Supporting information

Investigation of Drug for Pulmonary Administration-Model
Pulmonary Surfactant Monolayer Interactions Using
Langmuir-Blodgett Monolayer and Molecular Dynamics
Simulation: A Case Study of Ketoprofen

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Figure S1. Tilt angle of tail chains in lipid molecules with z-axis (a) DPPC molecules (b) DPPG molecules and the average tail order parameter $S_{CD}$ of lipid molecules (c) DPPC molecules (d) DPPG molecules in the ketoprofen/lipids system ($R = 1/5$) under different mean molecular areas. (the carbon number is counted from the head group of lipid molecules)

The tilt angle of tail chains in lipid molecules with the z-axis of the ketoprofen/lipids system ($R = 1/5$) is shown in Figure S1a, b, which shows the orientation distribution of lipid molecules. The favorable tilt angle decreases from 45.0° to 26.1° with the decrease of the mean molecular area, and the full width at half maxima (FWHM) of peak decreases from 46.0° to 12.3° as the mean molecular area decreases. Finally, the favorable tilt angle of lipid molecules tends to be around 26.0° under 50.63 Å². Figure S1c, d also provide the order parameters ($S_{CD}$) of tail chains in lipid molecules of the ketoprofen/lipids system ($R = 1/5$) under different mean molecular areas. If the orientation of tail is fully random, $S_{CD} = 0$; if all tails are vertically aligned, $S_{CD} = 1$. The values of $S_{CD}$ decrease under higher mean molecular area, and keep almost constant when the mean molecular area is 50.63 Å². It can be observed that the order distribution of lipid tail chains increases with the increase of...
the mean molecular area. The further away from the head group of lipids, the more disordered it is. Those results indicate that the arrangement of lipid on the air-water surface changes from disorder to order with the decrease of mean molecular area.

**Figure S2.** RDF between different molecules $g_{(O-P)}$ between carbonyl oxygen atom in the carboxylic acid group of ketoprofen and phosphorus atom in DPPG.

The RDF between the drug molecule and DPPG is also investigated. The results are consistent with Figure 5a that the $g_{(O-P)}$ decrease with the mean molecular area, which means that the drug molecules flee away from the hydrophilic layer formed by lipids head group and enter the hydrophobic region composed by tail chains of lipids during the course of compression.

**Figure S3.** Distribution count of ketoprofen in umbrella sampling transports through lipid monolayer. (a) $A = 50.63 \text{ Å}^2$ (b) $A = 90.00 \text{ Å}^2$

The distribution count above shows a reasonable overlap between sampling windows with a centroid distance from approximately 0 to 5 nm under different mean molecular area. It indicates the umbrella sampling has been successfully completed.
Figure S4. The changes of temperature (T) and root-mean-square deviation (RMSD) in the NVT simulation.

Figure S4 provides the changes of temperature (T) and root-mean-square deviation (RMSD) in the NVT simulation; it can be observed that the temperature and the root-mean-square deviation are basically keep constant within 5000 ps.