Study Kinetics Models of Clindamycin Hydrochloride from Poly(D,L-lactic-co-glycolic acid) Particles

Chatchawan Soonklang, Chalermchai Tassanarangsan, Nopparuj Soomherun, Narumol Kreua-ongarjnukool, and Saowapa Thumsing Niyomthai
Department of Industrial Chemistry, Faculty of Applied Science, King Mongkut's University of Technology North Bangkok, Bangkok, Thailand
Email: {ccw.soonklang, C.Tassanarangsan, n.soomherun}@gmail.com, {narumol.k, saowapa.t}@sci.kmutnb.ac.th

***Abstract*—The aim of this research is to study the kinetic models of Clindamycin hydrochloride encapsulated in poly(D,L- lactic-co-glycolic acid) particles (CLH/PLGA). The CLH/PLGA particles were prepared by the double emulsion technique. The characterizations of CLH/PLGA particles were determined particle size, zeta potential, encapsulation efficiency, morphology, principle functional group, swelling, and *in vitro* drug release profile. The morphology of CLH/PLGA particles was the smooth and spherical shape. The maximum encapsulation efficiency of CLH/PLGA particles was 75% and the particle size of CLH/PLGA particles is from 216 to 222 nm and zeta potential value from -14.7 to -12.76 mV. The *in vitro* release of CLH/PLGA particles was carried out in pH 6.8 and pH 7.4. The model drug release profile result was fitting with the kinetic mathematic model. In addition, the kinetic models of CLH/PLGA particles released in pH 6.8 and pH 7.4 were *First order model* and *Korsmeyer-Peppas model*. The investigated of the kinetic model also gave a better of the effect on the CLH release pattern.**

***Index Terms*—poly(D,L-lactic-co-glycolic acid), clindamycin hydrochloride, nanoparticles, kinetic models**

I. Introduction

Nowadays, drug delivery system using nanotechnology are improving to target drugs with maximum, in order to controlled release to target. Drug delivery system was prepared from particles that prepare are various techniques for example spray drying [1], liposome [2], emulsion [3], etc. Emulsion technique is the most method for prepared particles by biopolymer because it could be used for insoluble or soluble drug and increase adsorption [4].

Poly(D,L- lactic-co-glycolic acid); PLGA is biopolymer and commonly used in drug delivery system because of biodegradable, biocompatibility and non-toxic [5]. PLGA is a linear copolymer between lactic acid (LA) and glycolic acid (GA) [6]. PLGA is widely used in medical applications, such as bone tissue [6], anti-tumor [7], etc.

Clindamycin hydrochloride (CLH) is a drug water soluble and antibiotics drug in macrolide group, that is a type of antibiotics drug [8]. CLH used for the treatment of bacteria in lung [9], vagina [10] or acne [11]. It is available by mouth, injection into a vein and a cream to be applied to the skin or vagina.

The drug dissolution is an important study to evaluate the CLH release of PLGA particles like the coefficient of drug diffusion and dependent on model fitting. In this research focus on fitting of the experimental dissolution data from drug release for the development of drugs that control release from particles will depend on the result of drug dissolution compared with mathematic equations, including *Zero order*, *First order*, *Higuchi*, *Hixson-Crowel and Korsmeyer-Peppas*, [12]. Factors affecting drug dissolution are capable of experimental planning, predicted development of CLH release and knowing mechanisms from particles in order to apply for patients to receive enough medicine. Mathematic equations used as a model for predict the kinetic of drug release [13].

Zero Order Model. It's an ideal model of drug release. The drug dissolved from solid dosage forms and drug released at a rate constant over time by Equation (1) [12].

$$Q_t - Q_0 = K_0 t \quad (1)$$

where Q_t is the drug amount dissolved in solution at time t. Q_0 is the initial drug amount in solution. K_0 is the constant of *Zero order* release.

First Order Model. This profile used for release drugs according to remaining of drug amount in drug solid forms by Equation (2) in logarithms forms [12].

$$\log Q_t = \log Q_0 + (K_1/2.303) \quad (2)$$

where Q_t is the drug amount dissolved in solution at time t. Q_0 is the initial drug amount in solution. K_1 is the constant of the *First order* release. The data get plotted as log cumulative percentage of drug remaining and time which is a slope –K/2.303.

Hixson-Crowell Model. The release of drugs from solid dosage forms, capsules or suspension. The CLH tablet particles became smaller as drug dissolves, causing the surface area of the tablet to decrease, the radius and weight of particles are not being constant by the Equation (3) [12].

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$$M_0^{1/3} - M_t^{1/3} = K_{HX}t \quad (3)$$

where M_0 is the initial drug amount in solid dosage forms. M_t is the drug amount in solid dosage forms. K_{HX} is the *Hixson-Crowell* constant. The data obtained from *in vitro* drug release were plotted as drug percentage in CLH tablet and time, line with a slope of K_{HX}.

Higuchi Model. This profile describes the release of the drug from the semi solid on matrix system. This profile is based on hypothesis that (1) The particles of drug regularly spread in tablet, (2) The drugs of initial concentration in the matrix of CLH tablet higher than drug solubility, (3) Drug diffusion occurs in only one dimension, (4) The particles of drugs are minor than the thickness of the tablets, (5) Swelling of tablets and dissolution are less or slight, (6) The drug diffusion coefficient is constant, (7) The solution is a perfect sink condition always release environment by the Equation (4) and (5) [12].

$$Q_t - Q_0 = K_H\sqrt{t} \quad (4)$$

$$K_H = A[DC_s(2C_{ini})]^{1/2} \quad (5)$$

where Q_t is the drug amount dissolved in solution at time t per unit area A. Q_0 is the initial drug amount in solution. K_H is the *Higuchi* dissolution constant. *D* is diffusion coefficient in diffusion layer. C_s is solubility of drug in diffusion layer. C_{ini} is initial concentration of drug. The data were plotted as square root of time and cumulative percentage drug release.

Korsmeyer-Peppas model. This profile described drug from a semi-empirical polymeric system. This profile is based on hypothesis that (1) Occurs under perfect sink condition, (2) Drug release occurs in only one dimension by Equation (6) [12].

$$\log\left[\frac{(Q_t - Q_0)}{(Q_\infty - Q_0)}\right] = n\log(t) + \log K_{KP} \quad (6)$$

by "n" is release exponent used to characterize different release. It depends on shape of particles describe in Table I.

TABLE I. RELEASE EXPONENT VERSUS DRUG TRANSPORT MECHANISM DEPEND ON SHAPE OF DRUG DELIVERY SYSTEM [12]

Drug transport mechanism	Release exponent (n)		
	sphere	cylinder	films
Fickian diffusion	0.43	0.45	0.5
Anomalous transport	0.43<n<0.85	0.45<n<0.89	0.5<n<1.0
Case-II transport	0.85	0.89	1.0

In this research was prepared PLGA particles encapsulating CLH by the double emulsion method ($w_1/o/w_2$) in order to study of drug release kinetics *in vitro* at pH 6.8 (as in urinary system condition) [14] and pH 7.4 (as in lung condition) [15] by compared with mathematic equations consists of *Zero order model, First order model, Hixson-Crowell model, Higuchi model and Korsmeyer-Peppas model* to be used as model release kinetic of Clindamycin hydrochloride from PLGA particles.

II. METHOD

A. Preparation of CLH/PLGA Particles

1) Materials

Poly(D,L-lactic-co-glycolic acid); PLGA with have average molecular weight of 24,000-38,000 Da and copolymer ratio of lactide : glycolide at 50:50 purchased from Sigma-Aldrich, USA) product of Germany. Used as the outer material for particles. Poly(vinyl alcohol) (PVA, Mw. ~115,000 Da, VWR International, UK) was used here as stabilizers. Clindamycin hydrochloride (CLH, DACIN – F300, Thailand). Dichloromethane and acetone were analytical reagent grade and purchased from RCI Lab-scan Limited (Thailand).

2) Method

According to Nopparuj and *et al.* [16]. 1 mL of 10 mg CLH in 0.5 %w/v of PVA was ultrasonicated (model VCX 500) with 3 mL of PLGA solution (115 mg) for the single emulsion. Next, PVA solution was added and stirred for solvent evaporation to achieve the double emulsion. PLGA particles were collected by centrifuge (Hettich Zentrifugen, UNIVERSAL 320) at 8000 rpm for 20 mins and washed with DI water to remove free drug completely. Finally, particles were dried by freeze dryer (Thermo electron corporation, Pirani 501) for 24 hrs. and then were characterized.

B. Particle Size of CLH/PLGA Particles, Polydispersity Index and zeta Potential Measurement of CLH/PLGA Particles

The diameter, polydispersity index (PDI), and zeta potential of CLH/PLGA particles were analyzed by dynamic light scattering (DLS) techniques (HORIBA Scientific NANO PARTICLE ANALYZER SZ-100V2).

C. Encapsulation Efficiency (%EE) of CLH/PLGA Particles

The encapsulation efficiency of CLH/PLGA particles was measured by UV-Visible spectrophotometer at wavelength of 197 nm and using standard curve of CLH calculated amount of CLH unencapsulated in PLGA particles [17]. The encapsulation efficiency was calculated by Equation (7).

$$\%EE = [(B - A)/B] \times 100 \quad (7)$$

where A was the unencapsulated CLH/PLGA particles. B was the total amount of CLH.

D. Morphology of CLH/PLGA Particles

The morphology of the CLH/PLGA particles was investigated by field emission scanning electron microscope and energy dispersive X-ray spectrometer (FESEM-EDS 7610F, JEOL JSM-7610f, Oxford X-Max 20). The specimens were coated with platinum and observed under different magnifications at 1 kV and 10,000x magnification.

E. Fourier Transformed Infrared Spectra of CLH/PLGA Particles

CLH, PLGA and CLH/PLGA particles were prepared in potassium bromide pellets. The spectrum was

characterized by FT-IR spectrophotometer (Perkin Elmer: Model spectrum 2000) in order to determine the functional groups of CLH adsorbed in PLGA particles.

F. Swelling Ratio of CLH/PLGA Particles

The swelling ratio of CLH/PLGA particles prepared after incubation at 37°C in 10 mL of PBS solution pH 6.8 and 7.4. After time stated, the size of swollen CLH/PLGA particle was analyzed by nanosizer and their swelling ratio was calculated by Equation (8) [18].

$$\text{swelling ratio} = \left(D_{swell}/D_{dry}\right) \times 100 \quad (8)$$

where D_{swell} and D_{dry} substitute the particle size of CLH/PLGA after and before the incubation.

G. In Vitro Drug Release Profile

The *in vitro* release kinetic of CLH/PLGA particles was examined in PBS solution at pH 6.8 and pH 7.4 at 37°C. Each of sample (50 mg) was incubated in Phosphate Buffer Solution (PBS) in pH 6.8 and pH 7.4. The samples were placed in a shaking bath with shaking at 35 rpm. At each time point, the supernatant was removed and replace with pure PBS solution in each day, and the amount of CLH in the supernatant was examined by UV-Visible spectrophotometer at a wavelength of 197 nm

H. Comparison Drug Release Profiles with the Kinetic Mathematic Equations

The R^2 and adj-R^2 were observed using the fitting curve (of the experimental dissolution data from drug release profile with the kinetic mathematic equation, including *First order*, *Zero order*, *Hixson-Crowell*, *Higuchi* and *Korsmeyer-Peppas)* [13].

III. Results and Discussion

A. Preparation of CLH/PLGA Particles

The purpose of this research was to study of preparations CLH/PLGA particles by the double emulsion technique and release CLH without PLGA particles in PBS solution pH 6.8 (as in urinary system condition) and pH 7.4 (as in lung condition), in order to predict kinetic drug release profiles of CLH without PLGA particles.

B. Particle Size, Polydispersity Index and Zeta Potential Measurement

Various definition factors were reported properties of nanoparticles formed [19]. In this research, CLH/PLGA particles were prepared by the double emulsion technique. The properties of CLH/PLGA particles were presented in Table II. The particle size of PLGA was 199.30±1.15 nm. The particle size increased when encapsulated CLH into the PLGA particles by particle size of CLH/PLGA was 219.77±3.02 nm. The size of CLH/PLGA particle was dependent on the initial concentration of drug as similar earlier results [19], [20].

Zeta potential is a evaluated of electro-kinetic potential on the surface of particles. The zeta potential value of CLH/PLGA particle was -13.84±0.94 mV, while for PLGA and CLH were -24.28±1.38 mV and +3.01±0.05 mV, respectively. This result showed that is the zeta potential important for the entrapment in PLGA particles. The PDI of CLH/PLGA particles was a narrow size distribution of about 0.136±0.081 which observed PDI value of less than 0.500 [21].

C. Encapsulation Efficiency (%EE) of CLH/PLGA Particles

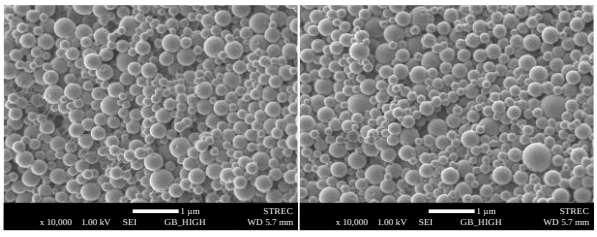
This study was presented with the encapsulation efficiency of CLH/PLGA particles. This result CLH/PLGA particles were encapsulated about 75.01±0.17%. Electrostatic interaction, the carboxylate anion ($-COO^-$) of PLGA particles was interacted with positive charge from amino salt ($-NH_2{}^+Cl^-$) of CLH lead to entrapped CLH, as shown in Table II.

TABLE II. Physical Properties of CLH/PLGA Particles

Sample	Mean particle size (nm±SD)	Zeta potential (mV±SD)	Encapsulation efficiency (%)
PLGA	199.30±1.15	-24.28±1.38	-
CLH	-	+3.01±0.05	-
CLH/PLGA	219.77±3.02	-13.84±0.94	75.01±0.17

D. Morphology of CLH/PLGA Particles

The morphology of PLGA and CLH/PLGA particles was analyzed by SEM micrograph, as illustrated in Fig. 1. The particles were observed the formation of spherical shape. Likewise, The SEM images were appeared of the surface particles with round and smooth. The morphology of PLGA and CLH/PLGA particles was a similarity characteristic shape.



(a) (b)

Figure 1. SEM micrograph of (a) PLGA and (b) CLH/PLGA (10,000x magnification).

E. Fourier Transformed Infrared Spectra of CLH/PLGA Particles

FT-IR study of CLH/PLGA particles was executed to characterize the functional groups of CLH in PLGA particles. Fig. 2 presented IR spectra of CLH, PLGA particles, and CLH/PLGA particles. The PLGA particles similar peaks were determined at 3424 cm^{-1} (O-H stretching), 3000 and 2955 cm^{-1} (C-H stretching), 1761 cm^{-1} (C=O stretching of carbonyl group), 1180 and 1091 cm^{-1} (C-O stretching). The CLH whereas 3467 cm^{-1} (O-H stretching), 3065 and 2921 (C-H stretching), 1686 and 1555 cm^{-1} (C=O stretching of amide carbonyl), 1453 cm^{-1} (C-N stretching of pyrrolidine), 1254 cm^{-1} (S-C-H stretching of thiol ether), 1080 and 1044 cm^{-1} (C-O

stretching) and 862 cm^{-1} (C-Cl stretching) [22]. When considering IR spectrum of CLH/PLGA particles compared with PLGA particles were investigated at 1429 cm^{-1} (C-N stretching of pyrrolidine), 1274 cm^{-1} (S-C-H stretching of thiol ether) and 865 cm^{-1} (C-Cl stretching) which the functional groups of CLH. The CLH/PLGA particles observed the principle functional group of CLH and PLGA particles [19].

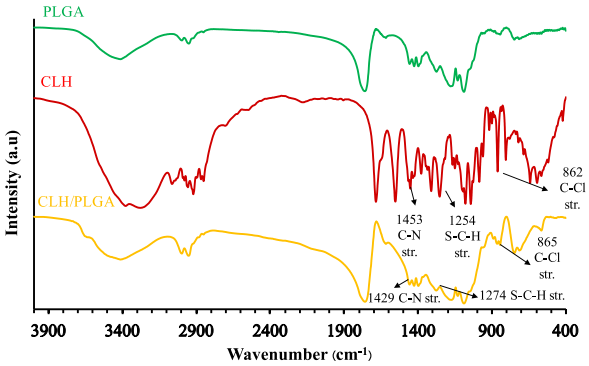


Figure 2. FT-IR spectra of PLGA, CLH and CLH/PLGA particles prepared by KBr pellets.

F. *Swelling Ratio of CLH/PLGA Particles*

The swelling ratio of CLH/PLGA particles in PBS solution at pH 6.8 and pH 7.4 on the first day demonstrated, the swelling increased swift due to diffusion of water into the CLH/PLGA particles. However, the swelling ratio from 2 to 9 days trend to be stable due to equilibrium of diffusion was illustrated in Fig. 3.

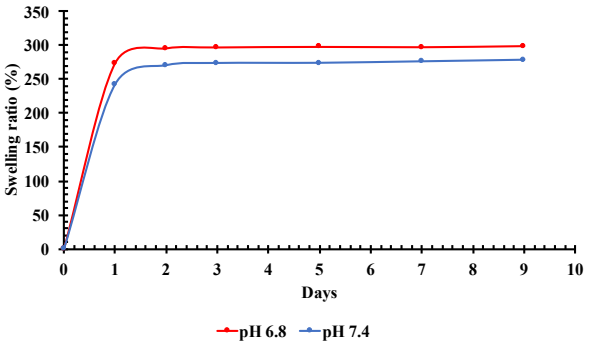


Figure 3. Swelling ratio of CLH/PLGA particles in pH 6.8 and pH 7.4 (n=9).

G. *In Vitro Drug Release Profile of CLH/PLGA Particles*

The CLH/PLGA particles were investigated to release in PBS solution pH 6.8 and pH 7.4, as shown in Fig. 4. The CLH release profile in PBS solution at pH 6.8 and pH 7.4 increase rapid in 1 to 20 days and trend to be stable in 21 to 30 days. This result was presented the release of CLH from CLH/PLGA particles in PBS solution pH 6.8 higher than pH 7.4. In case of release profile CLH in PBS solution pH 6.8 because in acidic conditions was accelerated degradation of PLGA particles (auto catalytic degradation) over time [23]. Causing PLGA particles was degraded amount of CLH released increase. Compared with release profile out of CLH/PLGA particles in PBS solution pH 7.4.

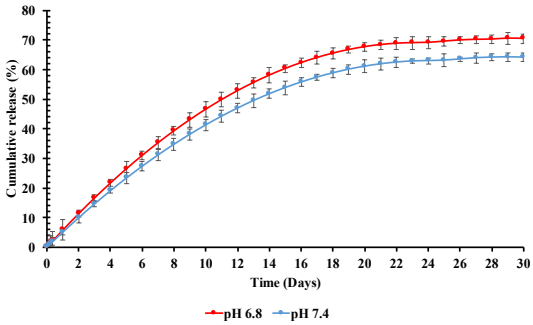
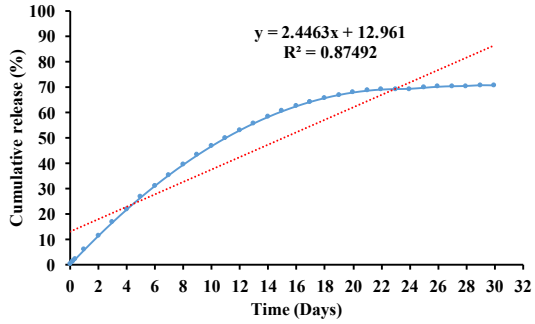
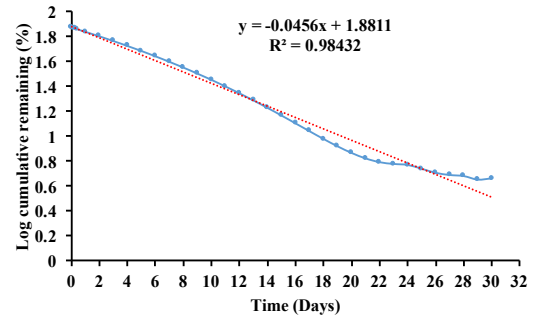


Figure 4. Cumulative release CLH/PLGA particles at time (n=9).

H. *Comparison Drug Release Profiles with the Kinetic Mathematic Equations*



(A)



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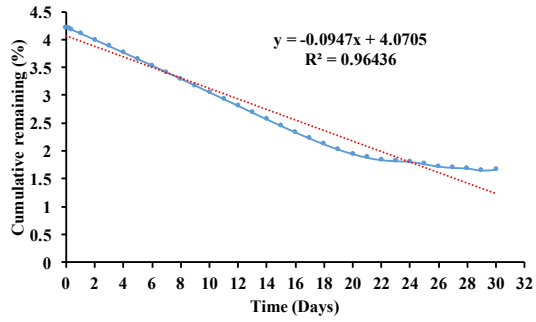

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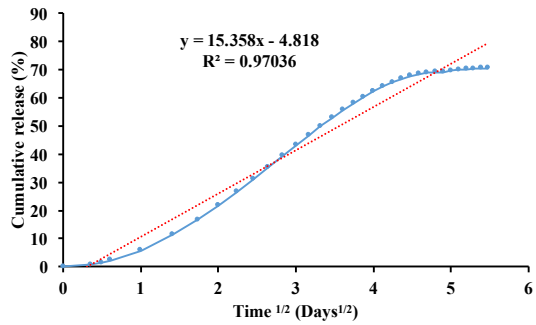

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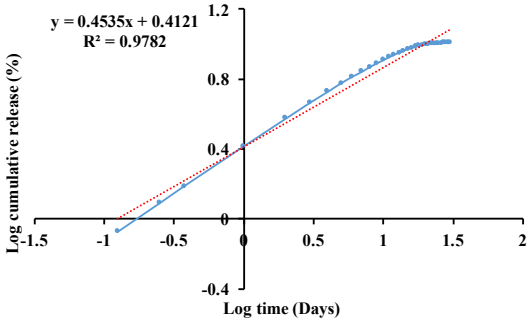
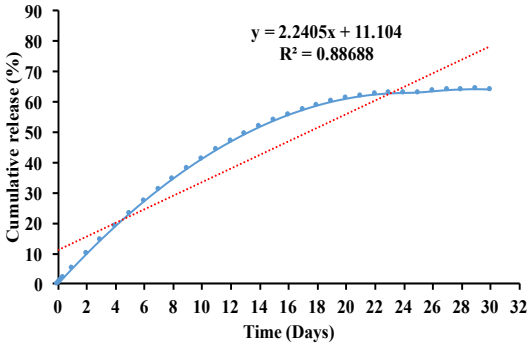


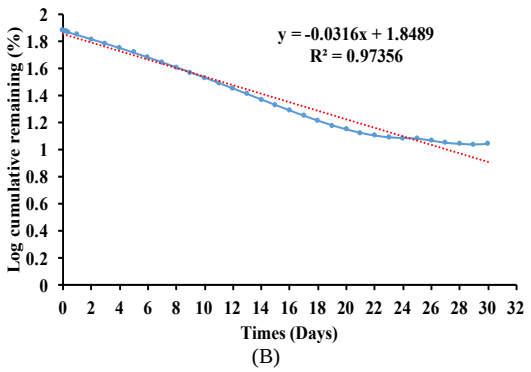
(E)

Figure 5. Drug release kinetic model plots in pH 6.8: (A) *Zero order*, (B) *First order*, (C) *Hixson-Crowell*, (D) *Higuchi*, and (E) *Korsmeyer-Peppas*.

The cumulative release data in pH 6.8 was fitted to the kinetic models. This analysis various parameters such as slope, interception, coefficient of determination (R^2) and adjusted coefficient of determination (Adj.-R^2) [24]. Kinetic study plots of *Zero order model*, *First order model* and *Hixson-Crowell* are fitted curve between time and cumulative release, log cumulative remaining, cumulative remaining$^{1/3}$, respectively. On the other hand, *Higuchi model* and *Korsmeyer-Peppas model* are plotted on cumulative release vs times$^{1/2}$ and log cumulative release vs log time respectively [12], [13], all plots are indicated in Fig. 5. Analyzing the data was exposed that, *First order model* was the best fit model due to the highest R^2 (0.984). The cumulative release data in pH 7.4 was fitted to the kinetic model like pH 6.8, as simulated in Table III and IV and Fig. 6 and analyzing the data were exposed that, *Korsmeyer-Peppas model* with the highest R^2 valve (0.981) and n=0.467. The release exponent (n) indicated the release mechanism is anomalous transport, as indicated in Table I.



(A)



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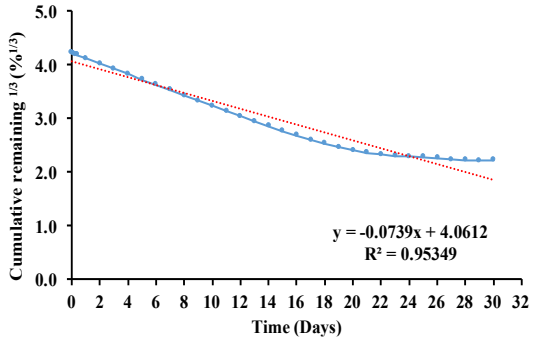

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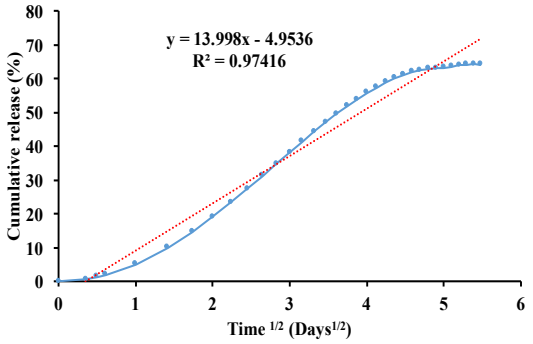

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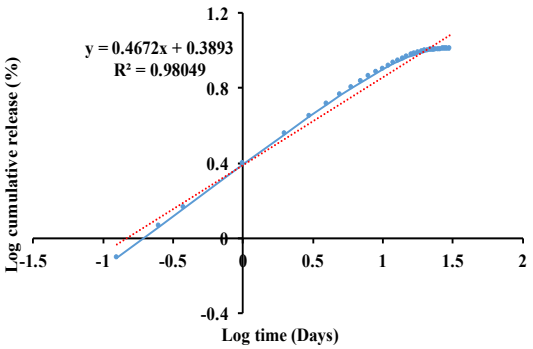

(E)

Figure 6. Drug release kinetic model plots in pH 7.4: (A) *Zero order*, (B) *First order*, (C) *Hixson-Crowell*, (D) *Higuchi*, and (E) *Korsmeyer-Peppas*.

TABLE III. INTERPRETATION OF SLOPE, INTERCEPTION, COEFFICIENT OF DETERMINATION AND ADJUSTED COEFFICIENT OF DETERMINATION FROM KINETICS OF CLH/PLGA PARTICLES IN PH 6.8

Models	Slope	Interception	R^2	Adj.-R^2
Zero order	2.466	12.961	0.875	0.871
First order	-0.046	1.881	0.984	0.984
Hixson-Crowell	-0.095	4.071	0.964	0.963
Higuchi	15.358	-4.818	0.970	0.969
Korsmeyer-Peppas	0.454	0.412	0.978	0.984

TABLE IV. INTERPRETATION OF SLOPE, INTERCEPTION, COEFFICIENT OF DETERMINATION AND ADJUSTED COEFFICIENT OF DETERMINATION FROM KINETICS OF CLH/PLGA PARTICLES IN PH 7.4

Models	Slope	Interception	R^2	Adj.-R^2
Zero order	2.241	11.104	0.887	0.883
First order	-0.032	1.849	0.974	0.973
Hixson-Crowell	-0.074	4.061	0.954	0.952
Higuchi	13.998	-4.954	0.974	0.973
Korsmeyer-Peppas	0.467	0.389	0.981	0.980

IV. Conclusion

The CLH/PLGA particles were prepared by the double emulsion technique. The average size of CLH/PLGA particles was approximately from 216 to 222 nm, zeta potential value from -14.7 to -12.76 mV, and encapsulation efficiency 75.01±0.17 percentage. The morphology of CLH/PLGA particles was spherical shape. Moreover, the functional groups of CLH/PLGA particles showed at 1429 cm^{-1} (C-N stretching of pyrrolidine), 1274 cm^{-1} (S-C-H stretching of thiol ether) and 865 cm^{-1} (C-Cl stretching). The kinetic model of CLH/PLGA particles released in pH 6.8 was *First order model* and pH 7.4 was *Korsmeyer-peppas model.*

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

C. Soonklang and C. Tassanarangsan carried out the experiment, performed the analytic calculations and fitted with the kinetic mathematic model, and co-wrote the paper with input from all authors; N. Soomherun helped to carry out the analytical methods and analyzed the data; N. Kreua-ongarjnukool and S. T. Niyomthai devised the main conceptual ideas, design, aided in interpreting the result, reviewing and editing paper; all authors had approved the final version submitted for publication.

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Chatchawan Soonklang was born in Thailand, in 1998. Now he is studying Master of Science degree in Industrial Chemistry, Department of Industrial Chemistry, Faculty of Applied Science, King Mongkut's University of Technology North Bangkok. He received the first class honors degree in the Bachelor of Science Degree in Industrial Chemistry, Department of Industrial Chemistry, Faculty of Applied Science, King Mongkut's University of Technology North Bangkok, Thailand. His research fields are nanotechnology, biopolymer, and drug delivery system.

Chalermchai Tassanarangsan was born in Thailand, in 1997. He received the second class honors degree in the Bachelor of Science Degree in Industrial Chemistry, Department of Industrial Chemistry, Faculty of Applied Science, King Mongkut's University of Technology North Bangkok, Thailand. His research fields are nanotechnology, biopolymer, and drug delivery system.

Nopparuj Soomherun (PhD. candidate) was born on April 30, 1991. He is a graduate of the second class honors degree in the Bachelor of Science Degree and Master of Science Degree in Industrial Chemistry from Department of Industrial Chemistry, Faculty of Applied Science, King Mongkut's University of Technology North Bangkok, Thailand. He received the Best Paper Award 2015 from the 2nd International Conference on Engineering and Natural Science, Waseda University, Japan. He has been practicing research assistant to develop an encapsulation at the Faculty of Medicine Ramathibodi Hospital, Mahidol University, Thailand since 2016. He is interested in nanotechnology, encapsulation, biopolymer, material science, and drug delivery system.

Narumol Kreua-ongarjnukool was born in Bangkok Thailand, in 1960. She received the second class honors degree in the Bachelor Degree in Chemistry from Srinakharinwirot University and Master of Science degree in Chemistry from the Department of Chemistry, Faculty of Science, Chulalongkorn University. She is an Associate Professor at the Department of Industrial Chemistry, Faculty of Applied Science, King Mongkut's University of Technology North Bangkok (KMUTNB). She is a member and the secretary of the Chemical Society of Thailand under the Patronage of Her Royal Highness Princess Chulabhorn Krom Phra Sri savangkavadhana. She received the outstanding research advisor award in 2017 from graduate school, KMUTNB. She has been joining the research to develop nanocarriers for drug delivery of in intraoperative Cerebrovascular Surgery at the Faculty of Medicine Ramathibodi Hospital, Mahidol University, Thailand since 2013. Her research interests include the fields of material science, micro/nano-encapsulation for biomedical application, biopolymer for drug deliver y system and wound dressings materials. She recently received the most outstanding employee award 2018 from KMUTNB. She has published the research paper in various journals and in the proceedings of the international conferences.

Saowapa Thumsing Niyomthai was born in Thailand, in 1986. She received the first honors degree in the Bachelor Science degree in Industrial Chemistry, Department of Industrial Chemistry, Faculty of Applied Science, King Mongkut's University of Technology North Bangkok, Thailand. and PhD. degree in Polymer Science from The Petroleum and Petrochemical College, Chulalongkorn University (An international program, in academic partnership with The University of Michigan, The University of Oklahoma, and Case Western Reserve University). In 2016, she joined the Department of Industrial Chemistry, Faculty of Applied Science, KMUTNB, Thailand as a Lecturer. She is a Life Member of the Chemical Society of Thailand. Her research fields are material science, micro/nanoencapsulation for biomedical application, electrostatic spinning of polymer, biopolymer for drug delivery system, wound dressings and cell/tissue scaffolding materials.