Supporting Information

Graphene quantum dot assisted translocation of drugs into a cell membrane

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Table S1. Details of all performed simulations in this study.

Method	Drug	Size of GQDs	Simulation time (ns)	Success of permeation (success / all)
MD	DOX	\	200	No (0/4)
		GQD7	200	No (0/4)
		GQD19	500	Yes (2/4)
		GQD61	200	No (0/4)
	DA	\	200	No (0/4)
		GQD7	200	No (0/4)
		GQD19	500	Yes (4/6)
		GQD61	200	No (0/4)

Method	Drug	Size of GQDs	Simulation time (ns)	velocity ($nm \cdot ns^{-1}$)	k ($kJ \cdot mol^{-1} \cdot nm^{-2}$)
SMD	DOX	GQD7	65	0.1	1000
		GQD19	65		
	DA	GQD7	65		
		GQD19	65		

Method	Drug	Size of GQDs	Simulation time (ns)	k ($kJ \cdot mol^{-1} \cdot nm^{-2}$)
Umbrella Sampling	DOX	GQD7	38*40	1000
		GQD19	52*40	
	DA	GQD7	38*40	
		GQD19	52*40	

Table S2. The interaction between GQDs and drugs in different systems.

Drug	Size of GQDs	Contact time (ns)	E_{vdW} (kJ·mol^{-1})	E_{ele} (kJ·mol^{-1})	E_{tot} (kJ·mol^{-1})
DOX	GQD7	0 ~ 200	-75.09	-4.05	-79.14
	GQD19	0 ~ 200	-125.38	-1.95	-127.33
	GQD61	0~100	-225.63	-1.22	-226.85
		100~130	-209.69	-0.54	-210.23
		130~200	-111.14	-3.91	-115.05
DA	GQD7	0 ~ 65	-49.66	-0.41	-50.07
		65~200	0	0	0
	GQD19	0 ~ 200	-81.84	-0.51	-82.35
	GQD61	0~150	-108.80	-0.55	-109.35
		150~180	-101.06	0.09	-100.97
		180~200	-72.80	1.60	-71.20

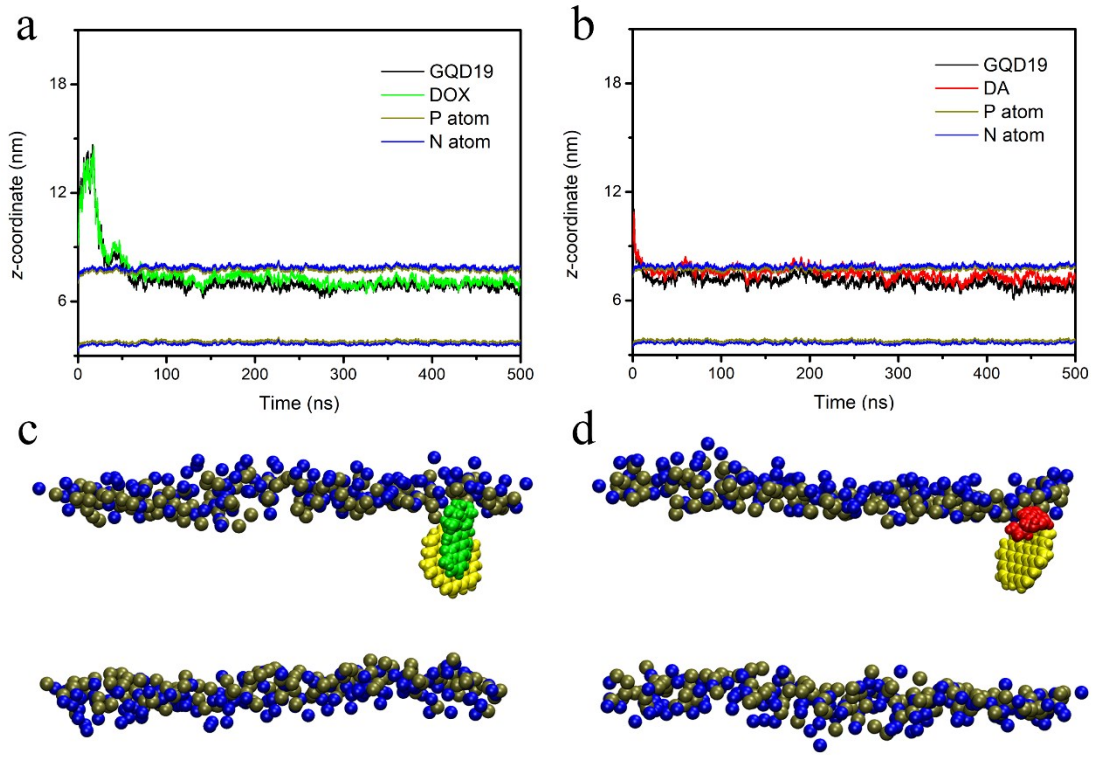

Figure S1. The *z*-coordinate of the center of mass (COM) of GQD19, the COM of drugs and the COM of P/N atoms from POPC lipid membrane as a function of simulation time: (a) GQD19-DOX and (b) GQD19-DA. The snapshots of each system were obtained from the end of 500 ns MD simulation: (c) GQD19-DOX and (d) GQD19-DA. GQD19 (yellow) and drugs (DOX: green; DA: red) are shown by VDW model with VMD software. N atoms (blue) and P atoms (tan) in the head group of membrane are also shown in a VDW model. Water molecules and lipid tails of membrane are not shown for clarity.

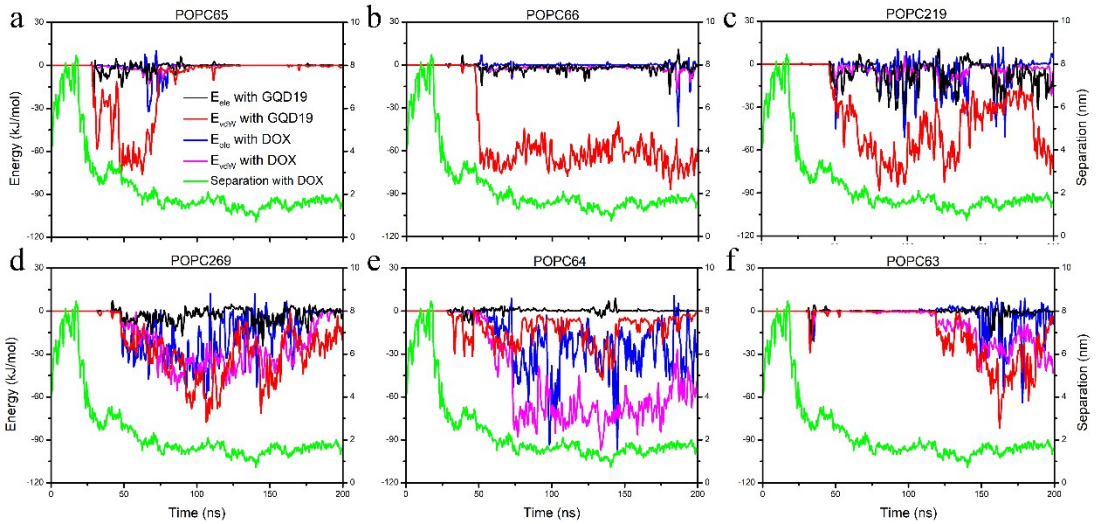

Figure S2. Time evolution of the interaction between GQD19 and certain POPC lipid molecule as well as the interaction between DOX and certain POPC lipid molecule during MD simulation time in (a) POPC65, (b) POPC66, (c) POPC219, (d) POPC269, (e) POPC64 and (f) POPC63.

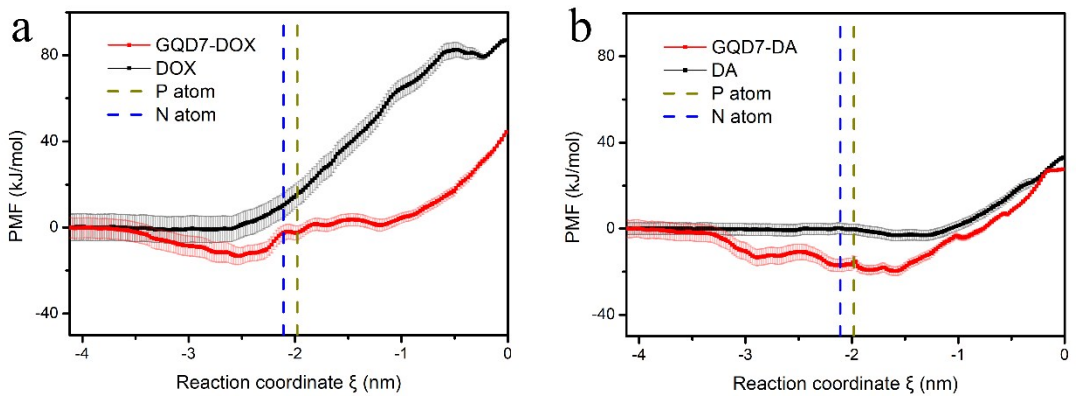

Figure S3. Potential of mean force (PMF) of drugs translocating through the POPC membrane in different systems. (a) The PMF of DOX translocation with and without GQD7 and (b) The PMF of DA translocation with and without GQD7. The blue line represents the average location of N atoms (ξ = -2.11 nm) on the tail of membrane lipid. The average location of P atoms (ξ = -1.97 nm) on the POPC membrane was displayed in dark yellow.

The translocation free energy of drugs could be affected by the company of GQD7, as shown in Figure S3. With the company of GQD7, the free energy minimum of GQD7-DOX complex in the water phase and lipid phase were -13.3 kJ·mol^{-1} (ξ = -2.54 nm) and -2.4 kJ·mol^{-1} (ξ = -1.97 nm), respectively. Compared with DA permeation without the company of GQD7, the free energy minimum of GQD7-DA complex permeation reduced 16.1 kJ·mol^{-1} in water phase and 26.4 kJ·mol^{-1} in lipid phase. PMF profiles for two drugs indicated that GQD7 have similar impact on drug translocation free energy reduction as GQD19. However, the extent of translocation free energy decrease with assistant of GQD7 was less than that with GQD19. Taking DOX as an example, the free energy minimum of DOX in lipid phase was -13.8 kJ·mol^{-1} (ξ = -1.97 nm) with the assistant of GQD19, which was obviously lower than -2.4 kJ·mol^{-1} (ξ = -1.97 nm) with the assistant of GQD7.

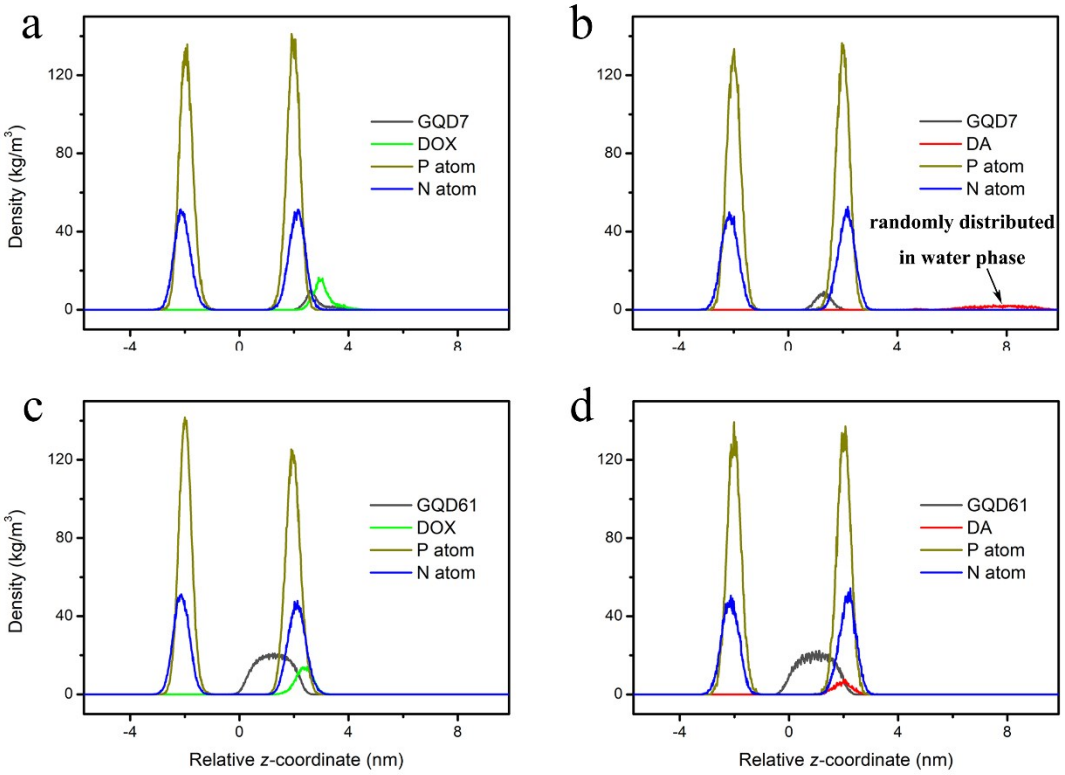

Figure S4. The density of GQDs, drug and P/N atoms of the lipid bilayer along the *z* direction when these systems were equilibrated: (a) GQD7-DOX, (b) GQD7-DA, (c) GQD61-DOX and (d) GQD61-DA. The *z*-coordinate of the middle of the lipid bilayer was set as the zero point in all systems.

In order to investigate the effect of GQDs size on the structure disrupting of membrane, the thickness of the POPC membrane and the area per lipid for different systems were calculated. As we mentioned in the paper, GQD7-DOX complex had difficulty permeating into the lipid bilayer and in the adsorption/desorption equilibration on the external surface of lipid membrane during the simulation. The thickness of the POPC membrane was around 3.99 nm, which was close to 3.97 nm in system with DOX alone. The permeation of GQD7 alone into the lipid membrane in GQD7-DA system also had little influence on the structure of POPC membrane, which accounted for only 0.03 nm thickness difference (3.98 nm for GQD7-DA system and 3.95 nm for system with DA alone). Meanwhile, GQD7-drug systems had similar area per lipid compared with the circumstance of drug alone. For GQD61with larger size, the thickness of lipid membrane in GQD61-DOX system was close to that in system with DOX alone. However, it intrigued asymmetrical distribution of the lipid

membrane, as seen in Figure S4c. The thickness of the membrane was about 4.02 nm in the system of GQD61-DA and this implied that the permeation of GQD61-DA into the lipid bilayer could have certain impact on the thickness of the POPC lipid membrane. The APL calculation also verified the structural changes in GQD61-DA system. The value of $(61.1\pm0.8) \times 10^{-2}$ nm^2 was relatively smaller than the value of $(62.3\pm1.0) \times 10^{-2}$ nm^2 for system with DA alone.