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# Structure and Dynamics of Curcumin Encapsulated Lecithin Micelles: A Molecular Dynamics Simulation Study

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# Abstract

Curcumin is a natural product with potential pharmaceutical applications that can be augmented by drug delivery technology such as nano emulsion. Our study focuses on microscopic structural and dynamics response of curcumin encapsulation in micellar system with lecithin as a natural surfactant under variations of composition and temperature using molecular dynamics (MD) simulations. The results highlight the self-assembly of lecithin micelle, with curcumin encapsulated inside, from initial random configurations in the absence of external field. The variation of composition shows that lecithin can aggregate into spherical and rod-like micelle with the second critical micelle concentration lies between 0.17-0.22 mol dm<sup>-3</sup>. The radial local density centering at the micelle center of mass shows that the effective radius of micelle is indeed defined by the hydrophilic groups of lecithin molecule and the encapsulated curcumin molecules are positioned closer to these hydrophilic groups than the innermost part of the micelle. The spherical micelle is shown to be thermally stable within the temperature range of 277-310 K without a perceivable change in the spherical eccentricity. The dynamics of micelle are enhanced by the temperature, but it is shown to be insensitive to the variation of lecithin-curcumin composition within the studied range. Simulation results are in agreement with the pattern obtained from experimental results based on particle size, polydispersity index, and encapsulation efficiency.

#### **Keywords**

Lecithin, Curcumin, Nanoemulsion, Micelle Formation, Molecular Dynamic Simulation.

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# 1. INTRODUCTION

Curcumin is a natural resource and versatile compound that shows anticancer (Tomeh et al., 2019), anti-inflammatory (Jurenka, 2009), anti-diabetic (Den Hartogh et al., 2020), antiviral, anti-bacterial and anti-fungal activity (Zorofchian M et al., 2014). Nevertheless, low solubility and bioavailability hamper its medical applications. Drug-nanotechnology is considered as a way to overcome the disadvantages and a deep understanding of components interactions in nano emulsion is essential to advance the technology.

Nowadays, the utilization of computer simulation in drug discovery becomes a routine which accelerate the finding of the compound with the highest efficacy with reduced intensive trial and error in laboratory. Computer simulation elaborate drug-target interaction, structure changes, thermodynamics and kinetics aspect which indicate structure stability (Bera and Payghan, 2019; De Vivo et al., 2016; Durrant and McCam-

mon, 2011). In more detail, computer simulation has also been applied in studying the formulation of active compoundloaded nanoemulsion involving liposomal or micellar system (Karjiban et al., 2012; Gupta et al., 2020; Marrink et al., 2000; Moghaddasi et al., 2018; Turchi et al., 2019). Nanoemulsion, which consists of active compound, oil-based solvent, emulsifier and water, has widely known to offer higher active compound bioavailability which increases its efficacy in delivering drugs to the targeted cells (Ochoa-Flores et al., 2017; Shelat and Acharya, 2016; Yu and Huang, 2012). Moreover, curcumin nanoemulsion is continuously being developed to improve curcumin solubility and bioavailability.

Despite the fact that curcumin has been developed vastly in nanoemulsion form (Esperón-Rojas et al., 2020; Franklyne et al., 2018; Kamel, 2019; Ningsih et al., 2021; Ochoa-Flores et al., 2017; Páez-Hernández et al., 2019; Shelat and Acharya, 2016; Sholihat et al., 2020; Silva et al., 2018; Teixeira et al., 2016; Yu and Huang, 2012), study of molecules interaction in

curcumin nanoemulsion system is relatively scarce. Simulation studies have been reported on the interaction of curcumin with lipid bilayer (Jalili and Saeedi, 2016; Kopeć et al., 2013) or with inorganic substance (Shi et al., 2019). Although experimental work has been attempted to study the formation of curcumin in soybean oil with Tween-80 surfactant (Jannah, 2020), the molecular-level details on structures and dynamics of the fundamental curcumin encapsulation in lecithin micelle are still not well understood. Molecular dynamics (MD) simulation is a powerful method to elucidate molecular interactions and advance our understanding on the aggregation behaviors at molecular level. The method has been used to study the binding patterns of micelles (Sammalkorpi et al., 2007; Wei et al., 2016), the effects of additive to non-ionic micelles (Piotrovskaya et al., 2006; Vierros and Sammalkorpi, 2018), micelle shape transition (Velinova et al., 2011), as well as surface/interfacial properties (Hakim et al., 2016). MD simulation has been also used to describe the interaction of Tween-80, multiple acid species in soybean oil and water in the absence or presence of curcumin (Moghaddasi et al., 2018), but the work is lacking of systematic approach that start from the fundamental chemical species and incrementally increase the system complexity. On the other hand, it is known that micelle shape in solution can be controlled through variations of temperature, concentration, additives, and ionic strength (Velinova et al., 2011). Here we investigate the curcumin encapsulated lecithin micelle morphological response to the variations of composition and temperature in microscopic details using MD simulation method. In particular, the work signifies the self-assembly process of micelle formation from a random configuration to spherical or rod-like micelles in the absence of an external driving force. These shapes are determined by the concentration of lecithin and less affected by the concentration of curcumin. Simulations also show that the encapsulated curcumins arrange themselves near the hydrophilic groups of lecithin that forms an interface with the surrounding water molecules.

# 2. EXPERIMENTAL SECTION

#### 2.1 Method

### 2.1.1 Simulation Cell and Potential Models

A cubic simulation cell is adopted where lecithin (1-palmitoyl-2-linoleoylphosphatidylcholine) and curcumin (5-hydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,4,6-trien-3-one) are randomly displaced using PACKMOL (Martinez et al., 2009), followed by insertion of water molecules. In this study, the effects of lecithin-curcumin composition to micelle formation are systematically investigated by preparing several systems whose labels and the corresponding compositions are given in Table 1. The system is labelled as L*xKy*, where *x* is the number of lecithin and *y* is the number of curcumin. The potential models for lecithin and curcumin are built using the Antechamber module in AMBER Tools 18 (Case et al., 2005) and Acpype according to General Amber Force Field (Wang, 2004). Water molecules are described using the rigid TIP4P/ $\epsilon$  water model (Fuentes-Azcatl and Alejandre, 2014). The model is a re-parameterization from the widely used TIP4P model and has been used to study biomolecular systems (Dominguez, 2016; Onufriev and Izadi, 2018).

#### 2.1.2 Molecular Dynamics Simulations

Molecular dynamics simulations are performed using GRO-MACS 2018.7 (Abraham et al., 2015). Three dimensional periodic boundary condition and minimum image convention are adopted. The equations of motion are solved using the leapfrog algorithm at a time step of 2 fs. The van der Waals interactions are smoothly truncated at 1.0 nm with a switching function that took effects from 0.8 nm. The long range coulombic interactions are treated using the smooth particle mesh Ewald method with a spline order of 4, a relative tolerance of  $10^{-5}$ , and the number of reciprocal space mesh was 25 for each of the x, y, and z directions. The temperature is maintained using Nose Hoover thermostat (Hoover, 1985; Nosé, 1984) at 277 K, 298 K, and 310 K, with a coupling time of 0.1 ps. The pressure is controlled at 1 bar using the Parrinello Rahman barostat (Parrinello and Rahman, 2005) with a coupling time of 1 ps. Chemical bonds that bind hydrogen atoms are fixed using LINCS algorithm (Hess et al., 1997). The simulation for each system is performed for at least 100 ns.

# **3. RESULTS AND DISCUSSION**

# 3.1 Micelle Shapes

The amphiphilic structure of lecithin is expected to lead the molecules to form a micelle in aqueous environment. MD simulations shows that the dispersed lecithin molecules in water rapidly form a micelle structure whose shape is dependent to the number of lecithin molecules as depicted in Figure 1 and their sizes are given in Table 2. The spherical micelle shape is further quantified in term of eccentricity, *e*, given by (Palazzesi et al., 2011; Wei et al., 2016).

$$e = 1 - \frac{3I_{\min}}{I_1 + I_2 + I_3} \tag{1}$$

with  $I_1$ ,  $I_2$ , and  $I_3$  are the three principal moments of inertia, and  $I_{min}$  is the minimum among those three. The equation above shows that the eccentricity value goes to zero when the micelle shape is close to a perfect sphere. The eccentricity values of the lecithin micelle formed under the studied composition are listed in Table 2. Although the parallelism of the eccentricity values with the compositions is not observed, their values that are close to zero shows that lecithin in most of the studied compositions tends to form a spherical micelle. The effective radius of this spherical micelle,  $R_s$ , is defined as (Palazzesi et al., 2011; Wei et al., 2016).

$$R_s = (5/3)^{1/2} < R_g > \tag{2}$$

~	Number of Molecules		Concentration (mol dm <sup>-3</sup> )		
System	Lecithin	Curcumin	Lecithin	Curcumin	
L25K5	25	5	0.06	0.01	
L50K5	50	5	0.12	0.01	
L75L5	75	5	0.17	0.01	
L100K5	100	5	0.22	0.01	
L25K10	25	10	0.06	0.03	
L25K15	25	15	0.06	0.04	
L25K20	25	<b>20</b>	0.06	0.05	
L25K25	25	25	0.06	0.06	

**Table 1.** Variations in The Number of Lecithin and Curcumin Molecules in The Simulated Systems. The Number of Water Molecules is Fixed to 20,189. The Volumetric Concentrations are Calculated from The Equilibrium Volume Given by MD Simulations at 1 bar and 298 K

**Table 2.** Characteristics of Micelle Formed at Various Composition of Lecithin and Curcumin. The Eccentricity *e*, Rod-like Parameter *s*, and Effective Micelle Radius  $R_s$  are Sampled in The Window of 50 - 100 ns Simulation Time. The Uncertainty Values Correspond to The Standard Deviation.

System	е	\$	Micelle Shape	$R_s$ (nm)
L25K5	$0.09 \pm 0.03$	-	spherical	$2.24\pm0.02$
L50K5	$0.08 \pm 0.03$	-	spherical	$2.76\pm0.01$
L75K5	$0.12 \pm 0.02$	-	spherical	$3.15 \pm 0.02$
L100K5	-	$0.024 \pm 0.013$	rod-like	-
L25K10	$0.10\pm0.03$	-	spherical	$2.28\pm0.02$
L25K15	$0.10\pm0.04$	-	spherical	$2.31 \pm 0.02$
L25K20	$0.13 \pm 0.04$	-	spherical	$2.36 \pm 0.02$
L25K25	$0.09 \pm 0.03$	-	spherical	$2.38 \pm 0.02$



**Figure 1.** Snapshots of Simulation Cell of Lecithin-curcumin System at The End of Simulation Time (100 ns) at 298 K: (a) L25K25, (b) L75K5, (c) L100K5 from Axial View, and (d) L100K5 from Lateral View. Curcumin molecules are marked with yellow color. The hydrophilic groups of lecithin molecules are displayed as balls, while the hydrophobic carbon chains are displayed as blue line. Water molecules are not displayed for the sake of clarity.

where  $R_g$  is the radius of gyration and the angled bracket denotes average. The calculated radii are listed in Table 2, which shows that the micelle size notably grows with the number of lecithin molecules. Figure 1 also shows that lecithin can form a cylindrical micelle, and thus the shape is quantified in term of rod-like factor, *s*, that is defined as (Vierros and Sammalkorpi, 2018).

$$s = \frac{I_3 - I_2}{I_3 - I_1} \tag{3}$$

Similar to the eccentricity value above, the value of *s* become close to zero when the micelle shape resembles a cylindrical rod. Table 2 shows that the value of *s* in L100K5 system suggests that the micelle shape is indeed rod-like, as depicted by Figures 1c and 1d. It is important to note, however, that the cylindrical shape is adopted by the micelle because of the presence of periodic boundary condition that connects both ends of cylinder. In other words, the volumetric concentration of lecithin is a determining factor for the shape transition of curcumin encapsulated lecithin micelle. A second critical concentration of micellization that characterize the transition to rod-like assemblies is then expected between L75K5 and L100K5 that correspond to 0.17-0.22 mol dm<sup>-3</sup>.





**Figure 2.** Potential Energy Arising from The Interaction of Lecithin Molecules with Water Molecules,  $\Phi_{LW}$ , during The First 20 ns of MD Simulations at 298 K. The values of  $\Phi_{LW}$  are normalized with the number of lecithin molecules.

In all compositions studied here, curcumin molecules are seen to be encapsulated inside the lecithin micelle. Dynamics analysis, as will be discussed later, shows that curcumin molecules are indeed moving together with the micelle. Table 2 shows that, under a fixed number of lecithin molecules, the increasing number of curcumin molecules does not profoundly affect the micelle sphericality as indicated by its eccentricity value. However, the effective micelle radius is found to slightly increase with the number of curcumin molecules encapsulated inside the micelle.

The profile of potential energies that arise from lecithinwater interactions, as shown in Figure 2, suggests that the formation of micelle stabilizes the solvation of lecithin in an aqueous system. The time required for the potential energy to converge also inversely proportional to the number of lecithin molecule, i.e. larger number of lecithin molecules requires more time to arrange themselves to form a larger micelle. The downward slope of potential energy for the system containing 25 molecules of lecithin, however, is not observable within the scale of Figure 2.

## **3.2** Micelle Structures

The spatial distributions of micelle components are useful to understand the structure of micelle. In spherical micelle, the distribution can be quantified in term of local radial density  $\rho_L$ centering at the micelle's center of mass under equilibrium conditions. Here we focus on the spatial distribution of hydrophilic group of lecithin, represented by N and P atoms; hydrophobic tail of lecithin, represented by the 8<sup>th</sup> carbon atom; and curcumin molecule, represented by its carbonyl group. Figure 3 shows the radial local density as a function of its distance from the center of mass of micelle for L25K5, L25K25, and L75K5 systems. As expected from a surfactant, the hydrophilic groups

of lecithin are shown to be located on the outermost part of the micelle, while the hydrophobic carbon tail is secluded in the inner part, near the center of mass. It is worth to note that the distance r of the peaks of hydrophilic groups are comparable to the effective spherical radius computed from the radius gyration shown in Table 2. This further emphasize that the hydrophilic groups correspond to the surface of spherical micelle and directly interacts with the water phase. Figure 3 also shows that curcumin molecules, as represented by their carbonyl group, arrange themselves close to the hydrophilic group of lecithin. However, the overall curcumin molecules are located inside the micelle and interact with the hydrophobic carbon chain of lecithin since curcumin is not an amphoteric species. As the number of curcumin increases, the peak broadening shows the curcumin molecules begin to distribute closer to the inner part of the micelle as shown by Figure 3b. Similar broadening is also observed when the number of lecithin molecules is increased. Figure 3c shows that spherical micelle of larger size allows broader distributions of atoms inside.

#### **3.3** Micelle Dynamics

The mean squared displacement (MSD) of lecithin, curcumin, and water molecules are displayed in Figure 4 for L25K5 system. Compared to the freely moving solvent molecules, the mobility of lecithin micelle is obviously limited. The inset in Figure 4 shows that the displacement of micelle is very limited under the reference of center of mass. Note that the smaller curcumin molecules have the similarly limited displacement with the lecithin molecules as a result of being trapped inside the micelle. The inset also shows that the displacements of lecithin and curcumin molecules are more limited in larger micelle. The MSD profiles for the other compositions are similar in trend.

Table 3 shows the self-diffusion coefficient, *D*, that quantitatively describes the mobility of each molecule species in the system. The diffusion coefficient is calculated from the slope of linear fitting of the mean squared displacement curve at interval 5 to 15 ns. The diffusion of lecithin and curcumin molecules decreases with the increase of lecithin composition that corresponds to the increase of micelle size. However, the variations of diffusion coefficients with the increase of curcumin composition are not discernable within the standard deviation.

#### **3.4** Thermal Stability

To further examine the effects of temperature to the micelle structure and dynamics, we choose L25K5 system, which produce the smallest effective radius as the subject, and apply three different simulation temperatures: 277 K, 298 K and 310 K. Within the investigated temperature range, increasing the temperature does not result in a spike in the potential energy of the interaction between the molecules in the system. The change of eccentricity values of micelle with the change in temperature are also not noticeable within the standard deviation as shown by Table 4. However, the thermal expansion on micelle size can be seen from the increase of its effective spherical



**Figure 3.** The Local Radial Density  $\rho$ L Profile of (a) L25K5, (b) L25K25 and (c) L75K5 System at 298 K. The distance of origin (r= 0) corresponds to the center of mass of the micelle. Each curve is normalized by the number density of the corresponding molecule species.

**Table 3.** Diffusion Coefficients of Lecithin, Curcumin, andWater Molecules at 298 K

G 1	$D (10^{-5} \text{cm}^2 \text{s}^{-1})$			
Sample	Lecithin	Curcumin	Water	
L25K5	$0.10 \pm 0.00$	$0.10\pm0.02$	$4.80\pm0.02$	
L50K5	$0.08 \pm 0.03$	$0.11 \pm 0.03$	$4.52 \pm 0.00$	
L75K5	$0.05 \pm 0.02$	$0.08\pm0.02$	$4.23 \pm 0.02$	
L100K5	$0.06 \pm 0.01$	$0.05 \pm 0.01$	$4.00 \pm 0.00$	
L25K10	$0.08 \pm 0.05$	$0.08 \pm 0.06$	$4.780 \pm 0.01$	
L25K15	$0.21 \pm 0.02$	$0.23\pm0.02$	$4.77 \pm 0.00$	
L25K20	$0.10 \pm 0.05$	$0.12 \pm 0.05$	$4.78 \pm 0.01$	
L25K25	$0.07\pm0.04$	$0.07\pm0.04$	$4.70 \pm 0.01$	



**Figure 4.** Mean Squared-displacement (MSD) of Lecithin, Curcumin and Water Molecules in L25K5 System at 298 K. The Enlarged Plot is Given as an Inset. In Addition, MSD of Each Molecule Species in L75K5 System, that Gives Larger Micelle, at 298 K is Also Plotted as Dashed Lines in The Inset.

radius, and the diffusion of each species increases with the increase of temperature. With relatively small changes in all of the scrutinized parameters, it signifies that nanoemulsion in L25K5 system is thermally stable within the studied different temperatures.

# 3.5 Relevance with Experimental Observations

In comparison with the previously reported experimental works on the formation of nanoemulsion in lecithin and curcumin with the addition of Tween-80 (Jannah, 2020), the results from MD simulations show some similar patterns. Although the predicted micelle size from all-atom simulations is generally smaller than the experimental results in the laboratory, the observed trend is mostly the same. Experimental works showed that the nanoemulsion size increases with the addition of lecithin, but relatively constant with the addition of curcumin. The experimental results on the efficiency of encapsulation also shows that the curcumin can be encapsulated inside the micelle under the corresponding concentration given in Table 1.

Experiment showed that polydispersity index increases when lecithin molecules number is increasing. At concentrations that correspond to L25K5 up to L75K5, the observed polydispersity index indicates uniformity of the particle size. In contrast, at a concentration that correspond to L100K5, we observed polydispersity index that implies non-uniform particle size, which might also portray a non-similar particle shape (Jannah, 2020). This observation is in line with simulation results where we could identify a shape transition from a spherical to a rod-like structure. It is possible that at higher lecithin concentration, micelle structure is diversified in rod-like as well as spherical structure. On the other hand, the above phenomenon is not observed in the addition of curcumin molecule where the size and shape of the micelles are relative constant. Poly-

•		Micelle Shape			$D(10^{-5} \text{cm}^2 \text{s}^{-1})$		
	T(K)	е	Shape	$R_s$ (nm)	Lecithin	Curcumin	Water
	277	$0.09 \pm 0.03$	Spherical	$2.20 \pm 0.01$	$0.07 \pm 0.01$	$0.07 \pm 0.00$	$3.28 \pm 0.02$
	298	$0.09 \pm 0.03$	Spherical	$2.24 \pm 0.02$	$0.10 \pm 0.00$	$0.10 \pm 0.02$	$4.80\pm0.02$
	310	$0.09\pm0.04$	Spherical	$2.25\pm0.02$	$0.16\pm0.00$	$0.15 \pm 0.00$	$5.78\pm0.02$

**Table 4.** Micelle Structure and Dynamics in L25K5 System at Three Different Temperatures. The Data at 298 K are Identical to Those in Tables 2 and 3, and are Shown in Here to Make the Comparison Easier.

dispersity index does not change drastically which indicates that the particles produced in this formulation are relatively homogeneous in size and it is possible that the shape of the particles is more uniform in spherical structure. These patterns are reproduced by the MD simulations.

# 4. CONCLUSIONS

The structures and dynamics of lecithin micelle encapsulating curcumin have been elucidated using MD simulations and the trends are in agreement with the reported experimental works. Within lecithin concentration of 0.06 - 0.17 mol dm<sup>-3</sup>, lecithin forms a spherical micelle whose size is proportional to the number of lecithin molecules. At higher concentration  $0.22 \text{ mol dm}^{-3}$ , lecithin forms a cylindrical micelle. By fixing the lecithin concentration at 0.06 mol dm<sup>-3</sup>, the addition of curcumin up to  $0.06 \text{ mol dm}^{-3}$  does not alter the micelle shape, but a slight increase in micelle radius is observed as a result of curcumin encapsulation. The local radial density profile shows that the spherical radius of micelle correspond to the hydrophilic groups of lecithin. These groups arrange themselves on the outermost part of the micelle and directly interact with water molecules. The encapsulated curcumin molecules are located close to the hydrophilic groups, instead of being in the innermost part of the micelle where the hydrophobic carbon chains of lecithin are positioned. The self-diffusion coefficients further show that the mobility of curcumin follows the mobility of lecithin. The nanoemulsion is shown to be thermally stable within 277-310 K.

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