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TRIBLOCK COPOLIMERIC
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SOLUBILITY ENHANCER

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SYNTHESIS, CHARACTERIZATION, AND OPTIMIZATION OF BIODEGRADABLE PCL-PEG-PCL TRIBLOCK COPOLIMERIC MICELLES AS NANOCARRIERS FOR HYDROPHOBIC DRUG SOLUBILITY ENHANCER

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ABSTRACT

Objective: This study aims to synthesize, characterize, and optimize biodegradable polycaprolactone-polyethylene glycol-polycaprolactone (PCL-PEG-PCL) triblock copolymeric micelles as a nanocarrier for hydrophobic drug solubility enhancer of ketoprofen (K).

Methods: PCL-PEG-PCL (PCEC) triblock copolymers was obtained from the synthesis of ϵ -caprolactone (ϵ -CL) and PEG by ring opening polymerization (ROP) method at different PCL: PEG ratio (2-5:1). The K-loaded PCEC triblock copolymeric micelles was obtained by solvent evaporation method. Optimization of PCEC triblock copolymers and analysis of the effect of PCL: PEG ratio factors on the responses toward particle size (PS), polydispersity index (Pdl), and entrapment efficiency (EE), were carried out through the design of experiments (DoE) approach of the 2² full factorial design method using the Design-Expert software to obtain the optimum formula.

Results: The higher the PCL: PEG ratio, the ZP value tends to be smaller while the PS, Pdl, EE, and drug solubility may be increased, but the addition of hydrophobic blocks to some extent does not affect the EE and drug solubility. The optimum K-loaded PCEC triblock copolymeric micelles with a PCL: PEG 2.0:1 ratio has a zeta potential (ZP) of -24.07 ± 0.35 mV, the particle size of 235.70 ± 6.03 nm, polydispersity index of 0.30 ± 0.06 , entrapment efficiency of $87.08 \pm 0.06\%$, and the solubility of the K increases by 10.60 times.

Conclusion: The 2² full factorial design has been proven to be the suitable optimization method to determine the optimum condition that yields to the optimum results of the PS, Pdl, and EE of the of the K-loaded PCEC triblock copolymer micelles.

Keywords: Optimization, Triblock copolymers, PCL, PEG, Ketoprofen

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INTRODUCTION

Biodegradable polymers such as polycaprolactone (PCL) and polyethylene glycol (PEG) are often used in drug formulations because they are easily degraded by metabolic reactions in the body so that they are safe to use and are not toxic after hydrolyzing [1, 2]. This polymer can be used in the form of triblock copolymers as carriers of drugs with the aim of increasing the low solubility of drugs in water (hydrophobic drugs) [3].

Ketoprofen (K) is a non-steroidal anti-inflammatory drugs (NSAIDs) derivative of propionic acid which reversibly inhibits the cyclooxygenase (COX_{1and2}) enzyme and causes inhibition of prostaglandin synthesis, which is used in the treatment of dysmenorrhea, rheumatoid arthritis, and osteo-arthritis [4]. K is a hydrophobic drugs which is classified into the Biopharmaceutical Classification System (BCS) Class II because of its low solubility in water (0,01 mg/ml). The trapping of K into PCL-PEG-PCL (PCEC) triblock copolymers is carried out in order to obtain K-loaded PCEC triblock copolymeric micelles. This system is expected to be able to increase the solubility of K [5, 6].

The composition of PCEC triblock copolymers is determined by its constituent factors (PCL: PEG ratio) which will affect the results of K-loaded PCEC triblock copolymeric micelles characteristics based on parameters of particle size (PS), polydispersity index (Pdl), and entrapment efficiency (EE) [7, 8]. Therefore, it is necessary to optimize PCEC triblock copolymers and analyze the effect of PCL: PEG ratio factors on the responses toward particle size, polydispersity index, and entrapment efficiency, using the design of experiments (DoE) approach in order to obtain the optimum formula.

MATERIALS AND METHODS

Materials

Ketoprofen (K) was purchased from Kalbe Farma (Bekasi, Indonesia), polyethylene glycol (PEG) 1000 and dichloromethane was purchased from Merck (Damstad, Germany), ϵ -caprolactone (ϵ -CL) and stannous 2-ethylhexanoate (Sn(Oct)₂) was purchased from Sigma-Aldrich (Singapore), diethyl ether was purchased from Smart-Lab (Tangerang, Indonesia), and deionized distillation water was purchased from Jaya Santosa (Yogyakarta, Indonesia).

Optimization method

The experiment design of 2² full factorial design for the formation of PCEC triblock copolymers is shown on table 1. Optimization of PCEC triblock copolymers and analysis of the effect of PCL: PEG ratio factors on the responses toward particle size, polydispersity index, and entrapment efficiency, were carried out through the design of experiment (DoE) approach of the 2² full factorial design method using the Design-Expert software (Stat-Ease Inc., Minneapolis, MN, US) [9-13].

Synthesis of PCEC triblock copolymers

The PCEC triblock copolymers was obtained from the synthesis of ϵ -CL and PEG by ring opening polymerization (ROP) method with different PCL: PEG ratio (2-5:1) [7]. Briefly, PEG was added to a two-necked flask under vacuum, melted, and stirred for 30 min at 130 °C to remove the water adsorbed to the PEG. Then, ϵ -CL and 0,5% (w/w) of Sn(Oct)₂ as catalyst were added and heated at 130 °C under stirring condition for 6 h. The mixture was further cooled at room temperature (25 °C) for 12 h and milky crude PCEC triblock copolymers was

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obtained. Subsequently, the crude copolymers was dissolved in dichloromethane and precipitated by slowly adding cold diethyl ether (4-8 °C) in an excess amount under stirring condition to remove the unreacted ε-CL monomers and PEG homopolymers for purification.

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The precipitate was then filtered and the purification process was repeated twice more. Then, the purified copolymers were dried under vacuum condition at room temperature to constant weight for 24 h and stored in a desiccator [8, 12, 14, 15].

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Table 1: Experiment design of 2² full factorial design for formation of PCEC triblock copolymers

Coded		Actual (g)		Ratio (Factors)	Parameter (Responses)	Target
PCL	PEG	PCL	PEG			
-1	+1	8	4	2.0:1	Particle size (nm)	Minimum
+1	+1	10	4	2.5:1	Polydispersity index	Minimum
-1	-1	8	2	4.0:1	Entrapment efficiency (%)	Maximum
+1	-1	10	2	5.0:1		

Characterization methods

The functional groups of ε-CL, PEG, and copolymers were characterized by fourier transform infrared-attenuated total reflectance (FTIR-ATR) spectroscopy Thermo Scientific Nicolet iS10 (Waltham, USA) with a ZnSe crystals and a deuterated triglysin sulphate (DTGS) detector. The scan was carried out in the range of 4000-650 cm⁻¹ at a resolution of 8 cm⁻¹ and 32 times of iterations [12].

The thermal properties of ε-CL, PEG, and copolymers were characterized by differential scanning calorimetry instrument (DSC)-60 Plus (Shimadzu, Japan). 2 mg of each sample was placed into a sealed aluminum pan and was heated in the temperature range of 25-100 °C at heating rate of 10 °C/min [12].

The structure of copolymers was characterized by Proton Nuclear Magnetic Resonance (¹H-NMR) spectroscopy 500 MHz Jeol Resonance JNM-ECZ500R (Peabody, USA) in CD₃OD (methanol-d₄). Less than 1 µg of each sample was placed into micro tube and analyzed in 500 MHz. [12, 16]

Formation of K-loaded PCEC triblock copolymeric micelles

K-loaded PCEC triblock copolymeric micelles was obtained by trapping K into PCEC triblock copolymers using a solvent evaporation method. 20 mg of PCEC triblock copolymers with different PCL: PEG ratio (2-5:1) was dissolved in 2 ml dichloromethana solution containing K (100 ppm) and then dichloromethana solvent was evaporated so that K-PCEC triblock copolymeric film layers were formed. 2 ml of deionized distillation water was added, shaken, and heated at 60 °C until it melted, and then cooled at 4 °C for 2 min. Subsequently, deionized distillation water was added up to 10 ml and homogenized by the vortex [17, 18].

Zeta potential (ZP), particle size (PS), and polydispersity index (Pdl)

ZP, PS and Pdl were determined by Zetasizer Nano ZS Version 7.01 Malvern (Worcestershire, England). Measurements were made at 25 °C using dynamic light scattering (DLS) technique at a wavelength of 632 nm, an angle of 173 °, refractive index 1,333, and absorbance of sample 0.1 [19].

Entrapment efficiency (EE)

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K-loaded PCEC triblock copolymeric micelles was centrifuged at 6000 rpm for 30 min. Supernatant was filtered by membrane filter 0,45 µm then determined by UV spectrophotometer (Thermo Scientific, Genesys 10S UV) at a wavelength of 239 nm to known unloaded K. Concentration of K in the PCEC triblock copolymeric micelles was obtained by difference between the concentration of initial K and unloaded K [20].

EE was calculated using the following equation:

$$EE (\%) = \frac{\text{Concentration K in micelles}}{\text{Concentration of initial K}} \times 100\% = \frac{(C_{\text{initial K}} - C_{\text{supernatant}})}{C_{\text{initial K}}} \times 100\%$$

RESULTS AND DISCUSSION

Characterization of PCEC triblock copolymers

The FTIR spectra of the synthesized PCEC triblock copolymers based on parameters of functional groups (specific vibration peaks) is displayed in fig. 1. The formation of PCEC triblock copolymers is indicated by the detection of several functional groups namely the ether group (C-O-C) and the alkaline group (C-H) from the bonding of PEG and PCL units with the peak of the band that appears in the frequency region of 1050-1300 cm⁻¹ (strong intensity) and of 2850-2970 cm⁻¹ (strong intensity), as well as the carbonyl ester group (C=O) and hydroxyl group (O-H) of the PCL unit bonding with the peak of the band that appears in the frequency region of 1690-1760 cm⁻¹ (strong intensity) and of 3200-3600 cm⁻¹ [12, 14].

The DSC thermogram of the synthesized PCEC triblock copolymers based on parameters of thermal properties (melting points) is displayed in fig. 2. In PEG and PCEC triblock copolymers, physical changes occur from solid to liquid which shows the endothermic transition (sample absorbs heat). The melting points of the PCEC triblock copolymers for the ratio of PCL: PEG 2.0:1; 2.5:1; 4.0:1; and 5.0:1 respectively were 50.67 °C; 54,25 °C; 55,49 °C; and 56.51 °C. These show that the greater the ratio of PCL: PEG, the longer the chain structure of PCL so that the higher the melting point of PCEC triblock copolymers [12].

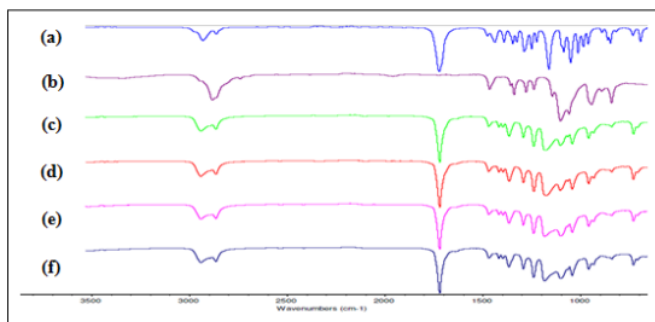


Fig. 1: FTIR spectra of ε-CL (a), PEG (b), PCEC triblock copolymers for the ratio of PCL: PEG 2.0:1 (c); 2.5:1 (d); 4.0:1 (e); and 5.0:1 (f)

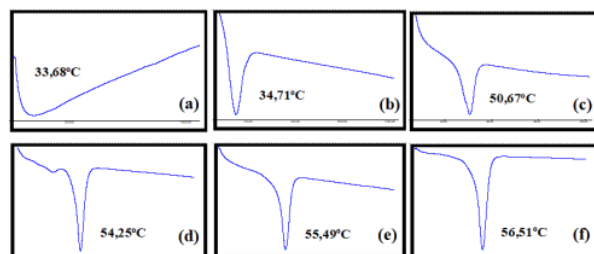


Fig. 2: DSC thermogram ϵ -CL (a), PEG (b), PCEC triblock copolymers for the ratio of PCL: PEG 2.0:1 (c); 2.5:1 (d); 4.0:1 (e); and 5.0:1 (f)

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The $^1\text{H-NMR}$ spectrum of the synthesized PCEC triblock copolymers based on parameters of structure (proton peaks) is displayed in fig. 3. The formation of PCEC triblock copolymers was demonstrated by the detection of proton peaks in PCL units at 1.422-1.442 ppm (CH_2), 1.666-1.667 ppm (CH_2), 2.333-2.334 ppm (OCCH_2), and 4.080 ppm (CH_2OOC), as well as the proton peak in the PEG unit at 3.638 ppm

($\text{CH}_2\text{CH}_2\text{O}$). In addition, there were differences in signal intensity (integration value) of each signal peak caused by differences in the number of hydrogen atoms (H) in each signal between each sample. This finding showed the differences in structure between each sample where the greater the ratio of PCL: PEG, the longer the chain structure of PCL so that the more the number of H atoms [12, 14, 16, 21, 22].

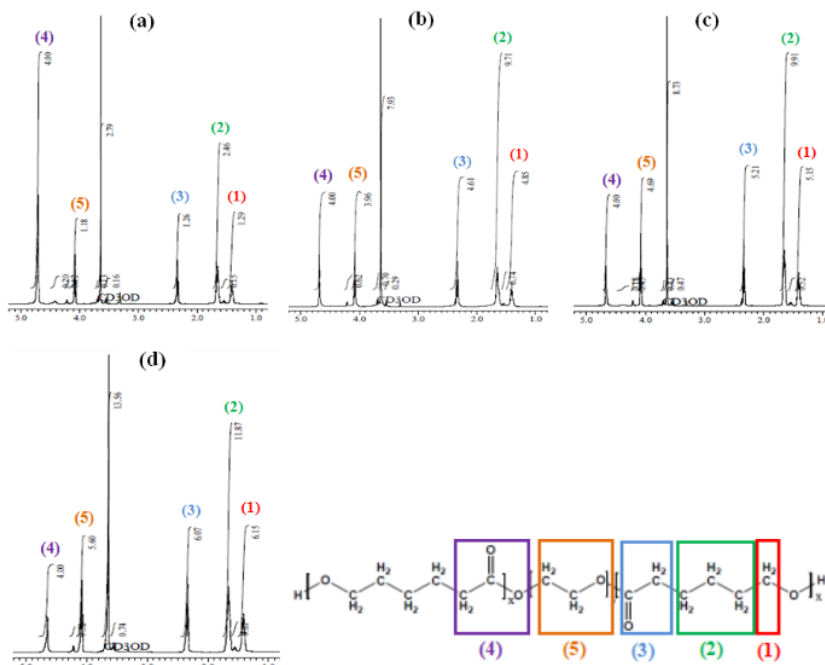


Fig. 3: $^1\text{H-NMR}$ spectrum PCEC triblock copolymers for the ratio of PCL: PEG 2.0:1 (a); 2.5:1 (b); 4.0:1 (c); and 5.0:1 (d)

Characterization of K-loaded PCEC triblock copolymeric micelles

The results of K-loaded PCEC triblock copolymeric micelles characterization is shown on table 2. The higher the PCL: PEG ratio, the ZP value tends to be smaller while the PS, Pdl, EE, and drug

solubility may be increased, but the addition of hydrophobic blocks to some extent does not affect the EE and drug solubility. K has a solubility of 9.15 ± 0.08 $\mu\text{g/ml}$ while the K-loaded PCEC triblock copolymeric micelles has a solubility of 70.51 ± 1.22 to 96.80 ± 2.39 $\mu\text{g/ml}$ (increasing from 7.71 to 10.61 times).

Table 2: The result of K-loaded PCEC triblock copolymeric micelles characterization

Sample	ZP (mV)	PS (nm)	Pdl	EE (%)	Drug Solubility ($\mu\text{g/ml}$)
K	-	-	-	-	9.15 \pm 0.08
K-PCEC 2.0:1	-21.33 \pm 2.46	232.53 \pm 2.02	0.25 \pm 0.01	86.69 \pm 0.03	96.80 \pm 2.39
K-PCEC 2.5:1	-19.63 \pm 1.40	240.73 \pm 5.29	0.41 \pm 0.12	87.71 \pm 0.02	97.07 \pm 2.66
K-PCEC 4.0:1	-17.83 \pm 0.55	580.50 \pm 68.29	0.66 \pm 0.07	88.82 \pm 0.06	72.48 \pm 1.47
K-PCEC 5.0:1	-17.80 \pm 0.40	725.83 \pm 12.07	0.67 \pm 0.02	88.82 \pm 0.04	70.51 \pm 1.22

Optimization

Optimization of PCEC triblock copolymers and analysis of the effect of PCL: PEG ratio factors on the responses toward PS, Pdl, and EE,

were carried out through the DoE approach of the 2² full factorial design method using the Design Expert software. The results of the analysis of the effect of ratio of PCL: PEG ratio factors on the responses toward PS, Pdl, and EE is shown on table 3.

Table 3: Experiment design of 2² full factorial design and the observed responses

Run	Factors		Responses		
	PCL	PEG	PS (nm)	Pdl	EE (%)
1	-1	-1	530.0	0.66	88.75
2	-1	1	234.7	0.24	86.72
3	1	1	236.1	0.27	87.73
4	1	1	246.5	0.48	87.68
5	1	-1	713.1	0.65	88.85
6	1	1	239.6	0.47	87.71
7	1	-1	737.1	0.69	88.83
8	-1	-1	553.3	0.6	88.88
9	-1	1	232.2	0.26	86.66
10	-1	-1	658.2	0.73	88.83
11	-1	1	230.7	0.26	86.70
12	1	-1	727.3	0.67	88.77

The results of the variance analysis (ANOVA) on the effect of PCL: PEG ratio factors toward the observed responses showed that the 3 observed responses gave significant results (p-value < 0.05). Therefore, the equation model of the 3 observed responses could be used to predict the optimum formula of K-loaded PCEC triblock copolymer micelles. The goodness of fit parameters (R², adjusted R², predicted R²,

Adequate precision) were used to determine the most appropriate model. The model in each response meets the acceptance criteria because the R² value is more than 0.7, the difference between the adjusted R² and the predicted R² values are no more than 0.2 and the adequate precision value is more than 4 [23, 24]. The results of the statistical analysis of the 3 observed responses is shown on table 4.

Table 4: The result of statistical analysis of the 3 observed responses

Parameter	PS (nm)	Pdl	EE (%)
R ²	0.9828	0.9090	0.9984
Adjusted R ²	0.9763	0.8748	0.9978
Predicted R ²	0.9612	0.7951	0.9964
Adequate precision	24.559	10.527	84.505

Contour plot interaction of PCL and PEG factors and the regression equation of the 3 observed responses is displayed on fig. 4 and table 5. PCL increases the particle size, polydispersity index and efficiency entrapment, while PEG and interactions between PCL and PEG cause a decrease in particle size,

polydispersity index, and entrapment efficiency. This is due to the greater PCL: PEG ratio, the longer the chain structure of PCL, causing the particle size, polydispersity index, and entrapment efficiency of K-loaded PCEC triblock copolymeric micelles to be greater [19].

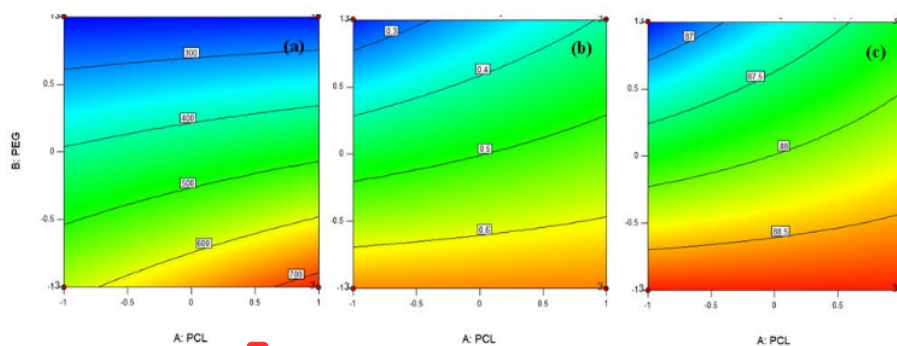


Fig. 4: Contour plot interaction of PCL and PEG factors on the observed responses toward PS (a), Pdl (b), and EE (c)

Table 5: The regression equation of the 3 observed responses

Responses	Regression equation
Particle Size (nm)	$Y_1 = 444.90 + 38.38X_A - 208.27X_B - 34.28X_A X_B$
Polidispersity Index	$Y_2 = 0.50 + 0.040X_A - 0.17X_B - 0.037X_A X_B$
Entrapment Efficiency (%)	$Y_3 = 88.01 + 0.25X_A - 0.81X_B - 0.25X_A X_B$

Optimum formula

The prediction of optimum formula of K-loaded PCEC triblock copolymer micelles is shown on table 6. The K-loaded PCEC triblock copolymeric micelles formula with the largest desirability value is selected as the optimum formula namely at a PCL: PEG ratio of 2.0:1 (solution number 1) with the predicted values of 232.533 nm for PS response, 0.253 for PDI response, and 86.693% for EE response. The optimum observed formula has a zeta potential of -24.07 ± 0.35 mV, particle size of 235.70 ± 6.03 nm,

polydispersity index of 0.30 ± 0.06 , entrapment efficiency of $87.08 \pm 0.06\%$, and the solubility of the K increases by 10.60 times. The verification result of observed values to predicted values is shown on table 7. The verification study by comparing the observed values to the predicted values used a 95% confident interval (CI) value and one sample t-test. The results are considered verified because all observed values is in the range of 95% CI and one sample t-test result using SPSS software indicate that no significantly different (p -value > 0.05) between the observed values and the predicted values.

Table 6: Prediction of optimum formula of K-loaded PCEC triblock copolymer micelles

No.	PCL	PEG	PS (nm)	PdI	EE (%)	Desirability	Status
1	-1.000	1.000	232.533	0.253	86.693	0.985	Selected
2	-0.952	1.000	232.731	0.257	86.718	0.981	
3	-0.940	1.000	232.778	0.258	86.724	0.980	
4	-1.000	0.986	235.008	0.256	86.708	0.979	
5	-1.000	0.961	239.392	0.261	86.735	0.969	
6	-0.809	1.000	233.315	0.268	86.790	0.969	
7	-0.783	1.000	233.424	0.270	86.803	0.966	
8	-0.165	1.000	235.957	0.317	87.116	0.913	
9	-0.014	1.000	236.575	0.329	87.193	0.899	
10	0.501	1.000	238.689	0.368	87.454	0.852	

Table 7: The verification result of the observed values to the predicted values

Responses	Prediction	Observation	95% CI	One sample t-test (p-value)
PS (nm)	232.533	235.70 \pm 6.03	195.18-269.88	0.909
PdI	0.253	0.30 \pm 0.06	0.18-0.33	1.338
EE (%)	86.693	86.71 \pm 0.04	86.65-86.74	0.871

CONCLUSION

The optimization study to obtain the optimum K-loaded PCEC triblock copolymer micelles has been successfully carried out using the 2² full factorial method. The PCEC triblock copolymers was obtained from the synthesis of ϵ -caprolactone (ϵ -CL) and PEG by ring opening polymerization (ROP) method with Sn (Oct)₂ as a catalyst. The K-loaded PCEC triblock copolymeric micelle was obtained by solvent evaporation method. The optimum K-loaded PCEC triblock copolymer micelles with a PCL: PEG 2.0:1 ratio has a zeta potential of -24.07 ± 0.35 mV, particle size of 235.70 ± 6.03 nm, polydispersity index of 0.30 ± 0.06 , entrapment efficiency of $87.08 \pm 0.06\%$, and the solubility of the K increases by 10.60 times.

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Nil

AUTHORS CONTRIBUTIONS

All of the authors listed in this manuscript has contributed equally.

CONFLICT OF INTERESTS

The author declares that there is no conflict of interest associated with this work.

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