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Simvastatin Biodegradation Using *Pleurotus florida*: Assessment of Isothermal, Kinetic Design and Thermodynamic Parameters

Pungayee Alias Amirtham P[1], Padamvathy S[2*]

[1]Department of Chemistry, Cauvery College for Women, Tiruchirappalli, Tamil Nadu, 620 018, India
[2]PG and Research Department of Chemistry, Bishop Heber College, Tiruchirappalli, Tamil Nadu, 620 017, India

ABSTRACT

Pharmaceutically active compounds are the emerging water contaminant and recently numerous studies have reported their continuous release in aquatic system posing an adverse impact on living organism on ecology. Simvastatin belongs to the drug class 3-Hydoxy-3-Methyl Glutaryl Coenzyme-A (HMG-CoA) reductase inhibitor. The present study focuses on the efficient loading of simvastatin drug onto the surface of Pleurotus florida biomass (PFB). The isothermal, kinetic and thermodynamic parameters were examined and the results showed that maximum simvastatin uptake was observed at 5.49 mg.g^{-1} with removal efficiency 72.56%. The maximum sorption capacity calculated from the Langmuir isotherm model was found to be 76.92 mg.g^{-1} and the separation factor value lies between zero and one indicating favorable isothermal process. The kinetic design was well illustrated by the pseudo second order model. Thermodynamic parameters imply that the adsorption of simvastatin on PFB was an endothermic process and the functionalities responsible for the simvastatin uptake were accomplished by Fourier Transform Infra-Red (FTIR) spectroscopy and Scanning Electron Microscopy (SEM). Results depict the applicability of oyster fungi as economically viable tool for the pharmaceutical enriched effluent treatment.

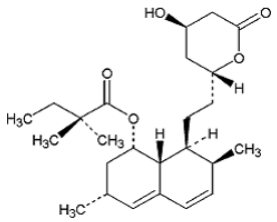
Keywords: Simvastatin, *Pleurotus florida*, Biomass, Biodegradation, Kinetic study

INTRODUCTION

Pharmaceutical compounds are considered as one of the emerging contaminant in the environmental matrices which creates a new challenge towards their detection and elimination owing to their lower concentration and large diversity of classes. Currently the scientific community pays greater attention towards the emerging contaminant which includes human and veterinary pharmaceuticals and the research surveys have reported that the potential impact of low range of pharmaceutical cannot be excluded. Recently intensive research has concentrated more on the removal of emerging micro pollutant with the aid of improvement in the analytical equipment and methodologies. The U.S Environmental Protection Agency, the Food and Drug administration, United States Geological survey and World Health organization have reported that there is a continuous release of pharmaceutical products into water resources [1] and trace levels of pharmaceutically active compounds are sufficient to induce toxic effects on living organisms in the ecosystem. The primary pathway of pharmaceuticals includes human and livestock excretion, improper disposal of unused dugs and manufacturing discharges [2]. The long term bioaccumulation of pharmaceutical residues eventually ends up in reduced fertility in male and feminization in aquatic species [3-8]. In the urban waste water, several of the following pharmaceuticals are detected and they are anti-inflammatory, antibiotic, lipid regulator, tranquilizer, estrogen and antidepressant [9]. Statin is a class of lipid-lowering drugs that reduces the production of cholesterol by the liver. The statin medication chiefly reduces cardiovascular risk and the most potent statin drugs are rosuvastatin (crestor), atorvastatin (atorva) and simvastatin (zocor). Simvastatin [2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4- hydroxy-6-oxo-2H-pyran-2-yl)-ethyl]-1-naphthalenyl ester] is more effective lipid-lowering drug commonly used to lower low density lipoprotein and triglycerides and increases high density lipoprotein in the blood. The physico-chemical properties of simvastatin [10,11] are signified in Table 1. It belongs to an antihyperlipidemic therapeutic class which inhibits 3-hydoxy-3-Methyl Glutaryl Coenzyme-A (HMG-CoA) reductase used in cholesterol synthesis [12,13]. The National Center for Health Statistics of USA described that the usage of statin drugs have been increased tenfold from 1998-2006 [14-16]. The lipid-lowering drugs such as fibrate and statin should be avoided in patients with high risk of coronary disease as they cause cancer in rodents [17]. There is a global necessity to preserve the water bodies since long term exposure of pharmaceutical poses ecological and human health challenges. The removal rate of pharmaceutical metabolite is influenced by the type of chemical constituent, their hydrophobicity, temperature, light intensity, hydraulic retention time and the treatment process. The conventional treatment technologies such as reverse osmosis, nano-filtration, ultra filtration, electro-dialysis, ion-exchange, ozonisation are associated with high energy consumption, production of sludge, operational condition problems and are designed to remove the pharmaceuticals from waste water only to a certain extent [18].

Advancement in current technology motivated the researchers to devise easy, rapid, reusable and cost effective, environment friendly techniques for the removal of pharmaceutical compounds using biologically available material. The main goal of the present study is to assess the utility of *P. florida* fungal biowaste for the removal of simvastatin drug from the aqueous solution with emphasis in the kinetic and thermal study.

Table 1: Physico-chemical properties of simvastatin drug

Properties simvastatin	
	
Molecular formula	$C_{25}H_{38}O_5$
Molecular mass	418.574 g/mol
Drug class	Antihyperlipidemic
Melting point	135-138°C
Solubility	Soluble in methanol
pK_a	14.91

Systematic name: [2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2- tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)-ethyl]-1-naphthalenyl ester.

MATERIAL AND METHODS

Chemicals

Zocor was supplied by MSD Pharmaceutical Limited and purchased from the local medical store. Hydrochloric acid, potassium permanganate, sodium hydroxide was obtained from High media chemicals were of analytical grades.

Biomass preparation

The *P. florida* biomass used in the study was prepared by collecting the *P. florida* biowaste from the mushroom cultivation center located at the Cauvery College for Women, Tiruchirappalli, Tamil Nadu. Prior to use, the fungal biomass were rinsed with water to remove the foreign particles adhere to the surface. Later they were dried in air and ground into a fine powder. The biomass was washed repeatedly with distilled water to attain mechanical strength, dried and stored in an airtight container for further use.

Preparation of simvastatin stock solution

The simvastatin tablet was finely powdered in a mortar and an accurate weight was transferred into the 100 ml volumetric flask. To this 50 ml of methanol solution was added and the mixture was sonicated for about 15 min and the solution was made up to the mark with methanol. From the stock solution various concentrations were prepared for the study.

Quantification of simvastatin

The residual concentration of simvastatin after the batch scale process was measured spectrophotometrically using NaOH and $KMnO_4$ solution. The zocor solution of varying initial concentrations (10-60 $mg.l^{-1}$) were prepared and treated with NaOH and KMnO4 solution ant The mixture was shaken occasionally and the corresponding absorbance was noted after 20 min at 610 nm [19,20] against the blank reagent. The linear standard calibration curve was obtained by a plot of absorbance versus concentration of the drug and the optical parameters are listed in the Table 2.

Table 2: Optical parameter of simvastatin

Parameters reported value	
λ_{max} (nm)	610
Beer's law range (µg/ml)	20–100
Molar absorptivity ($L.m^{-1}$ cm^{-1}	1.6×10^{-2}
Regression equation	y=0.016x+0.041
Correlation Coefficient	R^2 0.992
Slope (m)	0.016
Intercept (c)	0.041

Characterization of PFB

The FTIR of PFB before and after loading with simvastatin drug was recorded in the range of 4000-400 cm^{-1} and the specific active functional groups present in the PFB were identified. The thermo gravimetric analysis determines the physical and chemical properties of PFB as a function of an increase in temperature. The surface morphology of PFB and PFB-loaded simvastatin was pictured using scanning electron microscope.

Operating parameters effect on simvastatin uptake capacity

Simvastatin uptake by PFB at 30°C was investigated by varying the pH from 1-8. The mixture containing simvastatin and PFB was agitated by thermocouple stirrer at 150 rpm and simvastatin uptake by PFB was investigated for three different temperatures (25°C, 30°C and 35°C and 40°C). The residual concentration of simvastatin in the resultant filtrate was analyzed and amount adsorbed q_e was determined for each temperature.

Isotherm-kinetic design

Adsorption isotherm is an equation relating the amount of solute adsorbed onto the solid and solute equilibrium concentration in solution at a given temperature. The isothermal parameters provide an insight into surface properties, mechanism of sorption and affinity of sorbent for the maximum sorption capability. The most generally used isotherm models are Langmuir and Freundlich isotherm models. The distribution of simvastatin between the liquid and the PFB was explained in terms of Langmuir and Freundlich isothermal behavior. Langmuir isotherm describes the uniform monolayer coverage onto a surface with a finite number of identical sites as a function of concentration of adsorbed material in the liquid. The equilibrium parameter R_L predicts whether the Langmuir isotherm is favorable or not. Freundlich isotherm relates the concentration of a salute to the surface of an adsorbent to the concentration of the solute in liquid. The Freundlich parameters such as K_F, the adsorption capacity (mg/g), adsorption intensity 1/n and the amount adsorbed per gram of the adsorbent at equilibrium q_e (mg/g) are listed in Tables 3 and 4.

RESULTS AND DISCUSSION

Surface characterization

The surface active functional group actively responsible for the simvastatin uptake is listed in Table 3. The absorption peak around 3780.17 cm^{-1} is shifted slightly to 3777.92 cm^{-1} indicates that simvastatin uptake involves hydroxyl group replacement. The band at 1887.11 cm^{-1} showed no shift in simvastatin loaded PFB, which prominently implies that there was an interaction between the ester groups of lipids. From the FTIR spectrum the functional groups participated in the simvastatin uptake are hydroxyl groups, lipid esters and conjugated alkene. The XRD pattern reveals the amorphous nature of PFB. The TGA curve begins at 100°C and the degradation continues still 600°C. It shows PFB as thermally stable upto 600°C as in Figure 1. The SEM images of PFB control and PFB-loaded simvastatin are given in Figure 2A and 2B. The grooves and porous structure of control PFB was clearly visible in the image and it was glazed with simvastatin solid in the Figure 2B. This showed that the drug had been added to the surface of the PFB.

Table 3: Functional groups and classes of compounds involved in simvastatin uptake

Functional group classes of compounds frequency region (cm^{-1})	
Hydroxyl group alcohol	3780.17-3777.92
Alkane hydrocarbon	2923.81-2361.48
Alkane hydrocarbon	1887.11 - -
Acid Fatty organic acid	1598.80-1595.70

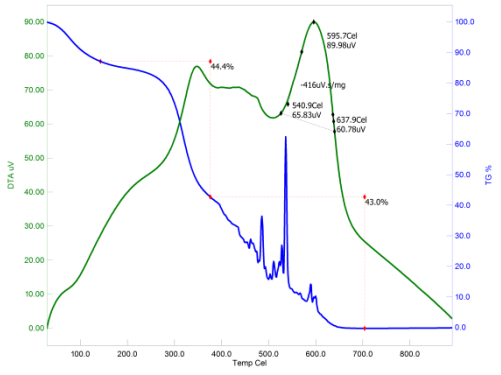


Figure 1: Thermogravimetric analysis of PFB

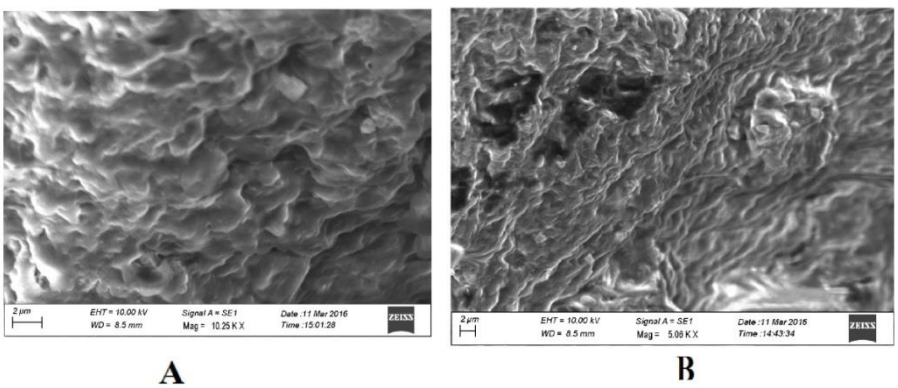


Figure 2: (A) PFB SEM image, (B) PFB loaded with simvastatin SEM image

Factors influencing the adsorption of simvastatin on PFB

Effect of pH and temperature

The pH factor decides the surface properties of PFB and simvastatin nature through either of the following such as pi-electron interaction, electrostatic interaction, hydrogen bonding or hydrophobic mechanism. The results depict that the uptake of simvastatin decreases from pH 5 due to the electrostatic repulsion [21-23] between the simvastatin and the negatively charged groups on the PFB (Figure 3). The increase in temperature disfavors the adsorptive efficiency of PFB. The rise in temperature increases the solubility of the solution and as a result the interaction between the simvastatin molecules decreases and thus uptake capacity decreased [24]. From the equilibrium concentration obtained from the thermal study, the distribution adsorption coefficient K_d, the standard free energy $\Delta G°$, enthalpy and entropy changes ($\Delta H°$ and $\Delta S°$) were also calculated.

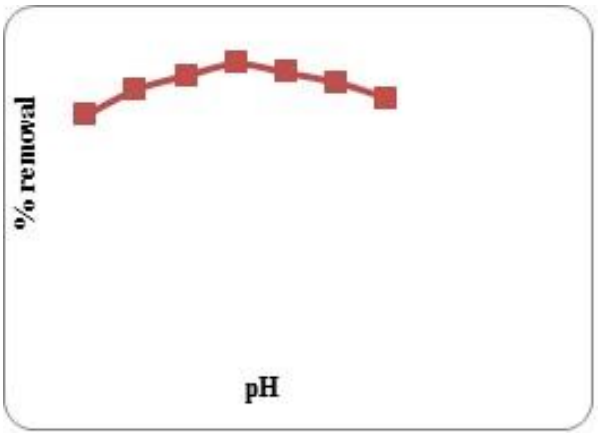


Figure 3: Effect of pH

Isothermal study and kinetic modeling

The isothermal model measures the uptake capacity of PFB for simvastatin and the Langmuir and Freundlich isothermal curves were depicted and isothermal parameters were determined from the slope and intercept of the linear plot and they are listed in the Table 4. The linear regression coefficient value R^2 for Freundlich adsorption isotherm as 0.997 and that for the Langmuir was 0.981. The experimental data reveal that increase in simvastatin concentration increases the uptake capacity confirming the multilayer physisorption [25,26] between the simvastatin and PFB.

Table 4: Isotherm and kinetic model parameters for simvastatin at 30°C

q_{max} (mg g^{-1})	76.92
Langmuir isotherm model (b.mg^{-1})	0.026
R^2	0.9810
R_L	0.287
K_F (mg g^{-1})	4.345
Freundlich isotherm model 1/n	0.5831
R^2	0.993
q_e (mg.g^{-1})	37.325
Pseudo-first order model (k_1.min^{-1})	0.1359
R^2	0.997
q_e (mg g^{-1})	166.67
Pseudo- second order model k_2 (g.mg^{-1}.min^{-1})	7.2×10^{-3}
R^2	0.997

The pseudo first and second order kinetic model was investigated using the following Equations 1 and 2:

$$\log (q_e-q_t)=\log q_e-(K/2.2303)t \quad (1)$$

$$t/q_t=1/k_2q_e^2+(1/q_e)t \quad (2)$$

The adsoprtion kinetic plot displayed in Figures 4 and 5. A linearised plot of t/q_t versus t and log (q_e-q_t) versus t as in Figure 5 were used to calculate q_e, k_1, k_2 from the slope and intercept values [22-27]. This suggests that pseuso second order was in good agreement illustrating the multilayer adsoption process between the simvastatin and PFB.

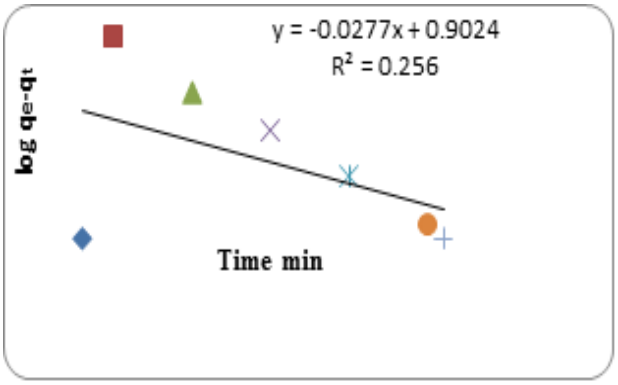


Figure 4: Pseudo first order kinetic model plot

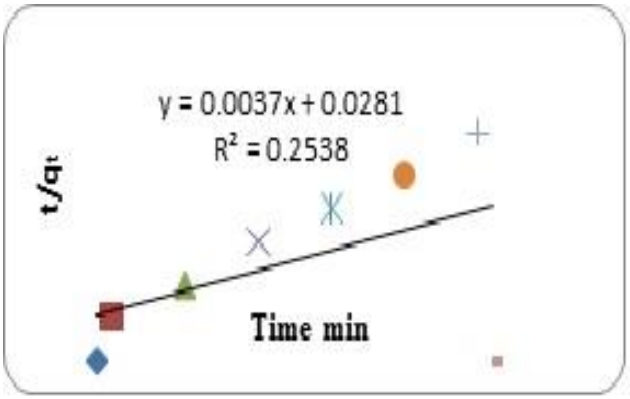


Figure 5: Pseudo second order kinetic model plot

CONCLUSION

The present study focuses on the feasibility of greater potential of PFB for the removal of simvastatin drug from the aqueous phase. The surface methodological response provides an efficient approach for the uptake of simvastatin by PFB in an eco-friendly manner under optimization conditions of pH, time, concentration, dose and temperature. The Freundlich model more competently describes the isotherm than the Langmuir model. The rise in temperature increases the equilibrium concentration and indicates the endothermic and non-spontaneous process of simvastatin removal by PFB due to the disorderliness of the system.

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