

## NANOMATERIAL AS RADIOPHARMACEUTICAL VEHICLE CANDIDATE ISOTHERM, THERMODYNAMIC, AND KINETICS STUDIES OF IODIDE ADSORPTION ON THE AL-SBA-16 MESOPOROUS

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### ABSTRACT

**NANOMATERIALAS RADIOPHARMACEUTICAL VEHICLE CANDIDATE ISOTHERM, THERMODYNAMIC, AND KINETICS STUDIES OF IODIDE ADSORPTION ON THE AL-SBA-16 MESOPOROUS.** In order to investigate the potential of Al-SBA-16 Mesoporous Nanomaterial as a candidate for radiopharmaceutical vehicles, the studies of kinetics, thermodynamic, and in vitro stability of Iodide adsorption onto the nanomaterial have been carried out. The adsorption study was conducted at different temperature, time, and iodide concentration and observed with spectrophotometric techniques. The isotherm adsorption was fitted with Langmuir and Freundlich model and the thermodynamic parameters were determined at temperatures of 293K, 301K, 308K, and 313K. Moreover, the adsorption kinetics was analyzed in terms of pseudo first order model for Al-SBA-16 Mesoporous Nanomaterial and Iodide and pseudo second order in overall reaction. The activation energy was determined by using Arrhenius equation, meanwhile, the in vitro stability testing was conducted in phosphate buffer saline at pH variation for 5.5 to 7.0, and at temperature variation for 20°C to 45°C and at testing time variation for 6 to 48 hours. The result indicate that the adsorption obeys the Langmuir isotherm model and has a tendency to be chemical adsorption with a value of DH was -116.641 kJ/mol and the nature of spontaneous reactions. The adsorption process followed the pseudo-first-order model and the apparent activation energy was 41.26 kJ/mol. In the present research work, the in vitro stability data were evaluated using P-Value and the theory of Hypothesis Testing or Fisher's significance test. The result of hypothesis testing show that, the adsorption of iodide onto Al-SBA-16 Mesoporous Nanomaterial were highly stable under the experimental conditions adopted.

**Keywords:** Mesoporous Nanomaterial, radiopharmaceutical vehicle, adsorption, in vitro stability

### ABSTRAK

**STUDI ISOTHERM, TERMODINAMIKA, DAN KINETIK DARI ADSORPSI IODIDA PADAMESOPORUS AL-SBA-16.** Untuk menyelidiki potensi mesopori nanomaterial Al-SBA-16 sebagai kandidat untuk kendaraan radiofarmaka maka dilakukan studi kinetika, termodinamika, dan stabilitas in vitro dari adsorpsi iodida ke dalam nanomaterial itu. Studi adsorpsi dilakukan pada

variasi suhu, waktu, dan konsentrasi iodida yang berbeda dan diamati dengan teknik spektrofotometri. Adsorpsi isoterm menggunakan model Langmuir dan Freundlich dan parameter termodinamika ditentukan pada suhu 293K, 301K, 308K, dan 313K. Selain itu, kinetika adsorpsi dianalisis terhadap model pseudo-first-order untuk Al-SBA-16 Nanomaterial Mesopori dan Iodida dan pseudo-second-order dalam reaksi keseluruhan. Energi aktivasi ditentukan dengan menggunakan persamaan Arrhenius, sementara itu, pengujian stabilitas in-vitro dilakukan dalam saline fosfat pada variasi pH 5,5 hingga 7,0, dan pada variasi suhu untuk 20 C hingga 45 C dan pada variasi waktu pengujian untuk 6 hingga 48 jam. Hasil menunjukkan bahwa adsorpsi mematuhi model isoterm Langmuir dan memiliki kecenderungan menjadi adsorpsi kimia dengan nilai  $H$  adalah -116.641 kJ/mol dan sifat reaksi spontan. Proses adsorpsi mengikuti model pseudo-first-order dan energi aktivasi jelas adalah 41,26 kJ / mol. Dalam penelitian ini, data stabilitas in vitro dievaluasi menggunakan P-Value dan teori Pengujian Hipotesis atau uji signifikansi Fisher. Hasil pengujian hipotesis menunjukkan bahwa, adsorpsi iodida ke Al-SBA-16 Mesopori Nanomaterial sangat stabil di bawah kondisi eksperimental yang diadopsi.

**Kata kunci:** Nanomaterial Mesopori, Kendaraan radiofarmaka, Adsorpsi, Stabilitas in vitro

## INTRODUCTION

One of the modified nanomaterial that have been made at STTN-BATAN is Al-SBA-16 that is, the Santa Barbara Amorphous-16 mesoporous silica material modified with the Al group by a direct synthesis grafting method. The Al-SBA-16 have specific surface area with a range of 1,000-1,412 m<sup>2</sup>/gram which is expected to be used as a carrier on radiopharmaceutical.

The use of Al-SBA-16 nanomaterial was chosen with consideration of the relatively large surface area of Al-SBA-16, uniform pore size and biocompatible [1-4] so that it is expected to be able to carry radionuclides as a vehicle of radiopharmaceutical [5-7].

The main purpose of this study was to determine the kinetic parameters and thermodynamic parameters of iodide ion adsorption as a substitute for iodine-131 radionuclides against Al-SBA-16 material. The study of the adsorption parameter was carried out in the form of an investigation of isotherms, kinetics, thermodynamics, and adsorption activation energy. These parameters are important to know chemical interactions such as monolayer absorption events that might occur between iodine and Al-SBA-16 material. This provides information on whether iodine adsorbed on Al-SBA-16 can be applied for radiopharmaceutical [8-12] and whether the dose resulting from iodine uptake with Al-SBA-16 is a suitable dose for radiopharmaceutical uses. The indicators if the Al-SBA-16 material has the potential as a good radiopharmaceutical carrier is the bonding of this material to radionuclides of interest is strong enough and stable, high loading capacity and has a relatively low activation energy [13-17].

The application of nanomedicine that selectively reach targets in tissues and contain large volumes of drugs, this can improve cancer detection and therapeutic effectiveness [18-20]. Nanoparticles as a medium for drug delivery will provide a better surface area thereby maximizing therapeutic effect while minimizing toxicity. The ability of nanoparticle drugs to pass through

obstacles in the body is better because of their very small size [18,21-23].

The nanomaterial stability testing is a procedure intended to establish the quality or reliability of the bond strength between radioisotope <sup>131</sup>I and Al-SBA-16 as a drug carrier in the variation of pH and temperature with respect to use time as a candidate for radiopharmaceutical preparations. The testing was carried out simulations using iodine isotopes of non-radioactive compounds. The Iodine that has been absorbed is expected to be strongly bonded with the Al group. The ability of the aluminum atom (Al) to attract electrons from the iodine (I) atom due to the difference in electronegativity between the two atoms [24,25]. The strength of these bonds can be observed by looking at the trend of iodine that is released from the particles after immersion in the media in vitro for up to 48 hours. It is hoped that in this study Al-SBA-16 is able to carry and maintain <sup>131</sup>I radioisotopes remain in the tissue of target and radiate the inflamed tissue that must be treated.

## EXPERIMENTAL METHOD

### Synthesis of Nanomaterial Al-SBA-16

Nanomaterial Al-SBA-16 was synthesized using TEOS, F-127, HCl, H<sub>2</sub>O and Al within 20 hours, followed by hydrothermal process inside the furnace for 2 days at 373K. The next step was conditioning into neutral pH, calcination and its characterization.

### Isotherm, Thermodynamic and Kinetics Determination

#### Isotherm Model Determination

Each amount of 25 mg Al-SBA-16 was dissolved into 25mL iodide solution at different temperatures of

293K, 301K, 308K, and 313K for 6 hours. The mixing solution of Al-SBA-16 and iodide was filtrated using Whatman 42 and being analyzed using UV-VIS spectrophotometry method. The study of the adsorption isotherm model is done by finding the value of  $Q_e$  and  $C_e$  of the Langmuir Equation or the value of  $\log Q_e$  and  $\log C_e$  of the Freundlich Equation as shown in Equations 1-2 and Equations 1-3. The curve from these results (Figure 5 and Figure 6) were used to determine the isotherm model, whether it is Langmuir or Freundlich model.

### Thermodynamic and Kinetics Determination

Arrhenius Equation was used to determine the thermodynamic and kinetics aspects. A common form of the equation is [32]:

$$k = k_0 e^{-E/RT} \quad \dots\dots\dots (1)$$

By determining the value of enthalpy ( $\Delta H$ ), entropy ( $\Delta S$ ) and Gibbs Energy ( $\Delta G$ ), it can be conducted the value of activation energy and its type, whether has a tendency to be chemical or physical reactions, and follows nature of spontaneous or unspontaneous reactions.

### In Vitro Analysis of Iodine Desorption with Al-SBA-16 nanomaterials

The passive in vitro loading of a simulated  $^{131}\text{I}$  solution into the Al-SBA-16 nanomaterial, was determined by maximum absorption of iodine ( $C_0$  concentration) in Al-SBA-16. The adsorption method is carried out by determining the optimum time of adsorption. After simulated  $^{131}\text{I}$  solution has been loaded then a stability test is carried out by measuring  $C_s$  (drug release). The stability test method is carried out by means of the results, loading results that have been filtered, dried at room temperature, then put 25 grams each into a 25 mL media solution of pH variations at room temperature  $37 \pm 1 \text{ }^\circ\text{C}$  (in a solution of  $28 \pm 1 \text{ }^\circ\text{C}$ ) and variations temperature against time in pH media 7. The solution was filtered and dried at room temperature then the filtrate obtained from the in vitro stability test was analyzed using a UV-Vis spectrophotometer instrument with a wavelength of 598 nm.

### Desorption Analysis with Standard Addition Method

The Filtrate of the isotherm model determination section was taken for 1 mL for the in vitro stability test. Each of them were added 1 mL of the standard solution with known absorbance value. Further addition of 1 mL of 1% starch solution, 5 drops of  $\text{H}_2\text{SO}_4$  and 1 mL of  $\text{H}_2\text{O}_2$  were conducted. The distilled water was then added until the volume of each samples reach 10 mL.

The filtrate was analyzed using UV-Vis spectrophotometer instrument with a wavelength of 598 nm.

## RESULTS AND DISCUSSIONS

### The Al-SBA-16 Character

The Al-SBA-16 material prepared for this study has the following characteristics: when characterized using a wide angle XRD has a diffractogram pattern at an angle of two theta between  $20^\circ$  to  $30^\circ$  as shown in Figure 1 that the nature of the material is amorphous.

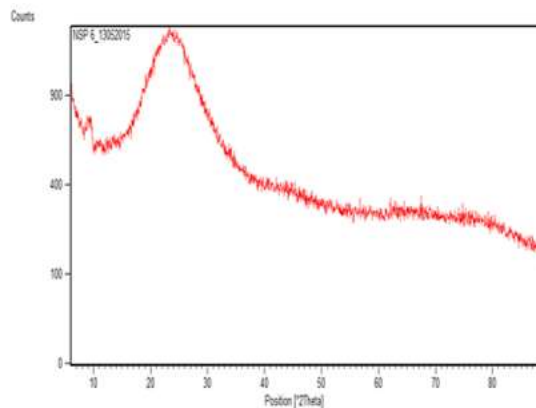


Figure 1. Al-SBA-16 material diffraction pattern at wide angle XRD

The amorphous nature of Al-SBA16 will make the material quite active considering drug compounds such as iodine and has less toxic properties compared to Al-SBA16 if it is crystalline(26–28).

The results of the characterization of Al-SBA-16 material using BET Surface Area Analyzer are shown in Table 1.

Table 1. The characterization of Al-SBA-16 material using BET Surface Area Analyzer.

No of Al-SBA-16 Material	Specific Surface Area ( $\text{m}^2/\text{gram}$ )	Pore Volume ( $\text{cc}/\text{gram}$ )	Pore Diameter ( $\text{A}$ )
1	1153.57	0.941	32.624
2	1407.44	1.156	32.858
3	1412.15	1.180	33.425
4	1038.73	0.879	33.843

Based on Table 1 it can be seen that the Al-SBA-16 material synthesized shows the surface properties of the material with specific surface area and high pore volume. On the other hand, the Al-SBA-16 material has a relatively uniform pore diameter, as evidenced from some material data that is characterized showing a pore diameter that is not much different. This is very beneficial if the Al-SBA-16 material is used as a drug delivery agent or drug vehicle because it is estimated to be able to carry large amounts of drugs(29–31).

The results of the characterization of Al-SBA-16 material using TEM are shown in Figure 2.

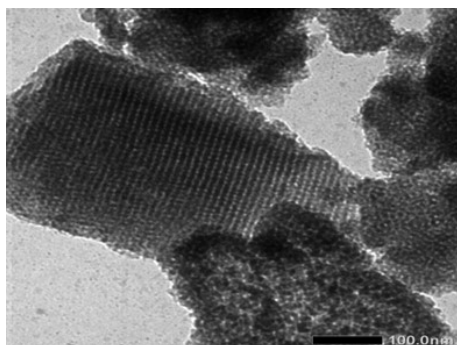


Figure 2. Transmission electron microscopy of the Al-SBA-16 material.

Based on Figure 2 it can be seen that the Al-SBA-16 material has a non-spherical particle shape with uniform nanometer sized pores. This supports the results of the characterization with the BET Surface Area Analyzer in terms of the pore pattern of the material. thus it can be predicted that the drug in the form of radioactive <sup>131</sup>I will be able to be loaded into the pores of Al-SBA-16 material properly.

### Determination of Optimum Adsorption Time

Figure 3. Graph of the effect of adsorption time on iodine.

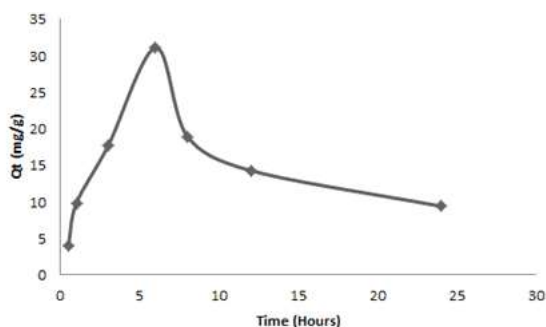


Figure 3. Graph of the effect of adsorption time on iodine

Adsorption process using initial concentration of 200 ppm and time 0.5; 1; 3; 6; 12; and 24 hours resulted highest adsorption rate occurred at 6 hours as indicated by the highest amount of absorbed concentration as shown at Figure 1. The decreasing adsorption ability after 6 hours contact time occurs because the adsorbate that has been adsorbed will be released back into the sample solution so that the concentration of adsorbate that is not adsorbed becomes greater. This can occur when the silanol group in mesoporous silica Al-SBA-16 prefers to bind to water molecules after interacting for longer than 6 hours [34].

### Effect of Temperature on Adsorption

The adsorption process is carried out with variations in the adsorption temperature of 20 °C, 28 °C, 35 °C and 40 °C as shown on Figure 4.

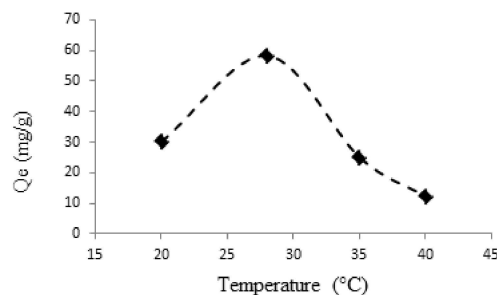


Figure 4. Graph of the effect of adsorption temperature on iodine.

Figure 4 shows that from 20 °C to 28 °C the amount of iodine absorbed increases while from 28 °C to 40 °C the amount of iodine absorbed decreases. Iodine absorption at temperature from 35 °C to 40 °C decrease relatively smooth than before. The reduced amount of iodine solution is due to the increasing of the temperature which make solubility of the iodine solution increases. Consequently, the energy of iodine interaction with the solvent increase as the probability of the interaction of adsorbate with adsorbent decrease.

### Determination of Adsorption Equilibrium

The mechanism of adsorption can be investigated by determining the type of adsorption that occurs in iodine by Al-SBA-16 material. Liquid solid phase adsorption can adhere to the Langmuir, Freundlich isotherm type or a combination of both. To find out the isotherm model that is suitable with the adsorption phenomena that occur between iodine and Al-SBA-16 material, the adsorption isotherm model is tested. Data obtained from iodine adsorption on Al-SBA-16 material was calculated using the Langmuir and Freundlich equation .

The Langmuir equation can be written in the following linear form [33]:

$$\frac{C_e}{q_e} = \frac{1}{q_m K_e} + \frac{C_e}{q_m} \dots\dots\dots (2)$$

The linear form of the Freundlich isotherm is as follows [33]:

$$\log q_e = \log K_F + \frac{1}{n} \log C_e \dots\dots\dots (3)$$

The data plotted on a linear graph as shown in Figure 5 and Figure 6.

Based on the value of R<sup>2</sup> obtained, iodine adsorption with Al-SBA-16 material follows the Langmuir isotherm model because the R<sup>2</sup> in the Langmuir isotherm is greater than that of the Freundlich isotherm. Adsorption of Langmuir isotherms is monolayer. The modification of Al groups on the surface of the material allows chemical bonds that are monolayer and follow the Langmuir isotherm [33,35]. This event shows that an

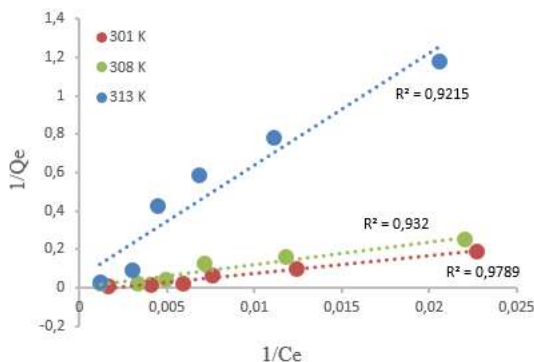


Figure 5. Plot model of Langmuir adsorption isotherm.

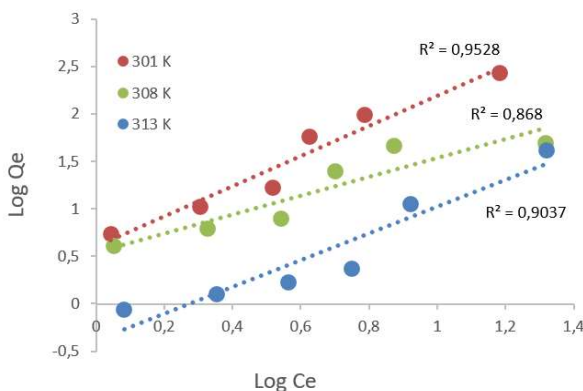


Figure 6. Plot of the Freundlich adsorption isotherm model

active group in the adsorbent binds to one adsorbate molecule, such as an  $Al^{3+}$  binds to one  $I^-$ .

### Determination of Adsorption Thermodynamic Conditions

Determination of thermodynamic conditions is done to find out the enthalpy values ( $\Delta H$ ), entropy ( $\Delta S$ ) and Gibbs free energy ( $\Delta G$ ) which is required by plotting  $\ln(K_d)$  vs  $1/T$  at each temperature.

The equation determine by following:

$$\ln K_d = \left( \frac{-\Delta H^\circ}{R} \right) \frac{1}{T} + \frac{\Delta S^\circ}{R} \quad \dots\dots\dots (4)$$

The results on the graph relationship  $1/T$  vs  $\ln K_d$  at Figure 7.

The adsorption process with the material at a temperature of  $28^\circ C$  gives a value of  $\Delta H = -116,641$  kJ/mol and  $\Delta S = -0,3657$  kJ/Kmol. A negative  $\Delta H$  value indicates an exothermic reaction. This is in accordance with the decrease in adsorption capacity as the temperature increases (2,33,35). The enthalpy of adsorption obtained was 116,641 kJ/mol. This value is in the range of 40-800 kJ/mol. This value indicates that the adsorption that occurs in iodine with Al-SBA-16 is a chemical adsorption. In this event chemical adsorption occurs between  $Al^{3+}$  and  $I^-$  ions. This indicates that

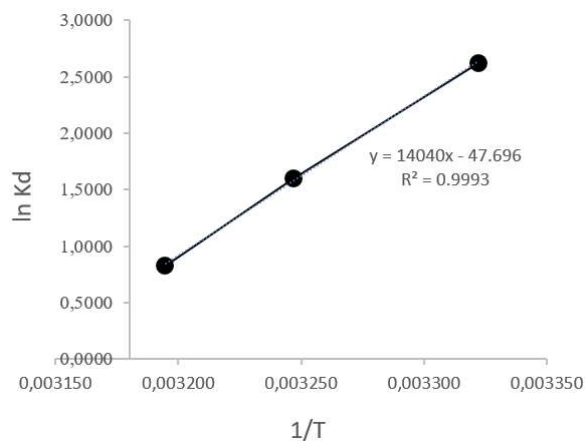


Figure 7. Curve of  $1/T$  with  $\ln K_d$

Al-SBA-16 can be used as a stable drug carrier for radioactive substances. That will be very useful in the field of medicine, especially radiotherapy.

In other temperature variations the value of iodine adsorption thermodynamic parameters is shown in Table 2.

Table 2. Thermodynamic Parameters

Temperature K	Entropy, $\Delta S$ kJ/K.mol	Gibbs Energy, $\Delta G$ kJ/mol	$\Delta H$ , KJ/mol
301	-0.3657	2.6615	-116.641
308	-0.3657	5.3387	-116.738
313	-0.3657	7.4320	-116.626

A positive value of  $\Delta G$ , 2.6615 kJ/mol; 5.3387 kJ/mol; and 7.4320 kJ/mol shows that the adsorption process is not spontaneous. The negative value of ( $\Delta S$ ) also indicates that the adsorption phenomenon involves an associative mechanism, while the positive ( $\Delta S$ ) corresponds to the dissociative mechanism<sub>(33,35)</sub>.

### Iodine Adsorption Kinetics on Al-SBA-16

Iodine adsorption data on Al-SBA-16 at various times was evaluated to get the kinetics that were suitable for the adsorption system. The pseudo first-order graph of the equation  $t$  versus  $\ln(q - q_t)$  is shown in Figure 8.

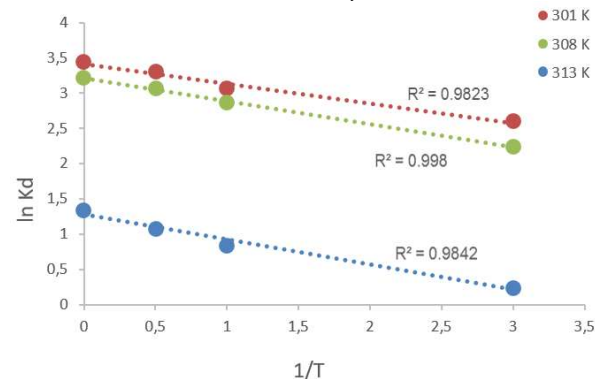


Figure 8. Time relationship curve with  $\ln (q_e - q_t)$

The plot  $t/q$  versus  $t$  of the equation shown in Figure 9.

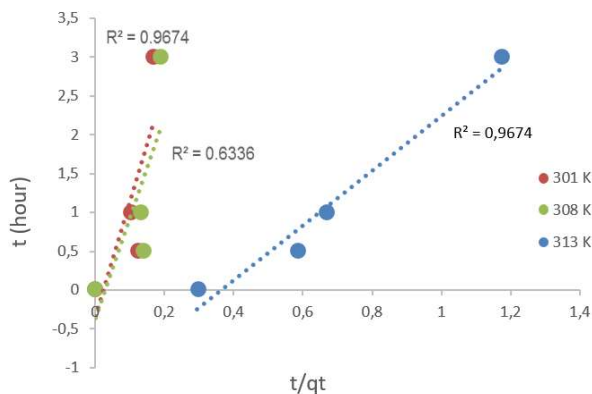


Figure 9. Curve of  $t/qt$  with  $t$ .

The curve shows that the regression value ( $R^2 = 0.63 - 0.96$ ) with the rate constants  $k$  and  $q$ . When compared with the results in first order kinetics, the regression value in second order is smaller so that the adsorption phenomenon that occurs in iodine with Al-SBA-16 follows the first order kinetics equation.

### Iodine Adsorption Activation Energy on Al-SBA-16

The value of the activation energy can be calculated from the value of the reaction rate constant at the three reaction temperatures using the Arrhenius equation. This Arrhenius equation is then modified to form a straight line equation (linear regression).

$$\ln(k) = \ln(k_0) - E/RT \dots\dots\dots (1-5)$$

The straight-line relationship of the Arrhenius equation for iodine adsorption process can be seen in Figure 10.

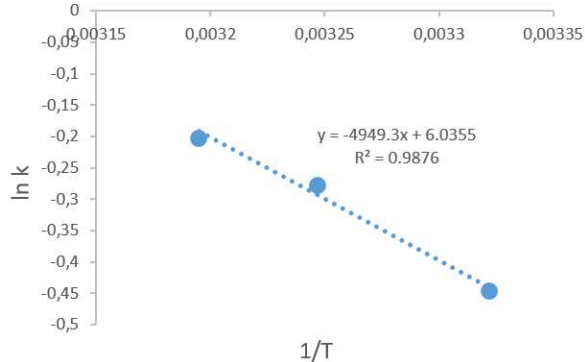


Figure 10. Curve of  $1/T$  with  $\ln K_d$

Based on the slope of the equation of the linear regression results on the curve obtained activation energy which is the slope times the gas constant ( $R$ ). The activation energy value obtained was 41.262 kJ/mol.

This value is more than 4.2 kJ/mol which indicates that adsorption occurs by chemisorption (33,35).

### Temperature Effect on Iodine Stability in Al-SBA-16 In Vitro Nanomaterials

To find out the stability of iodine bonds with Al-SBA-16, an analysis of samples was carried out on the variation of temperature in vitro by looking at the colour changes between the samples before and after each temperature variation using the UV-Vis spectrophotometer instrument with an instrument detection limit of 0.0002. The filtrate obtained later was complexed and analyzed by UV-Vis spectrometry using the standard addition method (spike concentration). This method is used if the sample concentration does not fall into the standard curve range or the concentration of the analyte in the sample is low. results of the calculation of the standard deviation obtained the upper and lower limits of 0.322 and 0.284. Analysis of absorbance of drug preparations by adding a standard concentration that has known absorbance value compared to the standard absorbance value obtained (standard addition method). If the absorbance value of the sample falls within the standard absorbance range then the Al-SBA-16 preparation with iodine does not undergo desorption or release so that the preparation can be declared stable to temperature(13), which is presented in Table 3 and Figure 11.

Table 3. Absorbance Stability Analysis Data Temperature Variation on Time (Standard Addition).

Temperature	Time (Absorbance)			
	6 hours	12 hours	24 hours	48 hours
20°C	0.3065	0.3098	0.3100	0.3108
28 °C	0.3066	0.3064	0.3070	0.3066
35 °C	0.3013	0.3063	0.3055	0.3138
40 °C	0.3063	0.3060	0.3070	0.3078
45 °C	0.3038	0.3063	0.3090	0.3120

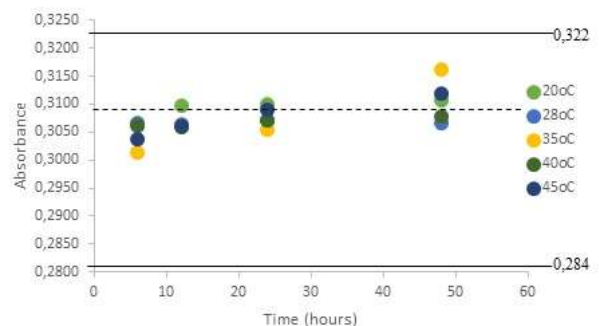


Figure 11. Graph of comparison of sample absorbance and standard temperature variation on time.

Based on the data obtained it is known that the temperature studied in the range of 20°C-45°C does not show any real difference evidenced from the value ( $p$ -value  $>$   $p$ -critical 0.02 with a confidence level of 98% (Patino et al, 2015) presented in the Table 4.



**Table 4.** Significance Test of Temperature Stability Variation using Anova Two Way Method Without Replication.

Category	F	P-value	F crit	ho	Significancy
Temperature	0.6324	0.6489	4.4187	Accepted	Not Significant
Time	4.0774	0.0328	4.8145		
Error	8.49E-05				
Total	0.00189				

In statistical hypothesis testing, the p-value or probability value is the probability of obtaining test results at least as extreme as the results actually observed during the test, assuming that the null hypothesis is correct. The value of p-value obtained for the temperature and time category each has a value of 0.6489 and 0.0328 which is greater than 0.02. This shows that Al-SBA-16 as a dosage loaded with iodine has strong bond so that iodine does not desorption into the simulation media. In storage the material can be carried out at a temperature of 20°C to 45°C because at that temperature no iodine is released (desorption) in the media but should be stored at room temperature.

## CONCLUSION

The optimum time for iodine adsorption is 6 hours and the optimum uptake temperature is 28°C, followed the Langmuir isotherm model with the evaluation results of thermodynamic parameters and activation energy of 41.26 kJ/mol iodine adsorption on Al-SBA-16 material is chemical adsorption and is exothermic. The result shows that, the adsorption of iodide onto Al-SBA-16 Mesoporous Nanomaterial were highly stable under the experimental conditions adopted. This indicates that Al-SBA-16 can be proposed as a stable drug carrier for radioactive substances, that will be very useful in the field of medicine, especially radiotherapy.

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