Extraction selectivity: A novel tool for green process development and design of solid-liquid extractor

Umar Isah Abubakar[1]* Lee Suan Chua[2]** and Ramalan Abdul-Aziz[3]

[1]*Product and Process Development (PPD) Research Group, Department of Chemical Engineering, Ahmadu Bello University, Zaria, Nigeria.*
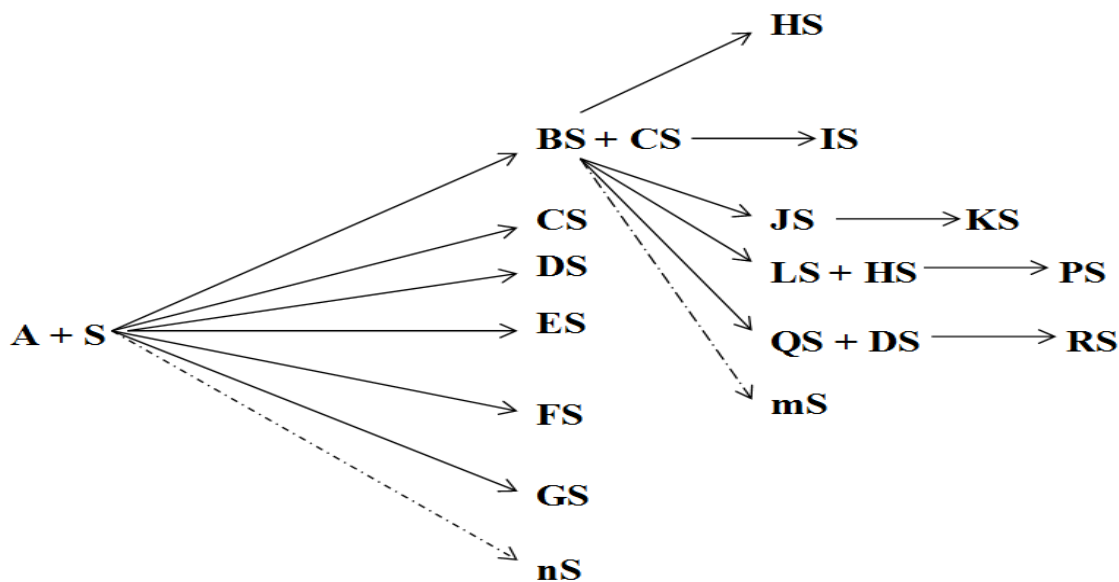[2]*Institute of Bioproduct Development (IBD), Universiti Teknologi Malaysia, Johor, Malaysia.*

*Corresponding author, Email address: iaumar@abu.edu.ng.
**Corresponding author, Email address: lschua@ibd.utm.my.

Graphical Abstract

Multiple competing solid-liquid extractions (SLEs) of desired and undesired extracts in series with multiple transformations of desired extract and its complex reactions with undesired extracts

*Corresponding author.
E-mail address: iaumar@abu.edu.ng.

Abstract

In process synthesis, design, and optimization of solid-liquid extractor, extraction yield (EY) has been the only process parameter used for centuries in determining the process performance. Solid-liquid extraction (SLE) is one of the crucial units in phytochemical processing. This communication introduces a concept of extraction selectivity (ES) as a new tool for green process analysis, design and development of solid-liquid extractor that overcomes the limitations of EY. New and simple equations have been developed based on the fundamental concepts of physical sciences, chemical, and process engineering. In addition, it proposes new schemes for the green SLE based on the concept of multiple extractions analogous to multiple reactions. Some of the equations were employed in the analysis of green SLE of andrographolide water extract and other phytochemical compounds from *Andrographis paniculata* (AP) as a case study. It was found that the performance indicator, ES is more sensitive and pronounced to changes in the process variables of SLE than EY.

Keywords: Extraction yield (EY); Extraction selectivity (ES); Multiple extractions; Green product and process development; Andrographolide water extract; *Andrographis paniculata*.

1. Introduction

For centuries, extraction yield (EY) has been the only process parameter for analyzing the solid-liquid extraction [1-33]. However, since EY relates the product extract(s) to the whole amount of feed rather than the actual quantity of feed that disappeared or consumed in the extraction, it has some limitations. Among other serious shortcomings, EY cannot accurately give the real performance and clearly reveal the effects of process variables on the extraction. The normal plot or equilibrium curve of EY experimental data generally follows the exponential growth and steady stationary curves. Moreover, EY cannot be conveniently and efficiently used as a criterion for quick evaluation of process economic potentials in either the so-called solvent selective single or multiple extraction(s) prior to the detailed profitability analysis and for minimization of undesired side extraction(s) that occur along with the desired extraction in multiple extraction(s). The SLE is one of the oldest practice unit processes or unit operations. It is the process of leaching out soluble components from multi-component solid mixture by contacting with the suitable solvent that selectively dissolves some but not all components in the solid. According to Johnson and Lusas [34], the ideal solvent does not exist based on the experience and practice. It is difficult to find a solvent that combined all of the properties of good solvent. A solvent that is abundant, inexpensive, nontoxic, nonreactive, non-flammable, stable, and selective to a single product of extract with high yield and purity. The SLE is mainly used in the production of sucrose from sugar beet, lipids from oil seeds, and phytochemicals from plants, etc [35-38]. The selectivity term is not new in the process industry or academia [39-45]. However, there is confusion within the industry

and academia about the actual meaning of selectivity. Most of the academicians and professionals are attributing this powerful process parameter to the only solvent selectivity or catalyst selectivity [1-2,46-53]. Again, most of the definitions given for selectivity are not well presented, cumbersomely defined and difficult to comprehend or in relative terms of desired and undesired products [40, 41, 44, 54-55] except the definitions given by Smith [43], and Wells and Rose [42]. This paper introduces a new concept called "extraction selectivity (ES)" as a novel tool for performance indication, and a criterion for the process analysis, design and development of solid-liquid extractor that overcomes the limitations of EY. It also proposes new schemes for the green or non-green SLE based on the concept of multiple extractions similar to multiple reactions. New and simple equations for estimating the two (2) basic forms of selectivity have been developed based on the fundamental concepts of physical sciences, chemical, and process engineering.

2. Material and Methods

2.1 Material and method development

In the development of new techniques for estimating ES, we combined the fundamental concepts of physical sciences, chemical, and process engineering. The green SLE of andrographolide from AP was used as a case study. The dried leaves of AP were purchased in ground form from Fidea Resource Sdn Bhd, and authenticated by Forest Research Institute of Malaysia (FRIM) with ID No.: SBID002/13. The sample was stored in a cool room at Institute of Bioproduct Development (IBD), Universiti Teknologi Malaysia (UTM). The samples were conditioned in an oven at 50 °C for 24 hours before extraction. Distilled water was collected from IBD pilot plant. Standard chemical of andrographolide (98 %) was procured from Sigma Aldrich®, USA. Deionized water was produced from NANOpure Diamond^{TM} Barnstead, USA. Methanol was of HPLC grade obtained from QRëc®, Malaysia. The extraction was performed in an automated pressurized liquid extractor (PLE), utilizing Dionex ASE 100®, USA under isothermal conditions at temperatures of 80°C, 100°C, and 120°C. In the sensitivity analysis of ES in comparison with EY, a set of 12 experimental runs were planned using design of experiment (DoE). The experiments were performed randomly under isothermal condition at 80°C based on the complete factorial experimental design (CFED) with center points as shown in Table 1. The statistical analysis was performed with aid of Design Expert software package version 9 (Stat Ease Inc., Minneapolis, USA). Then, the detailed investigations of the dependence of ES in comparison with EY on the process variables were examined at various conditions [56]. A high-performance liquid chromatography (HPLC), Waters 2690 Alliance equipped with Waters 996 photodiode detector absorbance (PDA) and auto sampler, USA, was employed for the analysis of the green extracts.

Table 1. Ranges and coded levels of independent process variables for CFED

Process variable	Range and level			
	Symbol	-1	0	+1
Solid-liquid ratio (g/mL)	A	1/50	3/50	5/50
Particle size (mm)	B	0.175	0.605	1.200
Time (min)	C	5	15	25

### 2.1.1   Holistic approach to process analysis of solid-liquid extraction

In reality, the SLE of phytochemical compound from plant materials using green or non-green solvents results into the product of multiple extracts [57-54]. In the multiple extractions, the process involves the extraction of the desired extract, other undesired extract(s), and undesired product(s) of a single or multiple transformation(s) and reaction(s). Generally, multiple extractions proceed in parallel. However, the product extract(s) can likely undergo multiple reactions in parallel, or in series, or in a combination of parallel and series (complex), or in separate independently. New schemes for the SLE are proposed based on the concept of multiple extractions similar to multiple reactions as shown in the following schemes 1 to 7 [1-2].

Scheme 1. *Single SLE of desired extract*
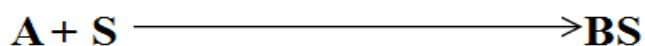
Scheme 1 represents the case of having a single solid-liquid extraction of desired extract **B** in solvent **S** from solid material **A.**
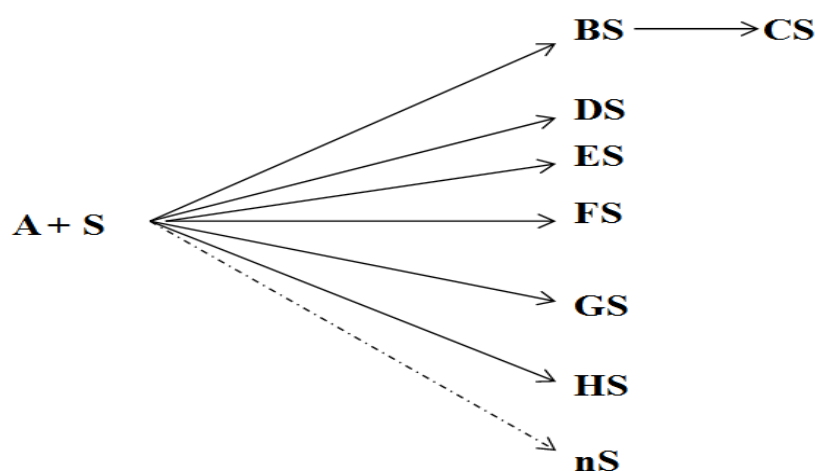
Scheme 2. *Multiple competing SLEs of desired and undesired extracts*
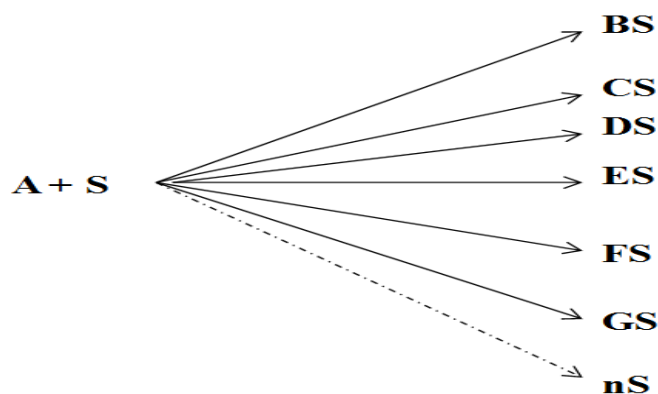
Scheme 2 illustrates the situation of having multiple competing solid-liquid extractions of desired extract **B** in solvent **S** and unwanted extracts **C, D, E, F, G** in solvent **S,** and unknown unwanted extracts **n**
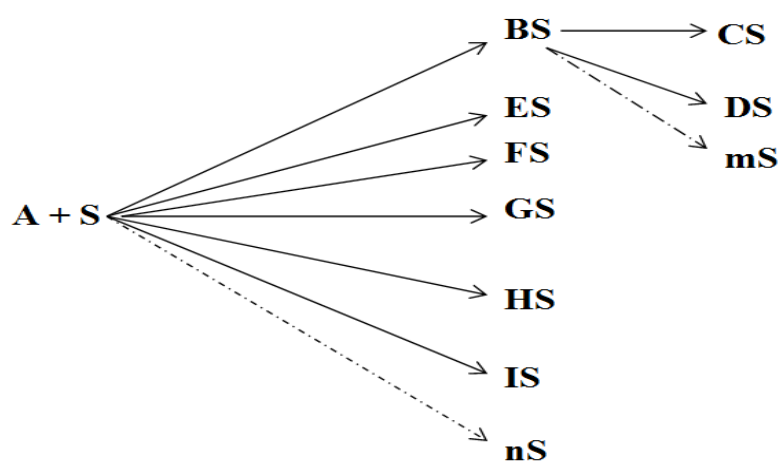
represented by dash line arrow in solvent **S** from solid material **A**.

Scheme 3. *Multiple competing SLEs of desired and undesired extracts in series with single transformation of desired extract*

Scheme 3 depicts the scenario of having multiple competing solid-liquid extractions of desired extract **B** in solvent **S** and undesired extracts **D, E, F, G, H** in solvent **S,** and unknown unwanted extracts **n** represented by dash line arrow in solvent **S** from solid material **A** in series with single transformation of desired extract solution into product **CS**.
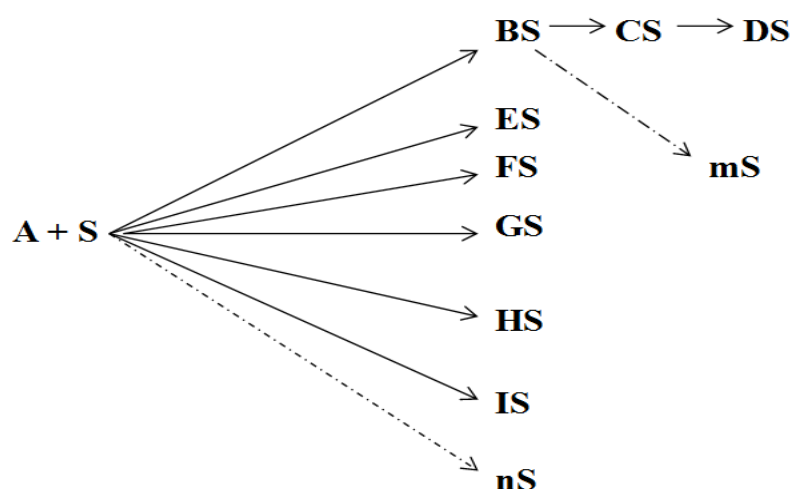
Scheme 4. *Multiple competing SLEs of desired and undesired extracts in series with multiple competing transformations of desired extract into unwanted products*

Scheme 4 exhibits the circumstance of having multiple competing solid-liquid extractions of desired extract **B** in solvent **S** and unwanted extracts **E, F, G, H, I** in solvent **S,** and unknown unwanted extracts

n represented by dash line arrow in solvent **S** from solid material **A** in series with multiple competing transformations of desired extract solution **BS** into solution of undesired products **CS, DS,** and unknown unwanted products of transformations **mS** represented by dash line arrow.
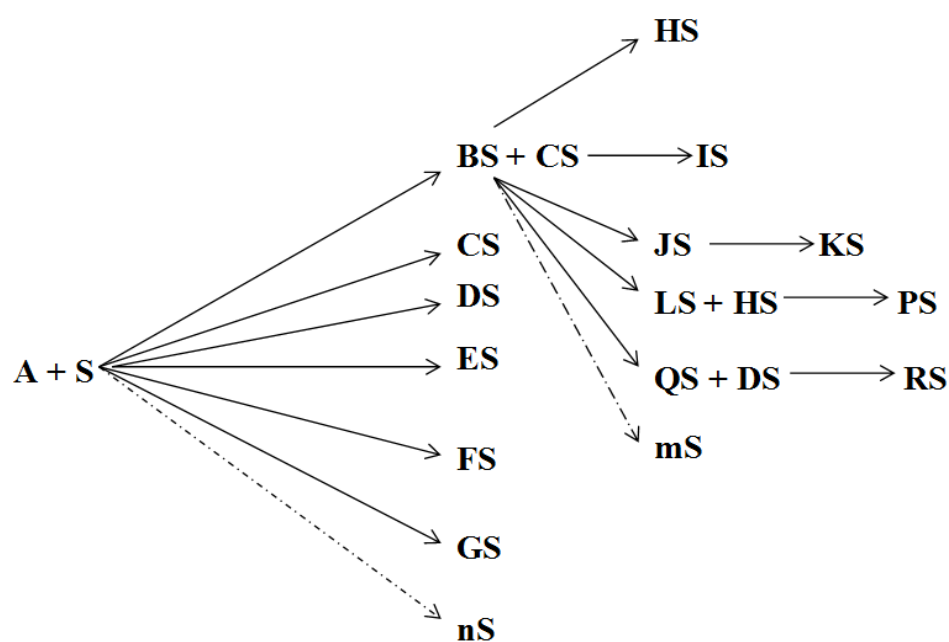
Scheme 5. *Multiple competing SLEs of desired and undesired extracts in series with multiple consecutive transformations of desired product extract*
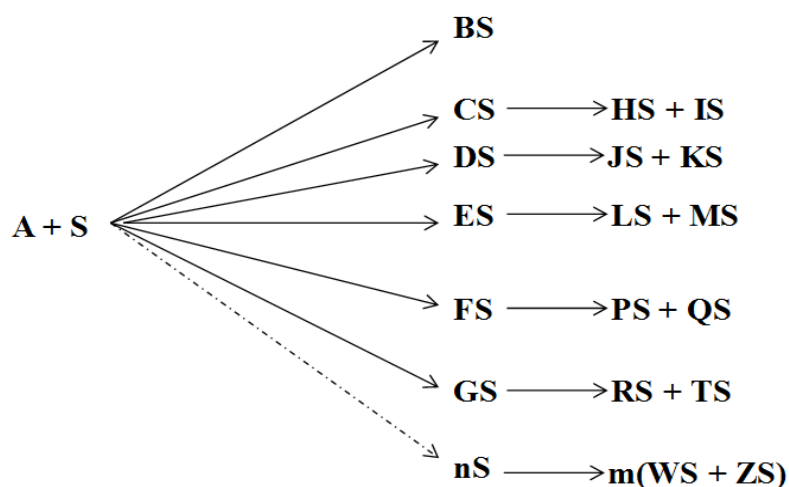

Scheme 5 represents the situation of having multiple competing solid-liquid extractions of desired extract **B** in solvent **S** and undesired extracts **E, F, G, H, I** in solvent **S,** and unknown unwanted extracts **n** represented by dash line arrow in solvent S from solid material A in series with multiple competing transformations of desired extract solution BS into unwanted products of CS to DS, and unknown unwanted products of transformations mS represented by dash line arrow.

Scheme 6. *Multiple competing SLEs of desired and undesired extracts in series with multiple transformations of desired extract and its complex reactions with undesired extracts*

Scheme 6 illustrates the scenario of having multiple competing solid-liquid extractions of desired extract **B** in solvent **S** and undesired extracts **C, D, E, F, G** in solvent **S,** and unknown unwanted extracts **n** represented by dash line arrow in solvent **S** from solid material **A** in series with multiple competing transformations of desired extract solution **BS** into unwanted products of **HS, JS** to **KS, LS** and **HS** to **PS, QS** and **DS** to **RS,** and unknown unwanted products of transformations **mS** represented by dash line arrow, and complex reactions of desired extract solution (**BS**) and undesired extract solution (**CS**) to unwanted product (**IS**).

Scheme 7. *Multiple competing SLEs of desired and undesired extracts in series with multiple independent transformations of undesired product extracts*

Scheme 7 exhibits the case of having multiple competing solid-liquid extractions of desired extract **B** in solvent **S** and undesired extracts **C, D, E, F, G** in solvent **S,** and unknown unwanted extracts **n** represented by dash line arrow in solvent **S** from solid material **A** in series with multiple independent transformations of undesired extracts **CS, DS, ES, FS, GS, nS** solution into unwanted products of **HS** and **IS, JS** and **KS, LS** and **MS, PS** and **QS, RS, TS,** and unknown unwanted products of transformations **m (WS** and **ZS),** respectively.

2.1.2   A case study of solid-liquid extraction of andrographolide from AP

The phytochemical qualitative screening and HPLC quantitative analysis for the green SLE of andrographolide water extracts from AP have shown the presence of both the primary and secondary metabolites.

Table 2. Phytochemical qualitative analysis of AP green extracts

| Constituents	Test	Observation	Inference
Carbohydrates	Molisch's test	A purple to violet coloration at interface	Present
Free reducing sugars	Fehling's test	A brick red precipitate formed	Present
Cardiac Glycosides	Salkowsk's test	A layer of reddish-brown color formed	Present
Tannins	Lead Sub-Acetate test $FeCl_3$ test	A color precipitate formed A blue-black precipitate formed	Present Present
Flavonoids	Shinoda's test NaOH test	A green color and heavy precipitate formed Yellow coloration formed	Present Present
Terpenes/steroids	Liebermann Burchard's test	A violet blue and finally green formed	Present
Alkaloids	Dragendoff's test Meyer's test Wagner's test	A blue-blackish precipitate A precipitate formed A white precipitate	Present Present Present
Saponins	Frothing test	A honey comb formed	Present
Anthraquinones derivatives	Borntrager's test	A pink color formed	Present
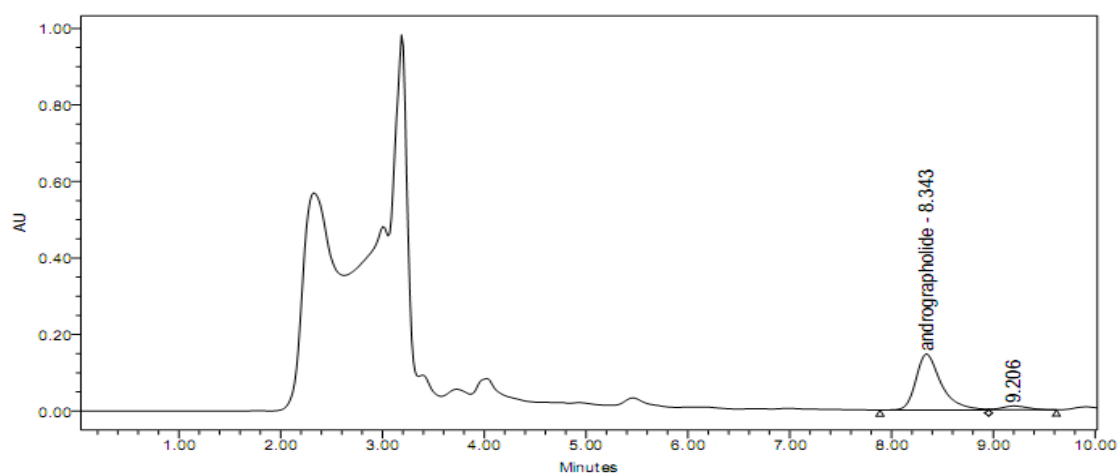
Figure 1. HPLC chromatogram of green extracts of *Andrographis paniculata*.

These include carbohydrates, free reducing sugars, cardiac glycosides, tannins, flavonoids, terpenes/steroids, alkaloids, saponins, and anthraquinones derivatives as shown in Table 2 and Figure 1. The identification and quantification of the andrographolide marker compound of the AP was performed using HPLC with aid of standard chemical of andrographolide procured from Sigma Aldrich, USA. The detection and measurement of andrographolide concentration were best observed at 223 nm using isocratic method with HPLC grade methanol: water system by modifying the ratio of methanol to water system (60:40) as the mobile phase.

The results obtained from our case study and some of the published reports for the SLE of andrographolide in accompany with other phytochemical compounds from AP can be best described to proceed based on the scheme 6 above of the new proposed schemes as depicted in Figure 2. The sequences of multiple competing green SLE of andrographolide with other phytochemical compounds from AP in series with multiple reactions of andrographolide and other phytochemical compound(s) in parallel or/and series is considered as a case study for demonstration. The letters in the scheme represent the following: **A**–AP*,* **S**–green solvent(water), **BS**–andrographolide (desired extract) in green solvent (water), undesired extracts (**C**–apigenin, **D**–glucose, **E**-7-O-methyl wogonin, **F**-skullcapflavone I, **G**-andrographidines A, B, C, D, E, and F; and **H**–unknown competing product extracts in relatively larger amounts from free reducing sugars, cardiac glycosidase, tannins, alkaloids, saponins, and anthraquinones derivatives) in green solvent **S**, undesired products of andrographolide reactions   (**I**–isoandrographolide,   **J**–14–deoxyandrographolide, **K**–deoxyandrographolide**,** **L**–andrograpanin, **P**–neoandrographolide,   **Q**–andrographiside,   **R**–14–deoxy–11,12–didehydroandrographolide**,**   **T**–dehydroandrographolide**,**   **U**–14–deoxy–11–hydroxyandrographolide,   and   **V**–14–deoxy–12–hydroxyandrographolide) in green solvent **S**.

2.2   Development of solid-liquid extractor

The development of the solid-liquid extractor should be based on complete understanding of the SLE for the desired product extract and the process characteristics. The performance indicator(s) that characterize the extraction should be the basis for the selection of optimal extractor, extractor design and scale-up or scale-down to any size [61]. In a situation whereby the desired product extract of multiple extractions undergo series of consecutive reaction(s) with itself, or one or more of the undesired product extract(s) to give another undesired product(s), the most important process variable for process control is the time (i.e. real time for a batch extractor or space time for a flow extractor). For instance, It will be extremely difficult to obtain the desired product extract **B** as illustrated in Figure 1, if the rate of extraction of **B** is slower than the rate of reaction (transformations of **B** into **I**, **J**,
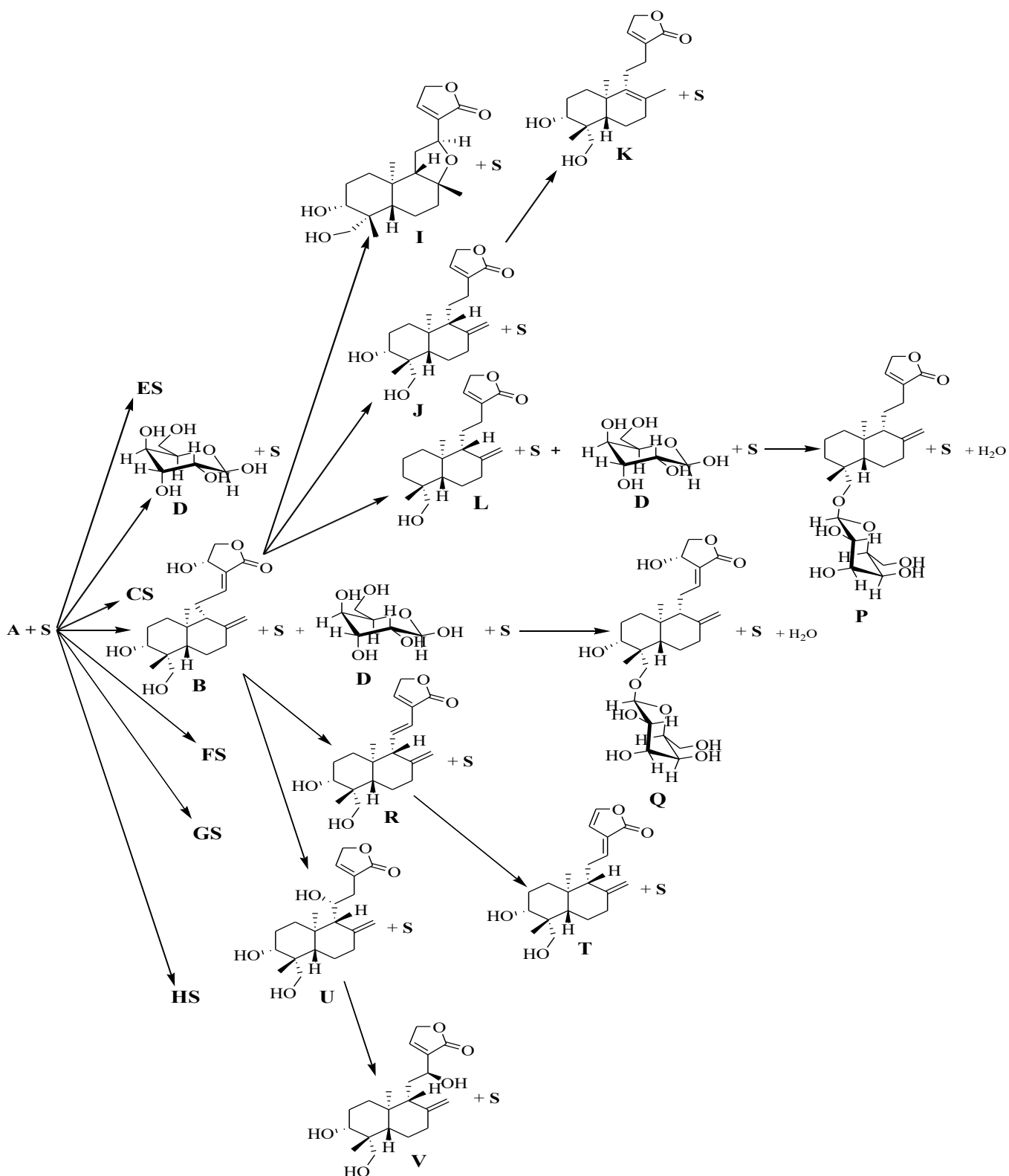
Figure 2. Multiple competing green solid-liquid extractions (SLE) of desired extract and undesired extracts in series with multiple transformations of a desired extract, and its complex reactions with undesired extracts.

K, L, R, T, U, and **V**). On the other hand, if the rate of extraction of B is faster than the rate of its transformation to unwanted products, a high selectivity and yield of B can be achieved. However, if the extraction is allowed to proceed for a long time in a batch extractor, the desired product extract **B** will be transformed into the undesired products **I, J, K, L, R, T, U,** and **V**. It is important to know the exact time for getting the maximum selectivity of the desired extract with the minimum selectivity of undesired extracts of multiple competing extractions and minimum reaction selectivity multiple reactions. Therefore, process research and development (R&D) should be focused on maximizing selectivity of the desired product extract while minimizing selectivity of undesired product extracts of multiple extraction(s), and reaction selectivity (RS) of multiple reactions.

3.   Results and discussion

The well-known equation for the calculation of the EY is presented in equation 1. New and simple equations of ES which have been developed, are for the instantaneous and overall selectivity parameter of the desired, undesired, and desired with respect to undesired product(s) at the end of extraction time in a batch extractor are summarized and shown from equations 2 to 7.

$$\hat{Y}_D = \frac{A_D}{A_{SM}} \quad\text{...} \tag{1}$$

$$\hat{S}_D = \frac{A_D}{A_{AASM}} \quad\text{...} \tag{2}$$

$$\hat{S}_U = \frac{A_U}{A_{AASM}} \quad\text{...} \tag{3}$$

$$\hat{S}_{D/U} = \frac{A_D}{A_U} \quad\text{..} \tag{4}$$

$$S_D = \frac{r_D}{r_{DPCs}} \quad\text{...} \tag{5}$$

$$S_U = \frac{r_U}{r_{DPCs}} \quad\text{...} \tag{6}$$

$$S_{D/U} = \frac{r_D}{r_U} \quad\text{...} \tag{7}$$

Where $\hat{Y}$ = Overall yield of desired product extract;

$\hat{S}_D,\ \hat{S}_U,\ and\ \hat{S}_{D/U}$ = Overall selectivity of desired, undesired, and desired with respect to undesired extracts(s);

$A_D,\ and\ A_U$ = Amount of desired and undesired product extract(s);

A_{AASM} = Actual amount of solid material disappeared in SLE;

A_{SM} = Whole amount of solid material used in SLE;

$r_D,\ and\ r_U$ = Rate of formation of desired and undesired product extract(s);

r_{DPCs} = Rate of dissolution of all phytochemical compounds;

S_D, S_U, and $S_{D/U}$ = Instantaneous selectivity of desired, undesired, and desired withrespect to undesired product extract(s), respectively.

Both EY and ES are process parameters that are or can be used as the performance indicators to characterize extraction process. The two parameters are similar to one another and are linearly related to the concentration or amount of product(s) produced. They relate product(s) with the most essential starting material or raw material, and disclose the effects of process variables on the performance of SLE. However, ES is more powerful in revealing the effects of process variables on the process than EY. This is because it uses only the actual amount of solid material (feed or raw material) that disappeared in SLE, unlike EY that uses the whole amount of solid material.

Table 3. CFED matrix and responses for the green SLE of andrographolide

		Independent process variables						Responses	
		Codded levels			Actual levels				
Std order	Run order	A	B	C	A	B	C	OYA (%)	OSA (%)
6	1	+1	-1	+1	5/50	0.175	25	2.98	13.11
7	2	-1	+1	+1	1/50	1.200	25	2.11	13.89
1	3	-1	-1	-1	1/50	0.175	5	4.36	22.32
9	5	0	0	0	3/50	0.605	15	2.59	13.97
10	4	0	0	0	3/50	0.605	15	2.5	13.69
2	6	+1	-1	-1	5/50	0.175	5	3.25	14.45
5	7	-1	-1	+1	1/50	0.175	25	1.82	8.75
11	8	0	0	0	3/50	0.605	15	2.55	13.91
12	9	0	0	0	3/50	0.605	15	2.67	14.29
4	10	+1	+1	-1	5/50	1.200	5	1.55	10.1
8	11	+1	+1	+1	5/50	1.200	25	2.47	14.8
3	12	-1	+1	-1	1/50	1.200	5	1.3	10.82

For the detailed and rigorous green process analysis, the first three (3) equations for the instantaneous selectivity (i.e., equations 5, 6, and 7) should be used in the ES computation when the rate of extraction of desired and undesired product extract(s) are fully established with all their specific extraction rate

constants, extraction order, and activation energies for extractions. On the other hand, the last three (3) equations for the overall selectivity (i.e., equations 2, 3, and 4) should be used in the estimation of ES in the absence of complete data.

Table 3 presents the CFED matrix and responses for the green SLE of andrographolide. In the sensitivity analysis, the CFED matrix and responses were empirically modelled using first-order model with double and triple factor interactions as shown in equation 8. The objective was to find the effects of individual, double and triple interactions of the process variables on the two performance indicators OYA and OSA and compare their sensitivity to changes in solid-liquid ratio (A), average particle size (B), and extraction time (C) in green SLE of andrographolide. The empirical models for the response variables of green SLE in terms of the coded process variables are shown in equations 9 to 10.

$$y_i = \beta_0 + \beta_1 A + \beta_2 B + \beta_3 C + \beta_{12} AB + \beta_{13} AC + \beta_{23} BC + \beta_{123} ABC \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (8)$$

Where y_i is the predicted response i while A, B, and C are the coded form of the process variables; β_0 is the intercept; β_1, β_2 and β_3 are the linear or partial regression coefficients relating responses (y_1 or y_2, etc) to the level of input variables (A or B or C); β_{12}, β_{13} and β_{23} are the interaction coefficients corresponding to the effect of double interactions (factor A with factor B, etc); and β_{123} is the interaction coefficient for the effect of triple interaction of process variables A, B and C.

$$OYA = +2.51 + 0.082A - 0.62B - 0.14C + 0.070AB + 0.30AC + 0.57BC - 0.27ABC \dots\dots\dots\dots\dots\dots (9)$$

$$OSA = +13.68 - 0.42A - 1.13B - 0.89C + 0.46AB + 1.73AC + 2.84BC - 1.33ABC \dots\dots\dots\dots\dots\dots\dots (10)$$

The models were significant at 95% confidence level. They were demonstrated to cover the following ranges for the overall yield of andrographolide from 1.3% (w/w) to 4.36% (w/w) and overall selectivity of andrographolide was from 8.75% (w/w) to 22.32% (w/w). The summary for the analysis of variance (ANOVA) performed at 95% confidence level of the models are presented is shown in Table 4. It can be observed from the coefficients of the model terms, F-values, significant probability values (p-values < 0.05), R^2-values, adequate precision and standard deviation values that OSA appears to be more sensitive to the changes in process variables than OYA.

Table 4. Analysis of variance (ANOVA) for the selected factorial models of OYA (%) and OSA (%)

Source	Sum of squares		DF		Mean squares		F-value		Prob > F	
	OYA (%)	OSA (%)	OYA (%)	OSA (%)	OYA (%)	OSA (%)	OYA (%)	OSA (%)	OYA (%)	OSA (%)
Model	7.21	122.0	7	7	1.03	17.43	199.6	283.7	0.0005[(+)]	0.0003[(+)]
A	0.054	1.38	1	1	0.05	1.38	10.56	22.43	0.0475[(+)]	0.0178[(+)]
B	3.10	10.17	1	1	3.10	10.17	601.0	165.6	0.0001[(+)]	0.0001[(+)]
C	0.15	6.37	1	1	0.15	6.37	28.26	103.7	0.0130[(+)]	0.0020[(+)]
AB	0.04	1.71	1	1	0.04	1.71	7. 60	27.86	0.0703[(+)]	0.0133[(+)]
AC	0.71	24.01	1	1	0.71	24.01	137.3	390.9	0.0013[(+)]	0.0003[(+)]
BC	2.58	64.30	1	1	2.58	64.30	499.5	1047	0.0002[(+)]	< 0.0001[(+)]
ABC	0.58	14.05	1	1	0.58	14.05	113.1	228.6	0.0018[(+)]	0.0006[(+)]
Curvature	0.03	0.50	1	1	0.03	0.50	4.91	8.21	0.1134[(-)]	0.0643[(-)]
Pure error	0.02	0.18	3	3	0.005	0.06				
Cor total	7.25	122.68	11	11						
R^2 squared	0.994	0.994								
Adeq. precision	37.1	40.0								
Std. dev.	0.10	0.41								

OYA–Overall yield of andrographolide
OSA– Overall selectivity of andrographolide
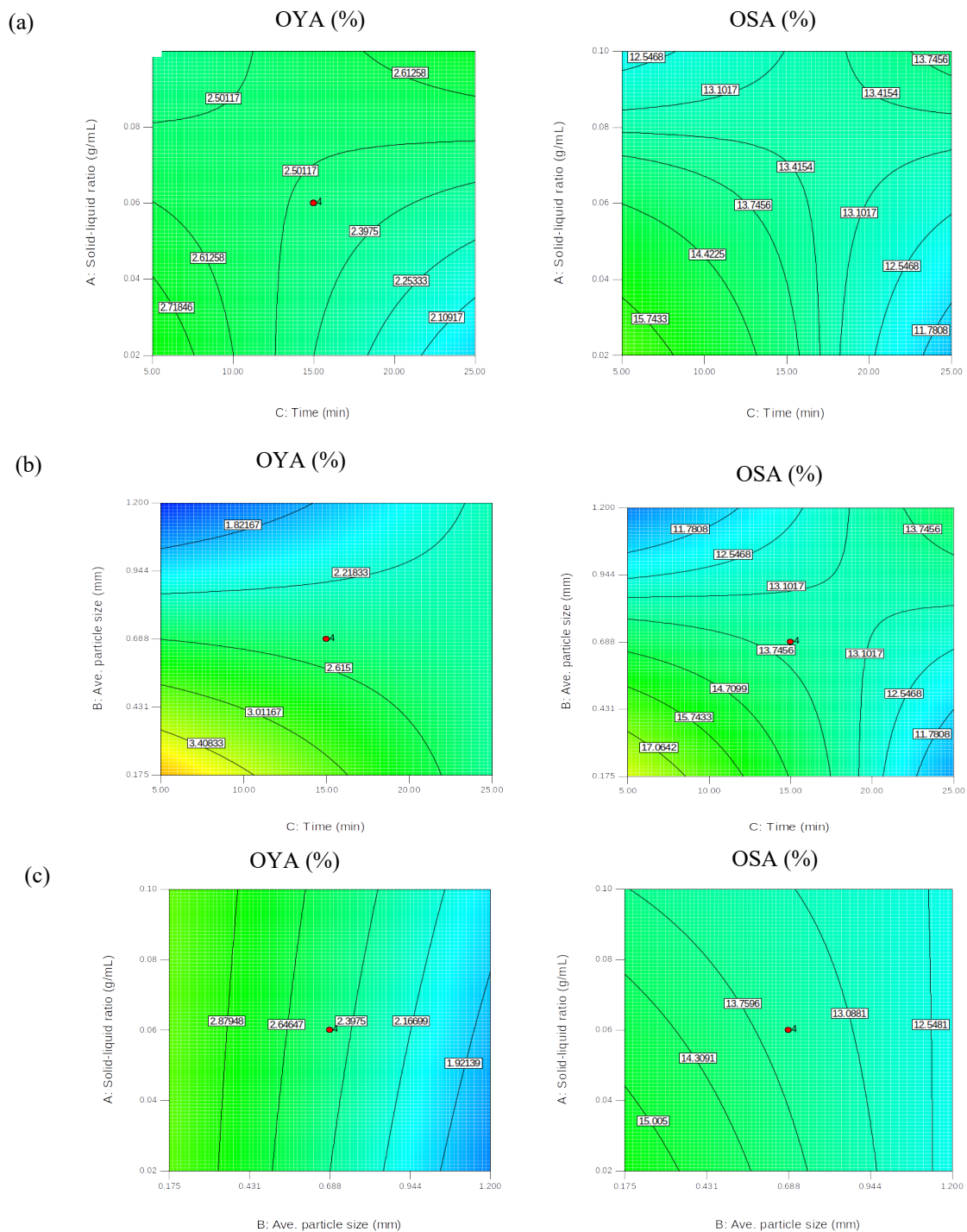*DF– Degree of freedom*
Prob.–Probability

Figure 3. Contour plots for OYA (%) and OSA (%) as a function of (a) solid-liquid ratio and time at ave. particle size of 0.69 mm, (b) ave. particle size and time at S-L ratio of 3/50 (g/mL) and (c) solid-liquid ratio and ave. particle size at time of 15 min.

The sensitivity of the two process parameters OYA and OSA to the impact of process variables can be visualized and compared in the contour plots as displayed in Figure 3. It exhibits and compares the contour plots of OYA and OSA as a function of solid-liquid ratio and extraction time, average particle size and extraction time as well as solid-liquid ratio and average particle size, while the third process variable is held constant at the centre levels in Figure 3 (a), (b) and (c) respectively. It can be observed from both plots that OYA and OSA increase with the decrease in both solid-liquid ratio and average particle size at shorter extraction time with stronger negative effects for the lower solid-liquid ratio and smaller average particle size at longer extraction time. However, both OYA and OSA increase at an extreme higher solid- liquid ratio (≥5/50 g/mL) and larger average particle size (≥1.200 mm) with the increase in extraction time (≥25 min). Unlike OYA, OSA increases with both decrease in average particle size and solid-liquid ratio at extraction time of 15 minutes with strong negative effect as average particle size increases.

Figures 4 and 5 exhibit the effects of average particle sizes, extraction time, and solid-liquid ratios on the overall yield of andrographolide (OYA) in comparison with the overall selectivity of andrographolide (OSA) in green SLE. The influences of process variables were studied under isothermal condition at 80° C for solid-liquid ratios of 1:10 (g/mL) and 1:50 (g/mL). The maximum OYA and OSA for solid-liquid ratio of 1/10 (g/mL) can be observed from Figure 4 (a) and (b) to be 4.11 %, and 17.45% at 20 minutes and 10 minutes, respectively for average particle size of 0.175 mm. In addition, the highest values obtained are 3.58 % and 15.48 % at 20 minutes for average particle size of 0.375 mm. Moreover, the maximums for average particle sizes of 0.605 mm, 0.855 mm, and 1.200 mm are found to be 3.11 % and 15.76 %; 2.68 % and 14.03 % and 2.47 % and 14.8 % at 25 minutes, respectively. On the other hand, the maximum OYA and OSA for solid-liquid ratio of 1:50 (g/mL) can be seen from Figure 5 (a) and (b) to be 5.59 %, and 26.37% at 15 minutes for average particle size of 0.175 mm. Besides, the highest values found are 3.94 % and 20.26 %; 3.02 % and 16.45 %; 2.43 % and 14.99 % and 2.14 % and 15.64 % for average particle size of 0.175 mm, 0.375 mm, 0.605 mm, 0.855 mm and 1.200 mm at 20 minutes, respectively. It can be observed that the plots of the OYA and OSA follow the pattern of exponential growth or law of diminishing returns as the concentrations of andrographolide keep increasing up to a different region of time to each class of particle size where andrographolide attains its equilibrium concentrations and starts to decline.
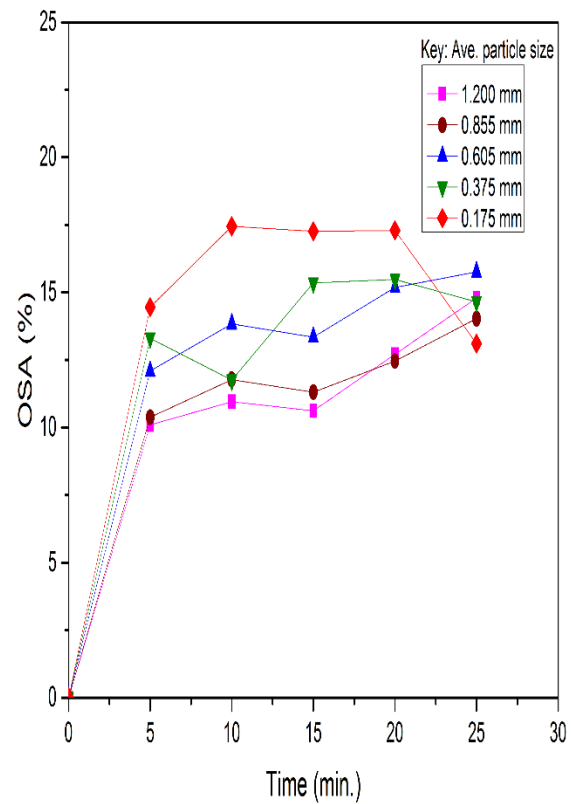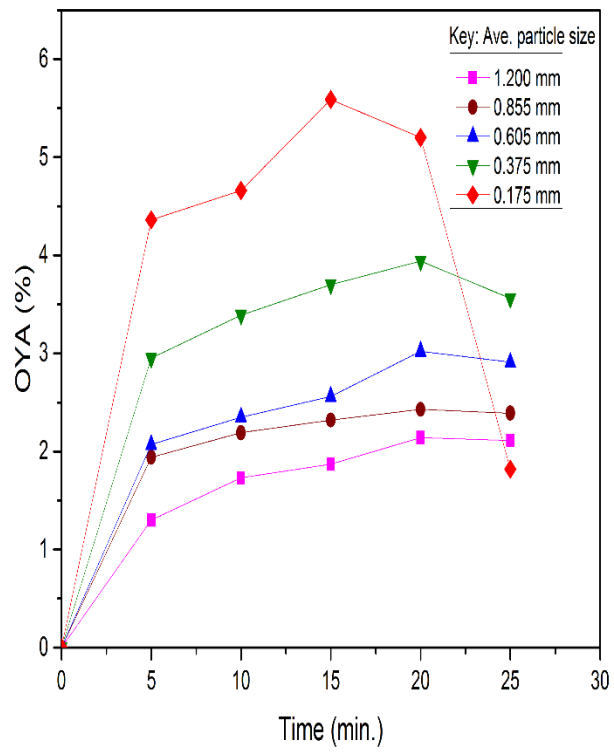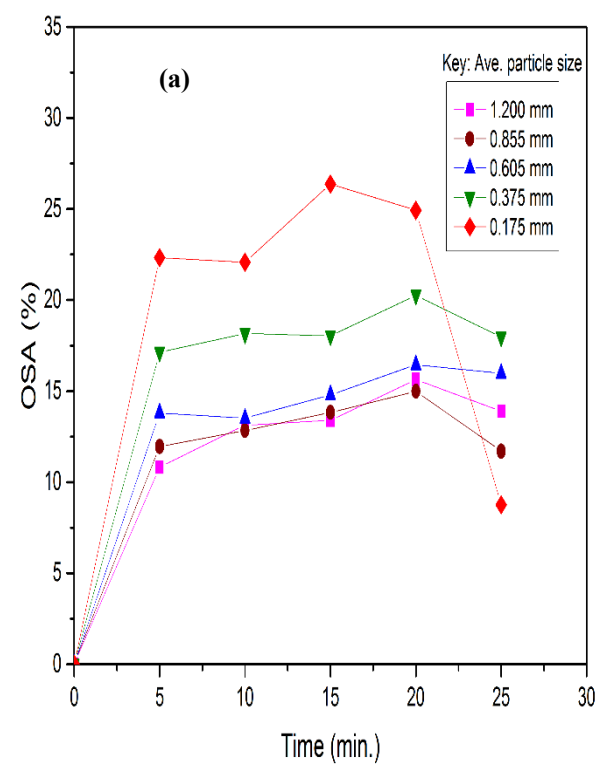
(a)
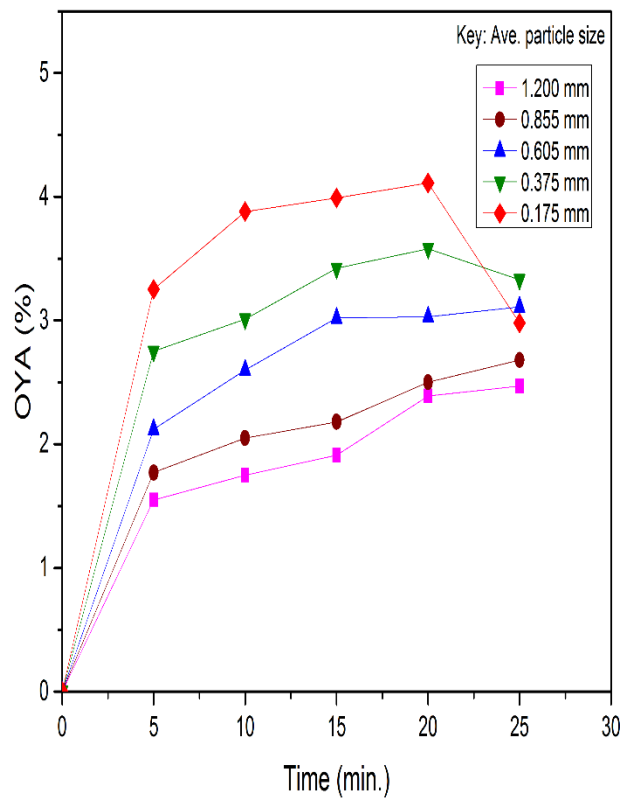
(b)

Figure 4. Effects of average particle sizes and extraction time on (a) overall yield of andrographolide (OYA), (b) overall selectivity of andrographolide (OSA) in green SLE for solid-liquid ratio of 1:10 (g/mL) under isothermal condition at 80 ^{o}C.
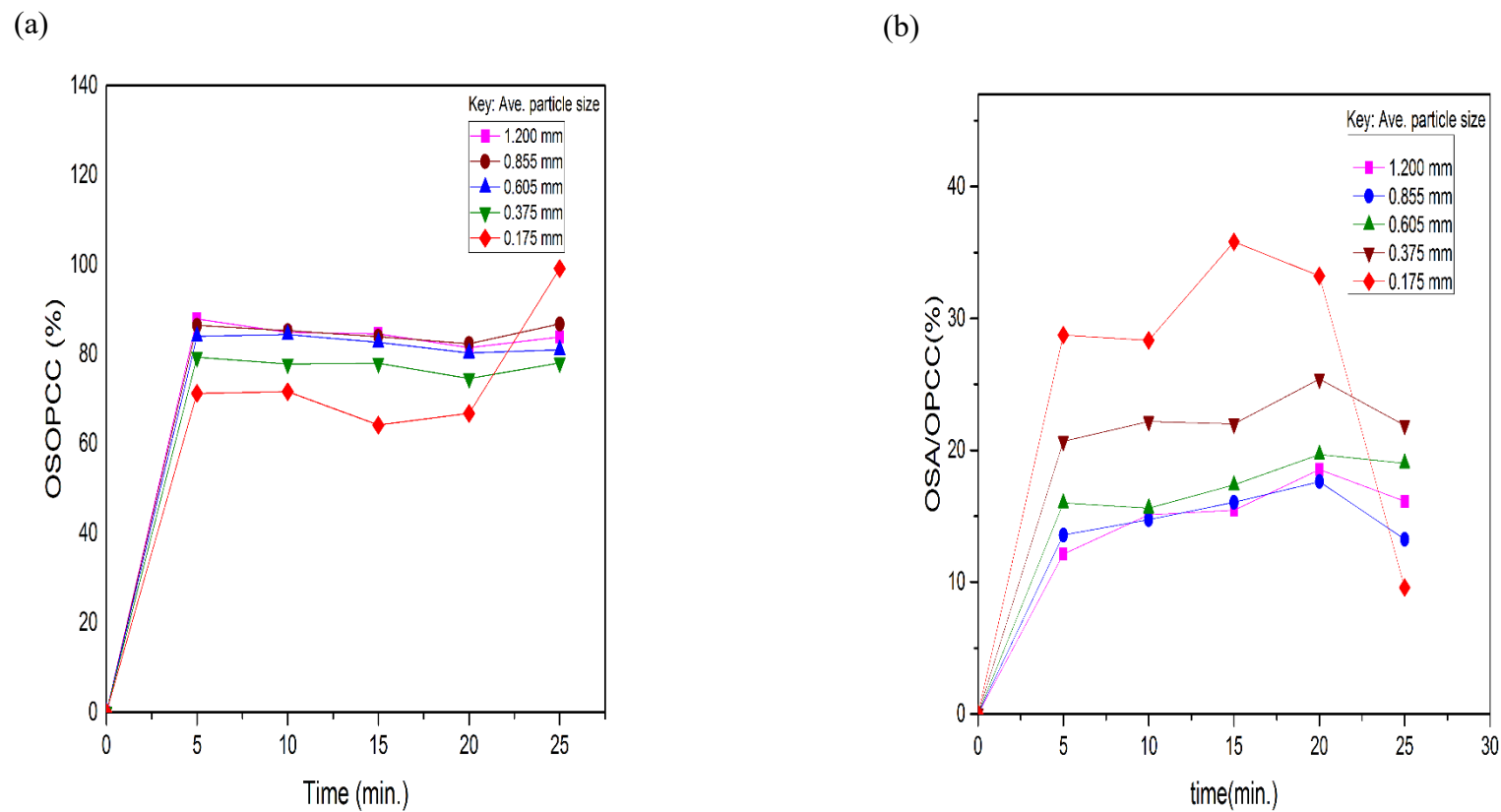
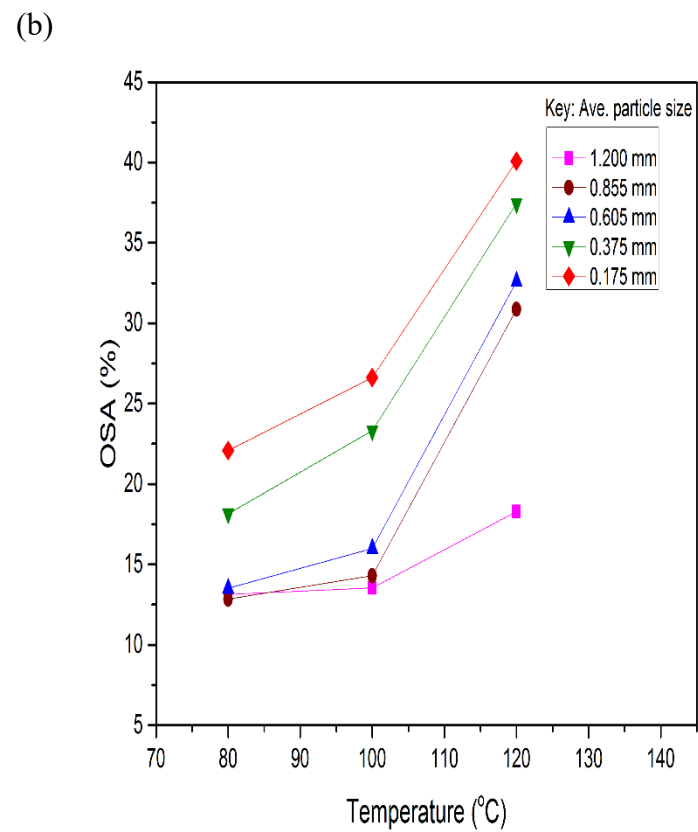(a)   (b)

Figure 5. Effects of average particle sizes and extraction time on (a) overall yield of andrographolide (OYA), (b) overall selectivity of andrographolide (OSA) in green SLE for solid-liquid ratio of 1:50 (g/mL) under isothermal condition at 80 ºC.

(a)

(b)

Figure 6. Effects of average particle size and extraction time on (a) overall selectivity of other phytochemical compounds (OSOPCC) and (b) overall selectivity of andrographolide with respect to other phytochemical compounds (OSA/OPCC) in green SLE for solid-liquid ratio of 1:50 (g/mL) under isothermal condition at 80 ℃.
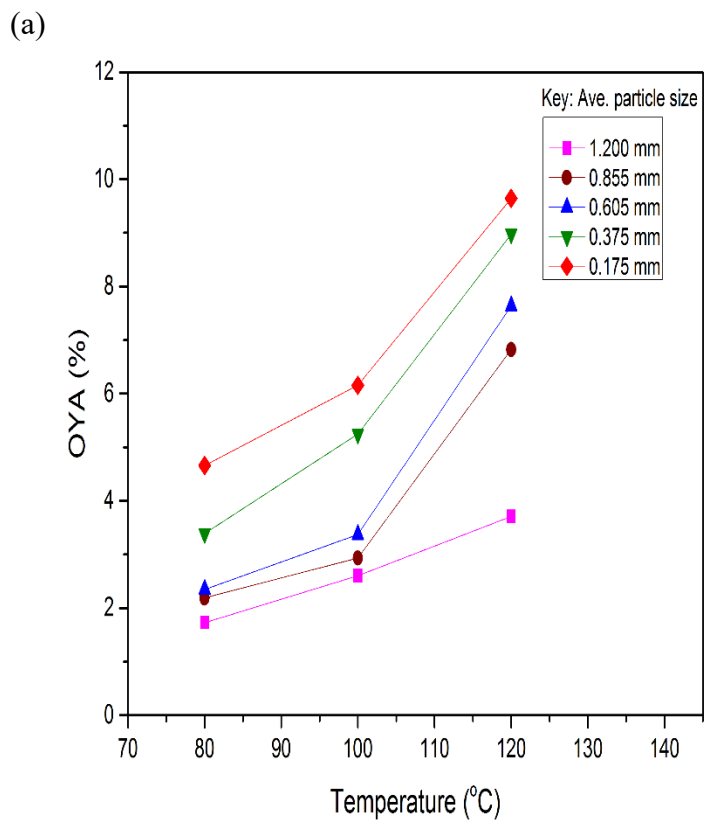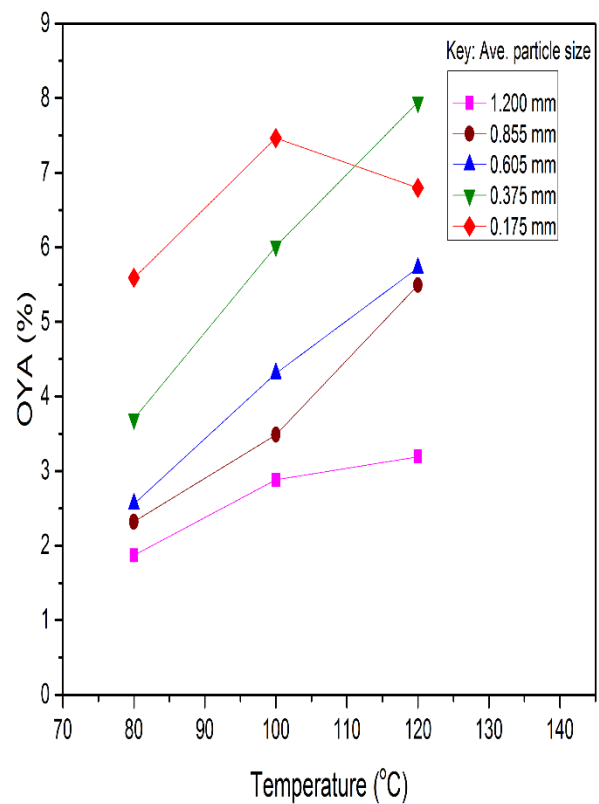
(a)

(b)

Figure 7. Effect of average particle size and temperature on (a) overall yield of andrographolide (OYA) and (b) overall selectivity of andrographolide (OSA) in green SLE for solid-liquid ratio of 1:50 (g/mL) at 10 minutes.
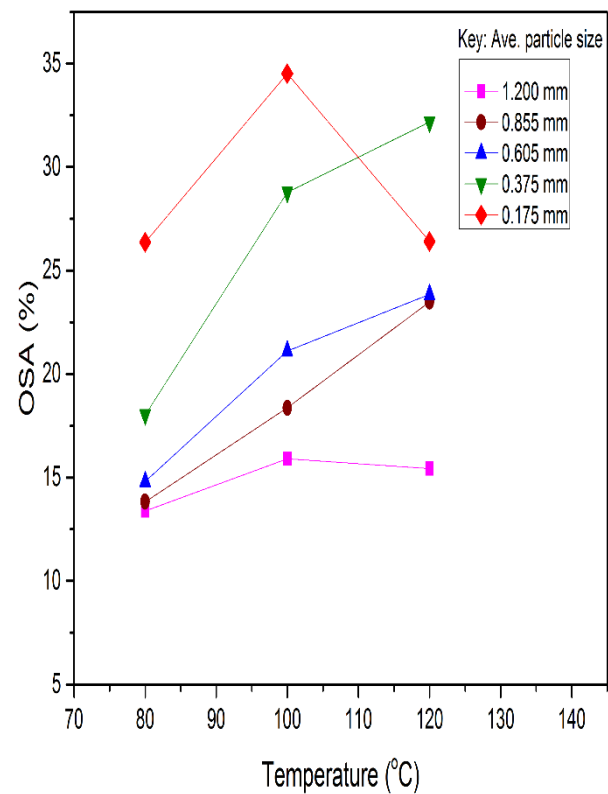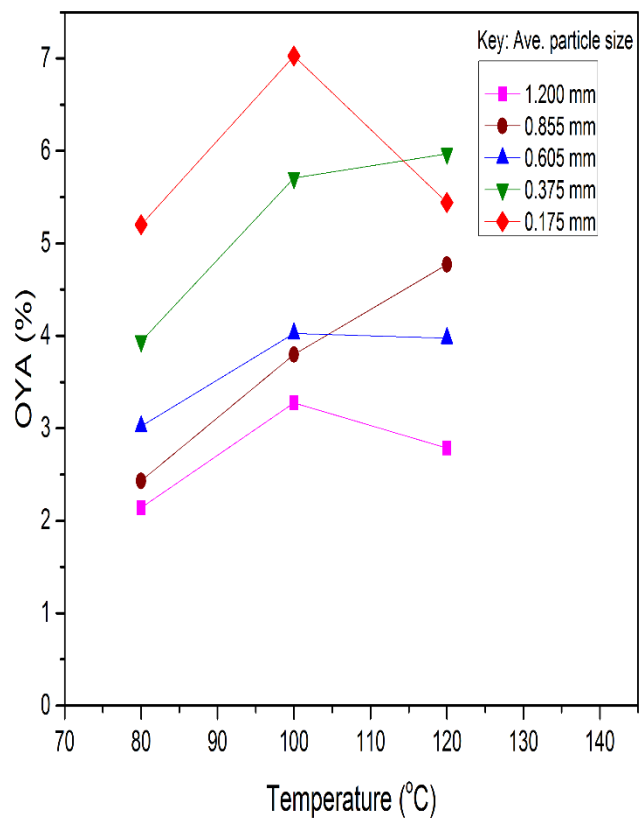
(a)

(b)

Figure 8. Effect of average particle size and temperature on (a) overall yield of andrographolide (OYA) and (b) overall selectivity of andrographolide (OSA) in green SLE for solid-liquid ratio of 1:50 (g/mL) at 15 minutes.
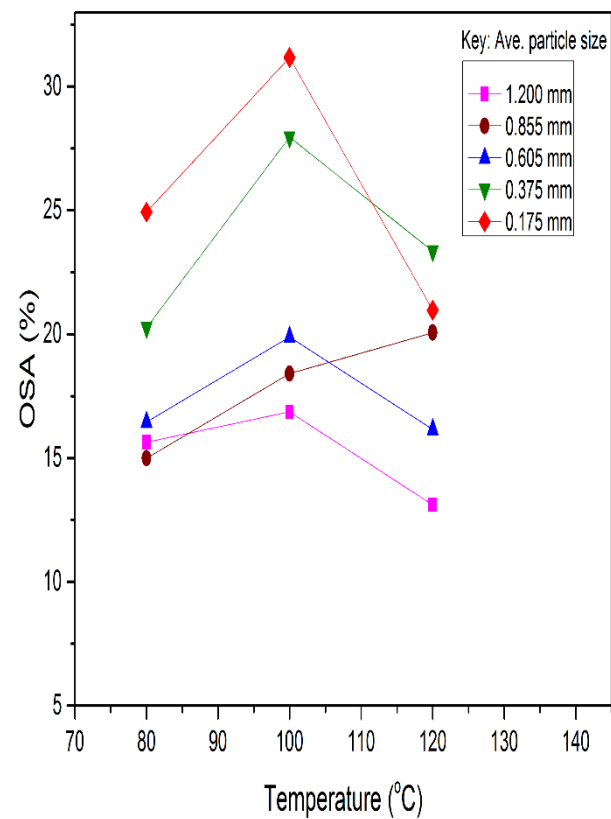
(a)

(b)

Figure 9. Effect of average particle size and temperature on (a) overall yield of andrographolide (OYA) and (b) overall selectivity of andrographolide (OSA) in green SLE for solid-liquid ratio of 1:50 (g/mL) at 15 minutes.

From the results on the plots of OYA and OSA, it can be noticed how OSA performance indicator sincerely discloses the truth about the real impact of the process variables on the SLE. These can be seen clearly for the curve of average particle sizes of 0.375 mm; and 0.855 mm and 1.200 mm as depicted on the plots.

Figure 6 depicts the effects of average particle size and extraction time on overall selectivity of other phytochemical compounds (OSOPCC), and overall selectivity of andrographolide with respect to other phytochemical compounds (OSA/OPCC) in green SLE. The condition was under isothermal at 80 C, and the solid-liquid ratio was 1:50 (g/mL). It proves how simple the concept of ES can be used to depict the performance of undesired extracts (i.e., other phytochemical compounds) and also relate the desired and undesired extract (s) in SLE.

Figures 7, 8, and 9 show the influences of average particle size and temperature on OYA and OSA in green SLE for solid-liquid ratio of 1:50 (g/mL) at 10, 15, and 20 minutes, respectively. They compare the responses of OYA and OSA based on the concepts of EY and ES to the changes of average particle sizes and temperatures at different time regimes. It can be observed from the Figures that the plots look similar to one another. However, it can be noted some of the plots slightly differ from their patterns. This is evident in the case of average particle sizes of 1.200 mm at 10 minutes, 0.855 mm, 0.605 mm, and 0.375 mm at 15 minutes, and 0.375 mm at 20 minutes as shown in Figures 7b, 8b and 9b, respectively. These further indicate how sensitive is the concept of ES in revealing the true performance of SLE process.

Conclusions

A new concept called extraction selectivity (ES) has been introduced as a performance indicator and a criterion in the green process analysis, design and development of solid-liquid extractor. New tools in the form of simple equations for determining the ES have been successfully developed. Some of the tools have been validated in the process analysis of the green SLE of andrographolide from AP. It was found that the ES is a function of not only solvent but also particle size, solid-liquid ratio, time, and temperature. The profiles of ES have shown the capability of debunking the plots of extraction yield (EY) and depicting the true picture of process performance for the efficient extractor design and profitable operations.

With the amazing abilities to overcome the limitations of EY, the following conclusions can be drawn:

1 ES can be used as a powerful criterion in choosing extraction schemes and extractors, process optimization and predicting profits that will optimize the extraction of desired product extract at the early stage of green product and process development.

2 ES can be used more conveniently in the green process analysis of SLE than the existing concept of atom economy developed by Trost [62] and proposed in the 12 principles of green chemistry by Anastas and Warner [63].

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Disclosure statements

Conflict of Interest: The authors declare that there is no known conflict of interest in this research paper.

Compliance with Ethical Standards: This research does not contain any studies involving human or animal subjects.

References

[1] A. Eiloart, Zur Extraction von Flüssigkeiten mit flüchtigen Lösungsmitteln*Zeitschrift für analytische Chemie*, *26*(1):233-234 (1887).

[2] H. D. Richmond, Fat extraction from milk solids. *Analyst,* 14(July), 121c-131(1889).

[3] J. F. Geisler, The relative merits of the Wanklyn and the Adams methods in the estimation of fat in milk analysis. *Journal of the American Chemical Society,* 12(10):488-500 (1890).

[4] F. B. Power, and H. Rogerson, Chemical examination of Jalap. *Journal of the American Chemical Society*, *32*(1):80-113 (1910).

[5] E. Newbery, XLI. —Unstable compounds of cholesterol with barium methoxide. *Journal of the Chemical Society, Transactions*, 105:380-386 (1910).

[6] D. T. Englis, R. T. Decker, and A. B. Adams, The preparation of raffinose from cottonseed meal. *Journal of the American Chemical Society*, *47*(11): 2724-2726 (1925).

[7] M. H. Thornton, M. H. Kraybill, and J. H. Mitchell Jr, Sterol Glucosides from Expressed Soybean Oil2, 3. *Journal of the American Chemical Society*, *62*(8):2006-2008 (1940).

[8] F. A. Kummerow, The composition of the oil extracted from 14 different varieties of *Andropogon Sorghum var. Vulgaris. Oil & Soap*, *23*(9):273-275 (1946).

[9] A. Klinkenberg, Calculation of the efficiency of counter-current stage-wise mass transfer processes with constant distribution factor, when in the stationary state: I. Distribution of one component only. *Chemical Engineering Science*, *1*(2):86-93 (1951).

[10] L. L. McKinney, E. H. Uhing, J. L. White, and J. C. Picken Jr, Vegetable Oil Extraction, Autoxidation Products of Trichloroethylene. *Journal of Agricultural and Food Chemistry*, *3*(5):413-419(1955).

[11] E. L. D'Aquin, J. Pominski, H. L. E. Vix, N. B. Knoepfler, E. A. Kulkarni, and E. A. Gastrock, Direct solvent-extraction of castor beans yields high grade oil. *Journal of the American Oil Chemists' Society*, *37*(2):93-97 (1960).

[12] W. Cowart, D. C. Tate, and J. Churchill, A study of the influence of storing wood on the yield and quality of tall oil. *Journal of the American Oil Chemists' Society*, *42*(3):202-207(1965).

[13] J. R. Balder, and J. M. Prausnitz, Thermodynamics of ternary, liquid-supercritical gas systems with applications for high pressure vapor extraction. *Industrial & Engineering Chemistry Fundamentals*, *5*(4):449-455 (1966).

[14] R. N. Nazar, H. G., Lawford, and J. T. F. Wong, An improved procedure for extraction and analysis of cellular nucleotides. *Analytical biochemistry*, *35*(2): 305-313 (1970).

[15] M. L. King, A. L. Forman, C. Orella, and S. H. Pines, Extractive hydrolysis for pharmaceuticals. *Chemical engineering progress*, *81*(5):36-39 (1985).

[16] A. Tamimi, and B. Z. Uysal, Parametric investigation of oil-shale extraction with organic solvents. *Separation science and technology*, 25(11-12):1151-1159 (1990).

[17] E. Reverchon, R. Taddeo, and G. D. Porta, Extraction of sage oil by supercritical C02: Influence of some process parameters. *The J. of supercritical fluids*, *8*(4):302-309 (1995).

[18] A. V. Yazdi, and E. J. Beckman, Design of highly CO2-soluble chelating agents. 2. Effect of chelate structure and process parameters on extraction efficiency. *Industrial & engineering chemistry research*, *36*(6):2368-2374 (1997).

[19] L. Prat, P. Guiraud, L. Rigal, and C. Gourdon, A one dimensional model for the prediction of extraction yields in two phases modified twin-screw extruder. *Chemical Engineering and Processing: Process Intensification*, *41*(9):743-751 (2002).

[20] G. Raman, V. G. Gaikar, Microwave-assisted extraction of piperine from Piper nigrum. *Industrial & engineering chemistry research*, *41*(10):2521-2528 (2002).

[21] C. Mantell, M. Rodrıguez, E. M. de la Ossa, Semi-batch extraction of anthocyanins from red grape pomace in packed beds: experimental results and process modelling. *Chemical Engineering Science*, *57*(18):3831-3838 (2002).

[22] S. Chemat, H. Aït-Amar, A. Lagha, and D. C. Esveld, Microwave-assisted extraction kinetics of terpenes from caraway seeds. *Chemical Engineering and Processing: Process Intensification*, *44*(12):1320-1326 (2005).

[23] T. H. Kao, J. T. Chien, and B. H. Chen, Extraction yield of isoflavones from soybean cake as affected by solvent and supercritical carbon dioxide. *Food Chemistry*, 107(4):1728-1736 (2008).

[24] I. Mota, P. C. Rodrigues Pinto, C. Novo, G. Sousa, O. Guerreiro, A. R. Guerra, and A. E. Rodrigues, Extraction of polyphenolic compounds from Eucalyptus globulus bark: process optimization and screening for biological activity. *Industrial & Engineering Chemistry Research*, *51*(20):6991-7000 (2012).

[25] A. Mehrkesh, T. Tavakoli, M. S. Hatamipour, and A. T. Karunanithi, Modeling and simulation of a rotating-disk contactor for the extraction of aromatic hydrocarbons from a lube-oil cut. Industrial & Engineering Chemistry Research, 52(27):9422-9432 (2013).

[26] C. H. Chan, R. Yusoff, and G. C. Ngoh, Modeling and kinetics study of conventional and assisted batch solvent extraction. Chemical Engineering Research & Design, 92(6):1169-1186 (2014).

[27] N. Rombaut, A. S. Tixier, A. Bily, and F. Chemat, Green extraction processes of natural products as tools for biorefinery. *Biofuels, Bioprod. & Biorefining*, *8*(4):530-544 (2014).

[28] U. A. Isah, "Optimization and Kinetics of Green Pressurized–Liquid Extraction for Andrographolide from *Andrographis paniculata,"* Submitted to Universiti Teknologi

Malaysia (UTM), Skudai, Johor Bahru, Malaysia, *Unpublished PhD Dissertation* (2016).

[29] P. M. Martins, B. N. Thorat, A. D. Lanchote, and L. A. Freitas, Green extraction of glycosides from Stevia rebaudiana (Bert.) with low solvent consumption: A desirability approach. *Resource-Efficient Technologies*, *2*(4):247-253 (2016).

[30] Y. Du, B. Schuur, and D. W. Brilman, Maximizing lipid yield in Neochloris oleoabundans algae extraction by stressing and using multiple extraction stages with N-ethylbutylamine as switchable solvent. *Industrial & engineering chemistry research,* 56(28):8073-8080 (2017).

[31] D. Cifá, M. Skrt, P. Pittia, C. Di Mattia, and N. Poklar Ulrih, Enhanced yield of oleuropein from olive leaves using ultrasound-assisted extraction. *Food science & nutrition,* 6(4), 1128-1137 (2018).

[32] S. Kim, S. C. Ko, Y. S. Kim, S. K. Ha, H. Y. Park, Y. Park, and S. H. Lee, Determination of Curcuma longa L. (Turmeric) leaf extraction conditions using response surface methodology to optimize extraction yield and antioxidant content. *Journal of Food Quality* (2019).

[33] H. Nawaz, M. A. Shad, N. Rehman, H. Andaleeb, and N. Ullah, (2020). Effect of solvent polarity on extraction yield and antioxidant properties of phytochemicals from bean (Phaseolus vulgaris) seeds. *Brazilian Journal of Pharmaceutical Sciences*, 56.

[34] L. Johnson, and E. W. Lusas, Comparison of alternative solvents for oils extraction. *Journal of the American Oil Chemists' Society*, *60* (2Part1), 229-242 (1983).

[35] U. A. Isah, "Process Development of a Pilot Plant for the Production of Anti-malarial Powdered Extract from Raw Herb 25," Submitted to Ahmadu Bello University (ABU), Zaria, Nigeria, *Unpublished M.Sc. Dissertation* (2009).

[36] U. A. Isah, L. S. Chua, and R. Aziz, (2015). Kinetics of green solid-liquid extraction of andrographolide from Andrographis paniculata: effects of particle size and solid-liquid ratio. *Green Processing and Synthesis*, *4*(5), 399-410.

[37] D. Naviglio, P. Scarano, M. Ciaravolo, and M. Gallo, Rapid Solid-Liquid Dynamic Extraction (RSLDE): A powerful and greener alternative to the latest solid-liquid extraction techniques. *Foods*, *8*(7):245 (2019).

[38] O. R. Alara, and N. H. Abdurahman, Kinetics studies on effects of extraction techniques on bioactive compounds from Vernonia cinerea leaf. Journal of food science and technology,

56(2):580-588 (2019).

[39] C. H. Deal, and E. L. Derr, Selectivity and solvency in aromatics recovery. *Industrial & Engineering Chemistry Process Design and Development*, *3*(4):394-399 (1964).

[40] M. Spielman, Selectivity in hydrocarbon oxidation. AIChE Journal, 10(4):496-501 (1964).

[41] J. M. Smith, Chemical Engineering Kinetics' 3rd edn McGraw-Hill. *New York* (1981).

[42] G. L. Wells, and L. M. Rose, *The art of chemical process design* (Vol. 2). Elsevier (1986).

[43] R. Smith, Chemical Process Design And Integration John Wiley and Sons (2005).

[44] H. S. Fogler, and P. H. PTR, Elements of Chemical Reaction Engineering, Prentice Hall International Series in the Physical and Chemical Engineering Sciences (2005).

[45] R. Hou, T. Wang, and X. Lan, Enhanced selectivity in the hydrogenation of acetylene due to the addition of a liquid phase as a selective solvent. *Industrial & Engineering Chemistry Research*, *52*(37):13305-13312 (2013).

[46] F. L. Moore, W. D. Fairman, J. G. Ganchoff, and J. G. Surak, Selective Liquid-Liquid Extraction of Iron with 2-Thenoyltifluoroacetone-Xylene. Application to Homogeneous Reactor Solutions. Analytical Chemistry, 31(7):1148-1151 (1959).

[47] J. L. Callahan, and R. K. Grasselli, A selectivity factor in vapor-phase hydrocarbon oxidation catalysis. AIChE Journal, 9(6):755-760 (1963).

[48] A. Z. Bikkulov, B. M. Groshev, and V. A. Popov, Selective solvents for the extraction of hydrocarbons. *Chemistry and Technology of Fuels and Oils*, *1*(6):435-440 (1965).

[49] E. I. Shcherbina, A. É. Tenenbaum, and O. P. Dmitrieva, Solvency and selectivity of ethylene glycol monoethers. Chemistry and Technology of Fuels and Oils, 11(6):432-435 (1975).

[50] E. J. Pretel, P. A. López, S. B. Bottini, and E. A. Brignole, Computer-aided molecular design of solvents for separation processes. AIChE Journal, 40(8):1349-1360 (1994).

[51] W. D. Seider, J. D. Seader, D. R. Lewin, Product and Process Design Principles: Synthesis, Analysis, and Evaluation; Second ed., John Wiley: New York, (2003).

[52] S. S. Rizvi, Separation, extraction and concentration processes in the food, beverage and nutraceutical industries; Woodhead Publishing Limited: New Delhi, (2010).

[53] B. Yang, R. Burch, C. Hardacre, G. Headdock, and P. Hu, Origin of the increase of activity and selectivity of nickel doped by Au, Ag, and Cu for acetylene, *ACS Catalysis*, 2(6):1027-1032 (2012).

[54] R. Turton, R. C. Bailie, W. B. Whiting, Shaeiwitz, J. A. Analysis, synthesis and design of chemical processes; Prentice-Hall, Inc.: New Jersey, (1998).

[55] R. Turton, R. C. Bailie, W. B. Whiting, J. A. Shaeiwitz, J. A. Analysis, synthesis and design of chemical processes; Pearson Education, Inc: New Jersey, (2009).

[56] U. A. Isah, L. S. Chua, R. Aziz, "Extraction selectivity–A new tool for green process analysis and design of solid-liquid extractor," A poster presented between 16-17 August 2014 at *1st International Conference on Industrial Pharmacy,* Swiss Garden Hotel, Kuantan, Pahang, Malaysia (2014).

[57] J. A. Henning, R. J. Core, and J. L. Gardea-Torresdey, Extracting volatile compounds from single plants using supercritical fluid extraction. *Crop science,* 34(4):1120-1122 (1994).

[58] A. Bucić-Kojić, M. Planinić, S. Tomas, M. Bilić, and D. Velić, Study of solid–liquid extraction kinetics of total polyphenols from grape seeds. *Journal of Food Engineering*, *81*(1):236-242 (2007).

[59] H. N. Rajha, N. El Darra, Z. Hobaika, N. Boussetta, E. Vorobiev, R.G. Maroun, and N. Louka, Extraction of total phenolic compounds, flavonoids, anthocyanins and tannins from grape byproducts by response surface methodology. Influence of solid-liquid ratio, particle size, time, temperature and solvent mixtures on the optimization process. *Food and Nutrition Sciences*, (2014).

[60] M. Radojković, Z. Zeković, S. Jokić, S. Vidović, Ž. Lepojević, and S. Milošević, Optimization of solid-liquid extraction of antioxidants from black mulberry leaves by response surface methodology. *Food Techn. & Biotechnology*, *50*(2), 167-176 (2012).

[61] A. Pfennig, D. Delinski, W. Johannisbauer, H. Josten, In *Industrial Scale Natural Products Extraction*; Bart, H. J., & Pilz, S. (Eds.). John Wiley & Sons (2011).

[62] B. M. Trost, The atom economy-a search for synthetic efficiency. *Science*, *254*(5037):1471-1477 (1991).

[63] P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and Practice*; Oxford University Press, New York, (1998).