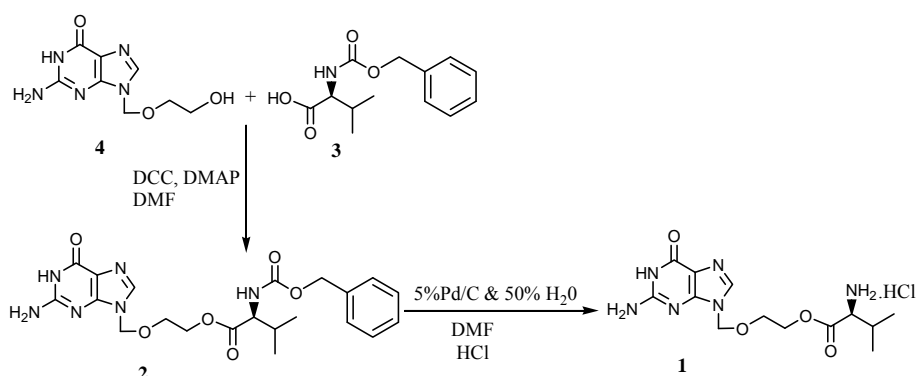
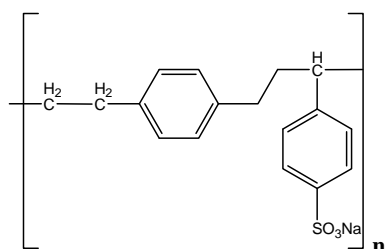
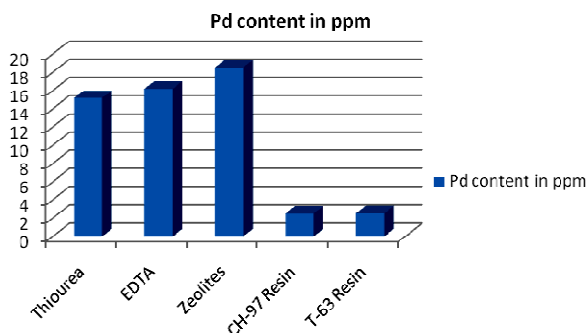


Table 1. Pd content results after treating with different resins.

S.No	Input Filtrate (2)	Trapping Reagents	Out Put Isolated (1)	Pd Content (ppm)
1)	10 g	Thiourea	8.3 g	15.16
2)	10 g	EDTA	8.3 g	16.19
3)	10 g	Zeolites	8.0 g	18.52
4)	10 g	CH-97 resin	8.5 g	2.50
5)	10 g	T-63 resin	9.5 g	2.54

**Figure 2. Structural framework of T-63 resin (5).****Figure 3. "Pd" content with different resins.**

move the undissolved by filtration and further concentrate the filtrate to obtain **2**. A mixture of **2** and 5% palladium on carbon catalyst-50% water and DMF were taken into par apparatus and maintained for 3 - 4 h and finally recrystallized in water/ethanol mixture (1:3 v/v) yield **1**.

A mixture of **2**, 10% palladium on carbon catalyst-50% water and DMF take in to par apparatus maintain for 3 - 4 h and further converted in to Hydrochloride by using HCl and followed by resin treatment (T-63 Resin) and finally isolation with acetone medium yields **1**.

4.1.1. Synthesis of Val Acyclovir Hydro Chloride (1): (Reported Process)

Compound **2** of 5.0 g (0.01 mol), 5% palladium on carbon catalyst-50% water (2 g), and DMF (50 mL) were taken into par apparatus applied 4.0 kg/cm² hydrogen pressures and maintained for 3 h. Filter the catalyst and concentrate the filtrate to give oil. Obtained oil was crystallized from water/ethanol (1:3 v/v) yields 1.5 g of **1**.

4.1.2. Synthesis of Val Acyclovir Hydro Chloride (1): (Improved Process)

Compound **2** of (50 g, 0.1 mol), 10% palladium on carbon catalyst-50% water (5.0 g) and DMF (500 mL) were taken into par apparatus applied 4.0 kg/cm² hydrogen pressures and maintained for 3 - 4 h. Filter the catalyst and wash with DMF (100 mL). Further concentrate the filtrate up to minimum volume obtain, cool the residue to 5°C - 10°C. Add water (125 mL). Adjust the pH up to 4.0 - 4.5 with 36% HCl (9.3 mL). Filter through Hyflow and wash with water (50 mL). Add T-63 resin **5** (1.4 g) to the filtrate and stir for 30 - 60 min. Filter through a 0.45 µm. Add acetone (375 mL) obtain filtrate and stir for 1 - 2 h. A product was isolated by filtration and washed with acetone (50 mL), and dry the product at 60°C - 70°C yields **1**.

4.1.3. Estimation of Pd Content in Valcyclovir Hydrochloride 1

The ¹HNMR spectra were measured in CDCl₃ and DMSO-d₆, using 200 and 50 MHz, respectively on a Varian Gemini 200 MHz FT NMR spectrometer. The chemical shifts are reported in δ ppm relative to TMS. FT-IR spectra were recorded in the solid state as a KBr dispersion using a perkin-Elmer 16428 FT-IR spectrophotometer. The mass spectrums were obtained using a shimadzu QP-8000α mass spectrometer with an electron energy set to 1.5 kV. The sample was introduced via the mass inlet using a LC pump (LC 10ADVP series) and an auto 1 injector (SIL 10ADVP). The heat block crossed dissolution line temperature at 230°C and 250°C respectively. Typical AAS conditions and furnace programme in AAS in the estimation of Pd content were presented in **Tables 2 & 3**. The Pd content observed 30 ppm in the reported process and 2.54 ppm in the present improved process using AAS (**Table 4**).

4.2. Preparation of Blank

Transfer 4.62 mL of 65% Suprapur Nitric acid (merk grade) into a 1000 mL flask and make up to the mark

Table 2. Typical AAS conditions in the estimation of Pd content.

TYPICAL AAS Conditions		
1)	Wavelength	24.76 nm
2)	Slit Width	0.7L nm
3)	Signal Type	AA-BG
4)	Measurement	Peak Area
5)	Read Time	5.0 sec
6)	Delay Time	0.0 sec
7)	BOC Time	2.0 sec

Table 3. Furnace programme in AAS in the estimation of Pd content.

Furnace Programme				
Temp °C	Ramp Time (Sec)	Hold Time (Sec)	Internal Flow	Gas Type
110	1	30	250	Normal
130	15	30	250	Normal
900	10	20	250	Normal
2200	0	4	0	Normal
2500	1	5	250	Normal

*Sample injection volume: 20 µl.

Table 4. Estimation of Pd content measured by atomic absorption spectroscopy.

S.No	Metal	Pd Content in PPM
1	Pd	30.0 (Reported Process)
2	Pd	2.54 (Improved Process)

with Milli Q Water. This gives the concentration of 0.3% Nitric acid solution and it is used as the blank.

4.3. Preparation of Sample

Weigh accurately about 200 mg of Valacyclovir sample into a 100 ml Vol. Flask dissolves and dilutes to the volume with 0.3% Nitric acid solution; sonicate this solution until the sample is totally dissolved. Then add the samples in the auto sampler vials for the estimation of Palladium by furnace.

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