

## Selective Separation and Preconcentration of Caffeine from Natural and Pharmaceutical Products using New Polyurethane Foams

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Two polyurethane foam-based sorbents (PUF) were synthesized by imprinting and grafting techniques and examined for selective separation and preconcentration of caffeine (CAF) in some pharmaceutical products and in black tea. Molecularly imprinted PUF was synthesized based on hydrogen-bonding interactions between CAF and alizarin yellow G (AYG) and subsequent polymerization into PUF. The static experiments indicated optimum sorption conditions at pH=6.5 and 5.5 for imprinted PUF (AY-IPUF) and grafted PUF (AY-GPUF), respectively. In the online experiments, the suitable preconcentration time was found to be 40 and 20s for (AY-IPUF) and (AY-GPUF), respectively, at a flow rate of 1.75 mL.min<sup>-1</sup>. Desorption of CAF has been affected by passing 500 µL of 0.05, 0.01 mol.L<sup>-1</sup> HCl eluent onto (AY-IPUF) and (AY-GPUF), respectively. The online methods have provided satisfactory enrichment factors of 8.4 and 10.5 for (AY-IPUF) and (AY-GPUF), respectively. The time consumed for preconcentration, elution and determination steps was 1.48 and 1.05 min, thus, the throughput was 42 and 57 h<sup>-1</sup>, for (AY-IPUF) and (AY-GPUF), respectively. The developed sorbents were studied for the determination of CAF in pharmaceutical samples which will be helpful to minimize caffeineism. Finally, *in silico* bioactivity, ADMET and drug-likeness predictive computational studies of caffeine were also carried out.

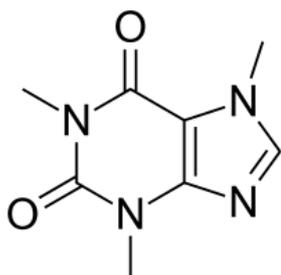
**Keywords:** Polyurethane foam (PUF). Alizarin yellow G. Caffeine separation. Adsorption isotherms. *in silico* screening.

### INTRODUCTION

Caffeine (CAF) or (1,3,7-trimethylxanthine) (Figure 1), is a naturally occurring alkaloid that can be found in coffeaesemen, theaefolium, cacao semen, colaesemen, mate folium and paulliniaecupanae semen (Ivanescu *et al.*, 2016). Due to its pharmacological effects, CAF can also be present in different pharmaceutical products, associated, for example, with aspirin for treatment of headaches, with

ergotamine for the antimigraine effect, with paracetamol and propyphenazone for pain relief or it can be used alone in the treatment of mild respiratory depression (Corciova, Ivanescu, 2016). CAF is a stimulant of the central nervous system that reduces fatigue, increases attention and generates a faster and clearer flow of thoughts (Ruxton, 2008). When CAF is consumed in moderate amounts; it can improve physical performance, so, it is sometimes used as a doping substance by athletes. If it is consumed in large amounts, it can produce constriction of blood vessels, increase the blood pressure and provoke arrhythmia because of the cardiac stimulation (Cristea, 2012; Ogah, Obebe, 2016).

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**FIGURE 1** - Caffeine structure (M.F:C<sub>8</sub>H<sub>10</sub>N<sub>4</sub>O<sub>2</sub>, M.W.=194.2).

Since there are several assorted factors that may regulate an individual's retaliation to CAF, it's then difficult to sketch a broad inference about its effects on the general population caused by the varied CAF's intake levels. For instance, pharmacokinetic factors might influence how rapidly the caffeine is absorbed, distributed, metabolized and eliminated (ADME) after being ingested. Meanwhile, this can also be governed by pharmacodynamic factors such as the interaction as well as the consequences of these interactions between CAF and its sites of action in the body (Turnbull, Rodricks, Mariano, 2016). CAF is a psychoactive drug widely used- and perhaps abused. Also, it can enter to the body from many different foods such as coffee and tea (Santos *et al.*, 2010).

The determination of CAF in various natural products is economically very important (Ahmad Bhawani, Fong, Mohamad Ibrahim, 2015). In most of the previous studies, CAF has been analyzed separately by PC (Horie *et al.*, 2002), TLC (Bhatia, Ullah, 1968), GLC (Forrest, Bendall, 1969), HPLC (Altun *et al.*, 2001; Franeta *et al.*, 2002; Ramos-Martos *et al.*, 2001), spectrophotometric methods (Hashimoto, Nonaka, Nishioka, 1989) and micellarelectro kinetic chromatography (MEKC) (Boonkerd *et al.*, 1995). However, these methods present the disadvantages of relatively high costs and time consumption. Another disadvantage is the possible interference of degradation products or an impurity that have the same chromatographic retention time as the target compound (Sena, Poppi, 2004).

The simplest and most cost-effective technique for the trace and ultra-trace determination of drugs is separation and preconcentration using solid-phase

extraction (SPE) (Talio *et al.*, 2014). The application of polyurethane foam (PUF) produces smaller resistance for fluid passage. Thus, it results in a low overpressure in the system, reducing the risk of leakage. PUF is safely disposable, not costly and needs only simple preparation procedures. Moreover, this sorbent is highly resistant to rough changes in pH values, despite of swelling in the presence of some concentrated organic solvents, such as ethanol (Marchisio *et al.*, 2005).

SPE is a fast method used for selective extraction, concentration and purification of target analytes prior to analysis. In SPE, solutes are extracted from a liquid-phase into a solid-phase, consisting of small and porous particles of silica or a cross-linked polymer. The extraction might be performed either in batch or column mode (Poole, 2003). Thousands of SPE applications are now available for the extraction of key analytes in the pharmaceutical, clinical/toxicological, environmental and biological fields, and new methods continue to be rapidly developed (Bojdi *et al.*, 2014; Ge *et al.*, 2013). The sorbents that permit faster reaction rates are preferred for the achievement of faster extraction and higher loading capacities (Camel, 2003). Amongst the various sorbents employed in SPE systems, the polyurethane foams (PUF) had a significant importance in the last few years. The PUF is an excellent sorbent material due to its high available surface area, as well as its comparatively low cost. In addition, it is stable in acids and bases (except for the concentrated nitric acid), it will not also change its structure when heated up to 180 °C (Gawargious, Abbas, Hassan, 1988). Thus, it is a very suitable material for both on-line and off-line preconcentration column packing. The on-line methods have the advantage of avoiding the sample manipulation between preconcentration and analysis steps, thereby minimizes the analyte loss and contamination probabilities, allowing higher precision of the analysis (Abdel Azeem, Mohamed Attaf, El-Shahat, 2013).

PUF can be directly used without previous pretreatment (Burham, Abdel-Azeem, El-Shahat, 2008). On the other hand, several chelating agents and liquid ion exchangers have been immobilized on PUF and used as a co-adjuvant in separate procedures (Wanyika *et al.*, 2010).

In our previous work (Azeem, Ali, El-Shahat, 2011), the untreated-PUF was employed for the sorption of CAF.

But due to the lack of selectivity of PUF, it can easily interfere with other co-existing substances. Herein, we attempted to graft PUF with Alizarine yellow G (AY) to increase the sensitivity and selectivity of the sorbent towards CAF. This shall improve the accuracy and precision of the new method.

In the present study, selective AY imprinted PUF (AY-IPUF) and AY grafted PUF (AY-GPUF) were prepared and used for clean-up, and the approach of preconcentration is applied prior to spectrophotometric measurement of CAF to introduce a simple, rapid, cost-effective and sensitive method for the evaluation of CAF in complex matrices. The sorbents were examined both in static batch and column dynamic modes to evaluate a suitable phase for continuous analysis. The proposed procedures will be validated by the fast determination of CAF in a representative pharmaceutical product as well as in black tea samples.

## MATERIAL AND METHODS

### Chemicals and solutions

All chemical reagents were of analytical grade. The pH adjustment was done using 0.1 mol.L<sup>-1</sup> HCl, acetic/acetate buffer and ammonia/ammonium buffer in pH ranges of 1-3, 4-6 and 7-9, respectively. A standard solution of CAF (0.25 mg.mL<sup>-1</sup>) was prepared using a high purity CAF supplied by The Egyptian Drug Authority (EDA). All solutions were prepared on daily basis by appropriate dilution of specified aliquots from the standard solutions using double-distilled water. AY was purchased from Aldrich, USA. Polyol (polyethylene oxide-polyethylene glycol), stannous octoate (C<sub>16</sub>H<sub>30</sub>O<sub>4</sub>Sn) and toluene diisocyanate (TDI) [CH<sub>3</sub>C<sub>6</sub>H<sub>3</sub>(NCO)<sub>2</sub>] were obtained from Safa Foam Company (Egypt) and were used without any further purification. The commercial pharmaceutical sample (Pronto-Plus, tablets) was purchased from October Pharma S.A.E. (Egypt) and was assayed.

### Apparatus

Absorbance measurements were carried out using a UV/Vis double-beam spectrophotometer (model 1601

Shimadzu, Kyoto, Japan). The pH measurements were carried out using a calibrated EDT (Dover Kent, UK) and pH-mV meter (model GP353) equipped with an EDT combined glass electrode ( $\pm 0.01$  accuracy). An automatic shaker with up to 200 rpm with a thermostatic water bath was used for stirring the samples. A Thermo-Nicolet Avatar FT-IR spectrometer (Thermo scientific, USA) was employed to record IR spectra. A homemade peristaltic pump was used to propel the samples into the mini-column to overcome backpressure and to minimize pulsation in the system and the connections were made by using Tygon tubes with 1.52 mm internal diameter. Two similar polyethylene tubes (3 mm internal diameter and 4 cm length) were used as mini-columns and were packed with 150 mg of AY-GPUF or AY-IPUF. The column was successively rinsed with 20 mL H<sub>2</sub>O then 5 mL of a 0.1 mol.L<sup>-1</sup> HCl solution and finally with distilled water until the effluent was neutral. The mini-columns were pre-conditioned individually prior to their use by passing 5 mL ammonia buffer (pH = 9.0) to activate the adsorption sites and solvate the functional groups in AYG. Afterwards, 20 mL of doubly distilled water was pumped through the mini-column, at a flow rate of 1.75 mL.min<sup>-1</sup> to eliminate the remaining ammonia buffer. This step was daily performed before starting the system operation.

### Method of computation: *In silico* predictive study

*In silico* studies of caffeine were conducted because the pharmacokinetic factors might influence an individual's response to CAF including how rapidly caffeine is absorbed, distributed, metabolized and eliminated (ADME) after being ingested. It also can be governed by pharmacodynamics factors such as the interaction as well as the consequences of these interactions between caffeine and its site(s) of action in the body. Differences in ADME [comprising retarded gastric emptying which can hinder absorption], and metabolism [explicitly differences in action of cytochrome P450 1A2 (CYP1A2)] can play a significant role in caffeine metabolism, escorting to differences in CAF levels in plasma and time course from the same dose.

Caffeine was gauged for its forecasted bioactivity, physicochemical, pharmacokinetic/ADMET (absorption,

distribution, metabolism, excretion and toxicity) traits, drug likeness scores and violations by employing Molinspiration Chem informatics server (<http://www.molinspiration.com>), Pre-ADMET server (<https://preadmet.bmdrc.kr>), Swiss ADME web interface (<http://www.sib.swiss>) and Molsoft server (<http://www.molsoft.com>).

### The pharmaceutical sample

Six tablets (Pronto-Plus product) were weighed individually to obtain the average mass. Tablets were then ground into fine powder and mixed well. The mass corresponding to one tablet for each formulation was weighed and dissolved in 100 mL (ethanol/water- 20/80 v/v) in a volumetric flask, in an ultrasonic bath for 15 min.

### Sample preparation

Determination of caffeine in black tea was carried out by UV/Vis Spectrophotometry using a 0.25 g tea sample dissolved in boiling distilled water. Fresh distilled water was then added to reach a net volume of 20 mL. 20 mL sample solution was pipetted to 250 mL volumetric flask. A 10 mL 0.01 mol.L<sup>-1</sup> hydrochloric acid and 2 mL basic lead acetate solution were then added, and the contents were completed to the flask's mark with distilled water. The mixture was shaken up and filtered. 50 mL filtrate were pipette and added to a 100 ml flask, 0.2 mL 4.5 mol sulfuric acid was added and again distilled water was added up the flask's mark, shaken up and finally filtered (Wang, Li, Xu, 2006).

### Synthesis of AY-GPUF and AY-IPUF

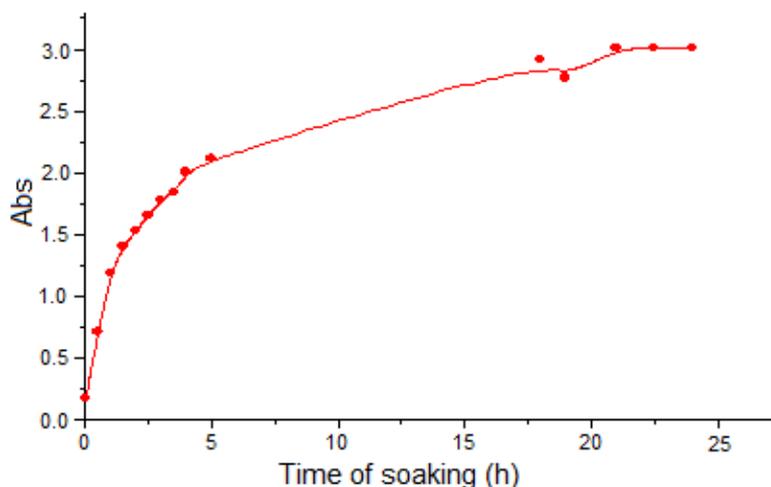
Alizarine yellow G was recommended as a reagent in the chemical modification of PUF due to its chemical structure which contains hydroxyl (OH) and carboxylic (COOH) groups (El-Shahat, Burham, Abdel Azeem, 2010). The OH groups can be grafted into the backbone of PUF by competing with a polyol to the toluene diisocyanate

groups during polymerization. The remaining COOH groups are easily ionized to form negative adsorption sites suitable for the adsorption of caffeine.

The preparation of AY-GPUF was based on a previously published work (El-Shahat, Burham, Abdel Azeem, 2010). 20.0 g liquid polyol were mixed with 0.5 g silicon oil, 0.02 g triethanolamine, 1.0 g double-distilled water, and 0.02 g ( $6.46 \times 10^{-5}$  mmole) of AY. Then, 0.02 g stannous octoate was added to the mixture and vigorously stirred for about 3 min. 13 g TDI were added at once under stirring for 30 s. Foaming reaction started in the liquid mixture by the evolution of carbon dioxide gas. Curing into solid polymeric material takes place afterward into a yellow-colored foam.

AY-IPUF was synthesized by mixing CAF and AY by the ratio 1:4 mmole to form a non-covalent complex. One milliliter aliquot of the complex solution was added to liquid polyol (20 g) and continued the same synthesis protocol as mentioned for AY-GPUF.

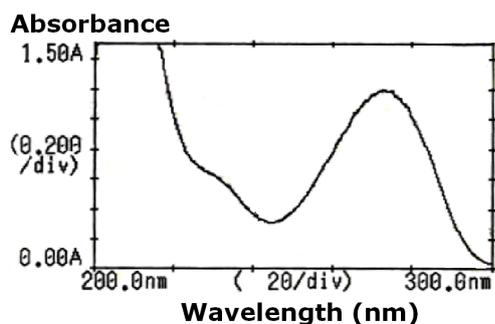
After the removal of the CAF template species, the cavity can then be used to selectively rebind the template from a mixture of chemical species. Desorption of CAF from the imprinted foam was examined by HCl solution at various concentrations and different soaking periods. The amount of recovered CAF was measured using spectrophotometry. The results shown in Figure 2 indicate that absorbance increase rapidly at the beginning; suggesting that most CAF was desorbed followed by a slow release. Also, the best concentration of HCl for complete desorption of CAF from AY-IPUF was found to be 0.1 mol.L<sup>-1</sup> in a volume of 15 mL. The soaking time was studied within the range of 0.5 - 24 hours, which is necessary to strip out the bound CAF without shaking the sorbent. Results indicated that the extraction of all CAF takes at least 24 hours. The HCl was recommended as it does not affect the base line of absorbance. Desorption under shaking or flow conditions was found to occur at shorter times as will be discussed later. The IR spectrum was used for characterizing CAF-free AY-IPUF and untreated PUF.



**FIGURE 2** - Soaking time Vs. UV absorbance of the released CAF from AY-IPUF sorbent.

### Off-line experiments

The optimum pH for CAF uptake was determined by using the batch equilibration technique. 20 millimeters of solutions, containing  $5.0 \mu\text{g}\cdot\text{mL}^{-1}$  CAF were adjusted to pHs in the range 1-10, then shaken with 0.1 g of foam for 30 min. After equilibration, the remained CAF was determined by the recommended method. The effect of shaking time on the extraction of CAF was studied using the batch experiment. For this propose, 20 mL solutions containing  $0.25 \mu\text{g}\cdot\text{mL}^{-1}$  CAF at optimum pH were automatically shaken with 0.1 g sorbent for time intervals 2, 5, 10, 15, 20, 25 or 30 min. The total capacity of each sorbent was then investigated. Typically, 0.1 g of foam was added to 20 mL of CAF containing  $5.0 \mu\text{g}\cdot\text{mL}^{-1}$  at optimum pH and shaken for 30 min at ambient temperature. After equilibration, the remaining CAF in the supernatant solution was spectrophotometrically determined at  $\lambda_{\text{max.}} = 274 \text{ nm}$ , as shown in Figure 3.



**FIGURE 3** - Full UV spectrum of pure caffeine.

### On-line preconcentration

In order to evaluate the performance of both AY-GPUF and AY-IPUF foams under dynamic conditions, adsorption studies were carried out using mini-columns integrated into the on-line preconcentration system, so 0.15 g foam was packed in a cylindrical polyethylene tube. The on-line system was operated in a time-based mode. Preconcentration of CAF was performed by pumping the CAF sample ( $0.25 \mu\text{g}\cdot\text{mL}^{-1}$ ) adjusted to pH 5.5 and pH 6.5 through the mini-column at a flow rate of  $1.7 \text{ mL}\cdot\text{min}^{-1}$  with 20 s and 40 s preconcentration time for AY-GPUF and AY-IPUF, respectively. Then, a double-distilled water carrier is passed through the mini-column till the absorbance baseline has been restored. Elution of CAF was achieved by injecting the carrier stream by  $500 \mu\text{L}$  from  $0.05 \text{ mol}\cdot\text{L}^{-1}$  and  $0.025 \text{ mol}\cdot\text{L}^{-1}$  hydrochloric acid solutions, respectively, at a rate of  $1.75 \text{ mL}\cdot\text{min}^{-1}$ . The displaced analyte from the sorbent was measured using UV spectrophotometer based on absorbance peak height at 274 nm. This procedure was applied for both standard and pharmaceutical samples.

## RESULTS AND DISCUSSION

### *In silico* predictive screenings

The work investigated here was carried out with the intent to forecast the bioactivity, drug-likeness and ADMET traits of caffeine utilizing *in silico* computational tools.

Molinspiration software was utilized for the prediction of bioactivity outcome of CAF for six different protein structures i.e. GPCR ligand (-0.53), ion channel modulator (-0.98), kinase inhibitor (-1.07), nuclear receptor ligand (-2.10), protease inhibitor (-1.23), and

enzyme inhibitor (-0.22). All the predicted values of the bioactivity score are negative, displaying a low affinity of CAF towards the selected protein structures.

Molsoft was used to predict drug-likeness score which is 1.03 in case of CAF as shown in Figure 4.

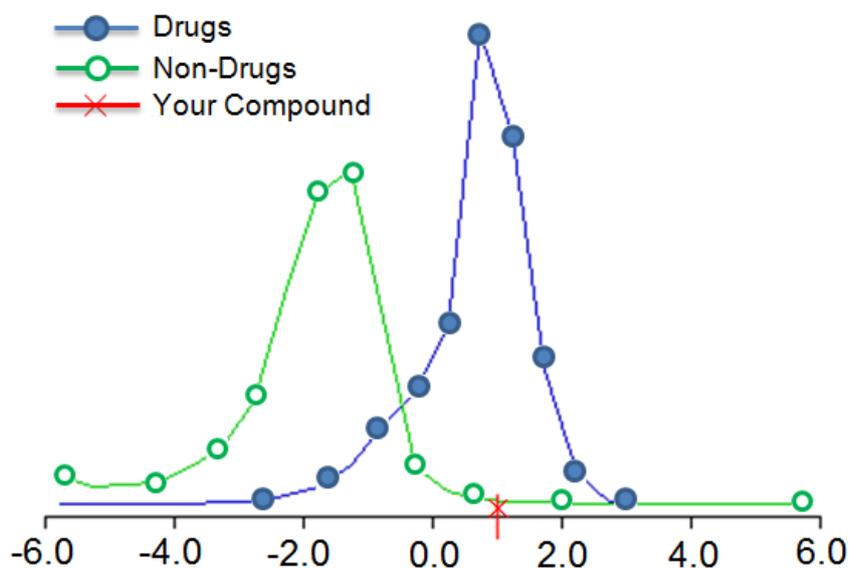
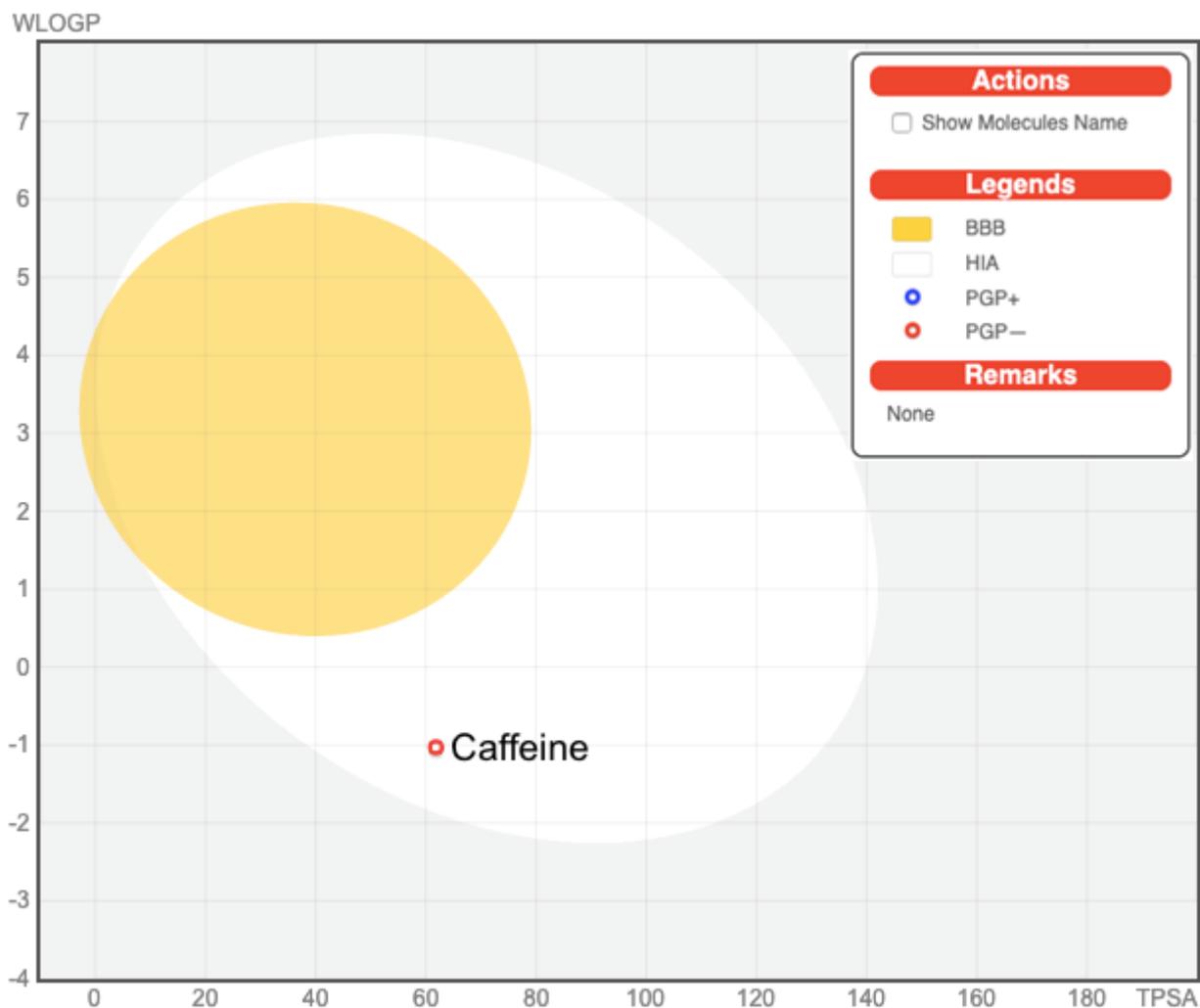


FIGURE 4 - Drug-likeness score model of caffeine.

Pre-ADMET and Swiss ADME were employed to foretell *in-vivo* ADMET attributes of CAF. Physicochemical properties of CAF were also predicted where the molecular formula is  $C_8H_{10}N_4O_2$ , molecular weight is  $194.19 \text{ g.mol}^{-1}$ , the number of heavy atoms is 14, fraction Csp<sup>3</sup> (the ratio of sp<sup>3</sup> hybridized carbons over the total carbon count of the molecule) being 0.38, with zero number of rotatable bonds, the number of H-bond acceptors are 3, number of H-bond donors being 0, molar refractivity is 52.04, TPSA (topological polar surface area) is  $61.82 \text{ \AA}^2$ . *In silico* % absorption of CAF was calculated to be 87.67% by the reported equation (%ABS =  $109 - (0.345 \times \text{TPSA})$ ) (Al-blewi *et al.*, 2019).

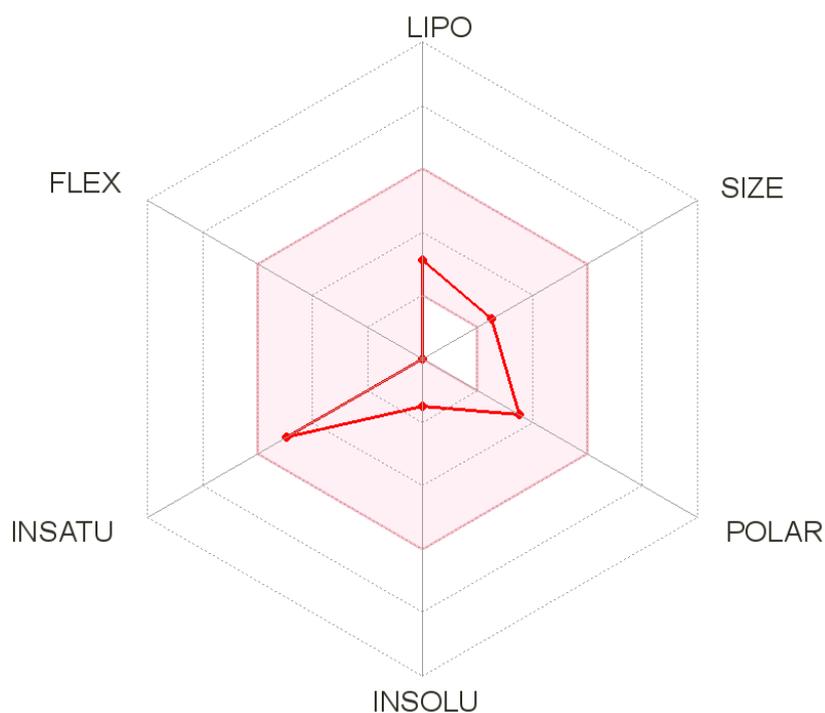
CAF is a non-BBB (blood-brain barrier) permeant but it has a high gastro intestinal absorption with an HIA (human intestinal absorption) percentage of 93.82%. It is a P-gp (p-glycoprotein) non-inhibitor. The PPB (plasma protein binding) emerged to be 14.08. The predicted passive HIA (human gastrointestinal absorption), permeation through BBB and P-gp substrates are ordered together in an instinctive graphical categorization model i.e. BOILED-Egg diagram as shown in Figure 5.



**FIGURE 5** - BOILED-Egg diagram of caffeine.

CAF does not inhibit any of the studied cytochrome P450 isomers. It displayed moderate Caco-2 cell permeability (21.26%) and low MDCK cell permeability (2.95%). Toxicological attributes of mutagenicity (Ames Test) and carcinogenicity (mouse and rat) for caffeine were also predicted. It is predicted as mutagenic by Ames test, carcinogenicity in mouse is negative, i.e. there is evidence of carcinogenic activities in mouse and in rats, the prediction is positive i.e. it is not carcinogenic in nature. Different drug-likeness rules in (Lipinski *et al.*, 2001), (Ghose, Viswanadhan,

Wendoloski, 1998), (Veber *et al.*, 2002), (Egan, Lauri, 2002) and (Muegge, Heald, Brittelli, 2001) were appraised to find out the number of violations if any by CAF. According to the drug-likeness rules of Lipinski, Veber and Egan, caffeine has drug likeliness as it does not violate any of these rules (0 violations). But predictions in terms of Ghose and Muegge rule flaunted that caffeine does not have drug-likeness as it has 1 violation in each set of rules. The bioavailability score of CAF is 0.55 and its bioavailability radar is shown in Figure 6.

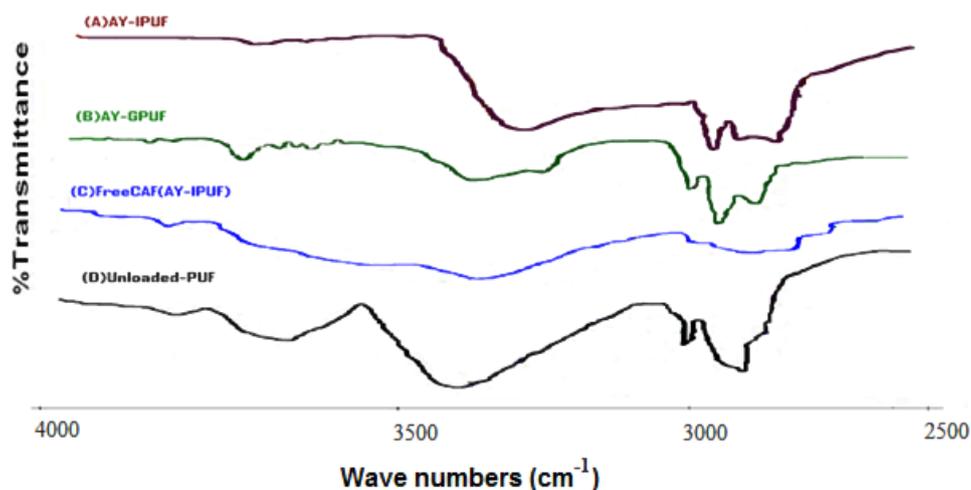


**FIGURE 6** - Bioavailability radar of caffeine: the pink area represents the optimal range for each property (lipophilicity: XLOGP3 between -0.7 and +5.0, size: MW between 150 and 500 g.mol<sup>-1</sup>, polarity: TPSA between 20 and 130 (Å<sup>2</sup>), solubility: log S not higher than 6, saturation: fraction of carbons in the sp<sup>3</sup> hybridization not less than 0.25, and flexibility: no more than 9 rotatable bonds). In this example, the compound is predicted not orally bioavailable, because too flexible and too polar.

#### Fourier transfer infra-red (FTIR)

The IR spectra of the untreated PUF exhibited the absorption bands correlated to  $\nu$ NCO,  $\nu$ OH,  $\nu$ CO and  $\nu$ NH<sub>2</sub> groups at 2100, 3509, 1655, 3111 and 3299 cm<sup>-1</sup>,

respectively. However, the spectra of AY-GPUF and AY-IPUF showed disappearance of the bands corresponding to  $\nu$ NCO,  $\nu$ OH groups and appearance of two bands corresponding to  $\nu$ CO and  $\nu$ NH<sub>2</sub> at 1700-1663 and 3231-3346 cm<sup>-1</sup>, respectively, as shown in Figure 7.

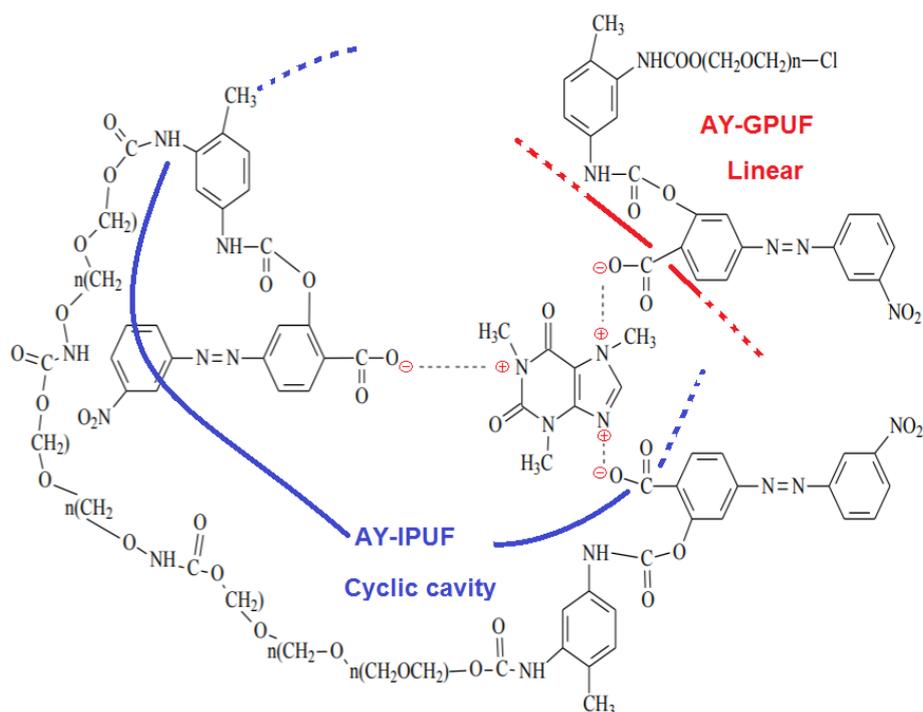


**FIGURE 7** - IR spectra of various polyurethane foam phases: (A) AY-IPUF, (B) AY-GPUF, (C) CAF-free AY-IPUF, (D) unloaded-PUF.



Evidently, CAF-free AY-IPUF showed characteristic absorption bands at 3467, 1714, 1663 and 3330  $\text{cm}^{-1}$  corresponds to  $\nu\text{OH}$ ,  $\nu\text{CO}$  and  $\nu\text{NH}_2$ , which indicate the incorporation of these groups during complex formation to CAF. At  $\text{pH} \geq 4.0$ , the  $\text{COOH}$  of alizarin will be ionized into the negatively charged form ( $\text{COO}^-$ ) making the polymer surface negatively

charged in AY-GPUF. Meanwhile, positive charges are formed in the protonated nitrogen atoms in CAF causing attraction forces between the protonated CAF and the polymer surface. While in the case of AY-IPUF, similar adsorption mechanism takes place but the sorbent forms a cyclo-polymeric chain around the CAF molecule as shown in Figure 8.



**FIGURE 8** - The proposed structure of sorbents, and the mechanism of adsorption by the AY-GPUF and AY-IPUF.

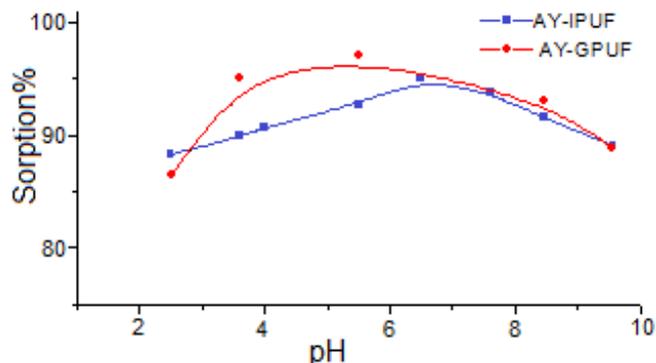
### Effect of pH on adsorption of CAF

The effect of solution's pH on the retention of CAF was studied in the range of  $\text{pH} = 2.5\text{-}9.5$ . For AY-IPUF sorbent, the sorption % has increased in the range of  $\text{pH} = 2.5\text{-}6.5$  which might be attributed to the presence of CAF on it is protonated form. While at  $\text{pH}$  range of  $5.5\text{-}9.5$ , the sorption % has slightly decreased, which might be due to reduction in the concentration of the positively charged protonated CAF which is available for ion-pair formation and less extent of a negatively charged ionized form of AY and independence of extraction on  $\text{pH}$  due to hydrophobic sorption by  $\pi\text{-}\pi$  interaction rather than electrostatic interaction. In case of AY-GPUF, the maximum sorption % was observed at  $\text{pH}$

$= 5.5$  which reveals the optimum  $\text{pH}$  value for ionization of  $\text{COOH}$  in AY reagent. Before  $\text{pH} 5.5$ , the sorption % is lower due to the persistence un-dissociated form of AY, while beyond this value the proportion of protonated CAF decreases as can be seen in Figure 9. Therefore, the optimum  $\text{pH}$  values for adsorption of CAF are 6.5 and 5.5 for AY-IPUF and AY-GPUF, selected for the present study. The percentage of sorption was determined using Eq. 1 (Azeem, Ali, El-Shahat, 2011):

$$\text{Sorption (\%)} = [(C_0 - C)/C_0] \times 100 \quad (\text{Eq. 1})$$

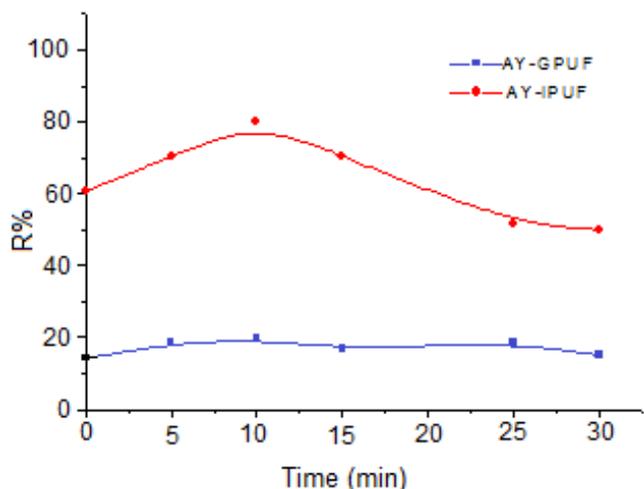
where  $C_0$  and  $C$  are initial and remaining concentration ( $\mu\text{g.L}^{-1}$ ) of CAF, respectively.



**FIGURE 9** - The effect of sample pH on the sorption of CAF: 0.25  $\mu\text{g}\cdot\text{mL}^{-1}$ , 0.1 g sorbent, 30 min shaking time.

### Influence of shaking time

The influence of shaking time on the sorption of CAF was investigated by the batch off-line procedure in the range 5-30 min at optimum pH. The results are shown in Figure 10. Obviously, both sorbents have shown fast kinetics for the sorption of CAF. The equilibrium state has been reached for both AY-GPUF and AY-IPUF after a 10 min shaking period. So, a stirring interval of 10 min would be recommended to reach the equilibrium state. The faster sorption of CAF ions on the modified PUFs probably reflects a good accessibility of the studied analytes ions to the new chelating sites in the sorbents and ensure surface phenomenon and that readily accessible to CAF ions solutions.

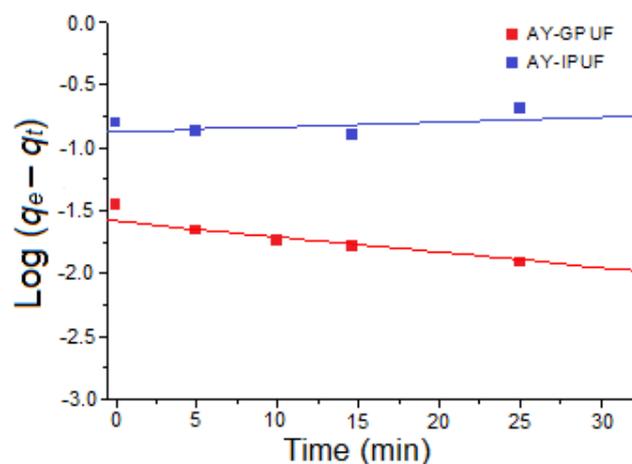


**FIGURE 10** - The effect of shaking time on the sorption of CAF: 0.25  $\mu\text{g}\cdot\text{mL}^{-1}$ , 0.1 g sorbent, pH 5.5 AY-GPUF and pH 6.5 AY-IPUF.

Kinetics of sorption was found to verify the first-order rate equation represented by Lagrangren relation (Eq. 2) (Salam, 2008):

$$\text{Log}(q_e - q_t) = (-K/2.303) t \quad (\text{Eq. 2})$$

where  $q_e$  and  $q_t$  are the amount of CAF ( $\mu\text{g}\cdot\text{g}^{-1}$ ) extracted at equilibrium and at any shaking time  $t$  (min),  $K$  is the first-order rate constant ( $\text{min}^{-1}$ ). The data presented in Figure 11 reveals a negative slope for the imprinted foam while a positive slope was obtained for the grafted one. The values for the rate constant ( $K$ ) were found to be 0.028 and 0.0087  $\text{min}^{-1}$  and half-life times are 33.06 and 106.2 min for AY-GPUF and AY-IPUF, respectively.



**FIGURE 11** - Lagrangren plot for adsorption of CAF onto AY-GPUF and AY-IPUF.

### Sorption capacity

The maximum exchange capacity of the sorbent (maximum amount extracted per gram of the sorbent) was determined by shaking 100 mg of the sorbent with excess CAF concentration ( $5.0 \text{ mg}\cdot\text{L}^{-1}$ ) for 30 min at ambient temperature. The remaining amount of CAF in the supernatant solution was determined as described in the recommended procedure. The sorption capacity  $Q$  ( $\mu\text{g}\cdot\text{g}^{-1}$ ) was calculated from (Eq. 3) (Huo *et al.*, 2019):

$$Q = [(C_0 - C) \times V]/m \quad (\text{Eq. 3})$$

where  $V$  is the sample volume (L) and  $m$  is the weight of sorbent (g). The maximum capacity for AY-GPUF and AY-IPUF was found 6500 and 1400  $\mu\text{g}\cdot\text{g}^{-1}$ , respectively. Variation in the sorption capacity with the sorbent type is expected to be parallel to the stability of the CAF-AY complex. The increased capacity of the grafted foam could be due to non-selective binding of CAF and extraction is mainly occurred on the polymer surface. However, the imprinted foam is highly selective and the capacity is mainly dependent on the number of template sites previously formed in the polymer backbone.

### Equilibrium adsorption isotherms

The sorption isotherm of CAF was carried out by determination of the sorbent uptake ( $\mu\text{g}\cdot\text{g}^{-1}$ ) at varying of the CAF concentration. Typically, 0.1 g foam sorbent was equilibrated with CAF solutions in the concentration range 1-600 and 1-40  $\mu\text{g}\cdot\text{mL}^{-1}$  in case of AY-GPUF and AY-IPUF, respectively.

The isotherm of AY-GPUF shows an “L” isotherm as shown in Figure 12(A). It shows one increasing section in the range 1-300  $\mu\text{g}\cdot\text{mL}^{-1}$  followed by plateau indicating saturation of sorbent by CAF.

The isotherm of AY-IPUF shows an “S” isotherm, as shown in Figure 12(B). The first section occurred in the concentration range of 1-20  $\mu\text{g}\cdot\text{mL}^{-1}$  and exhibited lower slope which may be due to the slow sorption of CAF at early stages by the highly selective imprinted sites. Further increase in CAF concentration leads to a saturation of the selective adsorption sites and the analyte becomes adsorbed by electrostatic forces at the surface which has a quite faster rate as indicated by the higher slope within the concentration range 30-40  $\mu\text{g}\cdot\text{mL}^{-1}$  then the sorbent total capacity was reached. Obviously, the extracted amount by grafted foam is much greater than that for the imprinted foam which emphasis the conclusion mentioned in the section: *Sorption capacity*.

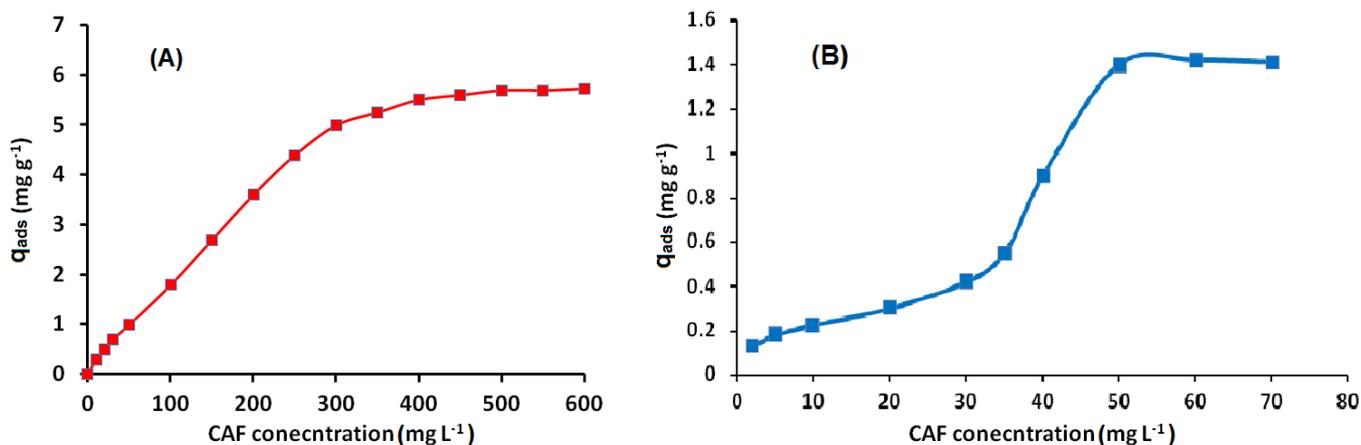


FIGURE 12 - Extraction isotherms for CAF with: (A) AY-GPUF and (B) AY-IPUF sorbents.

Modeling of the adsorption isotherm by Langmuir and Freundlich equations is represented in Figure 13. The Langmuir isotherm takes into consideration that sorption occurs on uniform surfaces containing sites with an equivalent adsorbing capacity in relation to the solute. Also, it considers adsorption occurs on a monolayer (de Almeida *et al.*, 2007). Therefore, for a solute-solvent system in which only the solute is significantly adsorbed

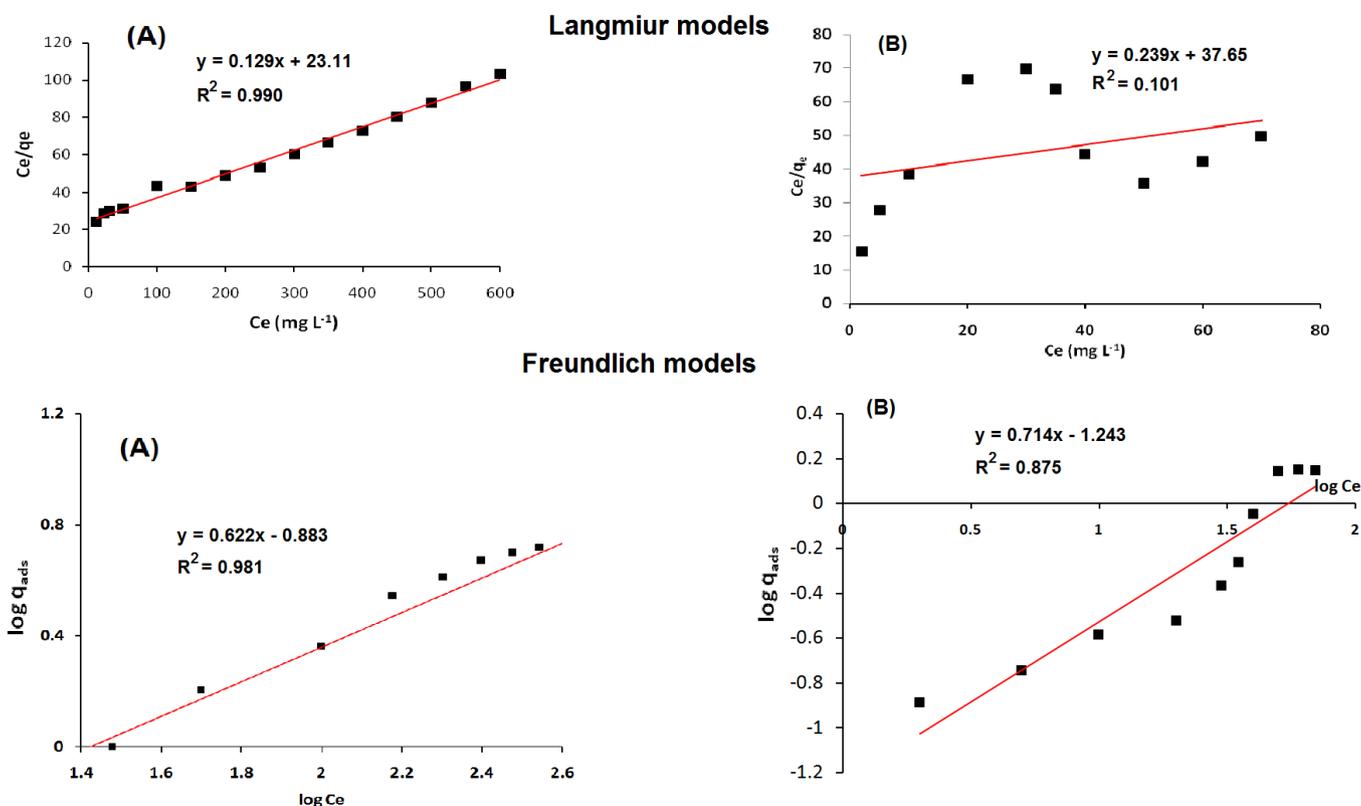
onto the solid surface, the Langmuir isotherm can be expressed as in Eq. 4:

$$C_e/q_{\text{ads}} = 1/(Q \cdot b) + C_e/Q \quad (\text{Eq. 4})$$

where  $C_e$  is the concentration of the solute after equilibrium is achieved ( $\text{mg}\cdot\text{L}^{-1}$ ),  $q_{\text{ads}}$  is the amount of solute retained on the adsorbent at equilibrium ( $\text{mg}$ .

$g^{-1}$ ),  $Q$  is the maximum adsorption capacity of the monolayer, and the term  $b$  can be assumed as apparent adsorption equilibrium constant. The application of the Langmuir isotherm to the present results yielded a linear relationship and the observed intercept is positive. Similarly, both grafted and imprinted foams

have shown similar straight-line plots with positive slopes. The linear correlation coefficients for the grafted and imprinted sorbents are 0.990, and 0.101, respectively. The values for  $Q$  and  $b$  are 4.2  $mg \cdot g^{-1}$  and 0.006  $L \cdot mg^{-1}$  for AY-IPUF and 7.75  $mg \cdot g^{-1}$  and 0.006  $L \cdot mg^{-1}$  for AY-GPUF, respectively.



**FIGURE 13** - Langmuir and Freundlich models for adsorption of CAF by: (A) AY-GPUF and (B) AY-IPUF sorbents.

Freundlich isotherm assumes that multiplayer adsorption of analyte takes place on a heterogeneous surface and the extent of solute adsorption increases infinitely with increasing the analyte concentration (Ababneh *et al.*, 2019; Avila, 2005). The empirical equation of Freundlich isotherm can be represented by Eq. 5 (Kumar *et al.*, 2012):

$$C_{ads} = K_F C_e^{1/n} \quad (\text{Eq. 5})$$

where  $C_{ads}$  is the amount of solute retained on the adsorbent,  $C_e$  is the solute concentration in solution after equilibrium

was reached, and  $1/n$  and  $K_F$  are the isotherm parameters that measure of adsorption intensity and adsorption capacity, respectively. The equation of Freundlich isotherms was linearized by applying a logarithm as in Eq. 6 (Pragathiswaran, Sibi, Sivanesan, 2013):

$$\log C_{ads} = \log K_F + 1/n \log C_e \quad (\text{Eq. 6})$$

The values of  $K_F$  and  $n$  could be obtained by plotting  $\log C_{ads}$  against  $\log C_e$ .

The calculated constants of Langmuir and Freundlich parameters are shown in Table I.

**TABLE I** - Isotherm parameters for the adsorption of CAF onto AY-GPUF and AY-IPUF sorbents at 25°C

Foam Type	Capacity	Langmuir Isotherm			Freundlich Isotherm		
	Q (mg.g <sup>-1</sup> )	q <sub>m</sub> (mg.g <sup>-1</sup> )	b (L.mg <sup>-1</sup> )	R <sup>2</sup>	K <sub>F</sub>	n	R <sup>2</sup>
AY-GPUF	6.5	7.75	0.006	0.990	0.131	1.61	0.981
AY-IPUF	1.4	4.2	0.006	0.101	0.049	1.29	0.875

Sorption by AY-GPUF is better described by Langmuir model ( $R^2=0.990$ ) than the Freundlich model ( $R^2=0.981$ ). The Freundlich isotherm is usually employed for the modeling of heterogeneous systems, being successfully used for the description of adsorption processes in solution (Hameed, Din, Ahmad, 2007; Li *et al.*, 2009). It can be observed that all the values of  $n$  are higher than 1.0, which can be attributed to the molecular interaction between adsorbent and adsorbate.

In the controversy, adsorption by AY-IPUF showed a sigmoidal curve ( $S$  isotherm) and has a point of inflection which may be a result of at least two types of opposing mechanisms leading to a phenomenon of cooperative adsorption. This can be observed from the nonlinear behavior of the two isotherms described by Langmuir and Freundlich models. The correlation coefficient was 0.101 and 0.875 for Langmuir and Freundlich models, respectively, which are considered insignificant.

Moreover, the value of  $n$  for the adsorption of CAF onto AY-IPUF is less than that for AY-GPUF, which is probably ascribable to the two adsorption cavities in AY-IPUF (De Boer, 1968). This may be due to adsorption to the imprinted cavity necessitates a particular orientation of the CAF molecule at the solid-liquid boundary phase as well as one CAF molecule may need more than one AY i.e the ratio adsorption stoichiometry of CAF:AY is 1:2, 1:3, or higher. The equation of the Freundlich isotherms commonly fits solute adsorption onto rough surfaces better than Langmuir isotherms (Ferreira, Andrade, dos Santos, 2004), once it takes into account the heterogeneity

of the solid surface and the variable energy distribution of the adsorption sites. However, it can be applied only to a narrow range of solute concentrations, which, in turn, limits its application in the prediction of adsorptive capacities (Banerjee, Chattopadhyaya, 2017). The AY-GPUF showed higher adsorption capacity and affinity for CAF, as the sorbent surface is readily available for attracting CAF since the AY reagent is anchored to the outer functional groups causing the adsorption process to suffer less steric hindrance. Also, the ratio of CAF:AY is expected to be 1:1 due to the linear grafted polymeric chain of AY-GPUF (See Figure 8).

### Selectivity

The effect of foreign ions which might interfere with the sorption of CAF was examined. Model solutions containing 5  $\mu\text{g.mL}^{-1}$  of CAF and interfering substance at various concentrations were prepared and mixed to the sorbent for batch extraction. The recovery of CAF was compared to the presence of the tested substance to a reference value obtained in the absence of the foreign compound. The results are shown in Table II. The tolerance limit is defined as the amount of interference causing an error in the recovery by  $\geq \pm 5\%$ . Starch, serine, histidine, citrate, could be tolerated at up to 200  $\text{mg.L}^{-1}$ , at least. Alkali and alkaline earth elements do not form stable complexes and are not retained on the sorbents under the working conditions used for the system (Anthemidis, Ioannou, 2006).

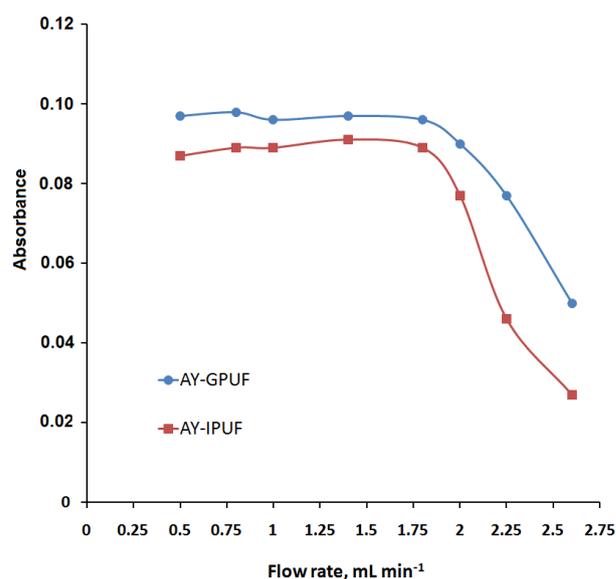
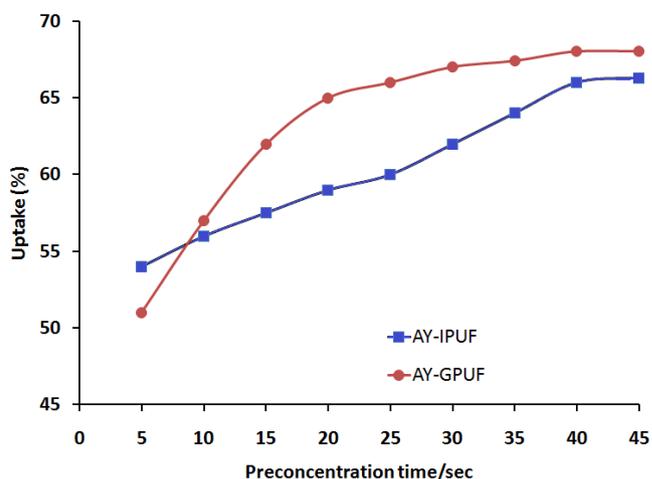
**TABLE II** - Tolerance levels of CAF (5 mg L<sup>-1</sup>) in the presence of interfering substances

Foreign Substance	Tolerance level, (mg.L <sup>-1</sup> )	Recovery (%)	
		AY-IPUF	AY-GPUF
Urea	600	99	100
Starch	3422	104	109.8
Glycine	>750	100	100
Serine	1050	100	100
Glutamine	1460	100	100
Histidine	200	97	100
Phenyl alanine	>1668	100	98
NaCl	850	100	100
Citrate	2940	99	100
Arginine	1742	100	100
CaCl <sub>2</sub>	1100	99	100

### Performance under flow conditions

The sample's flow rate is a very important parameter which affects the sorption's efficiency as well as the analysis time (Figure 14). In investigating the flow rate between 0.5 and 2.6 mL.min<sup>-1</sup>, there was a maximum and constant absorbance in the range 0.5-1.8 in case of both sorbents followed by a decrease in absorbance at higher flow rates. Therefore, a 1.75 mL.min<sup>-1</sup> flow rate was recommended for further experiments. The dynamic capacities of the AY-GPUF and AY-IPUF sorbents were also determined from breakthrough point. In this experiment, a model solution of 5 µg.mL<sup>-1</sup> CAF was adjusted to pH = 6.5 and pH = 5.5 for AY-IPUF and AY-GPUF, respectively. The column dynamic capacities were calculated from the breakthrough point and were found to be 32.88 mg.g<sup>-1</sup> and 42.02 mg.g<sup>-1</sup> for AY-GPUF and AY-IPUF, respectively. These values are well above the content of CAF in the analyzed pharmaceutical sample. Preconcentration time was investigated in the range of 5-45 s using 5 µg.mL<sup>-1</sup> CAF solution at a flow rate of 1.75 mL.min<sup>-1</sup> as presented in Figure 15. Linear relationships were observed within the preconcentration

time range of 1-20 and 1-35 s for AY-IPUF and AY-GPUF, respectively, which reflect quantitative sorption of CAF. At extended preconcentration periods, the recovery becomes nonlinear, perhaps due to the washing effect of the sample (Wells, 2003). The calculated enrichment factors were found 8 and 10 for AY-IPUF and AY-GPUF, respectively. The time consumed for preconcentration, elution and determination steps was 1.48 and 1.05 min, thus, the throughput was 42 and 57 h<sup>-1</sup> for (AY-IPUF) and (AY-GPUF), respectively.

**FIGURE 14** - Effect of sample's flow rate on the adsorption of CAF onto AY-GPUF and AY-IPUF sorbents.**FIGURE 15** - Effect of preconcentration time on the uptake of CAF.

## Desorption of CAF

Since CAF extraction occurred via electrostatic attraction forces between positively charged protonated CAF and negatively charged  $\text{COO}^-$  in AYG, consequently, the desorption should be performed by the suitable electrolyte which neutralizes the negative charge on the ligand. The use of acids as eluents for desorption was found to be highly effective because acids can rapidly neutralize the charge by immediate adjustment of pH. Different acids, including  $\text{HNO}_3$ ,  $\text{CH}_3\text{COOH}$  and  $\text{HCl}$ , were tested. The best results were obtained by using  $\text{HCl}$  as it gives a very weak background signal at the wavelength of measurements. Subsequently, various concentrations from  $\text{HCl}$  were studied and the best recovery was obtained at 0.01 and 0.05  $\text{mol.L}^{-1}$  for AY-GPUF and AY-IPUF, respectively. Furthermore, the elution volume was optimized by studying the recovery of CAF at eluent volumes varying between 200 and 1200  $\mu\text{L}$ . It was found that quantitative desorption was achieved by 500  $\mu\text{L}$   $\text{HCl}$  in both sorbents, therefore it was chosen for adequate desorption.

## Analytical performance

The limit of detection, defined as three times the standard defined deviation of the blank ( $3\sigma$ ) (Thomsen, Schatzlein, Mercurio, 2003), was found to be 2.26 and 0.98  $\mu\text{g.mL}^{-1}$  for AY-IPUF and AY-GPUF, respectively. Similarly, the limit of quantification ( $10\sigma$ ) was found to be 7.54 and 3.25  $\mu\text{g.mL}^{-1}$  for AY-IPUF and AY-GPUF, respectively. Also, the precision for 5 replicate determinations expressed as RSD was 0.3 and 1.2%, respectively, at the concentration of 5  $\mu\text{g.mL}^{-1}$  CAF. The linear range obtained by using the on-line preconcentration system is 1-80  $\mu\text{g.mL}^{-1}$  with a correlation coefficient of 0.982, and 0.993 for AY-IPUF, and AY-GPUF, respectively. Table III comprises the analytical performance data for the on-line preconcentration procedure using AY-IPUF and AY-GPUF sorbents. The accuracy of the proposed preconcentration methods was investigated by the add-found test (Abdel Azeem, Mohamed Attaf, El-Shahat, 2013). The recovery was found to be in the range of 99-104% and the corresponding RSD varied from 0.05 to 7.4% as indicated in Table IV.

**TABLE III**- Analytical parameters of on-line preconcentration by AY-IPUF and AY-GPUF sorbents

Parameter	AY-IPUF	AY-GPUF
pH range	6-8	4-6
Enrichment factor	8.4	10.5
Precision (RSD, n=5) (%)	0.28	1.24
Regression equation	$y = 0.005x + 0.015$	$y = 0.005x - 0.017$
Correlation Coefficient	0.982	0.993
Detection limit ( $\mu\text{g.mL}^{-1}$ )	2.26	0.98
Quantification limit ( $\mu\text{g.mL}^{-1}$ )	7.54	3.25

**TABLE IV** - Accuracy of the proposed methods for CAF determination by add-found test

Sorbent	Taken (mg)	Found (mg)	Recovery (%)	RSD (%)
AY-GPUF	0.50	0.49	98.0	1.20
	3.00	3.13	104	7.40
	10.0	9.97	99.7	7.30
AY-IPUF	0.50	0.51	102	1.40
	3.00	2.98	99.0	0.10
	5.00	4.99	99.0	0.05

## Application to real samples

Extraction of CAF from black tea was achieved by using AY-GPUF, AY-IPUF as an extracting media. The RSD of extraction of CAF from black tea solution was 0.33 and 0.257% for AY-IPUF and AY-GPUF, respectively. The results are summarized in Table V. The validity of the proposed procedures was also tested by determining CAF in pharmaceutical preparations. The recovery was found to be 100 and 108% and RSD 0.9 and 0.4% for AY-GPUF and AY-IPUF, respectively (Table VI). Therefore, the proposed sorbents are highly sensitive and could be used successfully for routine analysis of natural samples as well as pharmaceutical products.

**TABLE V** - Isolation and determination of Caffeine from tea (n=3) using imprinted and grafted foam

Material	AY-IPUF		AY-GPUF	
	mean(mg)±SD	RSD (%)	mean(mg)±SD	RSD (%)
Tea	6.90 ± 0.0023	0.33	6.72 ± 0.0017	0.257

**TABLE VI** - Determination of CAF in its pharmaceutical dosage (Pronto Plus tablets) applying standard addition technique using imprinted and grafted foam

Sorbent	Reported (mg)	Found* (mg)	Recovery (%)	RSD (%)
AY-GPUF	3.00	3.02	100.8	0.90
AY-IPUF	2.50	2.72	108.8	0.40

\*mean value of five replicates

## Comparison with other methods

A comparison of the analytical performance data of our developed AY-IPUF and AY-GPUF method to other reported procedures for preconcentration/separation of CAF is presented in Table VII. The developed AY-GPUF showed a higher capacity than the untreated-PUF. The detection limit for AY-GPUF was slightly higher than the hypercrosslinked polystyrene method (Andreeva, Dmitrienko, Zolotov, 2010). The analytical range of the methods under investigation was wider than all reported methods which conveys the validity for analysis of samples with varying concentrations. Also, the enrichment factor was found comparable to the homogeneous liquid-liquid microextraction method (Amini, Hashemi, 2018). Finally, the developed procedure provided a successful alternative for the preconcentration/separation and determination of CAF with a sufficient accuracy and precision.

**Table VII** - Comparison of the analytical performance of the AY-GPUF and AY-IPUF sorbents to other reported methods for preconcentration and determination of caffeine

Extracting Substance	Technique	Capacity (mg.g <sup>-1</sup> )	Detection limit (µg.mL <sup>-1</sup> )	EF <sup>a</sup>	Analytical range, (µg.mL <sup>-1</sup> )	Ref.
AY-GPUF	On-line/Off-line SPE	6.5	0.98	10.5	1.0-80.0	This work
AY-IPUF	On-line/Off-line SPE	1.4	2.26	8.4	1.0-80.0	This work
Untreated-PUF	Off-line SPE	4.1	0.016	-	0.05-30	Azeem, S. et al., 2011
MWCNTs <sup>b</sup>	Off-line SPE	-	0.3 µg.L <sup>-1</sup>	-	0.0011-9.7	Talio et al., 2014
HCLPS <sup>c</sup>	Off-line SPE	1.26 mmol.g <sup>-1</sup>	0.6	-	1.8-9.5	Andreeva et al., 2010
DCM <sup>d</sup>	HLLME <sup>e</sup> /GS	-	0.05	11	0.16-50	Amini et al., 2018

<sup>a</sup>EF: Enrichment factor.<sup>b</sup>MWCNTs: Multi-walled carbon nanotubes.<sup>c</sup>HCLPS: Hypercrosslinked polystyrene.<sup>d</sup>DCM: Dichloromethane.<sup>e</sup>HLLME<sup>b</sup>: Homogeneous liquid-liquid microextraction.



## CONCLUSION

CAF was explored for its physicochemical, pharmacokinetic, and pharmacodynamic traits utilizing computational tools along with *in silico* predictive bioactivity and drug-likeness scores. Apart from these predictive studies, a novel, rapid, yet sensitive, method has been developed for quantification of caffeine in pharmaceutical and natural samples. The proposed imprinted and grafted sorbents have shown fast sorption/desorption characteristics and allowed the on-line determination of the CAF. The extensive sample preparation is not needed which allows easy and rapid method development. The run-time for each sample was 5 min. Adequate sensitivity and selectivity were achieved with a traditional UV detector. The attained LOD in this study allows for the quantification of CAF in pharmaceutical preparations as well as in pure samples. Overall, the proposed method is highly sensitive and selective for the determination of CAF in complex matrices.

## DECLARATIONS

- Competing interests: all authors participating in this work declare that no conflict of interest exists.
- Ethics approval and consent to participate: this work does not contain any studies with human or animals participants.
- Consent for publication: all authors have agreed to publish this work.
- Availability of data and material: data and materials used/produced by this work are available and/or reproducible.
- Funding: not applicable.
- Authors' contributions: authors have equally participated in all stages of production of this work

## REFERENCES

Ababneh AN, Abu-Dalo MA, Horn C, Hernandez MT. Polarographic determination of benzotriazoles and their sorption behavior on granular activated carbon. *Int J Environ Sci Technol.* 2019;16(2):833-42.

Abdel Azeem SM, Mohamed Attaf SM, El-Shahat MF. Acetylacetone phenylhydrazone functionalized polyurethane foam: Determination of copper, zinc and manganese in environmental samples and pharmaceuticals using flame atomic absorption spectrometry. *React Funct Polym.* 2013;73(1):182-91.

Ahmad Bhawani S, Fong SS, Mohamad Ibrahim MN. Spectrophotometric Analysis of Caffeine. *Int J Analyt Chem.* 2015;2015:7.

Al-blewi F, Rezki N, Naqvi A, Qutb Uddin H, Al-Sodies S, Messali M, et al. A Profile of the In Vitro Anti-Tumor Activity and In Silico ADME Predictions of Novel Benzothiazole Amide-Functionalized Imidazolium Ionic Liquids. *Int J Mol Sci.* 2019;20(12):2865.

Altun ML, Ceyhan T, Kartal M, Atay T, Özdemir N, Cevheroğlu Ş. LC method for the analysis of acetylsalicylic acid, caffeine and codeine phosphate in pharmaceutical preparations. *J Pharm Biomed Anal.* 2001;25(1):93-101.

Amini T, Hashemi P. Preconcentration and GC-MS determination of caffeine in tea and coffee using homogeneous liquid-liquid microextraction based on solvents volume ratio alteration. *J Chromatogr B.* 2018;1092:252-7.

Andreeva E, Dmitrienko S, Zolotov Y. Sorption of caffeine and theophylline on hypercrosslinked polystyrene. *Moscow Univ Chem Bull.* 2010;65:38-41.

Anthemidis AN, Ioannou K-IG. Evaluation of polychlorotrifluoroethylene as sorbent material for on-line solid phase extraction systems: Determination of copper and lead by flame atomic absorption spectrometry in water samples. *Anal Chim Acta.* 2006;575(1):126-32.

Avila MAS. Experiment and modelling of the competitive sorption and transport of chlorinated ethenes in porous media: Cuvillier Verlag; 2005.

Azeem SMA, Ali S, El-Shahat MF. Sorption characteristics of caffeine onto untreated polyurethane foam: application to its determination in human plasma. *Anal Sci.* 2011;27(11):1133.

Banerjee S, Chattopadhyaya MC. Adsorption characteristics for the removal of a toxic dye, tartrazine from aqueous solutions by a low cost agricultural by-product. *Arabian J Chem.* 2017;10(Supplement 2):S1629-S38.

Bhatia I, Ullah MR. Polyphenols of tea. IV. - Qualitative and quantitative study of the polyphenols of different organs and some cultivated varieties of tea plant. *J Sci Food Agric.* 1968;19(9):535-42.

Bojdi MK, Behbahani M, Sahragard A, Amin BG, Fakhari A, Bagheri A. A palladium imprinted polymer for highly selective and sensitive electrochemical determination

- of ultra-trace of palladium ions. *Electrochim Acta*. 2014;149(Supplement C):108-16.
- Boonkerd S, Lauwers M, Detaevernier MR, Michotte Y. Separation and simultaneous determination of the components in an analgesic tablet formulation by micellar electrokinetic chromatography. *J Chromatogr A*. 1995;695(1):97-102.
- Burham N, Abdel-Azeem SM, El-Shahat F. Determination of lead and cadmium in tap water and apple leaves after preconcentration on a new acetylacetone bonded polyurethane foam sorbent. *Int J Environ Anal Chem*. 2008;88(11):775-89.
- Camel V. Solid phase extraction of trace elements. *Spectrochim Acta Part B*. 2003;58(7):1177-233.
- Corciova A, Ivanescu B. Determination of caffeine content from different pharmaceutical and natural products. *Eur Chem Bull*. 2016;5(4):138-41.
- Cristea AN. *Tratat de farmacologie*. Editura Medicală, București. 2012.
- de Almeida GN, de Sousa LM, Pereira Netto AD, Cassella RJ. Characterization of solid-phase extraction of Fe(III) by unloaded polyurethane foam as thiocyanate complex. *Journal J Colloid and Interface Sci*. 2007;315(1):63-9.
- De Boer JH. *The Dynamical Character of Adsorption*, 2nd ed. London Oxford University Press; 1968.
- Egan WJ, Lauri G. Prediction of intestinal permeability. *Adv Drug Delivery Rev*. 2002;54(3):273-89.
- El-Shahat MF, Burham N, Abdel Azeem SM. Flow injection analysis–solid phase extraction (FIA–SPE) method for preconcentration and determination of trace amounts of penicillins using methylene blue grafted polyurethane foam. *J Hazard Mater*. 2010;177(1):1054-60.
- Ferreira SLC, Andrade HMC, dos Santos HC. Characterization and determination of the thermodynamic and kinetic properties of the adsorption of the molybdenum(VI)–calmagite complex onto active carbon. *J Colloid Interface Sci*. 2004;270(2):276-80.
- Forrest GI, Bendall DS. The distribution of polyphenols in the tea plant (*Camellia sinensis* L.). *Biochem J*. 1969;113(5):741-55.
- Franeta J, Agbaba D, Eric S, Pavkov S, Aleksic M, Vladimirov S. HPLC assay of acetylsalicylic acid, paracetamol, caffeine and phenobarbital in tablets. *Farmaco*. 2002;57(9):709-13.
- Gawargious Y, Abbas E, Hassan H. Determination of Traces Of Bismuth in Water with Polyurethane Foak Thin-Layer Spectrophotometry. *Anal Lett*. 1988;21(8):1477-86.
- Ge L, Wang S, Yu J, Li N, Ge S, Yan M. Molecularly imprinted polymer grafted porous au-paper electrode for an microfluidic electro-analytical origami device. *Adv Funct Mater*. 2013;23(24):3115-23.
- Ghose AK, Viswanadhan VN, Wendoloski JJ. Prediction of hydrophobic (lipophilic) properties of small organic molecules using fragmental methods: an analysis of ALOGP and CLOGP methods. *J Phys Chem A*. 1998;102(21):3762-72.
- Hameed BH, Din ATM, Ahmad AL. Adsorption of methylene blue onto bamboo-based activated carbon: Kinetics and equilibrium studies. *J Hazard Mater*. 2007;141(3):819-25.
- Hashimoto F, Nonaka G-i, Nishioka I. Tannins and Related Compounds. LXXVII.: Novel Chalcon-flavan Dimers, Assamicains A, B and C, and a New Flavan-3-ol and Proanthocyanidins from the Fresh Leaves of *Camellia sinensis* L. var. *assamica* KITAMURA. *Chem Pharm Bull*. 1989;37(1):77-85.
- Horie H, Nesumi A, Ujihara T, Kohata K. Rapid determination of caffeine in tea leaves. *J Chromatogr A*. 2002;942(1):271-3.
- Huo Q, Li J, Liu G, Qi X, Zhang X, Ning Y, et al. Adsorption desulfurization performances of Zn/Co porous carbons derived from bimetal-organic frameworks. *Chem Eng J*. 2019;362:287-97.
- Ivanescu B, Vlase L, Lungu C, Corciova A. HPLC analysis of phenolic compounds from artemisia species. *Eur Chem Bull*. 2016;5(4):119-23.
- Kumar PS, Ramalingam S, Sathyaselvabala V, Kirupha SD, Murugesan A, Sivanesan S. Removal of cadmium (II) from aqueous solution by agricultural waste cashew nut shell. *Korean J Chem Eng*. 2012;29(6):756-68.
- Li J-M, Meng X-G, Hu C-W, Du J. Adsorption of phenol, p-chlorophenol and p-nitrophenol onto functional chitosan. *Bioresour Technol*. 2009;100(3):1168-73.
- Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliv Rev*. 2001;46(1-3):3-26.
- Marchisio P, Sales A, Cerutti S, Marchevski E, Martinez L. On-line preconcentration/determination of lead in *Ilex paraguariensis* samples (mate tea) using polyurethane foam as filter and USN-ICP-OES. *J Hazard Mater*. 2005;124(1):113-8.
- Muegge I, Heald SL, Brittelli D. Simple selection criteria for drug-like chemical matter. *J Med Chem*. 2001;44(12):1841-6.
- Ogah CO, Obebe OT. Caffeine content of cocoa and coffee beverages in Lagos, Nigeria. *J Innovative Res Eng Sci*. 2016;3(1):404-11.
- Poole CF. New trends in solid-phase extraction. *Trends Anal Chem*. 2003;22(6):362-73.

Pragathiswaran C, Sibi S, Sivanesan P. Comparison studies of various adsorption isotherms for aloe vera adsorbent. *Int J Res Pharm Chem.* 2013;3(4):886-9.

Ramos-Martos N, Aguirre-Gómez F, Molina-Díaz A, Capitán-Vallvey LF. Application of liquid chromatography to the simultaneous determination of acetylsalicylic acid, caffeine, codeine, paracetamol, pyridoxine, and thiamine in pharmaceutical preparations. *J AOAC Int.* 2001;84(3):676-83.

Ruxton C. The impact of caffeine on mood, cognitive function, performance and hydration: a review of benefits and risks. *Nutr Bull.* 2008;33(1):15-25.

Salam SMAAA. Chemically modified polyurethane foam for pre-concentration and separation of inorganic and organic species: Duisburg, Essen, 2008; 2008.

Santos C, Costa J, Santos J, Vaz-Carneiro A, Lunet N. Caffeine intake and dementia: systematic review and meta-analysis. *J Alzheimer's Dis.* 2010;20(s1):S187-S204.

Sena MM, Poppi RJ. N-way PLS applied to simultaneous spectrophotometric determination of acetylsalicylic acid, paracetamol and caffeine. *J Pharm Biomed Anal.* 2004;34(1):27-34.

Talio MC, Acosta MG, Alesso M, Luconi MO, Fernández LP. Quantification of caffeine in dietary supplements and energy drinks by solid-surface fluorescence using a pre-concentration step on multi-walled carbon nanotubes and Rhodamine B. *Food Addit Contam Part A.* 2014;31(8):1367-74.

Thomsen V, Schatzlein D, Mercurio D. Limits of detection in spectroscopy. *Spectroscopy.* 2003;18(12):112-4.

Turnbull D, Rodricks JV, Mariano GF. Neurobehavioral hazard identification and characterization for caffeine. *Regul Toxicol Pharmacol.* 2016;74:81-92.

Veber DF, Johnson SR, Cheng H-Y, Smith BR, Ward KW, Kopple KD. Molecular properties that influence the oral bioavailability of drug candidates. *J Med Chem.* 2002;45(12):2615-23.

Wang S, Li H, Xu L. Application of zeolite MCM-22 for basic dye removal from wastewater. *J Colloid Interface Sci.* 2006;295(1):71-8.

Wanyika HN, Gatebe EG, Gitu LM, Ngumba EK, Maritim CW. Determination of caffeine content of tea and instant coffee brands found in the Kenyan market. *African J Food Sci.* 2010;4(6):353-8.

Wells MJ. Principles of extraction and the extraction of semivolatile organics from liquids. *Sample Preparation Tech Anal Chem.* 2003;162:37.

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