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Development of Effervescent-assisted Liquid Phase Microextraction using 1-dodecanol for Determination of Ketoprofen Drug in Water

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A rapid and straightforward method based on effervescent-assisted dispersive liquid-liquid microextraction combined with high-performance liquid chromatography-ultraviolet (HPLC-UV) detection for preconcentration of ketoprofen in water samples was developed. The extraction efficiency of ketoprofen drug was investigated using 2^3 central composite design. The values of optimum extraction condition were set as 300 µL volume of 1-dodecanol, three pieces of tablets, and 30°C extraction temperature. The runtime was conducted in less than 6 min using a non-polar C_{18} column and an isocratic mobile phase (acetonitrile: water of 40:60 (v/v)) at a controlled flow rate of 1 mL min^{-1}. A good linear response was achieved in the range of 0.01–0.50 µg mL^{-1} (R^2 > 0.990). Detection and quantification limits were calculated at 0.001 and 0.004 µg mL^{-1}, respectively. The average recoveries at three spiking concentration levels were within the range of 85%–108% with RSD < 10% (n = 3). Real sample analysis was fortified using gel and standard solutions, and the calculated values were close to the actual values at 0.059 µg mL^{-1} (KET gel, initial concentration 0.075 µg mL^{-1}) and 4.49 µg mL^{-1} (standard solution, initial concentration 5 µg mL^{-1}), respectively.

Keywords: analgesic drug; central composite design; microextraction

I. INTRODUCTION

Ketoprofen (IUPAC name 2-(3-benzoylphenyl)propanoic acid), which is abbreviated as KET (Figure 1), belongs to non-steroidal anti-inflammatory drugs. KET has medicinal properties such as analgesic and antipyretic drugs. The pharmacological activity of KET is based on the inhibition of the COX-1 and COX-2 activity (Hatami & Farhadi 2013).

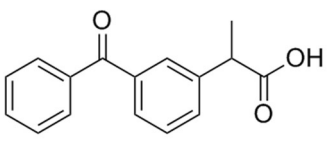

Figure 1. Formula structure of the molecule

Due to various KET applications in medicine, researchers find it challenging to develop a simple, sensitive, and low bias method for residual extraction or simultaneous determination on multiple matrices in which analyte always present at low concentration. Once consumed, 80% of KET is eliminated as an uncharged drug, and its degradation in wastewater is subjected to biological treatment (Kermia *et al.,* 2016). Different analytical methods, including solid phase extraction (Madikizela *et al.,* 2014), solid-phase microextraction (Vera-Candioti *et al.,* 2008), and liquid microextraction (Park & Myung 2015), were applied for the determination of KET in environmental waters.

Sample preparation technique such as solid-phase extraction commonly used for preconcentration and cleaning up the drugs from different samples. This traditional technique put up to major limitations, including tiresome procedures, high cost, and high demand on large volumes of toxic organic solvents. Liquid phase microextraction offers new benefits such as minimal organic solvent usage, fast extraction, high accuracy, and precision. In advanced microextraction exploration, dispersive liquid-liquid microextraction was first introduced by Rezaee *et al.* (2006). The working principle is based on the combination

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of an extraction solvent and a dispersion agent to form fine dispersion when the solvent comes into contact with the aqueous solution. The microextraction becomes a popular method due to its usefulness, simplicity, free energy, low consumption of organic solvents, high enrichment factor, and wide applications for analytes of different polarity (Xiao-Huan *et al.,* 2009; Zgoła-Grześkowiak & Grześkowiak 2011).

Dispersion techniques are commonly accelerated using manual shaking, magnetic stirring, air, vortex, surfactant emulsion, ultrasound, microwave, or effervescent tablets (Leong *et al.,* 2014). An effervescent tablet is a soluble tablet that involves acid-base reaction that produces carbon dioxide (CO_2) bubbles, thus making it possible for fine dispersion of extraction solvent in an aqueous sample (Yıldız & Çabuk 2018). This method is very rapid, effective, and reliable. Previous work indicated an effervescent tablet helps to improve extraction efficiency for the determination of herbicide (Liu *et al.,* 2014) and fungicide (Jiang *et al.,* 2014); however, the study on pharmaceutical drugs as model compounds is still limited.

In the present work, dispersive liquid-liquid microextraction (DLLME) with the acceleration of dispersion mode by effervescent tablets was utilised for the extraction of KET in the water samples. The influence of variables, such as the volume of extraction solvent, number of tablets, and the effect of temperature change was investigated and optimised using response surface methodology namely 2^3 central composite design (CCD). The developed method was then validated using the Association of Official Analytical Chemist (AOAC) criteria to assess their performance.

II. MATERIALS AND METHOD

A. Chemical and Reagents

Ketoprofen standard (purity > 98%) was purchased from Sigma-Aldrich (Steinheim, Germany). Methanol, acetonitrile (HPLC-grade), glycerine, 1-dodecanol (purity 99%), sodium bicarbonate (purity 95%), and sodium hydrogen phosphate (purity 95%) were purchased from Merck (Darmstadt, Germany). Ketoprofen gel 2.5% (Kop brand) was purchased from a local pharmacy. The stock solution of ketoprofen (5 µg mL^{-1}) was dissolved in methanol. The working solutions were prepared by appropriate dilution of the stock solution using deionised water produced by a Milli-Q system (Millipore, Bedford, MA, USA). All the standard solutions were stored at 4°C and brought to ambient temperature before use.

B. Instrumentation

The chromatographic separation was carried out with an HPLC system equipped with an autosampler (SIL-10ADVP), a vacuum degasser (DGU-14A), a system controller (SCL-10AVP), a quaternary pump (LC-10ATVP), an oven (CTO-10ASVP), a detector (SPD-10AVP), and an Apollo C_{18} column (250 mm × 4.6 mm, 5 µm). The final determination of ketoprofen was carried out at the optimum separation condition by HPLC with the isocratic binary mobile phase comprised 40:60 of acetonitrile: water. A flow rate set at 1 mL min^{-1}. The run time was 6 min, and the retention time of KET was integrated at 3.26 min. The optimum wavelength was set up at 252 nm. Injection volume per analysis was 20 µL.

C. Preparation of Tablet

In this study, the effervescent tablets were produced using the wet granulation method. Sodium bicarbonate (1 g) and sodium hydrogen phosphate (1 g) were weighed into a glass mortar, and sufficient ground to achieve homogenous mixing, and adopted as the effervescent precursors. The mixture was then transferred into a weighing boat with the dimension of 44 mm × 44 mm and subsequently added with 1 mL glycerine (binder). The binder was used to enhance the tablet hardness to a level where handling is possible. Finally, the homogenous mixture was transferred into a tablet mould with the dimension of 2.5 cm × 3.7 cm and subsequently compressed for 60 s to produce an effervescent tablet using a tablet press hammer. The effervescent tablets (internal diameter of 15 mm, shown in Figure 2) were stored in a 30 mL plastic bottle with a screw cap at 4°C and brought to ambient temperature before use.

Figure 2. The dimension of the effervescent tablet

D. Extraction Procedure

Deionised water (80 mL) was placed in a 100 mL beaker. Then, X_1 of 1-dodecanol (as the extraction solvent) was added into the beaker. Next, the beaker was placed in a water bath positioned on a hot plate to control water temperature and investigate the effect of temperature change, X_3. Subsequently, the desired number of tablets, X_2 was introduced into the solution for the extraction process. The generation of effervescent occurred from the bottom to the top of the beaker (Figure 3). Thus, it accelerated the KET movement towards the extractant solvent, which was positioned at the top of the solution. Once the effervescent reaction finished, the top portion of the solution (approximately 5 mL) was taken and transferred to a 12 mL vial.

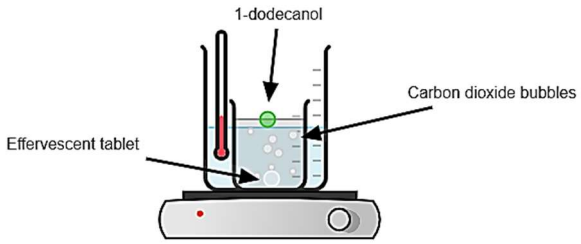

Figure 3. Graphical illustration of the extraction procedure

Then, the solution was vortexed for 5 min before the separated organic phase was collected by a pipette, filtered (0.45 µm cellulose membrane filter), and dissolved in 1 mL of methanol before injected into the LC system for final determination. No adjustment on solution pH and addition of salt was made as the mechanism was based on the acid-base reaction. Thus, acid neutralised carbonate salt, and the reaction was allowed to proceed in a neutral condition. Under an optimum condition, the enrichment factor was calculated using Equation 1:

$$EF = \frac{C_{Org}}{C_{aq}} \quad (1)$$

where C_{Org} and C_{aq} are the concentrations of KET in organic and aqueous phases, respectively.

E. Experimental Design

In CCD, 16 experiments were conducted randomly to minimise the bias of uncontrolled variables, and the respective design matrix is shown in Table 1. Three variables, namely volume of extraction solvent (X_1), number of effervescent tablets (X_2), and extraction temperature (X_3), were subjected to optimisation in this study. Satisfaction rotate-ability was set at $\alpha = \pm 1.68$. The peak height was selected as the response (i.e., dependent variable) of the study.

Table 1. Experimental variable and their levels

Parameter	-α	-1	0	+1	+α
Effect of extraction solvent (X_1)	132	200	300	400	468
Effect no. of tablet (X_2)	1	2	3	4	5
Effect of temperature (X_3)	13	20	30	40	47

The main effects, interaction effects, and quadratic effects were optimised and evaluated through this design. A 2^3 full factorial design of CCD was generated with STATISTICA version 10 (TIBCO software, Germany). A quadratic model was developed between the dependent and independent variables. The most important effects and variable interactions were assessed following Analysis of Variance (ANOVA). A p-value < 0.05 in the ANOVA table indicates the statistical significance of an effect at a 95% confidence level, including the decision either the model is accepted or rejected. Three-dimensional graphs were used to evaluate the interactive effect of two variables on the response.

F. Method validation

An analytical figure of merits was evaluated based on linearity, precision, accuracy, the limit of detection, and limit of quantification. A calibration curve was obtained by a series of six standard solutions ranging from 0.01 to 0.50 µg mL^{-1}. Detection and quantification limits were calculated using the linear regression method. The lowest concentration spiked was 0.01 µg mL^{-1}, and triplicate analysis was performed. The extraction recovery was calculated using the following mathematical expression (Equation 2):

$$\%\ ER = EF \times \frac{V_{Org}}{V_{aq}} \times 100\% \quad (2)$$

where V_{Org} and V_{aq} are the concentrations of KET in organic and aqueous phases, respectively.

Concentration levels tested at 0.5, 0.1, and 0.03 μg mL^{-1}, respectively. The precision was evaluated through the repeatability (intra-day), and reproducibility (inter-day) assay of the method with water samples spiked with KET. Both assays were calculated as %RSD with respect to the measurements made in triplicate (n=3). Concentration levels tested at 0.5 and 0.1 μg mL^{-1}, respectively. For real sample analysis, water samples were extracted in the same manner, and the standard addition method was applied.

III. RESULT AND DISCUSSION

A. Optimisation of CCD model

The optimisation plot (Figure 4) shows the predicted conditions for the optimum point and the desirability of the prediction. The second-order polynomial equation obtained for the optimised variables is given by Equation 3:

$$\text{Peak Height} = 8978 + 598X_1 + 768X_2 + 66X_3 - 967X_1^2 - 1915X_2^2 - 3200X_3^2 - 1238X_1X_2 + 1549X_1X_3 - 506X_2X_3$$

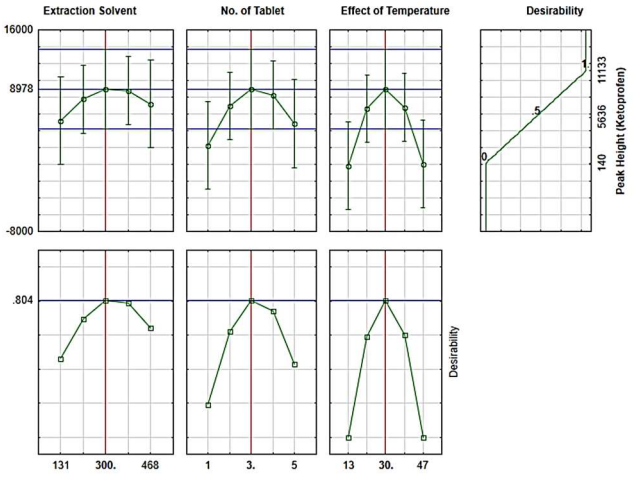

Figure 4. Optimiser plots for studied variables

The positive or negative sign reveals the case when the response (i.e., peak height) is enhanced or reduced, respectively, when passing from the lowest to the highest-level set for a specific variable (Vidal *et al.,* 2007). For interaction effects, a positive value gives a good sign that the response will increase once both variables change to the same level, such as X_1X_3. The ANOVA summary showed that the model was significant, with *p*-value < 0.05. The R^2 statistic indicated that the model explained 87% of the variability. The adjusted R^2 was calculated at 84% of the variability. An excellent fitted model should have a minimum R^2 of 80% (Joglekar & May 1987).

In this model, the desirability function of 0.80 was recorded. Desirability function takes values between 0 and 1, where 0 corresponds to a completely undesirable value and 1 to a completely desirable value (Joglekar & May 1987). The desirability of 1 was assigned for the maximum response of peak height (11133), 0.5 for the middle (5436), and 0 for the minimum (140). A lack-of-fit *p*-value of 0.72 implies that it is not significantly associated with the pure error. Thus, the acquired dataset is reliable.

The optimum working condition of extraction procedures as suggested by the model is 300 μL 1-dodecanol, 3 pieces of tablets, and 30°C extraction temperature. A *p*-value < 0.05 signifies the statistical significance of an effect at a 95% confidence level (Table 2). The enrichment factors were recorded at 89. Good enrichments are needed to increase the high probability of extraction, especially when dealing with a low-level concentration of pollutant like KET.

Table 2. Analysis of variance (ANOVA) for the second-order regression model

Factor	SS	Df	MS	F	P
(1) Extraction Solvent (L)	489346	1	489346	0.652	0.450
Extraction Solvent (Q)	883844	1	883844	1.178	0.319
(2) No. of Tablet (L)	807001	1	807001	1.076	0.339
No. of Tablet (Q)	3399552	1	3399552	4.533	0.047
(3) Effect of Temperature (L)	5957	1	5957	0.007	0.931
Effect of Temperature (Q)	9491115	1	9491115	12.657	0.011
1L by 2L	1226115	1	1226115	1.635	0.248
1L by 3L	1919520	1	1919520	2.559	0.160
2L by 3L	205436	1	205436	0.273	0.619
Error	4499074	6	749845		
Total SS	19365653	15			

The normality assumption was satisfied as to the residuals in the plot distributed along a straight line (Figure 5). The errors were normally distributed, and there were no critical violations of the assumptions that underlay the analysis. This latent information will ensure that the model provides an adequate approximation to the optimisation process (Khodadoust *et al.,* 2013).

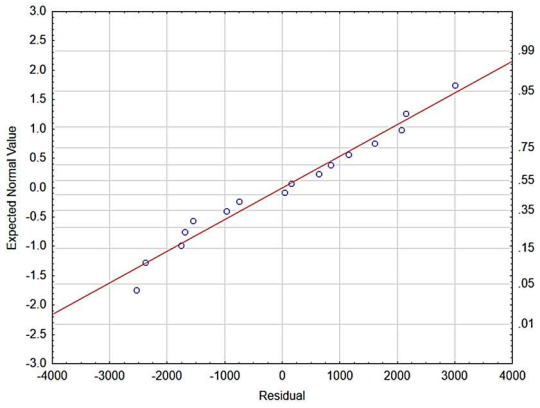

Figure 5. Normal probability plot

B. Effect Volume of Solvent Extraction

The effect of the volume of 1-dodecanol (extracting solvent) on the extraction efficiency was investigated. An ideal volume required is important to determine if KET is effectively extracted in the organic phase. The results illustrated in Figure 6 show that by increasing the volume of 1-dodecanol, the peak height response increased and reached 300 µL. For the remaining volume, the response remained constant or insignificantly different. The 1-dodecanol (log k_{ow} 5.13) becomes a good extractant as the solvent fulfils several requirements, such as immiscible with water, capable of dissolving analyte in water, low volatility, low density (0.830 mg L^{-1}), and low melting point below room temperature (Przyjazny, 2019). 1-dodecanol is a good extraction solvent owing to its hydrophobic end and hydroxyl group that can extract target analytes by hydrophobic or hydrogen bond effect (Hu *et al.,* 2017).

Similar to other non-steroidal anti-inflammatory drugs (NSAIDs), KET has high log P = 3.12, which implies that the compound is preferred in an organic phase. The contribution of 1-docecanol to extract KET in the CCD model reached 36.09%. The elliptical contour plot designated a significant interaction between extraction solvent volume and number of tablets on the effectiveness of KET extraction. When a low volume of 1-dodecanol and a small number of tablets were introduced into water samples, the extraction efficiency was low. This may be attributed to the facts that when a low amount of 1-dodecanol was used, the effective surface areas for adsorption process reduced and the acceleration of dispersion phenomena decreased due to insufficient tablets (Khodadoust *et al.*, 2013).

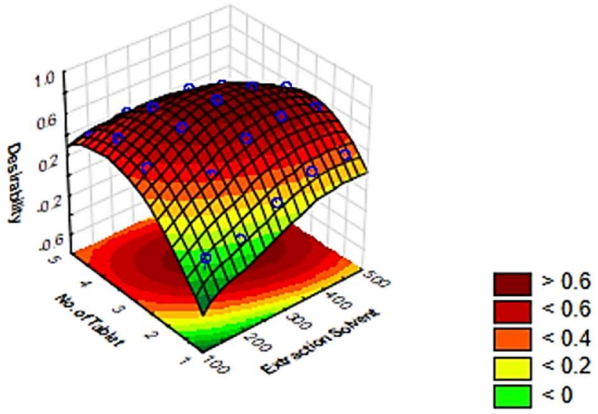

Figure 6. 3D response of interaction term between no. of tablet *vs* extraction solvent

C. Effect Number of Tablets

Adding a high number of effervescent tablets to an aqueous sample can produce more bubbles and accelerate the dispersion of the extraction solvent but simultaneously induce the increment of ionic strength and viscous resistance effect (Li *et al.,* 2019). In this work, 3 tablets were sufficient to assist 1-dodecanol for extracting KET in the aqueous phase. The formation of CO_2 bubbles was a quick process, and the probability of bicarbonate ions to come in contact with hydrogen ions was affected by temperature. The higher the temperature, the faster the molecules moved to the top of the aqueous solution, which led to the enrichment of KET by 1-dodecanol. The role of the tablets in enhancing the peak height response contributed up to 59.52% (Figure 7). Thus, it gave a good sign that the effectiveness of analyte transfer highly depends on the formation of CO_2 bubbles, which were generated in the condition without external energy.

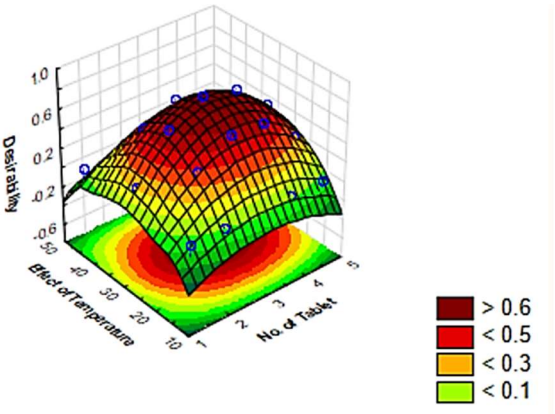

Figure 7. 3D response of interaction term between the effect of temperature *vs* no. of tablet

D. Effect of Temperature Change

Temperature affects the mass transfer process and thus influences extraction efficiency. The influence of extraction temperature was investigated in the range of 13–47°C. This range included the melting point of 1-dodecanol at 24°C. The response of peak height showed an increment from 13 to 30°C but decreased significantly afterwards. At low temperature, 1-dodecanol tends to remain in solid form, thus making extraction inefficient because the dissolution of tablets is still incomplete. The contour line appeared in a circular pattern, which indicated sensitive interaction effects between the number of tablets and temperature change at a narrow scale. Thus, at a suitable condition, the adjustment of temperature has a synergistic effect towards solvent extraction, by considering 57.28% contribution of the interaction of X_1X_3 (Figure 8).

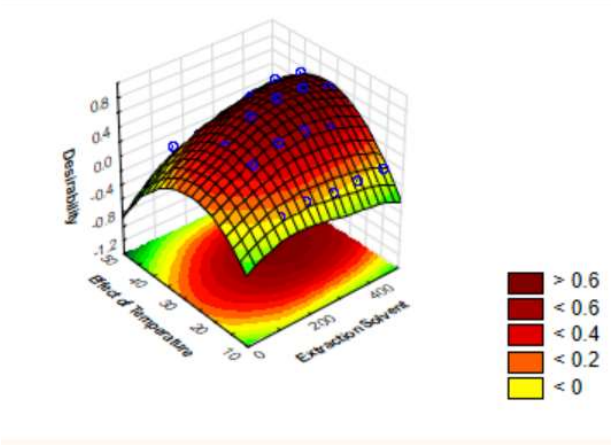

Figure 8. 3D response of interaction term between the effect of temperature *vs* extraction solvent

E. Analytical Figure or Merits

A good linearity range was achieved at a satisfactory level of R^2 > 0.990. The sensitivity of the developed method was shown by calculating the limit of detection and quantification (LOD and LOQ), which were recorded at 0.001 and 0.004 µg mL^{-1}, respectively. Good extraction recovery of 85%-108% was recorded when three concentrations of spiked KET (0.5, 0.1, and 0.03 µg mL^{-1}) were introduced into matrix samples. The repeatability test indicated low bias measurement (i.e., < 10 RSD), which was below the acceptable value proposed by AOAC guidelines.

Table 3. Analytical performance of the extraction method for determination ketoprofen in water samples

Merit	Ketoprofen
Linearity, r^2	0.990 (range 0.01–0.50 µg mL^{-1})
LOD	0.001 µg mL^{-1}
LOQ	0.004 µg mL^{-1}
ER	85-108%
RSD (Intra-day), n = 3	0.05 µg mL^{-1} (8); 0.01 µg mL^{-1} (10)
RSD (Inter-day), n = 3	0.05 µg mL^{-1} (1); 0.01 µg mL^{-1} (10)
Real sample	0.059 µg mL^{-1} (KET gel, 0.075 µg mL^{-1}); 4.49 µg mL^{-1} (standard solution, 5 µg mL^{-1})

To evaluate the efficiency of the proposed method, tap water samples were fortified with KET gel, and standard solutions were studied. The results showed acceptable extraction recoveries for the spiked samples, calculated at 0.059 µg mL^{-1} (KET gel, 0.075 µg mL^{-1}) and 4.49 µg mL^{-1} (standard solution, 5 µg mL^{-1}), respectively (Table 3). Chromatographic detection of spiked standard solution and KET gel, as shown in Figure 9.

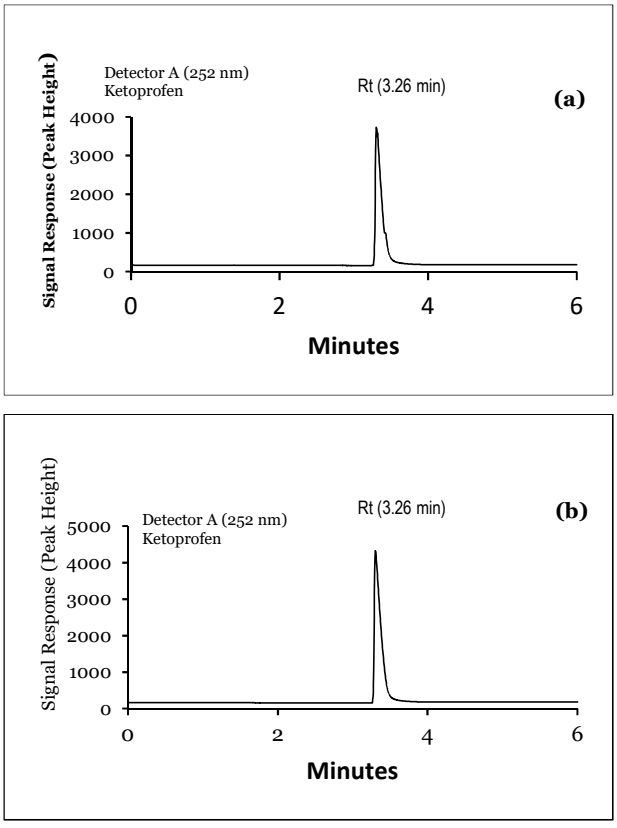

Figure 9. Chromatograms of KET detection in (a) standard solution, 0.01 µg mL^{-1} and (b) spiked solution contain KET gel

F. Comparison with other Methods

No similar analytical techniques to determine KET in water samples using effervescent-assisted microextraction were found in the literature. Thus, a comparison with the analytical figure of merits is subjected to other extraction techniques, which have been reported previously by researchers. The developed method shows comparable performance in terms of recovery assay. Thus, it is proven that the replacement of the halogenated solvent with 1-dodecanol does not detriment method capability. The application of effervescent tablets indirectly leads to the elimination of energy dependence on the acceleration of fine dispersion. Limit of detection may reach lower value if determined using sophisticated methods, such as liquid chromatography (LC-MS) that reflects the sensitivity levels of the instrument itself. Nonetheless, the enrichment factor calculated in this work reported higher than literature studies, EF < 12 (Park & Myung 2015). A comparison of the represented method with other approaches reported in the literature for the extraction of KET in water samples is given in Table 4.

Table 4. Comparison of method performance with other extraction techniques

Method	Instrument	LOD ($\mu g\ L^{-1}$)	%ER
SPE[a]	HPLC-PDA	0.08	83-102
SPME[b]	LC-DAD	2.2	-
DLLMME[c]	UHPLC-DAD	0.5	89.1-132
DLLME[d]	LC-MS-DAD	0.88	98-102
DLLME[e]	LC-MS	0.0003	76
This work	HPLC-UV	1.0	85-102

[a] Madikizela *et al.* 2014, [b] Vera-Candioti *et al.* 2008, [c] Montesdeoca-Esponda *et al.* 2008, [d] Park & Myung 2015, [e] Zgoła-Grzeskowiak *et al.* 2011

IV. CONCLUSION

The research work illustrated the successful application of the dispersive liquid-liquid microextraction combined with the effervescent tablet as a dispersive agent. The chemometric approach, namely 2^3 central composite design, was operated to find the optimal condition for microextraction. The statistical model and 3D response surfaces showed detail effect of factors on each variable and also on the extraction efficiency in combination mode. The optimised method shows good performance to extract KET drug in water samples at low-level concentration. Low bias values obtained in calculated data explain that the method seems suitable to use for routine analysis. In addition, the developed method may be utilised for the determination of other NSAID drugs to strengthen the effectiveness in future work.

V. ACKNOWLEDGEMENTS

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