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Physicochemical Studies on Interacting Some Cardiovascular Drug Pairs

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Abstract

Are increasingly seen to be important, some drugs, can undergo direct physical or chemical interaction with other drugs and render both drugs inactive. In the light of the above, this study aims to examine some pharmaceutical studies of physicochemical drug interactions including solubility and adsorption studies of selected cardiovascular drugs which are commonly involved in potential drug-drug interaction (pDDIs) in the cardiovascular department in order to pave the path for preventing or at least reducing the incidence of pDDIs. To reach this objective, study encountered some practical consequences of the physical chemistry of drugs, especially their interactions with each other, or with various pharmaceutical adsorbents. The solubility of three cardiovascular drugs was tested in the presence of other drugs using the shake-flask method. Those drugs were: aspirin, furosemide and amiodarone. Our results showed that spironolactone can affect the hydrolysis of aspirin if co-administered at equivalent clinical doses, and therefore might reduce the efficacy of protective low-dose aspirin. Moreover, the solubility of furosemide decreased in the presence of gentamicin. .The solubility of amiodarone decreased in presence of warfarin, theophylline and lidocaine.

In the adsorption experiments, aspirin and furosemide were selected as adsorbates: aspirin and furosemide. The adsorbents used were: activated charcoal, cholestyramine, kaolin, sodium hydroxide and sodium alginate. The experimental adsorption data were fitted to four isotherm models by both linear and non-linear regression analyses. Freundlich isotherm provided the best fit for most adsorption data followed by Temkin and Langmuir isotherms. The highest adsorption capacity of activated charcoal and cholestyramine was for furosemide.

Key words
Physicochemical interaction, cardiovascular drugs, adsorption isotherm

1. Introduction

Are increasingly seen to be important Drug interactions may occur inside the body and are called a drug-drug interaction (DDI) or outside the body and are known as a drug incompatibility. These interactions could result in favorable, toxic or no clinical effects [1-3]. Physicochemical incompatibilities are generally given little attention during inpatient care. They are, nevertheless, potential sources of drug interactions [4]. In particular settings, the consequences of drug incompatibilities can be severe. For example, physical changes to the solution may lead to precipitate formation that can cause some drugs, because of their physical or chemical properties, can undergo direct interaction with other drugs. Direct physical and chemical interactions usually render both drugs inactive. Direct drug interactions may not always leave visible evidence [5, 6]. Hence simple visual inspection is not enough to reveal all direct interactions. Because drugs can interact in solution, it is essential to consider and verify drug incompatibilities when ordering medications [6, 7].

Since solubility of a drug can be affected by mixing with other drugs or agents, it is vital to understand the way in which drugs dissolve in solution and the factors that maintain solubility or cause drugs to precipitate. Interactions that interfere with drug absorption as a result of chemical or physical reactions between drugs are called pharmaceutical drug interactions. Most of these occur during release or absorption after drug administration, such as in the stomach when two oral drugs are given concurrently [1].

Adsorption interactions are nonspecific and arise when molecules of a drug physically bind to the surface of another solid that acts as an adsorbent, reducing the concentration of drug available for absorption [8-9]. Adsorption at the solid–liquid interface plays a significant role in many fields including medicine and pharmacy with applications in drug formulation, antidotes and haemo perfusion for treating cases of severe drug overdoses [4, 10].

The present study is a contributing aimed at the proper understanding and studying of possible interactions in solution between selected cardiovascular drugs administered via the same route: By examining the solubility of a drug in the presence of another drug. Further insight into the drug -drug interactions, per se, necessities the undertaking of a parallel investigation and characterization of possible adsorbate-adsorbent interactions. Cardiovascular drugs were tested with different adsorbents and dietary fibers utilizing in vitro adsorption tests under simulated in vivo adsorption condition.

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2. EXPERIMENTAL

2.1. Materials

Amiodarone hydrochloride and theophylline were kindly provided by T3A Pharma Group, Giza, Egypt. Aspirin and Lidocaine hydrochloride: kindly provided by PHARCO. Pharmaceuticals, Alexandria, Egypt., furosemide, gentamicin sulfate and warfarin were kindly donated by GÜTEMED, USA.. Spironolactone: kindly provided by SEDICO Pharmaceuticals Company, Cairo, Egypt. Cholestyramine: by Bristol-Myers Squibb, England. Kaolin (aluminum silicate hydroxide Al2Si2O5 (OH) 4): ISO-CHEM Fine Chemicals, Egypt. Sodium alginate (sodium polymannuronate): Oxford Laboratory. Reagent, Oxford Lab Chem, India. Activated charcoal, acetic acid, sodium acetate, hydrochloric acid, methanol, aluminum hydroxide and sodium hydroxide: ADWIC; by El- Nasr Pharmaceutical Chemicals Co., Cairo, Egypt.

2.2. METHODS

2.2.1. Solubility measurement of drugs

The effect of the presence of certain drugs on the solubility of amiodarone, aspirin and furosemide in water was studied using the shake flask method as follows: Amiodarone hydrochloride (Amiodarone HCL + lidocaine HCL), (amiodarone HCL + theophylline), (amiodarone HCL + warfarin) , Aspirin (Aspirin + spironolactone) and Furosemide (Furosemide + gentamicin sulphate).

The UV spectra were run for all eight drugs, in order to exclude the spectral overlap of the tested drug pairs at the selected λmax where amiodarone (λmax 345), aspirin (λmax 278) and furosemide (λmax 271). Known excess of each of these drugs was shaken horizontally with 5 or 10 mL of distilled water in ten screw capped cylindrical glass vials. Vials were immersed in a thermostatically controlled shaking water bath (GFL® 1083, Germany) at a temperature of 37±0.5 °C and a speed of about 50 rpm. At specified time intervals (0.25, 0.5, 1, 2, 4, 6, 8, 12, 24 and 48 hrs), one vial was withdrawn and contents were filtered through a 0.45 μm disk filter. Filtrate was properly diluted with distilled water for spectrophotometric measurement ((Jenway, UV-6305, Staffordshire, UK) at the respective wavelength of maximum absorption to measure drug concentration, against blank solutions prepared in the same manner. Each measurement was performed thrice.

To determine the effect of the presence of other drugs on the solubility of tested drugs, a parallel run of ten more vials were prepared following the same procedure but with adding a specified weight of the interacting drug which was determined based on the dose ratio used of both drugs in clinical practice. Each interacting drug was tested alone at the same concentration to confirm no or negligible UV absorbance at the λmax of the drug tested for solubility. **(Table 1)** shows the amounts of drugs tested for interactions. The pH of solutions containing one or two drugs was measured using a Jenway digital pH meter after 24 hrs.

Table 1: Amounts of interacting drugs used in solubility studies

Interacting drugs	Tested drug (weight/volume)		
	Amiodarone (10 mg/ 10 mL)	**Aspirin (87.5 mg/ 5 mL)**	**Furosemide (5 mg/ 10 mL)**
Gentamicin	-	-	10 mg, 20 mg
Lidocaine	10 mg	-	-
Theophylline	10 mg	-	-
Spironolactone	-	25 mg, 25 μg	-
Warfarin	1 mg	-	-

2.2.2. Fourier-Transform infrared spectroscopy (FT-IR)

To help interpret solubility results, separate FT-IR spectra for single drugs and physical mixtures of drug pairs at a weight ratio of 1:1, were recorded using Shimadzu IR-470 spectrophotometer, at a range of 4000-400 cm-1. Potassium bromide (KBr) disc method was used. The samples were ground, mixed thoroughly with KBr and compressed into discs using the IR compression machine.

2.2.3. Statistical analysis of solubility studies

Experimental solubility data were statistically analyzed using IBM Statistical package for Social Science (SPSS) version 22.0 (SPSS Inc., Chicago, IL, USA). Assumptions of different statistical tests were first checked to ensure the model goodness-of-fit and validation of the model results. Statistical tests that were used for analysis were independent t-test which applied to determine if the presence of a possibly interacting drug had a statistically significant effect on solubility and the Mann–Whitney U non-parametric test which used for comparisons when the t-test did not meet the usual assumptions (normality, absence of significant outliers and homoscedasticity).

2.2.4. Adsorption studies

Equilibrium adsorption runs were carried out in 25 mL screw-capped cylindrical glass vials containing a final volume of 10 mL of the stock solution and the corresponding solvent. Stock solution of Aspirin and Furosemide were prepared in the appropriate solvent with determined pH. Specified volumes of the stock were added to the vials to produce suitable final working concentrations. A constant weight of adsorbents was added to all vials (**Table 2**).

Five adsorbents were used in the study namely; activated charcoal, kaolin, cholestyramine, aluminum hydroxide and sodium alginate. Each drug at a constant concentration was initially tested for adsorption on all five adsorbents. The adsorbents that have shown the highest capacity for each drug were used for further analysis and isotherm modelling. Both appropriate working dilutions of tested drugs and adsorbent weights were determined by preliminary experiments

considering solubility limits of each drug. A blank for the adsorbing materials was also prepared in the same way without the drug. In addition, a vial containing the same volume (10 mL) of the drug solution of known concentration without the adsorbent was prepared and treated in the same manner. This solution was used as a control to check for any change in drug stability. The screw-capped vials were then placed in a thermostatically controlled shaking water bath at temperature of 37±0.5 °C and agitated horizontally at 75 rpm over night to assure equilibrium was attained. In experiments concerning aspirin, the vials were left for only 2 hours at a temperature 25±0.5 °C to avoid hydrolysis of the drug. At the end of this time, the content of each vial was filtered through a Double Rings® filter paper (qualitative No. 102).

Table 2: Testing Conditions of Batch Adsorption Studies

Drug (Stock concentration mg/100 mL)	Stock solvent (pH)	Working Dilutions mg/mL
Aspirin (300)	acetate buffer (5)	0.1 – 3
Furosemide (50)	0.01 N NaOH (12.1)	0.1 – 1

2.2. 5. Analysis of adsorption studies

The residual concentration of each drug in the filtrate was determined spectrophotometrically at their respective wave length of maximum absorbance, λmax after appropriate dilution with the corresponding solvent. Each batch experiment consisted of three parallel runs. The equilibrium adsorption capacity qe (mg/g) of each adsorbent for each drug concentration at equilibrium and the removal rate (adsorbed percentage) were calculated as in the following equations, 1 and 2 (11):

$$q_e = (C_o - C_e)V/W \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

$$\text{"Removal \%"} = [(C_o\text{-}Ce)/C_o] \times 100 \ldots\ldots\ldots\ldots (2)$$

where C_o and Ce are the initial and equilibrium drug concentrations (mg/L), respectively, V is the solution volume (L), and W is the weight of adsorbent per one liter of solution (g/L).

2.2.6. Adsorption isotherms

Adsorption isotherm models were used to understand the adsorption mechanism and the energy involved in adsorption process [12]. In any single component isotherm study, determining the best-fitting model is a key analysis to mathematically describe the involved sorption system. [13]. In general, the modeled adsorption isotherm is an invaluable non-linear curve describing the adsorption phenomenon at a constant temperature and pH. On the other hand, linearization of isotherm models is an alternative easier mathematical approach to predict the overall adsorption behavior [14, 15]. Four two-parameter isotherm models were used in this study to fit the adsorption data applying both linear and non-linear regression; Langmuir, Freundlich, Dubinin–Radushkevich, and Temkin.

a. Langmuir model

The Langmuir model can be used to describe monolayer coverage where the adsorbed layer is one molecule in thickness [16]. It allows for the evaluation of the maximum adsorption capacity (qm), which is normally used to compare the efficiencies of adsorbents with which have been tested for the adsorption of drugs. The non-linear expression of Langmuir isotherm model can be illustrated as in equation [4] [17]:

$$q_e = q_m K_L \frac{C_e}{1+K_L C_e} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3)$$

where qe (mg/g) is the amount of adsorbate at equilibrium bound per unit mass of adsorbent, Ce (mg/L) is the concentration of adsorbate remaining in solution at equilibrium, qm (mg/g) is the maximum adsorption capacity to form a complete monolayer on the surface.bound at high Ce, and K_L (L/mg) is the Langmuir constant, which is associated with the energy of adsorption. The linear form of Langmuir isotherm known as Scatchard's linearization (linearization I) can be presented as [15, 18]:

$$\frac{C_e}{q_e} = \frac{1}{q_m K_L} + \frac{C_e}{q_m} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (4)$$

The plot of Ce/qe versus Ce usually leads to very good model fits to the experimental data and is usually selected as the best linear form of the Langmuir isotherm [18].

The essential characteristics of the Langmuir isotherm can be expressed by a dimensionless constant referred to as the separation factor or equilibrium parameter R_L which is calculated using the following equation [19]:

$$R_L = \frac{1}{1+K_L C_o} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (5)$$

where K_L is Langmuir constant (L/mg) and C_o is initial concentration of adsorbate (mg.g^{-1}). R_L values indicate the adsorption to be unfavorable when $R_L > 1$, linear when $R_L = 1$, favorable when $0 < R_L < 1$, and irreversible when $R_L = 0$.

b.

b. Freundlich model

The Freundlich model assumes multilayer adsorption that occurs on a heterogeneous surface, suggesting that binding sites are not equivalent. The non-linear form of the isotherm is generally given as [20]

$$q_e = K_f C_e^{1/n} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (6)$$

where K_f [mg/g(L/mg)$^{1/n}$] and n are Freundlich isotherm constants. The constant K_f is the measure of adsorption capacity, and 1/*n* is the measure of adsorption intensity; when the amount lies between 0 and 1, this shows equal adsorption opportunities and energies for all active sites [21]. A value for 1/n above one is indicative for a cooperative adsorption [22] . The Freundlich exponent, *n*, should have a value lying in the range of 1–10 for classification as favorable adsorption [23].The linear form of the

equation is used to determine the Freundlich parameters ($\log q_e$ versus $\log C_e$) [18]:

$$\log q_e = \log K_f + \frac{1}{n}\log C_e \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots (7)$$

c. Dubinin-Radushkevich (D-R) model

The Dubinin-Radushkevich isotherm is an empirical model which was initially formulated for the adsorption process following a pore filling mechanism. It is generally applied to express the adsorption process and determine the maximum monolayer adsorption capacity onto both homogeneous and heterogeneous surfaces [11]. A characteristic feature of the D-R isotherm is the fact that it is temperature dependent; hence when adsorption data at different temperatures are plotted as a function of logarithm of amount adsorbed versus the square of potential energy, all suitable data can be obtained [12]. The non-linear expression of D-R isotherm model can be illustrated as [24]

$$q_e = q_D \exp(-K_D \varepsilon^2) \quad \ldots\ldots\ldots\ldots\ldots\ldots (8)$$

Where q_D is the theoretical maximum capacity (mg/g), K_D is the D–R model constant which is related to the mean free energy of adsorption $(\text{mol/kJ})^2$, ε is the Polanyi potential and is equal to:

$$\varepsilon = RT \ln\left(1 + \frac{1}{C_e}\right) \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots (9)$$

R (8.314 J/mol.K) is the gas constant; and T is the absolute temperature (K: Kelvin). The linear form of the isotherm can be expressed as follows:

$$\ln q_e = \ln q_D - K_D \varepsilon^2 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots (10)$$

by plotting $\ln q_e$ against ε^2, the D-R constants of K_D and q_D can be obtained. The mean energy of adsorption, E_D (kJ/mol), is calculated as follows:

$$E_D = \frac{1}{\sqrt{2K_D}} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (11)$$

The D-R isotherm can be employed to determine if adsorption had occurred by physical or chemical process. The magnitude of E_D is useful for estimating the type of the adsorption process: physical (1-8 kJ/mol), ion exchange (9–16 kJ/mol) and chemical (>16 kJ/mol) [25].

d. Temkin model

Temkin isotherm is useful for estimating the heat of adsorption (25, 26). The non-linear form of Temkin is expressed by the following relationship:

$$q_e = \frac{RT}{b_t} \ln K_t . C_e \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots (12)$$

where K_t (L/g) is Temkin isotherm constant corresponding to the maximum binding energy, b_t (J/mol) is a constant related to heat of adsorption. The Temkin isotherm has generally been applied in the following linear form [22]:

$$q_e = \frac{RT}{b_t} \ln K_t + \frac{RT}{b_t} \ln C_e \quad \ldots\ldots\ldots\ldots\ldots\ldots (13)$$

A plot of q_e versus $\ln C_e$ enables the determination of the isotherm constants K_t, b_t from the slope and intercept.

2.2.7. Statistical analysis of adsorption isotherms data

All the model parameters were evaluated by both non-linear weighted least squares regression and linear regression using Microsoft Excel software. Non-linear weighted least squares regression seeks to minimize the sum of the squared errors (SSE) between observed and calculated values of the dependent variable, in this case the adsorbed concentration, qe [27]:

$$SSE = \sum_{i=1}^{N} w_i \left[q_{exp} - q_{cal}\right]^2 \quad \ldots\ldots\ldots\ldots\ldots\ldots (14)$$

Where SSE is the objective function to be minimized, N is the number of observations, w_i is the i^{th} weighting factor, q_{exp} is the i^{th} experimental (measured) value of the dependent variable, and q_{cal} is the i^{th} model-predicted value of the dependent variable. Therefore, assessing the ability of a model to describe a data set was based on also the corrected Akaike's Information Criterion (AIC_c) and the coefficient of determination (r^2) were used to determine the best-fitting isotherm to the experimental data. The coefficient of determination statistic (or model efficiency) is considered by many to be the best overall indicator of model goodness-of-fit [15].

A correlation coefficient of 1 indicates a perfect fit to the data, whereas a correlation coefficient value of <0 indicates that taking the average of all the measured values would give a better prediction than the model [28]. The coefficient of determination was calculated as:

$$r^2 = 1 - \frac{\sum(q_{exp} - \bar{q}_{cal})^2}{\sum(q_{exp} - q_{cal})^2} \quad \ldots\ldots\ldots\ldots\ldots (15)$$

where q_{exp} and q_{cal} are the experimental and model-predicted values of the equilibrium adsorbate concentration, respectively. $\bar{q}_e$ is the mean of measured adsorption equilibrium values. The AIC_c is calculated by the following equation:

$$AIC_c = N \ln\left(\frac{SSE}{N}\right) + 2(p+1) + \frac{2(p+1)(p+2)}{N-p-2} \quad \ldots\ldots\ldots\ldots (16)$$

where N is the number of data points in the isotherm (data sample size) and p is the number of fitted parameters. The model with the lowest AIC_c is considered to be the most likely to be correct (15, 29). Since results of non-linear regression were used to choose the best model fit, SSE and AIC_c were calculated for results of non-linear analysis only.

3. RESULTS & DISCUSSION

3.1. SOLUBILITY STUDIES

3.1.1. Solubility measurement of drugs

Poor aqueous solubility scan be altered by addition of other agents or by various factors (30, 31). Therefore, the solubility of amiodarone, aspirin, and furosemide was determined in the absence and presence of other drugs which were frequently given concomitantly in the cardiovascular patients and are

known to cause potential pharmacological DDIs. **(Table 3)** shows the measured pH of solutions.

Table 3: pH of tested drug solutions after 24 hs

Drugs in solution	pH
Amiodarone 10 mg	3.38
Amiodarone 10 mg + Lidocaine 10 mg	3.70
Amiodarone 10 mg + Theophylline 10 mg	3.49
Amiodarone 10 mg + Warfarin 1 mg	3.34
Aspirin 87.5 mg	2.47
Aspirin 87.5 mg + Spironolactone 25 mg	2.47
Aspirin 87.5 mg + Spironolactone 25 mcg	2.45
Furosemide 5 mg	3.45
Furosemide 5 mg + Gentamicin 10mg	3.75
Furosemide 5 mg + Gentamicin 20mg	3.85

Table 4. Solubility of aspirin in absence and presence of spironolactone

Solubility of Aspirin ± SD (mg/mL) (n=3)			
Time (hs)	**Alone**	**+25mg Spironolactone**	**+25mcg Spironolactone**
0.25	6.72 ± 1.21	5.48 ± 0.95	7.22 ± 1.07
0.50	7.98 ± 0.97	6.94 ± 0.82	9.42 ± 1.05
1	9.57 ± 0.57	8.61 ± 0.82	4.77 ± 0.85
2	6.46 ± 0.36	9.35 ± 0.65	7.08 ± 1.55
4	6.25 ± 1.09	11.25 ± 0.77	7.22 ± 1.18
6	10.85 ± 0.3	11.40 ± 0.55	8.49 ± 0.85
8	11.10 ± 0.5	11.40 ± 0.65	10.50 ± 1.23
12	8.62 ± 0.75	11.40 ± 0.54	11.90 ± 0.91
24	13.64 ± 1.1	12.36 ± 0.61	13.56 ± 1.05
48	15.30 ± 1.5	12.40 ± 0.61	12.00 ± 1.51

a. Aspirin + Spironolactone

From the obtained data displayed in **(Table 4)**, it can be observed that the solubility profile of aspirin in presence of 25 mg spironolactone was completely different as compared to aspirin's solubility profile alone although change in the extent of solubility was statistically insignificant. A Fourier-transform infrared (FT-IR) spectrum was run to interpret solubility results. **(Figure 1)** shows the FT-IR spectrum of aspirin, spironolactone and a 1:1 physical mixture of both. There was no change in the fingerprint region of either drug.

Once administered, aspirin (acetyl salicylic acid) is readily absorbed and rapidly hydrolyzed to salicylic acid, which is the active agent responsible for its main therapeutic effects [32, 33]. This could explain the erratic solubility behavior of aspirin. The presence of an insoluble clinically equivalent concentration of spironolactone (25 mg/ 5mL) prevented this behavior and aspirin reached solubility equilibrium after about 4 hours. While at a lower soluble concentration of spironolactone (25 µg/5mL), the solubility profile of aspirin was almost unchanged. An infrared (IR) spectrum was run between a 1:1 physical mixture of aspirin and spironolactone to exclude the formation of a new complex. The presence of spironolactone did not alter the pH of the solution. As shown in the IR spectra in figure 1, the effect of spironolactone was not a result of complex formation. Consequently, such solubility profile might be explained by physical interactions between both drugs where insoluble spironolactone physically reduced the hydrolysis of aspirin. So spacing administration of both aspirin and spironolactone could be considered. In general, there is no need to avoid concurrent use, but if the diuretic response to spironolactone is less than expected this interaction should be considered as a cause [34, 35].

b. Furosemide + Gentamicin

The solubility of furosemide in presence of gentamicin was reduced **(Table 5).** However, this decrease in solubility was not statistically significant. FT-IR spectra in **(Figure 2)**, shows that both drugs did not form any complexes when physically mixed.

Variable compatibility results have been reported for the IV combination of furosemide and gentamicin possibly due to differing drug concentrations and/or testing methodologies [35, 36]. Since furosemide is a weak acid (reported acidic pKa 3.48), with a carboxylic acid functional group, its aqueous solubility increases as a function of medium pH [37]. Furosemide is soluble in alkaline solutions and is prepared as a mildly buffered alkaline product. It can usually be mixed with infusion solutions that are neutral or weakly basic (pH 7 to 10) and with some weakly acidic solutions that have a low buffer capacity. It should not be mixed with acidic solutions having a pH below 5.5 [38]. In the current study, the addition of gentamicin sulfate to furosemide in distilled water slightly raised the pH of the solution. However, the reduction in furosemide solubility was statistically insignificant. In this case, the solubility reduction was probably due to a salting out effect by gentamicin sulfate which is soluble in water and not a result of alteration in pH. Salting out of weak electrolytes may result from the removal of water molecules that can act as solvent because of competing hydration of the added more soluble ion [1].

Concurrent use should be avoided systemically as it may result in increased gentamicin plasma and tissue concentrations and additive ototoxicity and/or nephrotoxicity. It is generally advised that aminoglycosides should not be used with other drugs that may cause ototoxicity or nephrotoxicity, such as etacrynic acid

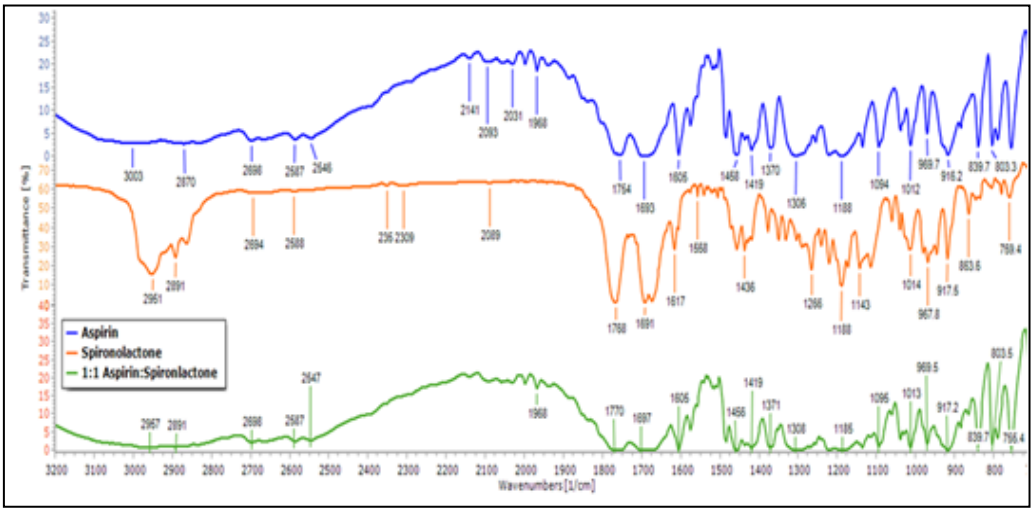

Figure 1: FT-IR of aspirin, spironolactone and 1:1 physical mixture of aspirin and spironolactone

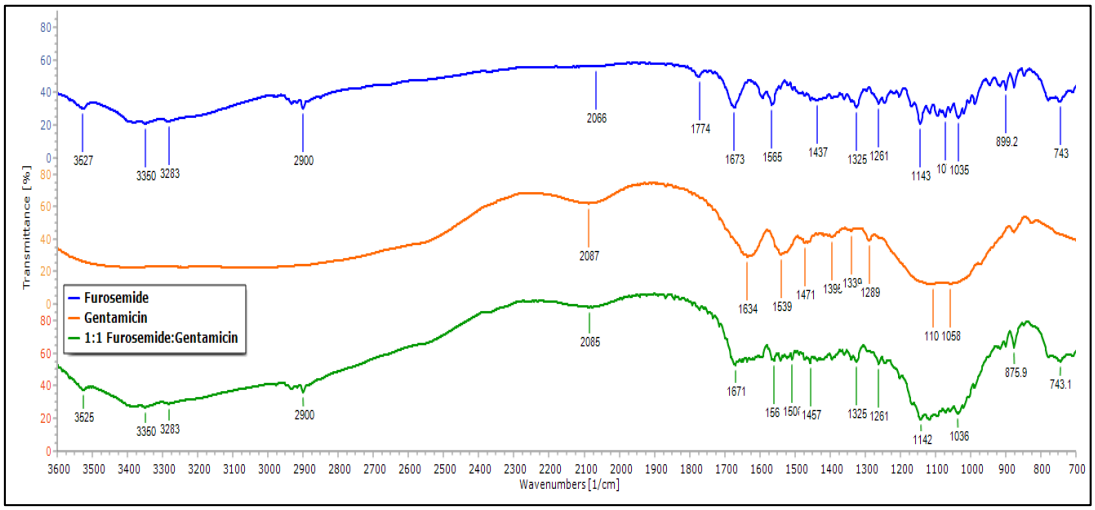

Figure 2: FT-IR of furosemide, gentamicin and 1:1 physical mixture of furosemide and gentamicin.

Table 5: Solubility of Furosemide in absence and presence of gentamicin

Solubility of Furosemide ± SD (mcg/mL) (n=3)			
Time (hs)	**Alone**	**+ 10 mg Gentamicin**	**+ 20 mg Gentamicin**
0.25	113.1 ± 8.35	163.1 ± 9.22	73.0 ± 10.50
0.50	181.9 ± 11.12	208.2 ± 12.97	161.9 ± 9.23
1	224.5 ± 12.33	213.6 ± 12.24	207.2 ± 14.05
2	196.3 ± 12.03	231.4 ± 10.55	186.9 ± 11.23
4	222.5 ± 13.12	238.9 ± 11.05	174.5 ± 12.13
6	232.4 ± 10.87	225.3 ± 9.11	198.3 ± 10.56
8	226.9 ± 11.11	237.8 ± 13.33	199.1 ± 10.33
12	235.9 ± 13.04	245.7 ± 12.31	207.2 ± 11.12
24	294.3 ± 10.31	269.6 ± 10.45	241.8 ± 10.17
48	294.3 ± 11.07	277.9 ± 9.43	241.5 ± 11.32

c. Amiodarone + Warfarin/ Theophylline/ Lidocaine

As evident in **(Table 6)** amiodarone exhibited lower water solubility at tested time intervals in the presence of all tested drugs; lidocaine, theophylline and warfarin. FT-IR spectra of amiodarone alone and in physical mixtures with all other three drugs indicate no complex formation **(Figures 3 (a, b, c))**. Lower amiodarone solubility in the presence of warfarin was statistically insignificant but was statistically significant in presence of theophylline and lidocaine. Scores of amiodarone solubility alone (mean rank=13.1) were significantly higher than for its solubility in presence of theophylline (mean rank=7.9), U=24, z=-1.97, p=0.049. Similarly, the scores of amiodarone solubility alone (mean rank=15.2) were significantly higher than for its solubility in presence of lidocaine (mean rank=5.8), U=3, z=-3.55, p<0.001.

Amiodarone has become the most widely prescribed antiarrhythmic because of its wide spectrum of efficacy and relative safety in patients with structural heart disease [39]. Although amiodarone can slow the ventricular response in atrial fibrillation, it should be used only after digoxin, beta-blockers, and calcium channel antagonists are ineffective, contraindicated, or not tolerated [40, 41]. Amiodarone may produce drug interactions with warfarin, digoxin, procainamide, and quinidine [42]. It has been suggested that the dosage of these drugs be reduced empirically by 50% when amiodarone is added and that QT and QRS intervals be monitored for excessive prolongation [40]. Concurrent use of amiodarone and theophylline may result in theophylline toxicity (nausea, vomiting, palpitations, and seizures). Theophylline serum concentrations should be closely monitored when amiodarone is added discontinued, or when dosing changes occur. Amiodarone may also increase the serum concentration of lidocaine through inhibition of CYP3A4 isozymes. Due to the long-half-life of amiodarone, this interaction is possible even after discontinuation of amiodarone. If coadministration is required, a reduced lidocaine dose should be initially used and toxicity carefully monitored [35].

Amiodarone is very slightly soluble in water (0.7 in 1 of water) [21]. All three tested drugs had little effect on the pH of the solution however; lidocaine increased the pH by 0.32 points. Theophylline is a weak basic drug with a pKa of 8.81 [43] which is higher than that of amiodarone, 6.56. Theophylline is reported to have a water solubility that is ten times (7.36 mg/ml) that of amiodarone (0.7 mg/ml) at 25 °C .As the pH of amiodarone solution was only slightly increased by the addition of theophylline, this suggests that reduced solubility is a result of a salting out mechanism. The significant reduction of amiodarone's solubility after addition of lidocaine hydrochloride could be explained by the salting out effect of lidocaine hydrochloride. Solubility of lidocaine hydrochloride is reported to be 0.68 g/ml in water at 25 °C [44]. Few studies examined the parenteral compatibility of amiodarone hydrochloride with theophylline which reported both drugs to be physically compatible [33].

3.2. ADSORPTION STUDIES

3.2.1. Analysis of adsorption data

The adsorption of selected drugs of aspirin and furosemide on commercial activated charcoal, a bile-binding resin, an antidiarrheal, an antacid and a dietary fiber have been studied. **(Table 7)** shows the percent of the drug adsorbed (constant initial concentration) per the specified amount of added adsorbent. Results recorded are the average of the triplicate adsorption runs. Under the adsorption conditions of the study, activated charcoal considerably adsorbed all the tested drugs.

3.2.2. Adsorption isotherms and parameters

Linear and non-linear fitting plots of Langmuir, Freundlich, Dubinin -Radushkevich and Temkin isotherm models for different adsorbents Non-linear regression plots compared different non-linear mathematical expressions of isotherms with experimental data for tested drugs on corresponding adsorbents.

Table 6: Solubility of amiodaone in absence and presence of lidocaine, theophylline and warfarin

Solubility of Amiodarone ± SD (mcg/mL)				
Time (hs)	**Alone**	**+ 1 mg Warfarin**	**+ 10 mg Theophylline**	**+ 10 mg Lidocaine**
0.25	198.53 ± 12.11	157.94 ± 9.47	199.71 ± 11.17	104.41 ± 8.97
0.50	312.65 ± 13.21	201.5 ± 12.02	241.5 ± 9.51	165.59 ± 10.23
1	316.2 ± 10.37	200.88 ± 13.76	240.9 ± 12.31	157.35 ± 10.53
2	352.1 ± 12.34	222.65 ± 10.65	311.5 ± 11.15	166.76 ± 10.23
4	413.24 ± 12.55	315 ± 12.01	312.1 ± 11.25	129.71 ± 9.07
6	436.76 ± 12.03	336.18 ± 11.33	296.2 ± 12.03	170.88 ± 9.66
8	376.18 ± 12.98	360.88 ± 11.51	315.7 ± 10.67	191.47 ± 11.24
12	437.94 ± 13.22	359.71 ± 11.12	336.8 ± 13.44	237.35 ± 10.07
24	512 ± 11.32	410.88 ± 10.15	398.53 ± 11.43	237.35 ± 10.15
48	570.3 ± 13.77	484.4 ± 12.58	448.53 ± 10.11	202.06 ± 11.01

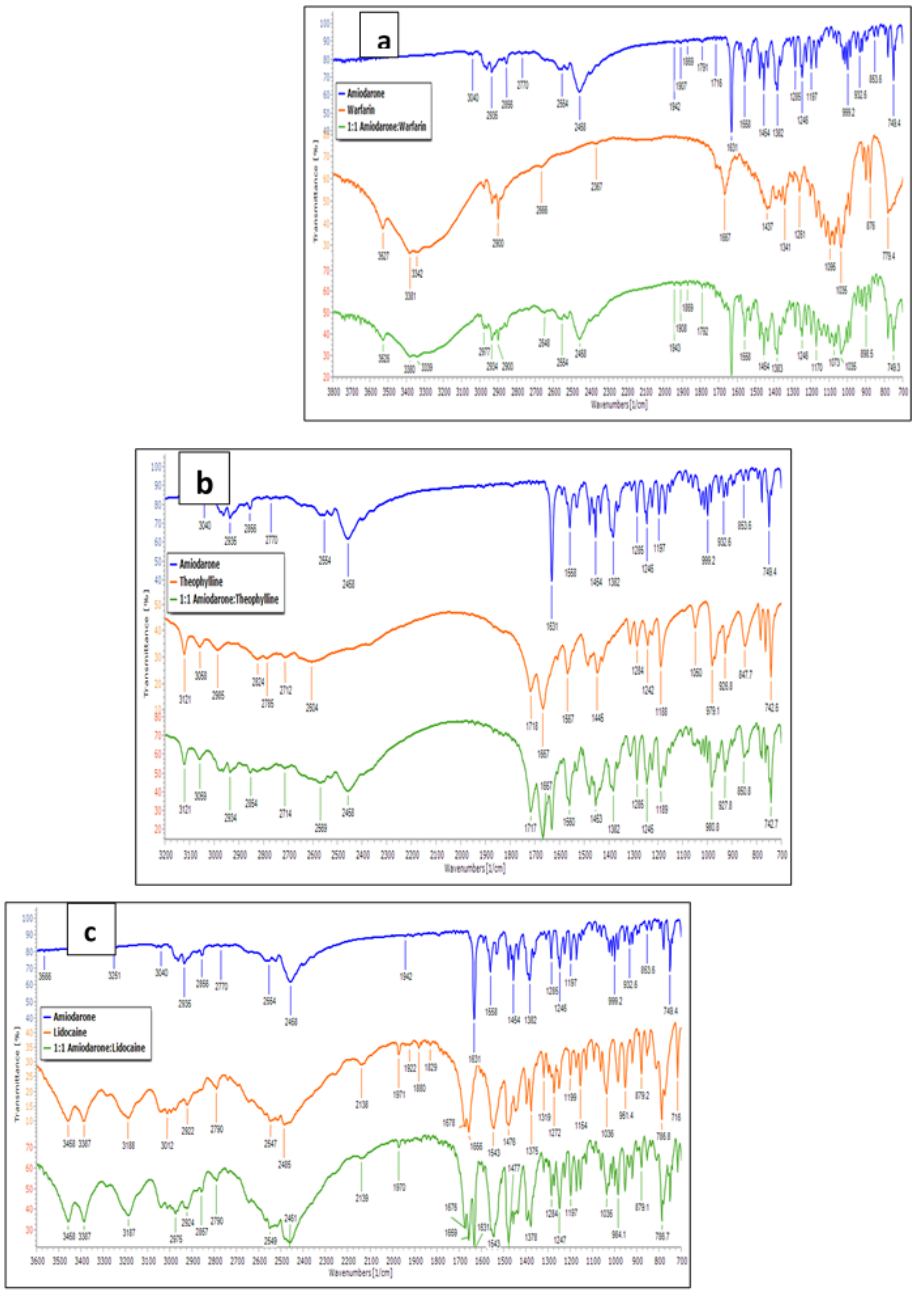

Figure 3(a): FT-IR of amiodarone, warfarin and 1:1 physical mixture of amiodarone and warfarin**. (b):** FT-IR of amiodarone, theophylline and 1:1 physical mixture of amiodarone and theophylline **(c):** FT-IR of amiodarone, lidocaine and 1:1 physical mixture of amiodarone and lidocaine

Table 7: Percent adsorbed of constant drug concentration per constant amount of adsorbent

Drug mg/100 mL	**Mean of percent (%) adsorbed per added adsorbent (g/10 mL)**				
	Activated charcoal	**Kaolin**	**Cholestyramine**	**Aluminium hydroxide**	**Sodium alginate**
Aspirin 100	76.66 ± 7.42/ (0.1)	- / (0.025)	31.14 ± 2.7/ (0.005)	- / (0.05)	- / (0.025)
Furosemide 50	45.72 ± 2.23/ (0.005)	6.6 ± 1.51/ (0.025)	95.14 ± 0.56/ (0.005)	10.3 ± 0.89/ (0.05)	18.2 ± 1.93/ (0.025)

Isotherm parameters derived from linearized and non-linearized fitting of data to Langmuir, Freundlich, Dubinin -Radushkevich and Temkin isotherms include isotherms constants for each fitted model as well as the adsorption capacities, coefficients of correlation (r2), SSE and AICc values.

The mechanism of uptake of drugs by solid adsorbents is mainly dependent on the physicochemical properties of both the adsorbents and the drugs in the tested medium [45]. The results of the present in vitro experiments indicate that activated charcoal had the capacity to adsorb all the tested drugs under the utilized experimental conditions of temperature, pH and amount of adsorbent added.

The values of the separation factor RL for initial concentrations of adsorbates, were over 0 and less than 1 which indicates the favorable adsorption among the studied adsorbent-adsorbate pairs under the conditions of the current study. The Freundlich exponent, n, for tested drugs pairs had a value between1–10 which denotes favorable adsorption.

a. Aspirin

Aspirin is a weak acid with a pKa value of 3.5 [46]. In the current study, aspirin was not adsorbed onto kaolin, aluminum hydroxide or sodium alginate, but was adsorbed onto activated charcoal, and with a greater capacity onto cholestyramine. Detailed adsorption data of aspirin onto both activated charcoal and cholestyramine are presented in **(Table (Supplement))** and plotted by linear regression in **(Figures 4 & 5**).

Aspirin possesses one aromatic ring which is reported to be involved in the formation of electron donor–acceptor complexes, where the basic surface oxygen and/or carbon surface electron rich regions of activated charcoal act as donors and the aromatic ring of the adsorbate serves as an acceptor [47]. Besides, aspirin has two characteristic polar groups: one hydroxyl (OH) and one carboxylic group. Equilibrium adsorption data on activated charcoal fitted well to the four isotherms (r2 > 0.8), where Langmuir was a better fit than Freundlich isotherm. This suggests monolayer coverage of aspirin molecules on activated charcoal surface. The value of the Freundlich constant n was significantly higher than unity indicating that the biosorption behavior of aspirin can be considered as favorable. Temkin isotherm proved to be a better model in explaining sorption energies as it showed better goodness of fit parameters compared to D-R **(Figure 6a).**

At the studied pH [5] of acetate buffer, aspirin is ionized. The cholestyramine-aspirin interaction is electrostatic in nature where the chloride ions of the resin being exchanged for the anions of the drug in solution. The interaction takes place between the carboxyl group of the ionized drug and the quaternary ammonium group of the positively charged resin. As exhibited in **(Figure 6b)**, a plot of the amount of adsorbate at equilibrium bound per unit mass of adsorbent qe (mg/g) against the concentration of adsorbate remaining in solution at equilibrium Ce (mg/L) yielded an "L" shape curve. This implies either that the adsorbed aspirin molecules are not vertically

Table: Adsorption data for *ASPIRIN*

Activated charcoal												
C_0 mg/L	**C_e mg/L**	**q_e(x/m) mg/g**	**ln C_e**	**ln qe**	**1/C_e**	**1/q_e**	**log C_e**	**log q_e**	**C_e/q_e**	**ε^2 J^2/mol^2**	**% Adsorbed**	**R_L**
300	44.33	25.567	3.791662	3.241302	0.022558	0.039113	1.646698	1.40768	1.733876	3308.736	85.22	0.404858
600	47.3	55.27	3.85651	4.01223	0.021142	0.018093	1.674861	1.742489	0.855799	2910.312	92.12	0.253807
900	94.7	80.53	4.550714	4.38863	0.01056	0.012418	1.97635	1.905958	1.175959	733.6648	89.48	0.184843
1200	177.26	102.274	5.177618	4.627655	0.005641	0.009778	2.248611	2.009765	1.733187	210.4252	85.23	0.145349
1500	292.85	120.715	5.679661	4.793432	0.003415	0.008284	2.466645	2.081761	2.425962	77.26668	80.48	0.11976
1800	457.15	134.285	6.125012	4.899964	0.002187	0.007447	2.660059	2.128028	3.404327	31.74659	74.60	0.101833
2100	643.89	145.611	6.467528	4.980939	0.001553	0.006868	2.808812	2.163194	4.421987	16.01276	69.34	0.088574
2400	771.67	162.833	6.648557	5.092725	0.001296	0.006141	2.887432	2.211742	4.739027	11.15162	67.85	0.07837
2700	986.48	171.352	6.894143	5.14372	0.001014	0.005836	2.994088	2.233889	5.757038	6.825697	63.46	0.070274
3000	1219.81	178.019	7.10645	5.18189	0.00082	0.005617	3.086292	2.250466	6.852134	4.465019	59.34	0.063694
Cholestyramine												
C_0 mg/L	**C_e mg/L**	**q_e(x/m) mg/g**	**ln C_e**	**ln qe**	**1/C_e**	**1/q_e**	**log C_e**	**log q_e**	**C_e/q_e**	**ε^2 J^2/mol^2**	**% Adsorbed**	**R_L**
100	66.56	66.88	4.198104	4.2029	0.015024	0.014952	1.823213	1.825296	0.995215	1478.606	33.44	0.959693
200	132.11	135.78	4.883635	4.911036	0.007569	0.007365	2.120936	2.132836	0.972971	378.1074	33.945	0.922509
300	199.89	200.22	5.297767	5.299417	0.005003	0.004995	2.300791	2.301507	0.998352	165.5821	33.37	0.888099
400	287.3	225.4	5.660527	5.417877	0.003481	0.004437	2.458336	2.352954	1.274623	80.27548	28.18	0.856164
500	352.85	294.3	5.866043	5.6846	0.002834	0.003398	2.54759	2.46879	1.198947	53.25422	29.43	0.826446
600	405	390	6.003887	5.966147	0.002469	0.002564	2.607455	2.591065	1.038462	40.43732	32.5	0.798722
700	473.52	452.96	6.160194	6.115804	0.002112	0.002208	2.675338	2.65606	1.04539	29.59175	32.35	0.772798
800	534.63	530.74	6.281575	6.274272	0.00187	0.001884	2.728053	2.724882	1.007329	23.21909	33.17	0.748503
900	660.56	478.88	6.493088	6.17145	0.001514	0.002088	2.819912	2.680227	1.379385	15.21535	26.60	0.725689
1000	716.11	567.78	6.573834	6.341734	0.001396	0.001761	2.85498	2.75418	1.261246	12.94786	28.39	0.704225

C_0: the initial concentration of the adsorbate; Ce: the equilibrium concentration of the adsorbent; qe: the amount of adsorbate at equilibrium bound per unit mass of adsorbent; ε: Polanyi potential; RL: separation factor.

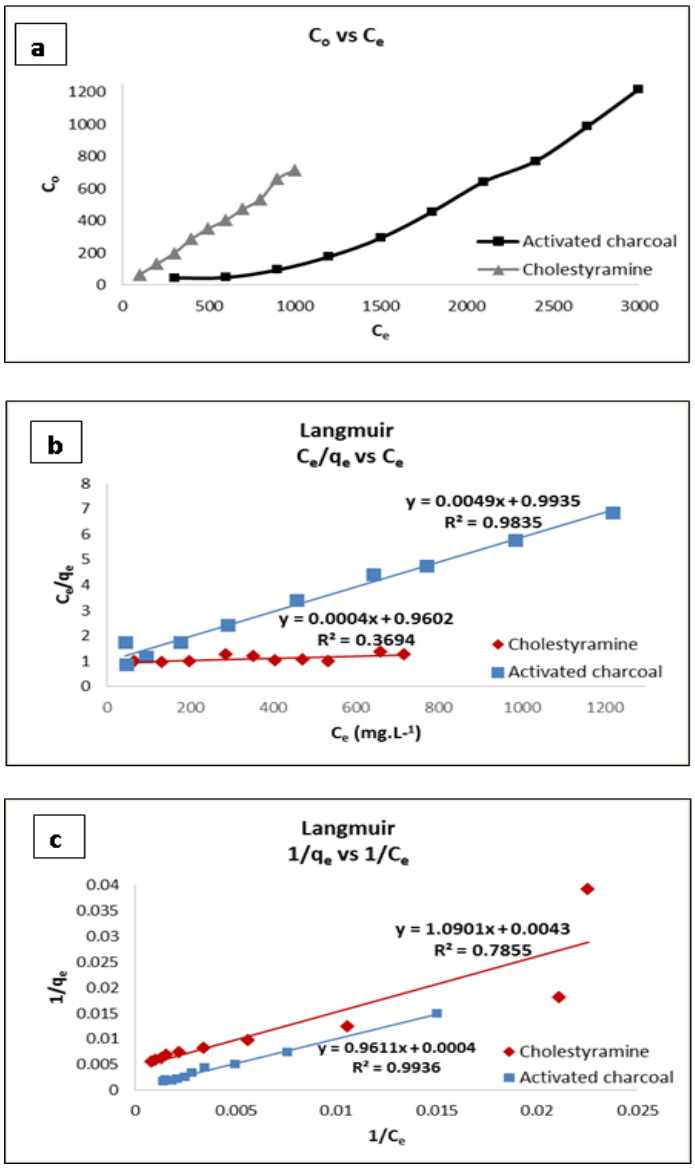

Figure 4: Plots of (**a**) amount adsorbed *vs* initial concentration, (**b**) Langmuir linearization I (**c**) Langmuir linearization II isotherm models for adsorption of ***aspirin*** onto activated charcoal and cholestyramine.

oriented or that there is no strong competition from the solvent [36]. Isotherm analysis shows that the equilibrium data was best represented by the Freundlich equation which suggests a multilayer coverage with a maximum adsorption capacity of about 578 mg/g as calculated by the D-R isotherm .The extremely high maximum adsorption capacity obtained by the Langmuir isotherm indicated that this isotherm was unsuitable for describing the adsorption process.

b. Furosemide

Furosemide, a widely used loop diuretic is a weak acid with an acidic pKa value of 3.9 and is slightly soluble in water [32, 46]. It possesses a carboxylic acid functional group and its aqueous solubility increases as a function of medium pH [37]. The highest adsorption capacity of furosemide was onto cholestyramine followed by activated charcoal as manifested in **(Table (supplement))**. Linear curves onto both these adsorbents are shown in **(Figures 7, 8).**

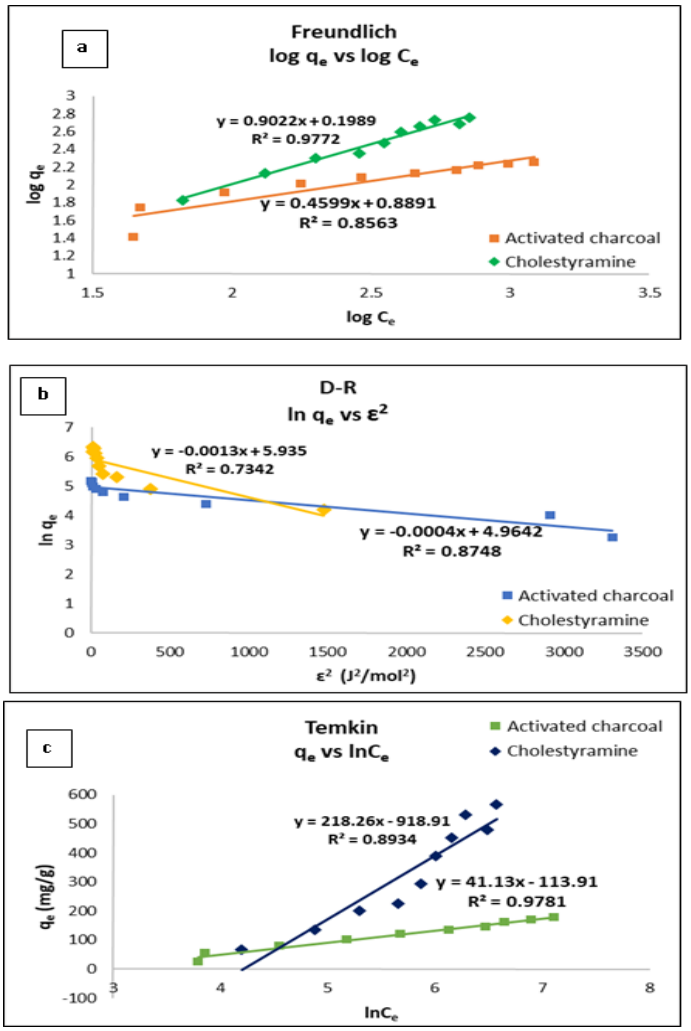

Figure 5: Linear fitting plots of (**a**) Freundlich, (**b**) Dubinin-Radushkevich and, (**c**) Temkin isotherm models for adsorption of ***aspirin*** onto activated charcoal and cholestyramine.

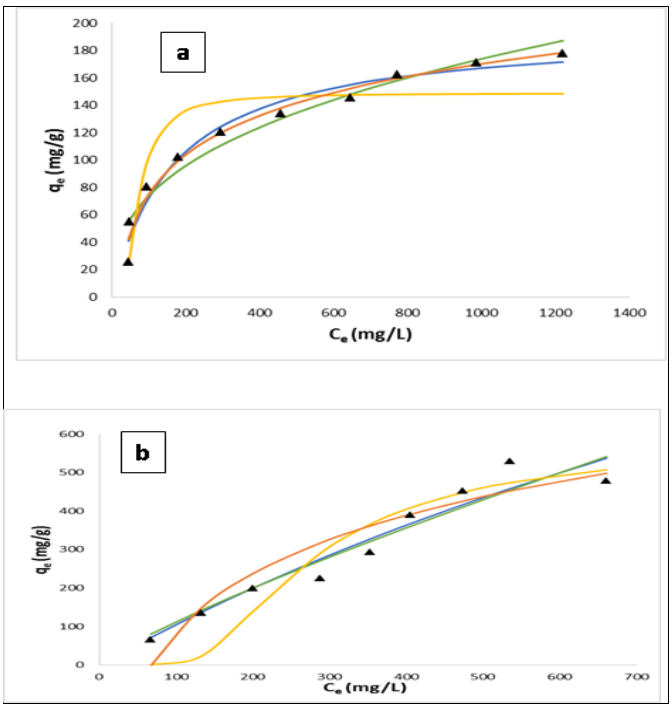

Figure 6: (a). Equilibrium isotherms for the adsorption of aspirin onto activated charcoal, **(b).** Equilibrium isotherms for the adsorption of aspirin onto cholestyramine

Table: Adsorption data for *FUROSEMIDE*

Activated charcoal												
C_0 mg/L	**C_e mg/L**	**q_e(x/m) mg/g**	**ln C_e**	**ln qe**	**1/C_e**	**1/q_e**	**log C_e**	**log q_e**	**C_e/q_e**	**ε^2 J^2/mol^2**	**% Adsorbed**	**R_L**
100	19.16	161.68	2.952825	5.085619	0.052192	0.006185	1.282396	2.208656	0.118506	17210.12	80.84	0.33557
200	52.72	294.56	3.964995	5.685483	0.018968	0.003395	1.721975	2.469174	0.178979	2347.683	73.64	0.201613
300	90.59	418.82	4.506344	6.037441	0.011039	0.002388	1.95708	2.622027	0.216298	801.366	69.80	0.144092
400	159.9	480.2	5.074549	6.174203	0.006254	0.002082	2.203848	2.681422	0.332986	258.4388	60.03	0.112108
500	283.66	432.68	5.647776	6.069998	0.003525	0.002311	2.452798	2.636167	0.655588	82.34526	43.27	0.091743
600	351.98	496.04	5.863574	6.206657	0.002841	0.002016	2.546518	2.695517	0.70958	53.51743	41.34	0.07764
700	462.87	474.26	6.137446	6.161756	0.00216	0.002109	2.665459	2.676016	0.975984	30.96764	33.88	0.067295
800	554.95	490.1	6.318878	6.194609	0.001802	0.00204	2.744254	2.690285	1.13232	21.55132	30.63	0.059382
900	615.35	569.3	6.422191	6.344408	0.001625	0.001757	2.789122	2.755341	1.080889	17.53129	31.63	0.053135
1000	727.23	545.54	6.589243	6.301776	0.001375	0.001833	2.861672	2.736827	1.333046	12.55519	27.28	0.048077
Cholestyramine												
C_0 mg/L	**C_e mg/L**	**q_e(x/m) mg/g**	**ln C_e**	**ln q_e**	**1/C_e**	**1/q_e**	**log C_e**	**log q_e**	**C_e/q_e**	**ε^2 J^2/mol^2**	**% Adsorbed**	**R_L**
200	7.18	385.64	1.971299	5.954904	0.139276	0.002593	0.856124	2.586182	0.018618	336.2291	96.41	0.166667
300	14.41	571.18	2.667922	6.347704	0.069396	0.001751	1.158664	2.756773	0.025228	173.0083	95.2	0.117647
400	20.84	758.32	3.036874	6.631105	0.047985	0.001319	1.318898	2.879853	0.027482	120.8556	94.79	0.090909
500	25.2	949.6	3.226844	6.856041	0.039683	0.001053	1.401401	2.977541	0.026537	100.3468	94.96	0.074074
600	27.97	1144.06	3.331133	7.042339	0.035753	0.000874	1.446692	3.058449	0.024448	90.58139	95.34	0.0625
700	31.86	1336.28	3.461351	7.197645	0.031387	0.000748	1.503246	3.125897	0.023842	79.69074	95.45	0.054054
800	43.32	1513.36	3.768614	7.322088	0.023084	0.000661	1.636688	3.179942	0.028625	58.84754	94.59	0.047619
900	46.19	1707.62	3.832763	7.442856	0.02165	0.000586	1.664548	3.232391	0.027049	55.22994	94.87	0.042553
1000	53.71	1892.58	3.983599	7.545696	0.018619	0.000528	1.730055	3.277054	0.028379	47.56798	94.63	0.038462

C_0: the initial concentration of the adsorbate; C_e: the equilibrium concentration of the adsorbent; q_e: the amount of adsorbate at equilibrium bound per unit mass of adsorbent; ε: Polanyi potential; R_L: separation factor.

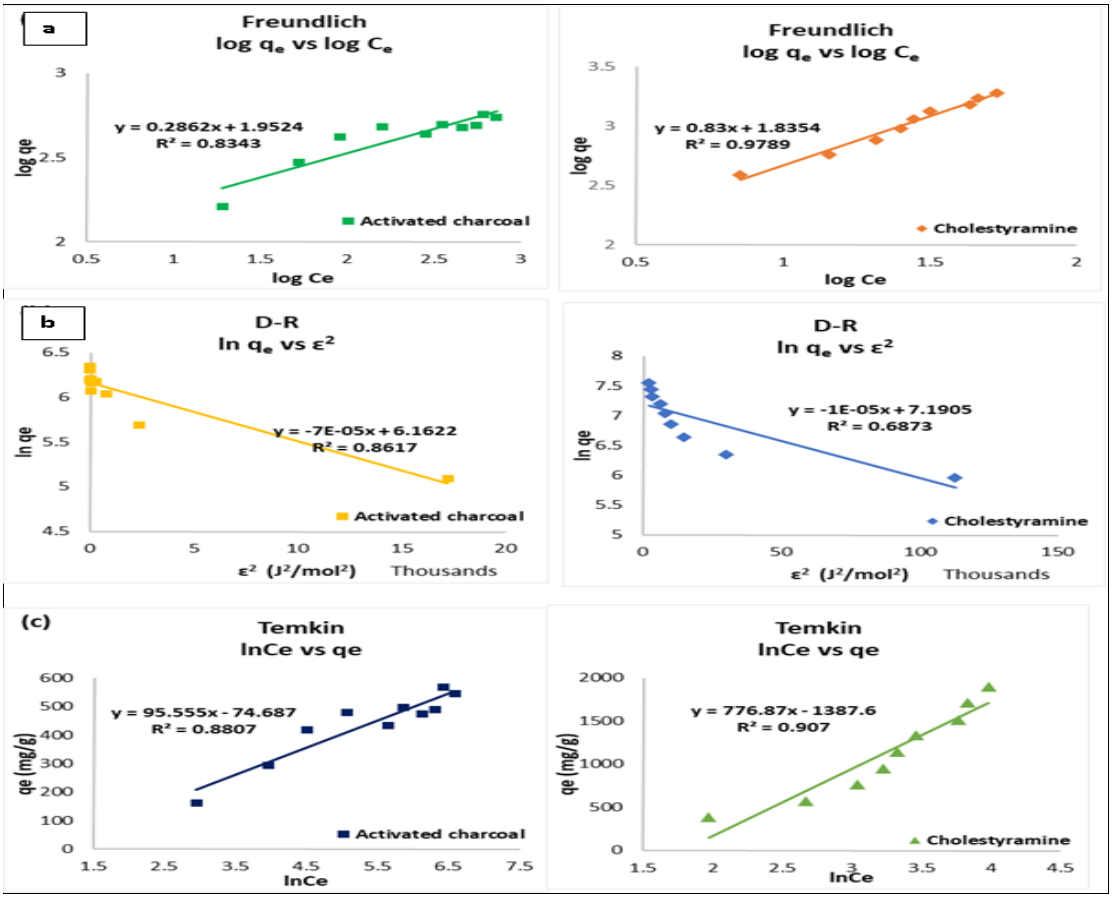

Figure 7: Linear fitting plots of (a) Freundlich, (b) Dubinin-Radushkevich and, (c) Temkin isotherm models for adsorption of furosemide onto activated charcoal and cholestyramine.

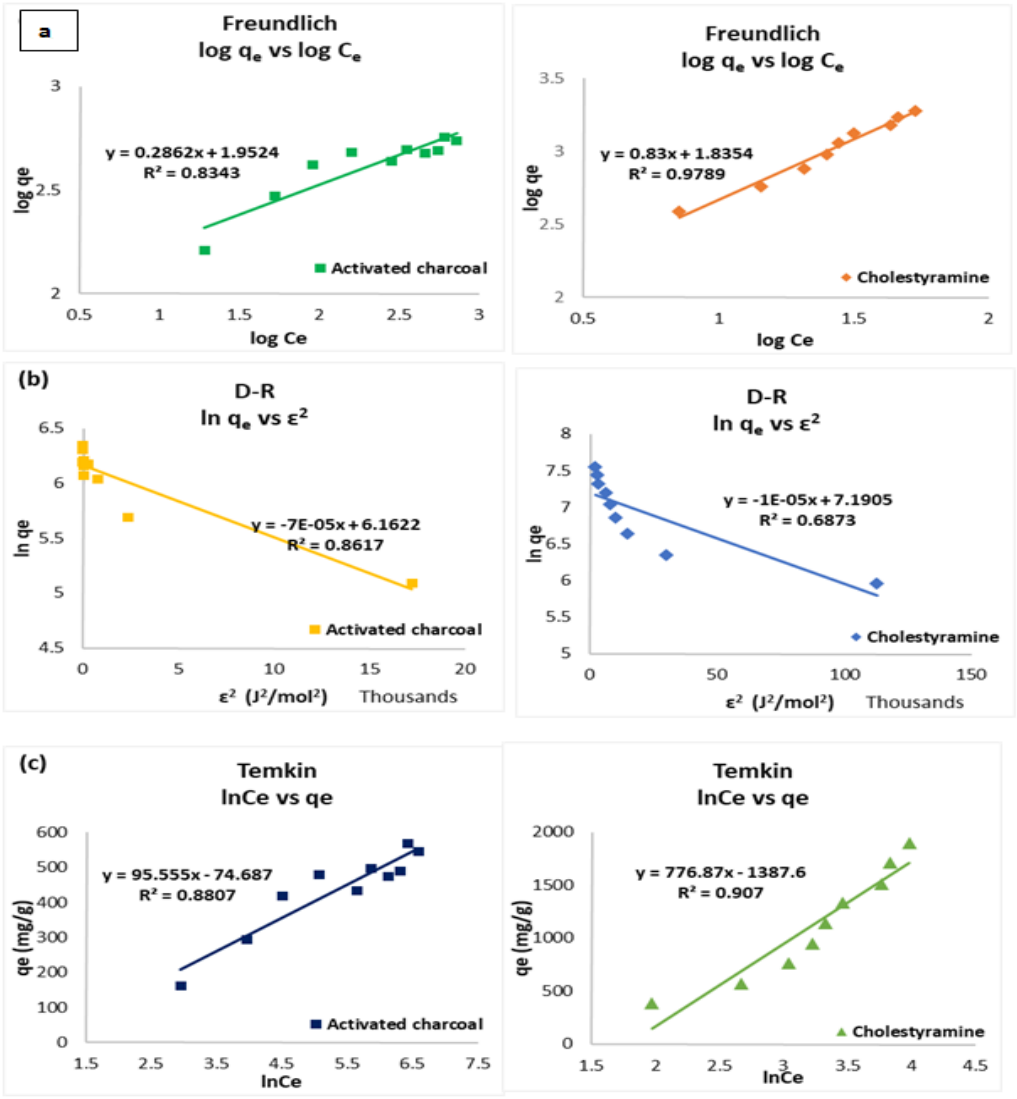

Figure 8: Linear fitting plots of (a) Freundlich, (b) Dubinin-Radushkevich and, (c) Temkin isotherm models for adsorption of furosemide onto activated charcoal and cholestyramine.

The extent of furosemide adsorption decreased as the initial concentration increased. Over 80 % of furosemide was adsorbed at the lowest initial concentration (100 mg/L). The maximum adsorption capacity showed a fair degree of adsorption (qm=555.46 mg/g). At the studied alkaline pH, the carboxyl group of furosemide is expected to be protonated rendering the molecule more polar and thereby may reduce affinity to activated charcoal. However, Furosemide is a hydrophobic molecule that can form hydrophobic bonds between itself and non-polar hydro-carbon molecules [48]. Langmuir isotherm more suitably described the adsorption of furosemide on activated charcoal, whereas Temkin was a better fit for representing the energy of adsorption **(Table 8).**

On the other hand, Cholestyramine adsorbed furosemide significantly where lower initial concentrations of furosemide used during the adsorption experiment disappeared in solution completely. With furosemide being ionized at the high pH of the solution, anion exchange with the resin takes place. The results obtained from the study of the influence of furosemide concentration on adsorption by the resin may be represented by the Freundlich equation **(Table 9).** Although Langmuir

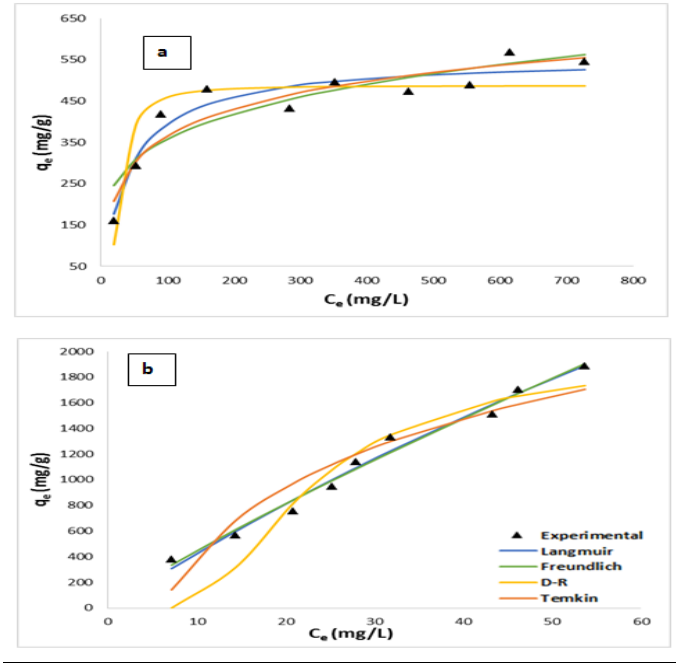

Figure 9: (a) Equilibrium isotherms for the adsorption of furosemide onto activated charcoal (b). Equilibrium isotherms for the adsorption of furosemide onto cholestyramine

Table 8: Isotherm Parameters for Adsorption of *Furosemide* onto *Activated charcoal* Obtained by Linearized and non-Linearized fitting of Data

Isotherm	Linear	Non-linear
Langmuir		
q_e (mg/g)	555.55	555.46
K_L (L/mg)	1.98E-02	2.4E-02
r^2	0.9853	0.9200
SSE		1.1E+04
AIC_c		79.92
Freundlich		
n	3.49	4.39
K_f[mg/g(L/mg)$^{1/n}$]	89.62	125.36
r^2	0.8343	0.8297
SSE		2.32E+04
AIC_c		87.49
Dubinin-Radushkevich		
q_D (mg/g)	474.47	487.07
K_D (mol/kJ)^2	7E-05	9.06E-05
E_D (kJ/mol)	0.1	0.074
r^2	0.8617	0.8021
SSE		2.78E+04
AIC_c		89.29
Temkin		
K_T (L/g)	26.99	26.98
b_T (J/mol)	0.42	0.46
r^2	0.8807	0.8807
SSE		1.61E+04
AIC_c		83.86

q_e: the maximum adsorption capacity; K_L: Langmuir isotherm constant, R_L: separation factor; n, K_f: Freundlich isotherm constants; q_D: the theoretical maximum capacity; K_D: D-R isotherm constant; E_D: mean energy of adsorption; K_T, b_T: Temkin isotherm constants; r^2: coefficient of determination; *SSE*: sum of squared errors; AIC_c: corrected Akaike's Information Criterion.

Table 9: Isotherm Parameters for Adsorption of *Furosemide* onto *Cholestyramine* Obtained by Linearized and non-Linearized fitting of Data

Isotherm	Linear	Non-linear
Langmuir		
q_e (mg/g)		8980.89
K_L (L/mg)	3333.33*	0.0049
r^2	0.017*	0.9827
SSE	0.9604*	3.74E+04
AIC_c		85.79
Freundlich		
n		1.16
K_f[mg/g(L/mg)$^{1/n}$]	1.20	61.51
r^2	68.45	0.9825
SSE	0.9789	3.75E+04
AIC_c		85.81
Dubinin-Radushkevich		
q_D (mg/g)		1994
K_D (mol/kJ)^2	1326.77	6.12E-05
E_D (kJ/mol)	1.E-05	0.0904
r^2	0.224	0.8732
SSE	0.6873	2.72E+05
AIC_c		103.6
Temkin		
K_T (L/g)	0.168	0.168
b_T (J/mol)	3.32	3.32
r^2	0.9070	0.9070
SSE		1.99E+05
AIC_c		100.83

q_e: the maximum adsorption capacity; K_L: Langmuir isotherm constant, R_L: separation factor; n, K_f: Freundlich isotherm constants; q_D: the theoretical maximum capacity; K_D: D-R isotherm constant; E_D: mean energy of adsorption; K_T, b_T: Temkin isotherm constants; r^2: coefficient of determination; *SSE*: sum of squared errors; AIC_c: corrected Akaike's Information Criterion. *Parameters computed by fitting data to Linearization II of Langmuir.

isotherm fitting had better goodness-of-fit values, the isotherm produced an inappropriate q_m with extreme confidence intervals. Plotted data showed an *"S"* shaped curve **(Figure 9b)** which is consistent with the polarity of furosemide in the alkaline solution and the increased adsorption with an average of over 95 %.Concentration of furosemide also decreased to variable degrees in presence of kaolin, aluminium hydroxide and sodium alginate which indicated potential interactions. Adsorption on natural clay nanotubes was investigated for offering sustained release of drugs and chemicals including furosemide [50].

4. Conclusions

It is critical to identify drug solubility and compatibility before ingesting with other drugs or mixing with other solutes and/or solvents in order to avoid changes in bioavailability, development of adverse reactions and toxicities. Spironolactone can affect the hydrolysis of aspirin if co-administered at equivalent clinical doses, and therefore might reduce the efficacy of protective low-dose aspirin. Furosemide can precipitate in the presence of other highly soluble drugs through a salting out effect, or if the pH of the solution is lowered by addition of other acidic drugs or acidic formulations of other drugs. Amiodarone is a drug with low solubility which could be further reduced in presence of other drugs with higher solubility or those which could alter the pH of the media.

The concomitant use of the tested drugs, aspirin and furosemide in this study with the tested adsorbents viz.; activated charcoal, cholestyramine, kaolin, aluminum hydroxide and sodium alginate is dependent upon the chemistry and physical properties of both adsorbents and adsorbates. The experimental data were fitted to four isotherm models by both linear and non-linear regression. Freundlich isotherm provided the best fit for most adsorption data followed by Temkin and Langmuir isotherms. While Langmuir isotherm was shown to be inadequate for fitting all tested adsorption systems onto kaolin and cholestyramine, which indicated that adsorption onto both of these adsorbents, does not follow a monolayer coverage pattern. Surface properties and areas of solids also played an important role in adsorption. Most surfaces of solids are heterogeneous, with the result that adsorption energies were variable. Activated charcoal adsorbed tested drugs. The highest adsorption capacity of activated charcoal and cholestyramine was furosemide.

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