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Supporting Information

Hydrogel-Assisted Delivery of Lipophilic Molecules into Aqueous Milieu for Transdermal Medication Capitalized on Environment-Specific, Regioselective Adsorption of Graphene Oxides

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Experimental details

Materials

Nile Red (NR) with octanol/water partitioning coefficient of 5.06, Methyl Red (MR) with octanol/water partitioning coefficient of 3.9, Ibuprofen (IBU, United States Pharmacopeia Reference Standard) with octanol/water partitioning coefficient of 1.8, phosphate buffered saline (PBS) tablets, agarose with gelation temperature of 36 °C, and graphite were purchased from Sigma-Aldrich. Hexane (HPLC, 99.5%) and ethanol (99.5%) were purchased from Sinopharm Chemical Regent Co. Ltd. All the chemicals were used as received. Water with a resistivity of 18 $M\Omega \cdot cm^{-1}$ was prepared using a Millipore Milli-Q system and used in all experiments.

Preparation of GO_xACHs

Graphene oxides (GOs) were produced from naturally occurring graphite flakes according to the Hummers protocol. One mL of the aqueous suspension of as-prepared GOs were warmed to 80 °C under stirring, followed by addition of 0.015 g of agarose powder. After the agarose powder was completely dissolved in the GO suspension under stirring at 80 °C, the resulting aqueous solution of GO/agarose mixtures were poured into molds and cooled down to room temperature for gelation, yielding the GO-loaded agarose composite hydrogel (GOACH) blocks with different shapes. The resulting warm GO/agarose mixture solution was also added dropwise to liquid nitrogen for quick gelation to produce GOACHs beads with sizes in range of 2−4 mm. The concentration of agarose in the aqueous suspensions of GOACHs beads was fixed as 1.5 wt. %, and the concentration of GOs were altered from 0.01 wt. %, 0.02 wt. %, and 0.03 wt. %. The same protocol was also applied to produce pristine agarose hydrogel blocks or beads by using the warm aqueous solution of agarose.

Transfer of GOACHs from water to hexane via stepwise solvent exchange

Firstly, the water phase of as-prepared GOACHs was thoroughly displaced by ethanol, which was executed by successive incubation of as-prepared GOACHs in a sufficient volume of ethanol for 5 times; the incubation time was 6 h each step. Subsequently, the ethanol phase of the GOACHs was thoroughly displaced by hexane by successively

incubating them in a sufficient volume of hexane for 5 times; the incubation time was 6 h each step.

Adsorption of GOACHs towards lipophilic molecules in hexane

NR , MR and IBU molecules were dissolved in hexane at different initial concentrations (C_o^i, mg·L^{-1}). As-prepared GOACHs were incubated with the resulting hexane solutions of lipophilic organic molecules at room temperature and the temporal evolution of the organic molecule concentration in hexane (C_o^t, mg·L^{-1}) was monitored with the help of UV-vis spectroscopy. When the organic molecule concentration in hexane reached the equilibrium value (C_o^e, mg·L^{-1}), the equilibrium organic molecule adsorption uptake (q_o^e, mg·g^{-1}) of GOACHs was calculated by Equation S1.

$$q_o^e = (C_o^i - C_o^e) \cdot V_o / W_{GOACH} \quad \text{S1}$$

where V_o is the volume of the organic molecule solution in hexane and W_{GOACH} is the total solid mass of GOACHs, namely, the mass sum of their GO and agarose content. The adsorption isotherms of GOACHs towards lipophilic organic molecules in hexane were obtained by plotting the calculated value of q_o^e, calculated according to Equation (S1) versus the experimentally measured values of C_o^e, and the resulting adsorption isotherms were fitted by Langmuir model and Freundlich Model, described as follows:

$$q_o^e = q_o^m K_L C_o^e / (1 + K_L C_o^e) \quad \text{S2a}$$

$$q_o^e = K_F (C_o^e)^{1/n} \quad \text{S2b}$$

where q_o^m (mg·g^{-1}) is the maximum adsorption capacity of GOACHs, K_L (L·mg^{-1}) is the Langmuir constant rate, K_F was the Freundlich adsorption constant, and 1/n was the measure of the adsorption intensity in Freundlich model. While the Langmuir isotherm model is based on the assumption of homogeneous monolayer adsorption of adsorbates on the adsorbent, the Freundlich model assumes heterogeneous adsorption:

Taking into account that lipophilic organic molecules are adsorbed on the edges of the GO guests in GOACHs in a monolayer adsorption manner via hydrogen bonding, the q_o^e can be correlated with the ratio of the number of the adsorbed organic molecules (N_{om}) to that of the GO edge polar groups (N_{EP}). For a given type of GOxACHs, their total solid mass (W_{GOACH}) can be correlated with the N_{EP} value of their GO guests by

$$N_{EP} = \frac{f_{GO} \cdot W_{GOACH}}{M_{GO}} \cdot N_A \cdot \phi_{EP} \quad \text{S3a}$$

where f_{GO} is the weight fraction of GO in the solid mass of GOACHs, M_{GO} is GO molecular mass, N_A is Avogadro number, ϕ_{EP} is the molar fraction of the GO edge polar groups. When the equilibrium adsorption of the GO_xACHs toward lipophilic organic molecules is established in hexane, the q_o^e value can be described as below:

$$q_o^e = W_{om}/W_{GOACH} \quad \text{S3b}$$

where W_{om} is the amount of the organic molecules loaded within the GO_xACH, described as below:

$$N_{om} = \frac{W_{om}}{M_{om}} \cdot N_A \quad \text{S3c}$$

By inserting Equations S3a and S3c into S3b, q_o^e can be described as below:

$$q_o^e = \phi_{EP} \cdot \frac{N_{om}}{N_{EP}} \cdot \frac{f_{GO} \cdot M_{om}}{M_{GO}} = \phi_{EP} \cdot \frac{N_{om}}{N_{EP}} \cdot A_{GO}^{NR} \quad \text{S3d}$$

Since the minimal number of the GO edge polar groups used for adsorption of one lipophilic organic molecules, referred to as α_o^{EP}, can be estimated according to the organic molecule structure, the utilization efficiency (ξ_o^{EP}) of the GO edge polar groups for adsorption of lipophilic organic molecules in hexane can be calculated as:

$$\xi_o^{EP} = \alpha_o^{EP} \cdot \frac{N_{om}}{N_{EP}} \quad \text{S3e}$$

By inserting Equations S3e into S3d, q_o^e can be described as:

$$q_o^e = A_{GO}^{NR} \cdot \phi_{EP} \cdot \xi_o^{EP}/\alpha_o^{EP} \quad \text{S3f}$$

Swelling of dried GOACHs and agarose hydrogels in water

After the water phase of GOACHs or agarose hydrogels were replaced by hexane via stepwise solvent exchange as described above, the composite and pristine hydrogels were thoroughly dried in air under ambient condition overnight. The completely dried gels were weighted and then immersed into PBS (or water) to swell; PBS was prepared by dissolving one PBS tablet into 200 mL of water. During incubation in PBS, the gels were taken out at regular time intervals and after their surfaces were dried by paper tissues, the PBS-swollen gels were weighted. Both the weights of dried gels (W_D) and those of PBS-swollen gels (W_S) were the averaged values of three experimentally measured values, which were utilized to the swelling ratio of the dried gels (SR) according to Equation S4:

$$SR = (W_S - W_D)/W_D \quad \text{S4}$$

To highlight the effect of stepwise solvent exchange on the swelling behavior of

agarose hydrogels, they were dried in air without undergoing stepwise solvent exchanged and their SR values were calculated based on Equation S4.

Release of the loaded lipophilic organic molecules from GOACHs into aqueous media

After as-prepared NR-GOACHs were immersed into PBS for 5h to reach their equilibrium swollen stage, they were taken out, dried by paper tissues and placed in 10 mL of PBS/ethanol mixtures in which the ethanol volume content was altered from 10 vol% to 20 and 30%. The concentration of NR molecules in alcoholic PBS (C_w^t), released from NR-GOACHs, was monitored by means of UV-vis absorption spectroscopy. Once the NR concentration in the alcoholic PBS reached the plateau value, which was usually took about 6 h, the NR-GOACHs were taken out and placed in freshly prepared alcoholic PBS for another release round. The release round was repeated for at least 3 times. The equilibrium adsorption uptake of dissolving NR molecules by GOACHs in water (q_w^e) was calculated by Equation S5:

$$q_w^e = (C_w^{max} - C_w^e) \cdot V_w / W_{GOACH} \qquad \text{S5}$$

where V_w was the volume of alcoholic PBS (10 mL), C_w^e was the equilibrium concentration of the released NR during NR-GOACH incubation in alcoholic PBS and C_w^{max} is the maximum concentration of NR in alcoholic PBS. The equilibrium NR concentration obtained in the second release round was utilized as C_w^e, while the NR-saturated concentration in alcoholic PBS was utilized as C_w^{max} for the amount of NR loaded in GOACHs, implemented in hexane, was far above the amount required to reach the NR-saturated concentration.

If we assume that the lipophilic organic molecules, liberated from the edges of the GO guests in GOACHs, are adsorbed onto the GO carbon lattice plane in a monolayer adsorption manner via hydrophobic interactions, the q_w^e can be correlated with the ratio of the number of the adsorbed organic molecules (N_{dye}) to that of the (non-oxidized) carbons of the GO carbon lattice planes (N_{PC}). Similar to Equation S3a, the total solid mass (W_{GOACH}) of GO_xACH can be correlated with the N_{PC} value of their GO guests by:

$$N_{PC} = \frac{f_{GO} \cdot W_{GOACH}}{M_{GO}} \cdot N_A \cdot \phi_{PC} \qquad \text{S6a}$$

where ϕ_{PC} is the molar fraction of the (non-oxidized) carbons of the GO carbon lattice planes; in the ideal case, $\phi_{PC} + \phi_{EP} = 1$. When the equilibrium adsorption of the GO_xACHs toward lipophilic organic molecules is established in water, the q_w^e value can be described as:

$$q_w^e = W_{om}/W_{GOACH} \quad \text{S6b}$$

where W_{om} is the amount of the organic molecules loaded within the GO_xACH, described as below:

$$N_{om} = \frac{W_{om}}{M_{om}} \cdot N_A \quad \text{S6c}$$

By inserting Equations S6a and S6c into S6b, q_w^e can be described as below:

$$q_w^e = \phi_{PC} \cdot \frac{N_{om}}{N_{PC}} \cdot A_{GO}^{NR} \quad \text{S6d}$$

Since the minimal number of the GO lattice plane carbons required to adsorb one NR molecule, referred to as α_o^{PC}, can be estimated according to the organic molecule structure, the utilization efficiency (ξ_o^{PC}) of the GO lattice plane carbons for adsorption of lipophilic organic molecules in water can be calculated as:

$$\xi_o^{PC} = \alpha_o^{PC} \cdot \frac{N_{om}}{N_{PC}} \quad \text{S6e}$$

By inserting Equations S6e into S6d, q_w^e can be described as:

$$q_w^e = A_{GO}^{NR} \cdot \phi_{PC} \cdot \xi_o^{PC}/\alpha_o^{PC} \quad \text{S6f}$$

In the case of MR-GOACHs, the MR release commenced immediately after the dried MR-GOACHs were placed in water at different pH values or PBS due to the high solubility of MR in water. The MR concentration in water (C_w^t), released from MR-GOACHs, was monitored by means of UV-vis absorption spectroscopy. When Equation S5 was applied to calculate the equilibrium adsorption uptake of dissolving MR molecules by GOACHs in water (q_w^e), the equilibrium MR concentration obtained in the first release round was utilized as C_w^e, while the C_w^{max} value was calculated from the q_o^e value of NR-GOACHs based on Equation (1) in the main text.

Calculation of the C_w^e of lipophilic organic molecules released from GOACHs into water

When a given amount of GO_xACHs with GOACH solid mass (W_{GOACH}) and equilibrium adsorption uptake of lipophilic organic molecules in hexane (q_o^e) are brought into a given volume (V) of aqueous milieu for the organic molecule release, the C_w^e of the lipophilic organic molecules released in water is established as a result of equilibrium balance of dissolution of the loaded organic molecules and the adsorption uptake of the dissolving organic molecules on the carbon lattice planes of the GO guests in the GO_xACHs. If dissolution is the sole contribution to the release of the loaded organic molecules from GOACHs to water, the maximal C_w^e value ($C_w^{e,\,max}$) will be given by:

$$C_w^{e,max} = K_D \cdot q_o^e \cdot W_{GOACH} / V \qquad \text{S7a}$$

In Equation S7a, K_D is introduced as a dissolution constant which incorporates all factors to affect the dissolution of the organic molecules loaded (at the edges of the GO guests) in GOACHs, including the contributions of the solubility and diffusivity of the organic molecules in water and the susceptibility of their hydrogen bonds with the GO edge polar groups to the environment nature switching from hexane to aqueous media. If the organic molecule adsorption on the carbon lattice planes of the GO guests in GOACHs is assumed to take place after the $C_w^{e,max}$ is reached, as suggested in Figure 2d, the contribution ($C_w^{e,red}$) to reduction of the organic molecule concentration in water from $C_w^{e,max}$ to C_w^e can be calculated as follows:

$$C_w^{e,red} = q_w^e \cdot W_{GOACH} / V \qquad \text{S7b}$$

As a result,

$$C_w^e = C_w^{e,max} - C_w^{e,red} = (K_D \cdot q_o^e - q_w^e) \cdot \frac{W_{GOACH}}{V} \qquad \text{S7c}$$

Note that K_D can be empirically derived from the release efficiency (E_w^r) of the loaded lipophilic molecules from GOACHs. Equations (1) and (2) can be used to deduce E_r^w as below:

$$E_w^r \approx K_D - q_w^e / q_o^e \qquad \text{S8a}$$

Comparing Equation S8 and Equation 5, K_D and τ can be calculated as below:

$$K_D = \delta \cdot {S_w}^k \qquad \text{S8b}$$

$$\tau = - q_w^e / q_o^e \qquad \text{S8c}$$

Ex vivo skin permeation study

The permeation study of IBU-GOACHs through a rat skin was carried out according the Chinese standards GB/T 27818-2011.After its abdominal hair was shaved, a rat was sacrificed under anesthesia, and its abdominal skin was surgically excised. The dermal surface of the rat skin was cleaned by isopropyl alcohol to remove sub-cutaneous fats without damaging the epidermal surface. Subsequently, the rat skin was washed with saline water and stored at 4 °C, which was subjected for ex vivo skin permeation study within 1 d. A Franz diffusion cell (TD12D, Shanghai Kaikai. Co., LTD) were used in the present skin permeation study (Figures 4b and S13). The receptor compartment of the Franz diffusion cell contained a magnetic bar and 6.5 mL of PBS buffer. The prepared rat skin was firstly hydrated with PBS buffer and slightly stretched and then sandwiched between the receptor and donor compartments with the stratum corneum facing the donor compartment and an available diffusion area (A) of ca. 3.14 cm^2. After the receptor and donor compartments were clamped together, a slab of 5g of IBU-$GO_{0.2}$ACH with q_o^e of 32.68 $mg.g^{-1}$ were placed to tightly and completely cover the rat skin in the donor compartment. Note that the dried IBU- $GO_{0.2}$ACH slab was initially placed on the rat skin in the donor compartment, followed by dropwise addition of PBS buffer atop to enable the dried gel to reach the equilibrium swollen state. After the upper opening of the donor compartment was tightly sealed with parafilm to inhibit the evaporation of water from PBS-swollen IBU-GOACHs, the receptor compartment was placed in a thermostatically controlled water bath at 32 °C ± 0.5 under magnetic stirring at 200 rpm. At 1 h intervals for the first 6 h and 2 h intervals for the following 18h, 2 mL of the PBS buffer were withdrawn from the receptor compartment for assessment of the C_w^t values of IBU in the receptor phase by means of UV-vis absorption spectroscopy and replaced by 2 mL of fresh PBS buffer to keep the volume of the receptor phase constant. The cumulative amount of IBU molecules per unit area (Q, μg $\cdot cm^{-2}$) permeated into the receiving PBS across the rat skin during transdermal delivery of IBU-GOACHs was calculated as below:

$$Q = (C_w^t \times 6.5ml + \sum_{t=1}^{t-1} C_w^t \times 2ml)/A \qquad \text{S9a}$$

The permeant rate (J /ug$\cdot cm^{-2}\cdot h^{-1}$) was calculated as below:

$$J = \Delta Q/\Delta t \qquad \text{S9b}$$

As a control, IBU molecules were directly loaded in agarose hydrogel. To do that, the

water phase of agarose hydrogel was replaced by the hexane solution of IBU via stepwise solvent, followed by evaporation of hexane in air. After being thoroughly dried, the resulting IBU-laden agarose hydrogel was used for the skin permeation study as described above.

Characterization

TEM imaging was implemented on JEOL(JEM-2010) electron microscope operating at 100 kV. The aqueous dispersion of GOs was dropped onto carbon-coated copper grids and dried by tissue paper for TEM observations. The zeta-potential of GOs was assessed by a Brookhaven ZetaPALS apparatus (90Plus Zeta). The rheological property was measured by using parallel plate geometry on a Peltier plate on an advanced rheometer (Discovery HR-2, TA Instrument, USA). The diameter of the steel plate was 25 mm with a gap of 1mm. The G' (storage modulus) and G" (loss modulus) of the hydrogels were calculated by taking the values at a particular angular frequency of 1 rad/s and a strain of 1% at mode of oscillation (temperature ramp); the ramp rate was 5^{o}C / min from 70 ^{o}C to 30 ^{o}C. The agarose and GOACHs samples were freeze dried in -50 ^{o}C overnight to remove the water and then submitted to characterization by means of Fourier transform infrared (FT-IR) spectroscopy (Thermo Fisher Scientific iS10), X-ray diffraction (XRD, PANalytical B.V. Empyrean), scanning electron microscopy (SEM) (Nova nano 450) and differential scanning calorimetry (DSC) (Q2000, TA Instrument, USA) from 25 to 500 ^{o}C at speed with 10 ^{o}C·min^{-1}. The The UV/vis absorption spectroscopy was carried out on a UV/vis 2700 spectrophotometer (Shimadzu). XPS spectra were obtained on a Kratos Axis Ultra with a Delay Line Detector photoelectron spectrometer using a monochromatic aluminum X-ray source running at 225 W with a characteristic energy of 1486.6 eV; the analysis depth was approximately 15 nm into the sample surface.

Figure S1. Scheme of fabrication of GOACHs.

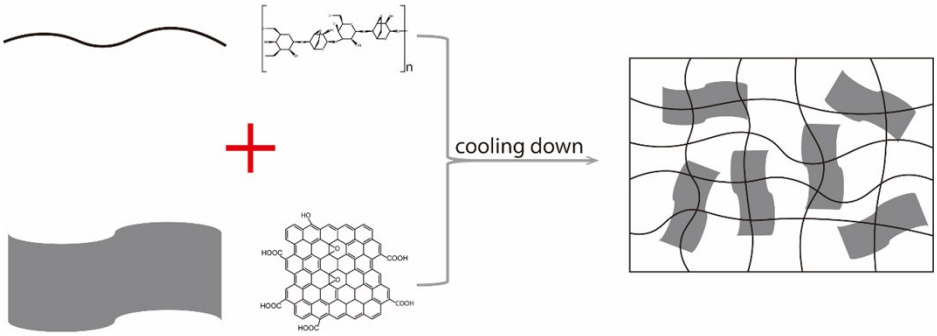


Figure S2. TEM images of graphene oxides on carbon coated cooper grids with circular holes.

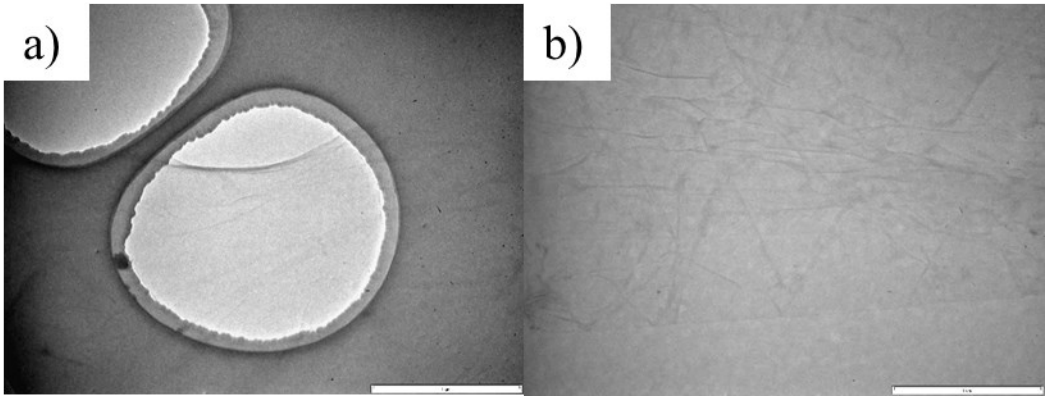


Figure S3. Zeta Potential of graphene oxides in water (0.1 mg/ml), which is around -45 mV.

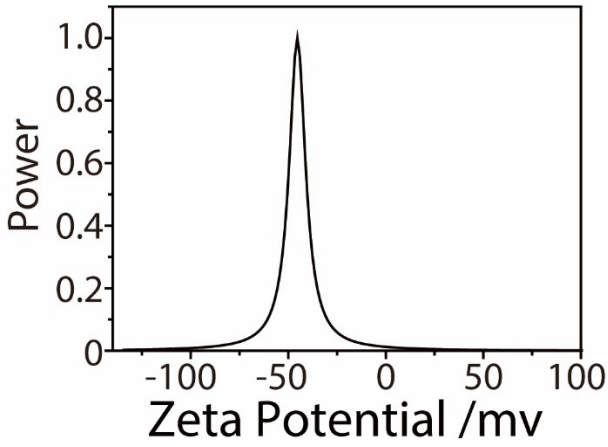
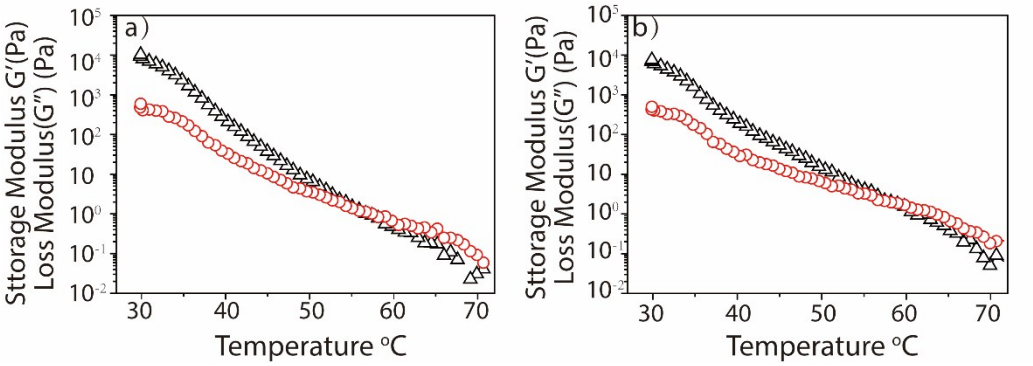
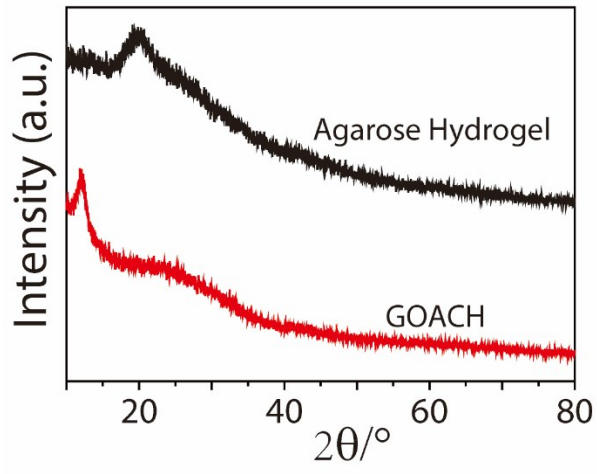


Figure S4. Plots of storage modulus G' and loss modulus G'' of agarose hydrogels (a) and GOACHs (b) versus temperature in the range of 50℃ to 30 ℃.



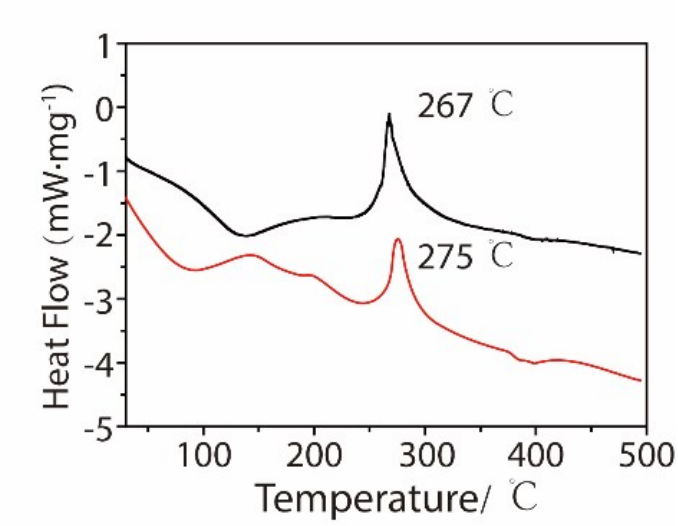
The following rheological measurement was performed for getting insight into the hydrogel thixotropy. The storage modulus (G') indicates the quantity of stored energy in the system, it will characterize the solid-liked property of the hydrogel, while the loss modulus (G'') presents the quantity of dissipated energy in the network. For the GOACHs, the thixotropic gel-sol transition occurs at 58 °C, similar to that of pristine agarose hydrogel. The G' and G'' values of GOACHs are also comparable to those of pristine agarose hydrogels.

Figure S5. X-ray diffraction (XRD) spectra of agarose hydrogels (black curve) and GOACHs (red curve).



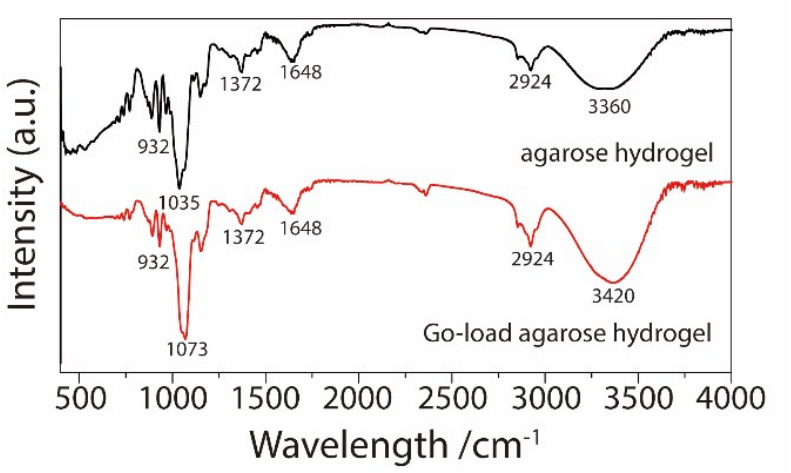
The peak of agarose hydrogel was 20°, which was similar as literature report. (Arvind Kumar et.al. Green Chem., 2010, 12, 1029–1035). After the graphene oxides added, the sharp peak at 12° was stand for the GO in the GOACHs.

Figure S6. DSC Curves of agarose hydrogels (black curve) and GOACHs (red curve).



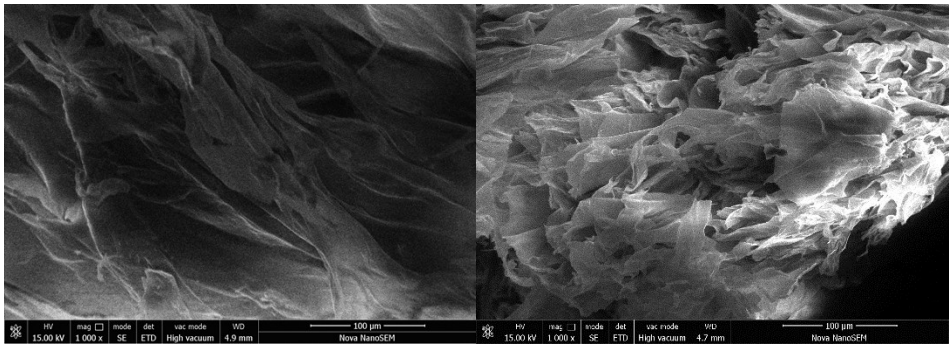
Both the agarose hydrogels and GOACHs show a sharp peak around 260 °C, which arise from the carbonization process of agarose.

Figure S7. FTIR spectra of agarose hydrogel (black curve) and GOACHs (red curve).



The FTIR spectra of agarose hydrogels and GOACHs show little difference and both of them show the band of C-H stretching at 2924 cm^{-1}, the band of C-H bending at 1372 cm^{-1}, the band of O-H stretching in the range of 3200 - 3600 cm^{-1}, and the band of 3,6-anydro-D-galactose skeletal bending at 932 cm^{-1}.

Figure S8. SEM images of agarose hydrogels (left panel) and GOACHs (right panel).



From Figure S3-S8, it is found that the presence of graphene oxides hardly affect the property of the composites hydrogel possibly due to their low content.

Figure S9. The swelling behaviors of pristine and composite agarose hydrogels are measured by the swelling ratio (SR), namely, the weight ratio of water-swollen gel to dried gel. (a) Temporal evolution of the SR values of dried agarose hydrogel bars obtained after treatment without (■) and with solvent exchange (□) and dried $GO_{0.1}$ACH (○), $GO_{0.2}$ACH (△), $GO_{0.3}$ACH bars (◇) during incubation in PBS. The Figure b-d are the optical images of agarose hydrogel bars obtained after treatment without (b) and with solvent exchange (c) and $GO_{0.2}$ACHs bars obtained after solvent exchange treatment (d) in the thoroughly dried state (left panels) and in the equilibrium swollen state obtained after 5h incubation in PBS (right panels). The solvent exchange is executed to stepwise convert the water phase of the pristine and composite hydrogels to hexane via ethanol.

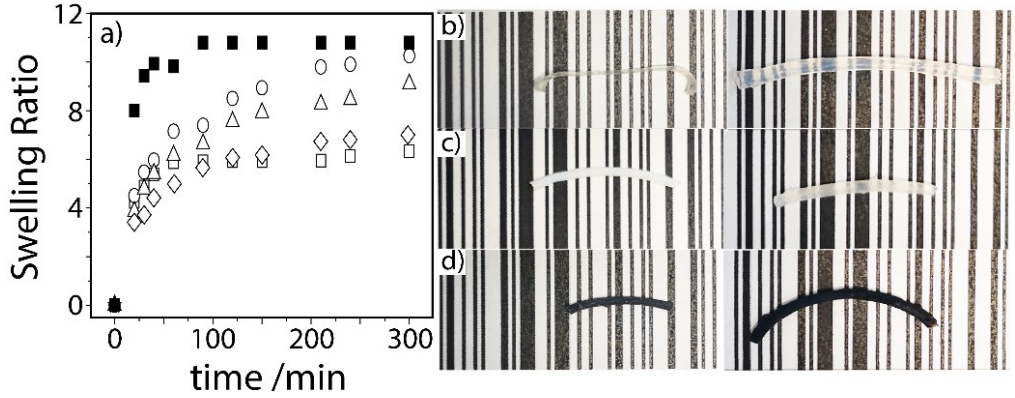


Figure S9a shows that stepwise solvent exchange from water to hexane via ethanol results in ca. 50% loss in SR for agarose hydrogels; the equilibrium SR values of the dried agarose hydrogels treated without and with solvent exchange are about 11 and 6, respectively, after 5 h incubation in phosphate buffer solution (PBS). This is justifiable because the displacement of water especially by a non-polar organic solvent such as hexane is expected to introduce more hydrogen bonds between the dehydrating local domains of the agarose hydrogel network and thus intensify the network physical cross-linking. In contrast, the presence of GO guests can minimize the impact of stepwise solvent exchange on the swelling performance of dried GOACHs, which can be rationalized as a result of that the presence of hydrophilic GO guests can foster the (re)hydration efficiency of the agarose hydrogel host. Figure S1 shows that after 5 h

incubation in PBS, the equilibrium SR value of the dried GO_xACHs is gradually reduced from 10 to 9 and 7 with the GO content (x) increases from 0.1 to 0.2 and 0.3 $mg \cdot g^{-1}$, which should reflect the fact that the GO guests loaded in the agarose hydrogel hosts incur noticeable aggregation with the Go content increasing and in turn their contribution to the hydration of the dried agarose hydrogel networks is largely reduced. Note that dried GOACHs show almost identical swelling performance in PBS and pure water, while the PBS was preferentially used in the current work for the purpose of verifying the applicability of GOACHs in drug formulation.

Figure S10. (a – f) UV-vis absorption spectra of NR solutions in hexane at the initial NR concentration (C_o^i) of 6 (a), 12 (b), 15 (c), 18 (d), 24 (e), and 30 □g·mL^{-1} (f) before (black curves) and after $GO_{0.1}$ACHs (red curves), $GO_{0.2}$ACHs (blue curves) and $GO_{0.3}$ACHs (purple curves) are incubated inside to reach the NR adsorption equilibrium.

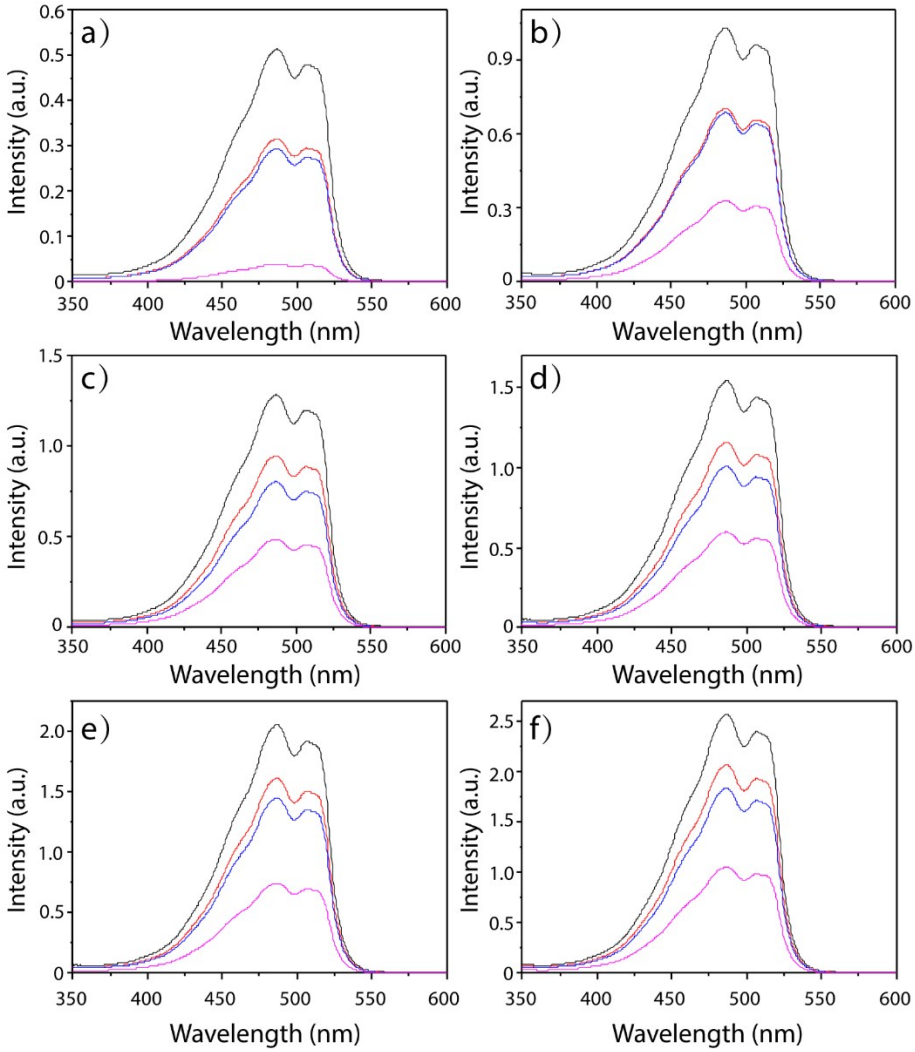


Table S1. Summary of the q_o^e values (mg·g^{-1}) of GO_xACHs towards NR molecules in hexane with different initial NR concentration (C_o^i, ug·mL^{-1}).

C_o^i	6	12	15	18	24	30
$GO_{0.1}$ACH	1.526	2.509	2.582	2.963	3.422	3.865
$GO_{0.2}$ACH	1.684	2.634	3.690	4.096	4.656	5.628
$GO_{0.3}$ACH	3.617	5.336	6.071	7.206	9.983	11.550

Figure S11. Adsorption isotherms of $GO_{0.1}$ACHs (□), $GO_{0.2}$ACHs (○), and $GO_{0.3}$ACHs (△) towards NR in hexane (solid curves), which are fitted according to Langmuir (dashed curves) and Freundlich models (dot curves)

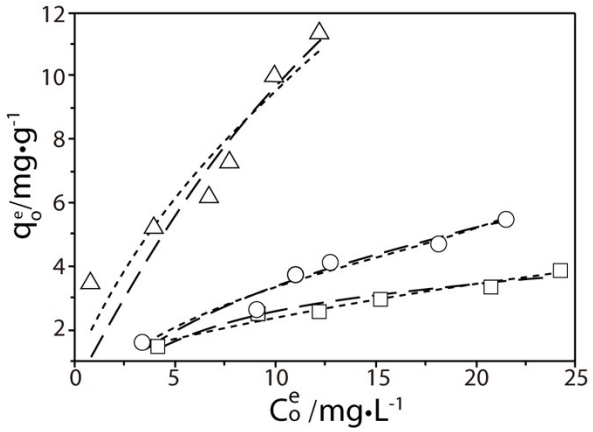


Table S2. Summary of the fitting results of the adsorption isotherms of GO_xACHs towards NR molecules in hexane obtained according to Langmuir and Freundlich models. The poor fitting based on Freundlich model is indicated by the 1/n value of < 1.

Samples	Langmuir model			Freundlich model		
	q_o^m (mg·g^{-1})	K_L (L·mg^{-1})	r^2	K_F (mg·g$^{1-1/n}$·g^{-1}·L$^{1/n}$)	1/n (g·L^{-1})	r^2
$GO_{0.1}$ACH	5.528	0.083	0.957	0.771	0.500	0.977
$GO_{0.2}$ACH	12.347	0.037	0.943	0.680	0.682	0.950
$GO_{0.3}$ACH	32.960	0.042	0.784	2.223	0.631	0.857

Figure S12. Determination of the solubility of NR in alcoholic PBS with 10% (a-c) and 20 % ethanol solution (d-f). A series of amounts of NR powder were introduced in the alcoholic PBS to produce NR-saturated solutions with the aid of ultrasonication. The red curves are the UV-vis spectra obtained immediately after the alcoholic PBS solutions of NR are prepared and the black curves are the UV-vis spectra obtained after the solutions are store overnight so that undissolved NR powders completely settle. When the absorption intensity of the black curves becomes almost identical to that of the red curves, the very amount of NR demanded to produce NR-saturated solution is introduced in the alcoholic PBS with a given volume. Accordingly, the solubility of NR is determined to be 0.2 ug·mL^{-1} (or mg·L^{-1}) in alcoholic PBS with 10% ethanol and 1.5 ug·mL^{-1} (or mg·L^{-1}) in alcoholic PBS with 20% ethanol.

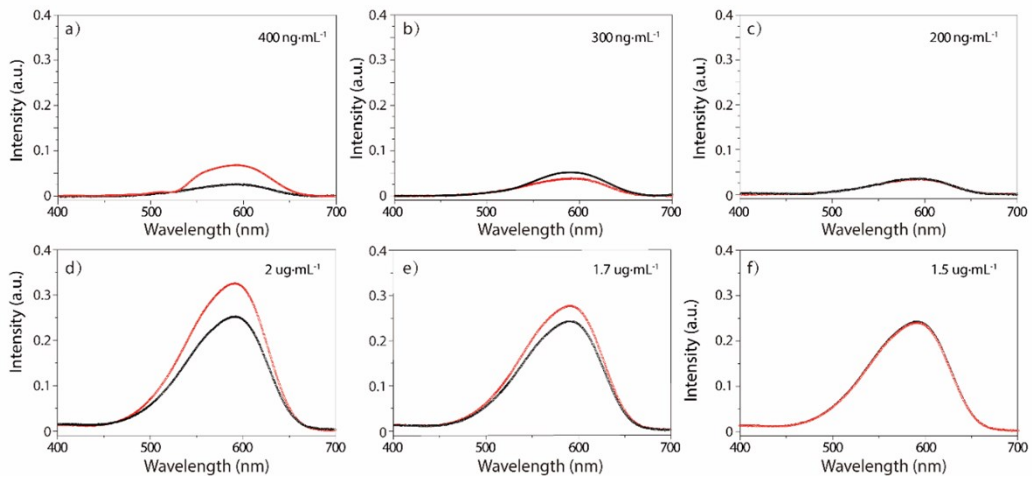


Figure S13. a) The UV-vis absorption spectra of alcoholic PBS during incubation of NR-$GO_{0.2}$ACHs with q_o^e of 5.628 mg.g^{-1} for 1 (black curve), 2 (red curve), 3 (blue curve), 4 (purple curve), 5 h (orange curve) and 6h (green curve). (b) Absorption spectra of the first (black curve), second (orange curve), and third batches (green curve) of alcoholic PBS used for incubation of NR-$GO_{0.2}$ACHs with q_o^e of 5.628 mg.g^{-1} to release the loaded NR molecules. Each incubation step is executed for 6 h to ensure the equilibrium release of the loaded NR molecules from the $GO_{0.2}$ACHs. (c) Absorption spectra of the second batches of alcoholic PBS used incubation for NR-$GO_{0.2}$ACHs with q_o^e of 4.096 (red curve), 4.656 (blue curve), and 5.628 mg.g^{-1} (black curve), respectively, and alcoholic PBS bearing 1 mg·g^{-1} urea used for incubation of NR-$GO_{0.2}$ACHs with q_o^e of 5.628 mg.g^{-1} (purple curve). In all figures, the ethanol content of alcoholic PBS media is 10 vol %.

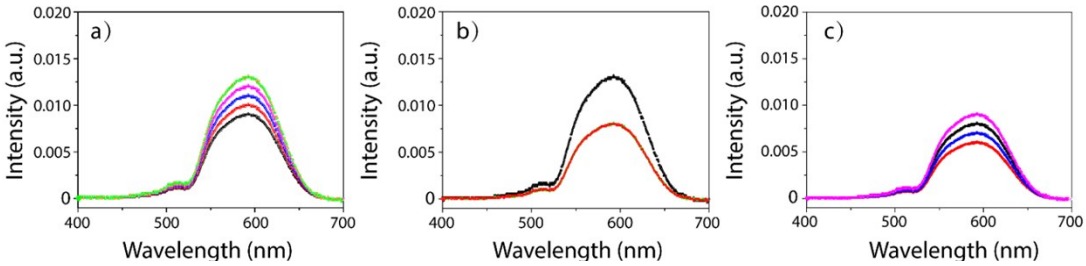


Figure S14. Temporal NR release profiles during incubation of NR-$GO_{0.2}$ACHs with q_o^e of 5.628 mg.g^{-1} in alcoholic PBS media with the ethanol content of 10 (a), 20 (b), and 30 vol % (c). When the NR concentration in alcoholic PBS media reaches the plateau value, the NR-GO_xACHs are taken out and placed in fresh alcoholic PBS media for new NR release round. The dashed lines indicate when GOACHs are brought into fresh alcoholic PBS media.

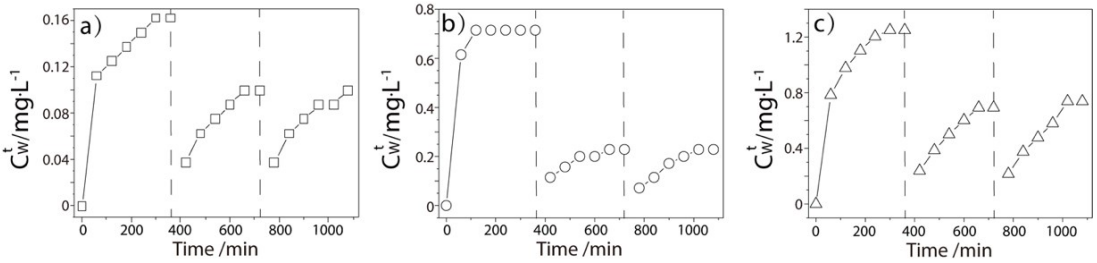


Figure S15. Temporal NR release profiles during incubation of NR-$GO_{0.1}$ACHs (a) and NR-$GO_{0.3}$ACHs (b) in alcoholic PBS media with the ethanol content of 10 vol%. The q_o^e values of NR-$GO_{0.1}$ACHs are 2.582 (◇), 2.963 (△), 3.422 (○), and 3.865 mg.g^{-1} (□).The q_o^e values of NR-$GO_{0.3}$ACHs are 6.071 (◇), 7.206 (△), 9.983 (○), 11.550 mg.g^{-1} (□). When the NR concentration in alcoholic PBS media reaches the equilibrium value, the NR-GO_xACHs are taken out and placed in fresh alcoholic PBS media for new NR release round. The dashed lines indicate when NR-GO_x ACHs are brought into fresh alcoholic PBS media.

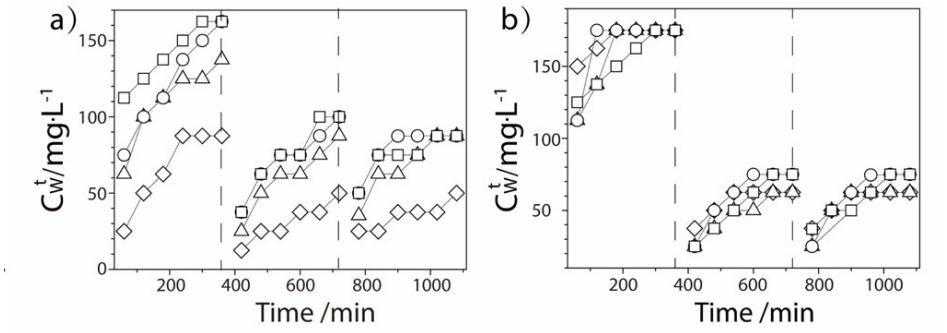


Table S3. Summary of the solubility (S) of MR in water at different values of pH (retrieved from the database of SciFinder@).

pH	1	2	3	4	5	6	7	8	9	10
S ($mg \cdot L^{-1}$)	240	38	7.8	12	81	650	2300	3000	3200	3200

Figure S16. (a – f) UV-vis absorption spectra of MR solutions in hexane at initial MR concentration (C_o^i) of 4 (a), 8 (b), 10 (c), 12 (d), 16 (e), and 20 $ug \cdot mL^{-1}$ (f) before (black curves) and after $GO_{0.1}$ACHs (red curves), $GO_{0.2}$ACHs (blue curves) and $GO_{0.3}$ACHs (purple curve) are incubated inside for to reach the adsorption equilibrium.

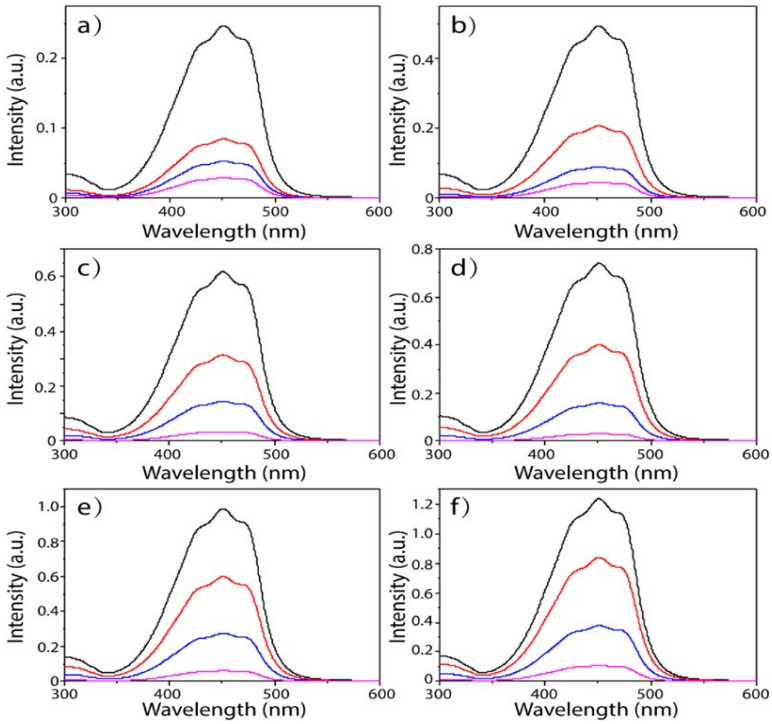


Table S4. Summary of the q_o^e values ($mg \cdot g^{-1}$) of GO_xACHs towards MR molecules in hexane with different initial MR concentration (C_o^i, $ug \cdot mL^{-1}$).

C_o^i	4	8	10	12	16	20
$GO_{0.1}$ACH	1.737	3.070	3.250	3.646	4.162	4.257
$GO_{0.2}$ACH	2.065	4.293	5.028	6.200	7.589	9.137
$GO_{0.3}$ACH	2.301	4.733	6.176	7.516	9.804	11.928

Figure S17. Adsorption isotherms of $GO_{0.1}$ACHs (□), $GO_{0.2}$ACHs (○), and $GO_{0.3}$ACHs (△) towards NR in hexane (solid curves), which are fitted according to Langmuir (dashed curves) and Freundlich models (dot curves).

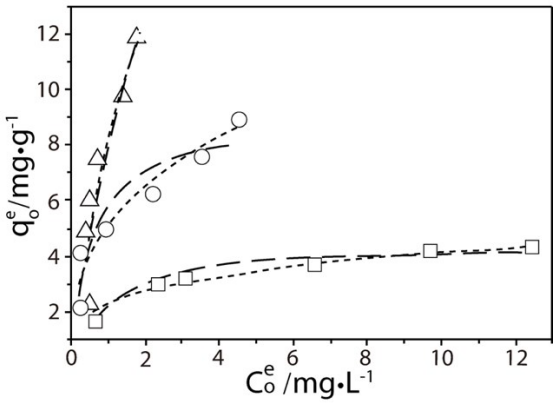


Table S5. Summary of the fitting results of the adsorption isotherms of GO_xACHs towards MR molecules in hexane, based on Langmuir and Freundlich models. The poor fitting based on Freundlich model is indicated by the 1/n value of < 1.

Samples	Langmuir model			Freundlich model		
	q_o^m (mg·g^{-1})	K_L (L·mg^{-1})	r^2	K_F (mg·g$^{1-1/n}$·g^{-1}·L$^{1/n}$)	1/n (g·L^{-1})	r^2
$GO_{0.1}$ACH	4.474	0.961	0.970	2.303	0.255	0.950
$GO_{0.2}$ACH	8.990	1.877	0.817	5.125	0.349	0.896
$GO_{0.3}$ACH	27.804	0.415	0.835	7.806	0.716	0.823

Figure S18. (a) Temporal evolution of the absorption spectra of PBS during 6 h incubation of MR-$GO_{0.2}$ACHs with q_o^e of 9.137 mg.g^{-1}. (b-c) Temporal MR release profiles during incubation of MR-$GO_{0.1}$ACHs (b) and MR-$GO_{0.3}$ACHs (c) in PBS. The q_o^e values of MR-$GO_{0.1}$ACHs are 3.250 (◇), 3.646 (△), 4.162 (○), and 4.257 mg.g^{-1}(□). (c) The q_o^e values of MR-$GO_{0.3}$ACHs are 6.176 (◇), 7.516 (△), 9.804 (○), 11.928 mg.g^{-1} (□). When the MR concentration in PBS reaches the equilibrium value, the MR-GO_xACHs are taken out and place in fresh PBS for new MR release round. The dashed lines indicate when MR-GO_xACHs are brought into fresh PBS.

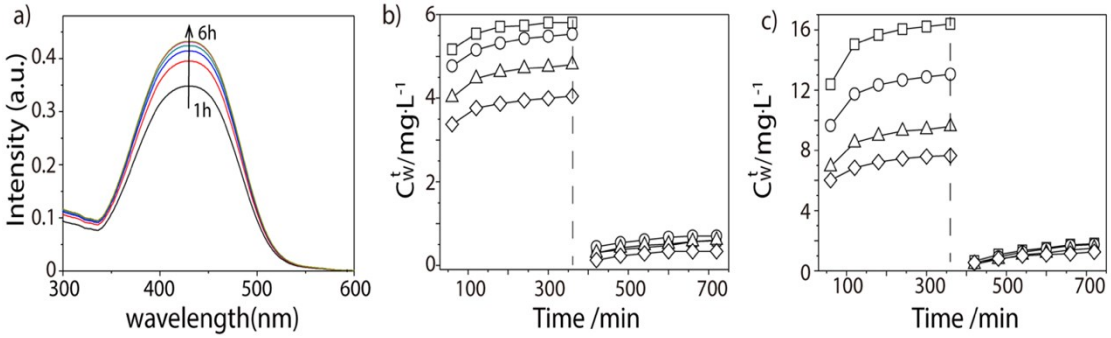


Figure S19. UV-Vis absorption spectra of IBU in hexane (a) and PBS buffer (b).

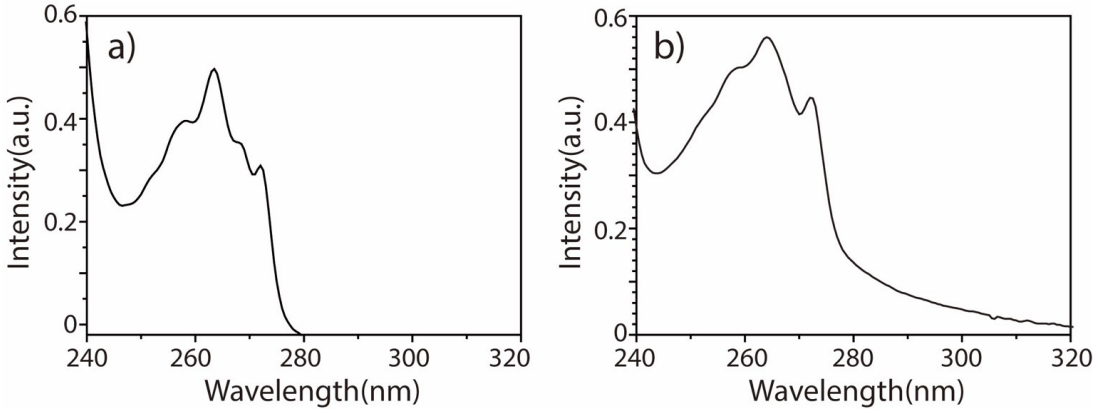


Table S6. Summary of the q_o^e values (mg·g^{-1}) of $GO_{0.2}$ACHs towards IBU molecules in hexane obtained at different initial IBU concentrations (C_o^i, □g·mL^{-1}).

C_o^i	50	100	200	300	400
$GO_{0.2}$ACHs	6.514	12.04	13.83	24.76	32.68

Table S7. Summary of the fitting results of the adsorption isotherms of $GO_{0.2}$ACHs towards IBU molecules in hexane based on Langmuir and Freundlich models. The poor fitting based on Freundlich model is indicated by the 1/n value of < 1.

Sample	Langmuir model			Freundlich model		
	q_m ($mg \cdot g^{-1}$)	K_L ($L \cdot mg^{-1}$)	r^2	K_F ($mg \cdot g^{1-1/n} \cdot g^{-1} \cdot L^{1/n}$)	1/n ($g \cdot L^{-1}$)	r^2
$GO_{0.2}$ACHs	153.895	$7.5*10^{-4}$	0.884	0.377	0.754	0.877

Figure S20. Temporal IBU release profiles during incubation of IBU-$GO_{0.2}$ACHs with q_o^e of 24.76 (○), 13.83 (△), and 12.04 $mg.g^{-1}$ (◇), respectively, in PBS. When the IBU concentration (C_w^t) in PBS reaches the equilibrium value, the IBU-$GO_{0.2}$ACHs are taken out and placed in fresh PBS media for new IBU release round. The dashed lines indicate when IBU-$GO_{0.2}$ACHs are brought into fresh PBS.

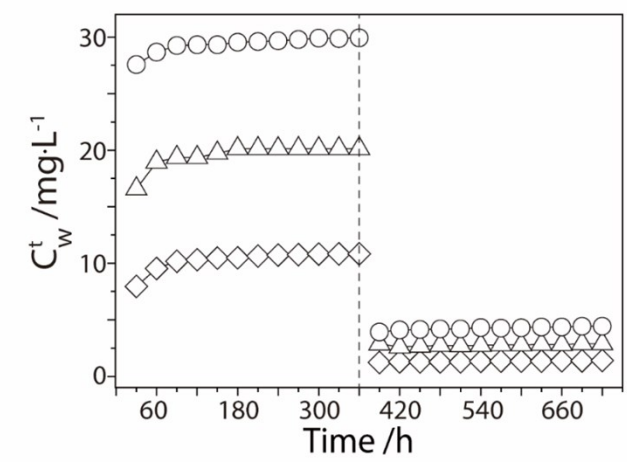


Figure S21. Photographs of a Franz diffusion cell (a) and its main components (b).

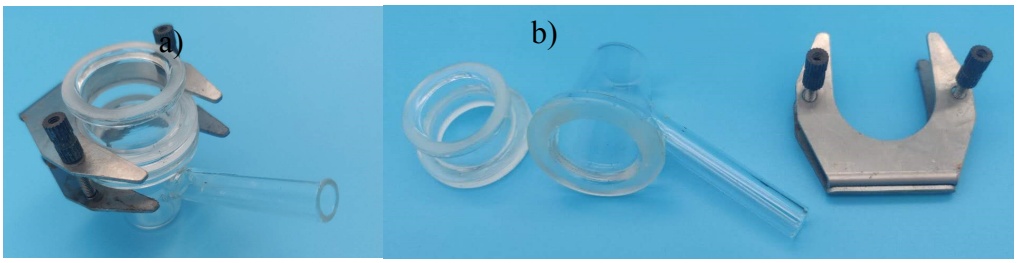


Figure S22. The experimental pictures about transdermal IBU delivery through rat skin.