The Eurasia Proceedings of Science, Technology, Engineering & Mathematics (EPSTEM)
ISSN: 2602-3199

The Eurasia Proceedings of Science, Technology, Engineering and Mathematics (EPSTEM), 2025

Volume 37, Pages 286-295

ICEAT 2025: International Conference on Engineering and Advanced Technology

Optimization of Thermal and Temporal Parameters in Ethanol-Assisted Soxhlet Extraction of Bioactive Drugs: A Kinetic Comparison of Eugenol and Caffeine

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Abstract: In this study, the temperature and time parameters for the extraction process of pharmaceutical compounds using a Soxhlet apparatus with ethanol as a solvent were optimized, comparing the kinetics of the compounds (eugenol) from clove buds and (caffeine) from dried Arabica coffee beans. A second-order kinetic model was used, and the effects of temperature (60-75 degrees Celsius), extraction time, and the solute-to-solvent ratio on the mass transfer coefficient KL were studied. The results showed that the efficiency of extracting eugenol compound increased significantly with the rise in temperature, reaching an optimal kL value of 0.019319 min^{-1} at 75 degrees Celsius due to the decrease in solvent viscosity, which led to increased molecular movement, as shown by the results, longer extraction times improved kL, although solvent saturation effects appeared after 6 hours. Conversely, caffeine extraction peaked near ethanol's boiling point at 75°C (kL = 0.004546 min^{-1}), with the solute-to-solvent ratio critically influencing yield—a 1:3 ratio achieved the highest efficiency. The mass transfer coefficient (kL) exhibited a near-linear relationship with both temperature and time, confirming its dominance in extraction efficiency. The second-order model elucidated both processes, demonstrating that temperature (75°C), time (6 hours), and solute-to-solvent ratio (1:3) enhance caffeine yield, offering significant insights for the augmentation of bioactive compound extraction in the pharmaceutical and industrial domains. Subsequent investigations may examine alternate solvents or hybrid methodologies.

Keywords: Eugenol extraction, Caffeine extraction, Soxhlet method, Kinetic modeling, Mass transfer coefficient

Introduction

Eugenol, an influential medicinal compound extracted from cloves (Syzygium aromaticum), is famous for its diverse medical and commercial applications. It is primarily sourced from clove buds and forms a significant component of clove essential oil, contributing up to 90% of its cosmetics (Santos et al., 2009). Eugenol is acknowledged for its antioxidant, antibacterial, and anti-inflammatory attributes, rendering it highly significant in the medicinal and food industries (Haro-González et al., 2021; Olas &Ulanowska, 2021). The extraction of eugenol can be accomplished using many processes, each offering unique advantages and differing efficiency.

The extraction of eugenol from cloves is significant due to its extensive uses in the medicinal, food, and cosmetic sectors. Diverse techniques have been devised to enhance the quantity and purity of eugenol derived from clove essential oil. The methods encompass classic techniques, such steam distillation, as well as advanced methods such as microwave-assisted extraction and supercritical fluid extraction. Every method possesses distinct benefits and limits, which are crucial for identifying the most appropriate strategy for certain industrial applications.

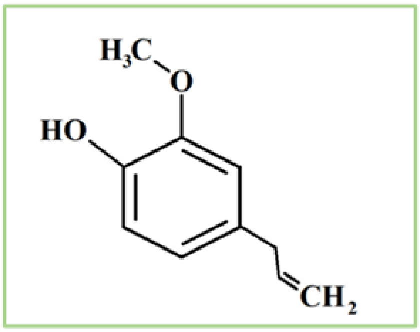

Figure 1. Chemical structure of eugenol (Olas & Ulanowska, 2021).

Benefits and Medical Uses of Eugenol

- ❖ Antimicrobial Properties: Eugenol shows considerable antibacterial efficacy against several pathogenic bacteria, such as Staphylococcus aureus and Escherichia coli, making it beneficial in addressing foodborne pathogens and spoiling organisms (Karm, 2019; Pavesi et al., 2018).
- ❖ Antioxidant and Anti-inflammatory Effects: It functions as a powerful antioxidant, neutralizing free radicals and decreasing oxidative stress, so aiding in the prevention of chronic illnesses, including cancer and cardiovascular problems (Haro-González et al., 2021; Khalil et al., 2017).
- ❖ Analgesic and Anesthetic Uses: Eugenol is employed in traditional medicine as an analgesic for dental and muscular pain, and it also exhibits anesthetic characteristics, which are utilized in dental care products (Salsabila et al., 2023).

Caffeine is an organic compound belonging to the methylxanthine group and is considered one of the most widely consumed stimulants worldwide. Its molecular formula is C8H10N4O2, and it is characterized by being alkaline and acting as a stimulant for the central nervous system (Reddy et al., 2024). Caffeine is naturally found in many plants such as coffee, tea, and cocoa, and it is also included in the composition of many beverages and medications (Saimaiti et al., 2023; Pavithra, 2021(.When caffeine is taken orally, it is rapidly and almost completely absorbed in the digestive system, reaching its peak concentration in the plasma within one hour of consumption. Caffeine is distributed in all body tissues and undergoes major metabolism in the liver by cytochrome P450 enzymes, especially CYP1A2, where it is converted into other compounds such as paraxanthine, theobromine, and theophylline, which also have biological effects similar to caffeine. The rate of caffeine metabolism varies among individuals, and its half-life in the body ranges from 2 to 12 hours depending on genetic, physiological, and environmental factors (Reddy et al., 2024).

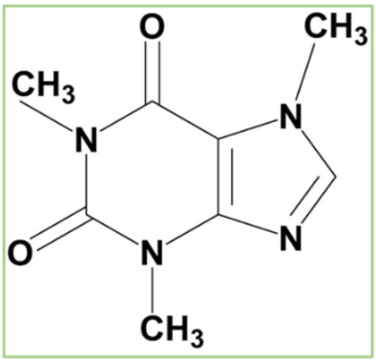

Figure 2. Chemical structure of caffeine (Song et al., 2024)

The extraction of caffeine from Arabic coffee involves different methodologies, each with its own advantages and challenges. These methods range from traditional techniques like Soxhlet extraction to more innovative approaches such as high-pressure and temperature extraction, and the use of deep eutectic natural solvents. Each method aims to improve the yield and purity of caffeine while considering factors such as environmental impact and cost-effectiveness.

Benefits and Medical Uses of Caffeine

- ❖ Improving cognitive functions and alertness :Caffeine acts as a stimulant and an activator of the central nervous system, which in turn leads to increased alertness, attention, and response speed. It blocks adenosine receptors in the brain, helping to reduce fatigue and improve mental performance, especially in cases of little sleep and tiredness (Rodak et al., 2021; Temple et al., 2017).
- ❖ Caffeine and neurological diseases: Studies confirm that moderate caffeine consumption reduces the risk of neurological diseases such as Alzheimer's and Parkinson's disease (Poole et al., 2017; Rodak et al., 2021).
- ❖ Caffeine and its effect on physical performance: There are many studies confirming that caffeine has the ability to improve physical capacity, increase endurance, and enhance muscle strength because it raises adrenaline levels in the body and improves muscle contractions (Rodak et al., 2021).
- ❖ Antioxidant and anti-inflammatory: Caffeine has antioxidant properties, which in turn helps reduce oxidative stress and inflammation in the body. It also contributes to its protective effects against some chronic diseases and cancers (Rodak et al., 2021).
- ❖ Caffeine and the reduction of certain types of cancer: Studies have shown that consuming large amounts of caffeine reduces the risk of developing several types of cancer, including liver, colon, endometrial, rectal, and skin cancer (Poole et al., 2017)
- ❖ Caffeine and its effect on reducing the incidence of heart and vascular diseases: Despite numerous studies indicating that consuming large amounts of coffee raises blood pressure, there are other studies that confirm moderate caffeine consumption reduces the risk of heart disease and strokes, provided the consumer is in good health (Poole et al., 2017).

Methodology

Materials

The materials utilized in this work are listed in Table 1.

Table 1. The list of materials

No	Materials	Properties
1	Dried Coffee Beans (DCB)	From local market
2	Clove buds	From local market
3	Ethanol	purity 99.8 % (v/v) Density 0.789 Molecular weight 64.07 g/ml Manufactured by chem-lab NV-Belgium

Experimental Procedure

Figure (3) shows the experimental apparatus for this process, The extraction process in this study is carried out according to the following:

- ❖ Experimental Design: Before starting the extraction process, the experiment was designed using the Minitab software and adopting the Taguchi experimental methodology to reduce the number of experiments while maximizing the variables. The design included three variables (the ratio of the weight of the dissolved raw material to the weight of the solvent, extraction temperature, extraction time). The design resulted in 25 experiments under different conditions.
- ❖ Sample preparation: The required weights of the raw material (clove buds or DCB) were determined, and five different weights (118, 78, 47, 33, 26) grams were used. Conversely, the weights of the solvent (pure ethanol) were determined based on the ratio used in the experiment according to the design, where five ratios were used (1:1, 1:3, 1:5, 1:7, 1:9).
- ❖ Starting the extraction process: The raw material is placed in the extractor, and the solvent is added to the round-bottom flask. Then, the Soxhlet apparatus is assembled with the condenser placed on top, and the heater mantle temperature is adjusted according to the experimental variables. The device is then turned on, and the extraction process continues for the specified duration according to the experimental design.
- ❖ Mechanism of action: When the heater mantle is heated, the solvent evaporates, then condenses through the condenser and drips onto the raw material. After the extractor is filled, the solvent level rises to return to the round-bottom flask, carrying the extracted materials with it. This cycle repeats throughout the experiment.

Figure 3. Soxhlet extractor.

Kinetic Model of Eugenol and Caffeine Extraction

Numerous studies employed diverse models to characterize the solid-liquid extraction process (Abed et al., 2019; Golshany et al., 2024; Ho et al., 2005; Rakotondramasy-Rabesiaka et al., 2008; Taralkar & Garkal, 2010). The second-order extraction kinetics model, frequently employed in the solid-liquid extraction process, was selected for this study.

$$\frac{dc_t}{dt} = k_L(c_s - c_t)^2 \tag{1}$$

Where:

KL (min^{-1}) is rate constant for2nd-order model, $C_t\left(\frac{g}{L}\right)$ and is the concentration of (caffeine or eugenol) at any time t (min), where the concentration of caffeine and eugenol was determined by examining the extract resulting from the extraction process using the GC-MS device for the clove extract and using the T80 dual-beam absorption spectrophotometer for the caffeine extract, determining the concentration of caffeine and eugenol resulting from the extraction process for each experiment, and $C_S\left(\frac{g}{L}\right)$ is the concentration of (caffeine or eugenol) at saturation (extraction capacity). By grouping variables, equation (2) is obtained:

$$\frac{dC_t}{(Cs - C_t)^2} = k_L\, dt \tag{2}$$

The boundary conditions at t = 0, Ct= 0 and Ct at time t. The integration of the rate equation for a second-order extraction yielded the equation (3):

$$C_t = \frac{C_S^2 k_L t}{1 + C_S k_L t} \tag{3}$$

arrange equation (3) to generate the equation (4):

$$\frac{t}{C_t} = \frac{1}{kLC_S^2} + \frac{t}{C_S} \tag{4}$$

By rearrange equation (4), the rate of extraction (equation 5) can be written as:

$$\frac{Ct}{t} = \frac{1}{(1/k_L C_S^2)+(t/Cs)} \tag{5}$$

When t approaches 0 the initial $\frac{t}{C_t}$ extraction rate, hi as can be written as equation (6):

$$h_i = k_L C_S^2 \tag{6}$$

At any time, the concentration of (caffeine or eugenol) can be expressed as:

$$C_t = \frac{t}{\left(1/h_i\right)+(t/C_S)} \tag{7}$$

Equation (3) can be rearranged to be as shown in equation (8):

$$\frac{t}{C_t} = \frac{1}{h_i} + \frac{t}{C_S} \tag{8}$$

By plotting experimental values of versus t, the values of the initial extraction rate hi, the saturation concentration addition to the constant of 2nd order extraction rate, can be determined using both the slope and intercept.

Results and Discussion

Kinetics of Eugenol Extraction

In Fig. 4, it is evident that the extraction rate gradually decreases over time under all studied operating conditions, where experiments were conducted at different times (4, 5, 6, and 7 hours) and temperatures (60, 65, 70, and 75 degrees Celsius). During the early stages of the process, the rate of transfer of eugenol from the clove buds to the solvent is high, attributed to the high concentration of eugenol in the solid material at the beginning of the extraction. As time progresses, the concentration of remaining eugenol in the cloves gradually decreases, leading to a reduction in its concentration in the extract and a slowdown in the extraction rate regardless of the temperature or time used. However, the results indicate that an increase in temperature or extraction time can lead to a significant improvement in the amounts of extracted eugenol, but the overall extraction rate continues to decline over time due to the gradual depletion of the active ingredient from the solid phase.

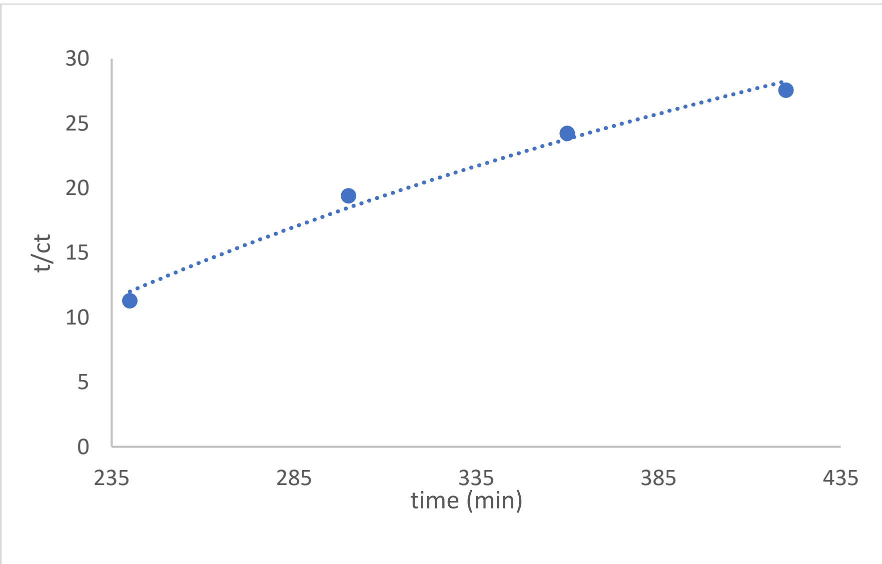

Figure 4. Second-order extraction kinetics of eugenol in Soxhlet method from clove buds at various temperatures

k_LThe values of and hi were calculated by slope and intercept following the linearization process, as shown in Table 2.

Table 2. Parameters of the second-order kinetic model at various extraction temperatures of eugenol extract by ethanol

Temperature °C	KL min^{-1}	hi (g / Lm)
60	0.000957	0.21844
65	0.00963	2.197396
770	0.010678	2.436503
75	0.019319	2.436503

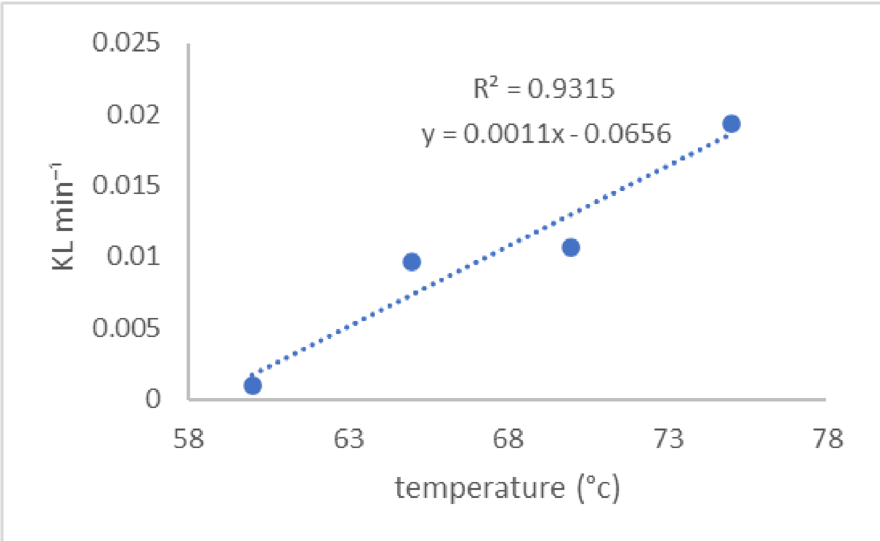

Figure 5. The effect of temperature on the mass transfer coefficient in the process of extracting eugenol.

In figure 5. notice that kL increases with the rise in temperature the reason for that is:
The increase in temperature reduces the viscosity of ethanol which improves mass transfer. Increasing the temperature increases the speed of molecular movement which accelerates the dissolution of eugenol and its transition from solid to solvent. The relationship is almost linear as shown by the value of $R^2 = 0.9315$

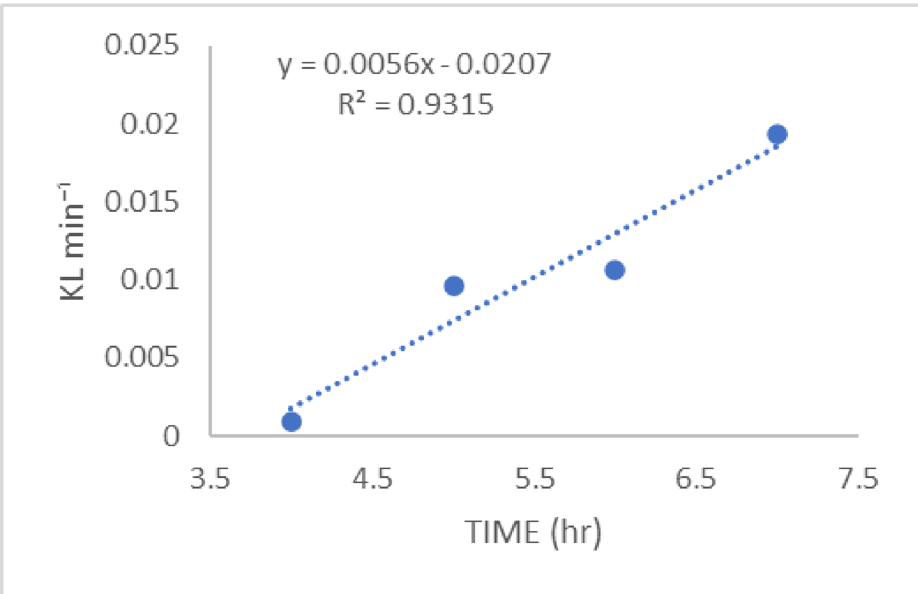

Figure 6. The effect of time on the mass transfer coefficient in the process of extracting eugenol

In figure 6. notice a nearly linear direct relationship between time and the transfer coefficient:

The longer the extraction time, the higher the value KL. The reason is that prolonged contact between the solid (clove buds) and the solvent (ethanol) increases the likelihood of eugenol transferring to the liquid.

The Soxhlet apparatus operates by continuously recycling hot solvent through the sample, making time an important factor in improving the extraction of the target compound. Notice that there is a point (at around 6 hours) where KL decreased. A bit less than expected from the line, which may indicate the beginning of the solvent's saturation with eugenol. Reducing the transfer rate due to the decrease in the concentration of the residual material in the solid sample.

Kinetics of Caffeine Extraction

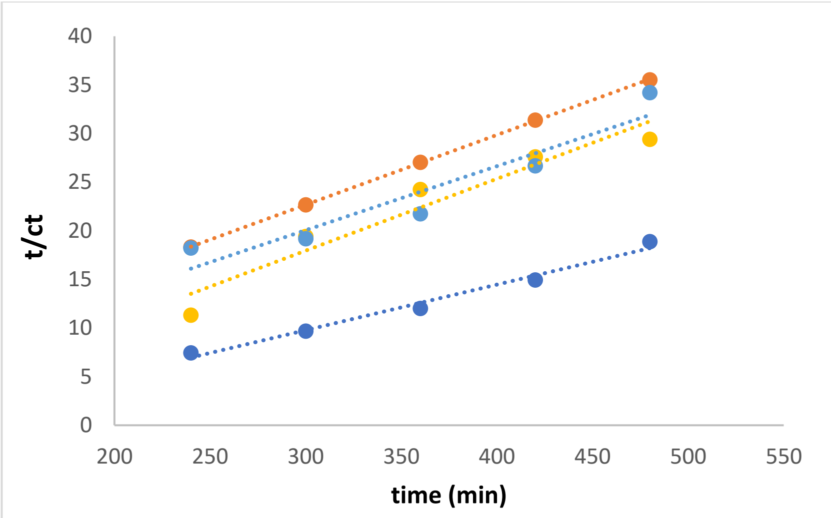

Figure 7. Second-order extraction kinetics of caffeine in Soxhlet method from Coffea arabica L

- orange line: the ratio 1:3
- dark blue line: the ratio 1:1
- yellow line: the ratio 1:7
- light blue line: the ratio 1:9

Fig. 7 showed that the ratio of solute weight to solvent weight had the greatest impact on the behaviour of the extraction process over time, as evidenced by the differences in the positions and slopes of the lines representing the various conditions. Where the ratio 1:3 (orange line) in this experimental condition showed a clear gradient in the values of t/ct over time, indicating a relatively high mass transfer rate under the specified conditions. This ratio represented a balance point between the amount of solid and the amount of solvent, leading to an effective continuation of the extraction process over time. The 1:1 ratio (dark blue line) showed a slowdown in the rate of change of t/ct over time compared to the other conditions. The explanation for this is often due to the rapid saturation of the solvent or weak mass transfer resulting from the small amount of solvent compared to the amount of solid, which limits the continuation of the process with the same efficiency. The ratios 1:7 and 1:9 (yellow and light blue) showed that with the increase in the amount of solvent, the extraction behavior remained stable and efficient, and the rate of change of t/ct over time continued at a good rate, reflecting the achievement of stability in the mass transfer process with reduced saturation effect. Although temperature is an influencing factor, the most apparent effect came from the ratio between solute and solvent, as evident from the variation in the main curves of the graph. The parameters of the second-order kinetic model at various extraction temperatures of caffeine extract by ethanol are shown in table 3.

Table 3. Parameters of the second-order kinetic model at various extraction temperatures of caffeine extract by ethanol.

Temperature °c	KL min^{-1}	$(\boldsymbol{g} / \boldsymbol{Lm})$hi
60	0.000312	0.076735
65	0.000759	0.08865
70	0.002313	0.054878
75	0.004546	0.048699

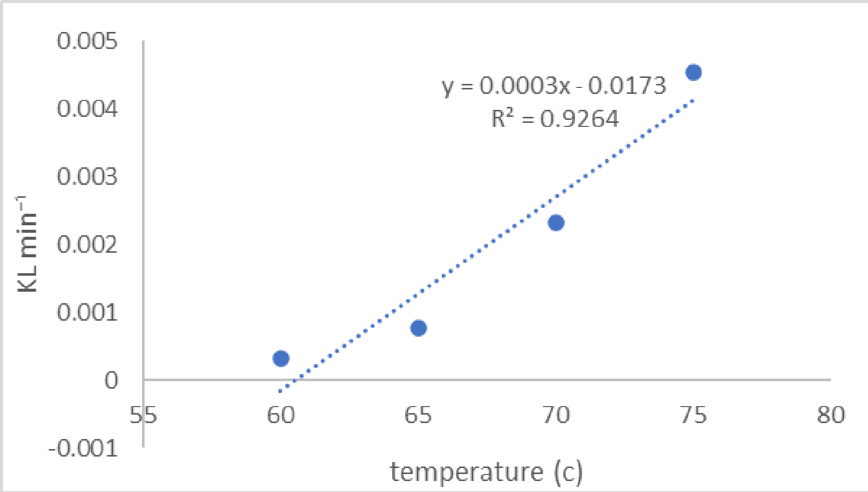

Figure 8. The effect of temperature on the mass transfer coefficient in the process of extracting caffeine

Fig. 8 shows that increasing the temperature leads to improve the value of KL, which means speeding up the transfer of caffeine. A temperature of 75°C provided the highest transfer rate, which is close to the boiling point of ethanol (78.4°C), indicating high efficiency without significant solvent loss.

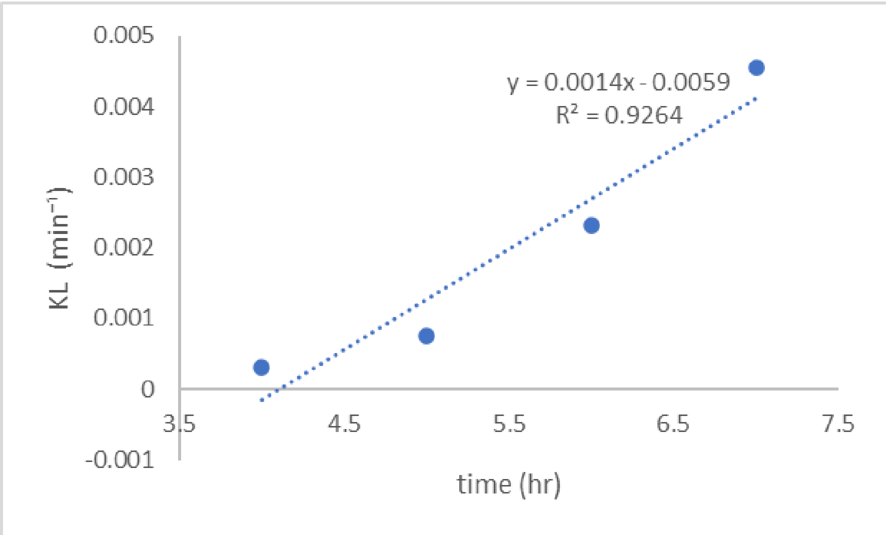

Figure 9. The effect of time on the mass transfer coefficient in the process of extracting caffeine

Fig 9 observes a clear linear direct relationship between time and the mass transfer coefficient. The longer the extraction time, the higher the value of KL, and this makes sense because:

As the hot solvent continues to circulate in the Soxhlet apparatus, more caffeine is continuously extracted from the beans. Increasing time means longer contact between the solvent and the solid increased amount of transferred substances. The Soxhlet apparatus repeatedly boils and condenses the solvent, which makes the time directly affect the amount of extracted material and the efficiency of transfer. There is one point at 5 hours that shows a slight deviation from the line, but its impact is not significant because the determination coefficient is still high.

Effect of KL on Extraction Process

The mass transfer coefficient is the most influential factor in the extraction process, as it directly determines the amount of material transferred per unit time. If kL is low, even under good operating conditions, the process will be slow and uneconomical. In industrial and pharmaceutical processes, the goal is always to increase kL to achieve the highest yield and fastest extraction, which is accomplished by controlling operational factors such as temperature, time, and solvent ratio.

Through the research, it was confirmed that increasing the mass transfer coefficient leads to a significant increase in the extraction yield of both substances (eugenol and caffeine), especially under optimal conditions (relatively high temperature and before solvent saturation).

Conclusion

The present study examined the Soxhlet method with ethanol as the solvent to extract eugenol from clove buds and caffeine from dried coffee beans. The second-order kinetic model proved to be more effective at explaining the extraction mechanism for both compounds. With the highest mass transfer coefficient (kL) seen at 75°C, attributed to lowered solvent viscosity and enhanced molecular movement, the extraction efficiency raised with temperature for eugenol. Additionally, caffeine extraction efficiency increased with increasing temperature, reached its peak close to ethanol's boiling point. Time also was important since longer extraction times raised the mass transfer coefficient and the best time was 6 hours, although effects on solvent saturation were observed beyond ideal durations. Coffee extraction was much influenced by the solute-to-solvent ratio; a 1:3 ratio produced the best efficiency. These results provide valuable information for both industrial and pharmaceutical uses since they show the need of optimizing temperature, time, and solvent ratios to maximize extraction yields for bioactive compounds. More investigation could look at substitute solvents or techniques to improve scalability and efficiency.

Scientific Ethics Declaration

* The authors declare that the scientific ethical and legal responsibility of this article published in EPSTEM journal belongs to the authors.

Conflict of Interest

* The authors declare that they have no conflicts of interest to report regarding the present study.

Funding

* This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Acknowledgements or Notes

*This article was presented as an oral presentation at the International Conference on Engineering and Advanced Technology (ICEAT) held in Selangor, Malaysia, on July 23-24, 2025.

* I would like to express my sincere gratitude to University of Al-Qadisiyah, Chemical Engineering Department.

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To cite this article:

Mohammed, W.N., & Rushdi, S. (2025). Optimization of thermal and temporal parameters in ethanol-assisted Soxhlet extraction of bioactive drugs: A kinetic comparison of eugenol and caffeine. *The Eurasia Proceedings of Science, Technology, Engineering and Mathematics (EPSTEM), 37,* 286-295.