Fusion of polymer-coated liposomes with forcespun microfibers as hybrid materials to enhance sustained release

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Supplementary Materials and Methods Information

Drug release kinetic models

Zero-order release kinetics

In zero-order release kinetics, the cumulative amount of drug release is directly proportional to time, as described by the following equation[1]:

$$C = (K_0.t)_,$$

where K_0 is the zero-order rate constant expressed as concentration per time and t is the time per hour.

First-order release kinetics

It is expressed as the log cumulative percentage of drug undissolved versus time, as described by the following equation[2]:

$$Log\ C = (Log\ C_0 - K_t/2.303)_,$$

where C is the amount of drug undissolved at time, C_0 is the drug concentration at t equal to 0, and K_t is the corresponding release rate constant.

Higuchi square root release model

It is expressed as the cumulative percentage of drug release versus the square root of time, as described by the following equation[3]:

$$Q = \left(K_H.t^{\frac{1}{2}}\right),$$

where Q is the amount of drug dissolved at time, K_H is the Higuchi constant.

Hixson-Crowell cube root release model

It is expressed as the cube root of the initial concentration minus the cube root of the percentage of drug undissolved versus time, as described by the following equation[4]:

$$\left(Q_0^{\frac{1}{3}} - Q_t^{\frac{1}{3}} = K_{HC}.t\right),$$

where Q_0 is the initial amount of the drug, Q_t is the amount of drug release at time, and K_{HC} is the rate constant for the Hixson-Crowell cube root model.

Korsmeyer-Peppas equation

It is a simple semi-empirical model that relates drug release to elapsed time exponentially, as described by the following equation[5]:

$$Q/Q_0 = Kt^n,$$

where Q/Q_0 is the fraction of drug released at time, K is the constant comprising the structural geometric characteristics, and n is the diffusion exponent that depends on the release mechanism.

Supplementary Figures

Fig. S1 A photograph of quercetin liposomal dispersion.

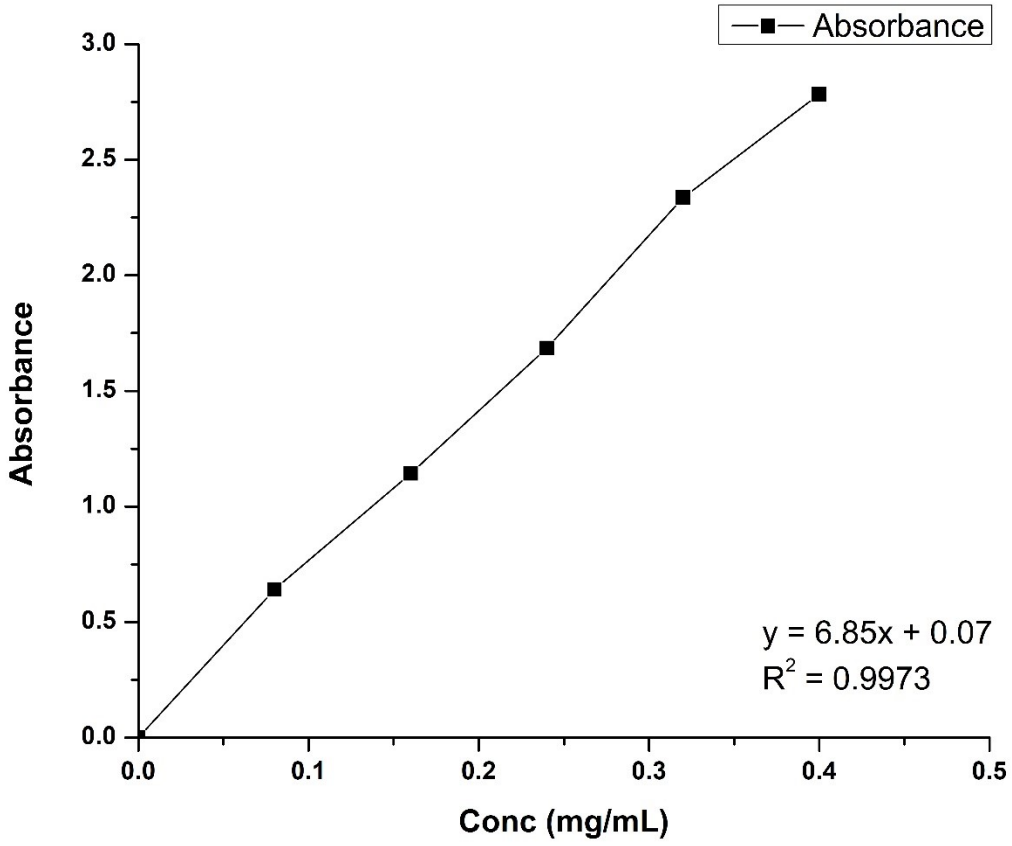

Fig. S2 Calibration curve of quercetin.

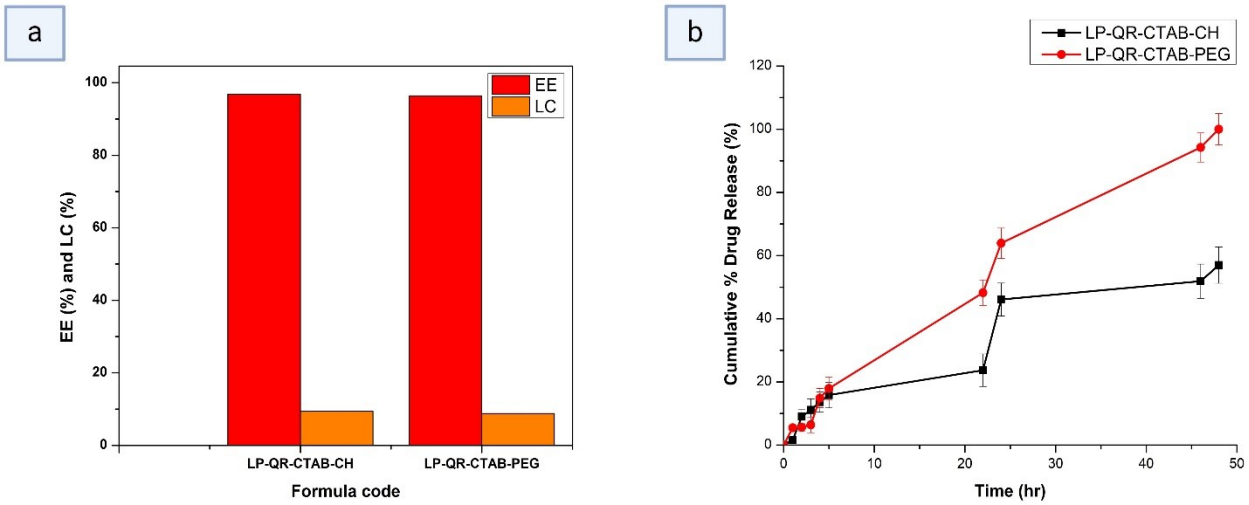

Fig. S3 shows (a) the EE% and LC% of LP-QR-CTAB-CH and LP-QR-CTAB-PEG liposomes; and (b) the *in vitro* drug release profiles of LP-QR-CTAB-CH and LP-QR-CTAB-PEG liposomes.

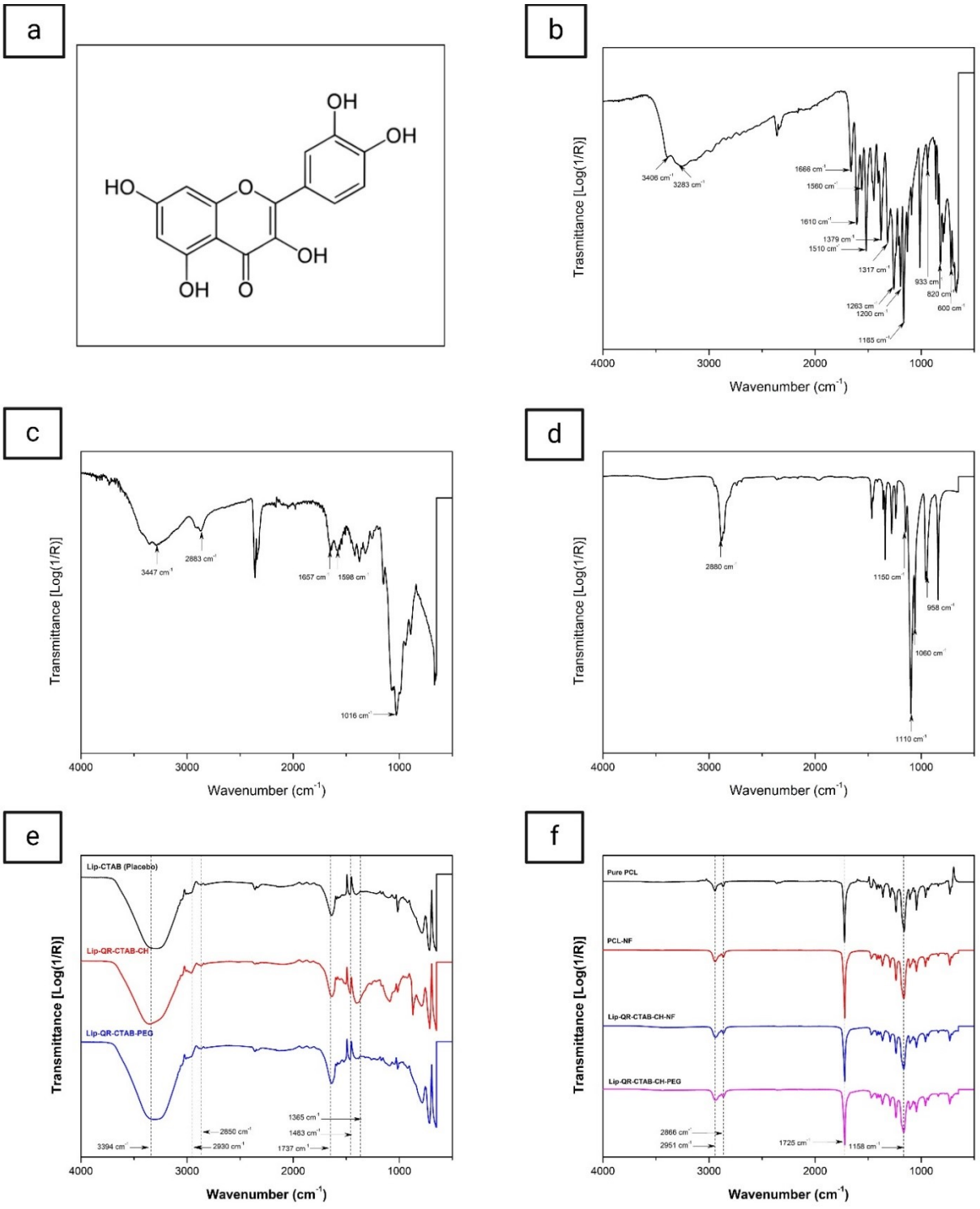

Fig. S4 Chemical structure of quercetin (a), the FT-IR spectra of quercetin (b), chitosan (c), and PEG-4000 (d); LP-CTAB, LP-QR-CTAB-CH, and LP-QR-CTAB-PEG (e); and PCL, PCL-NF, LP-QR-CTAB-CH-NF, and LP-QR-CTABPEG-NF (f).

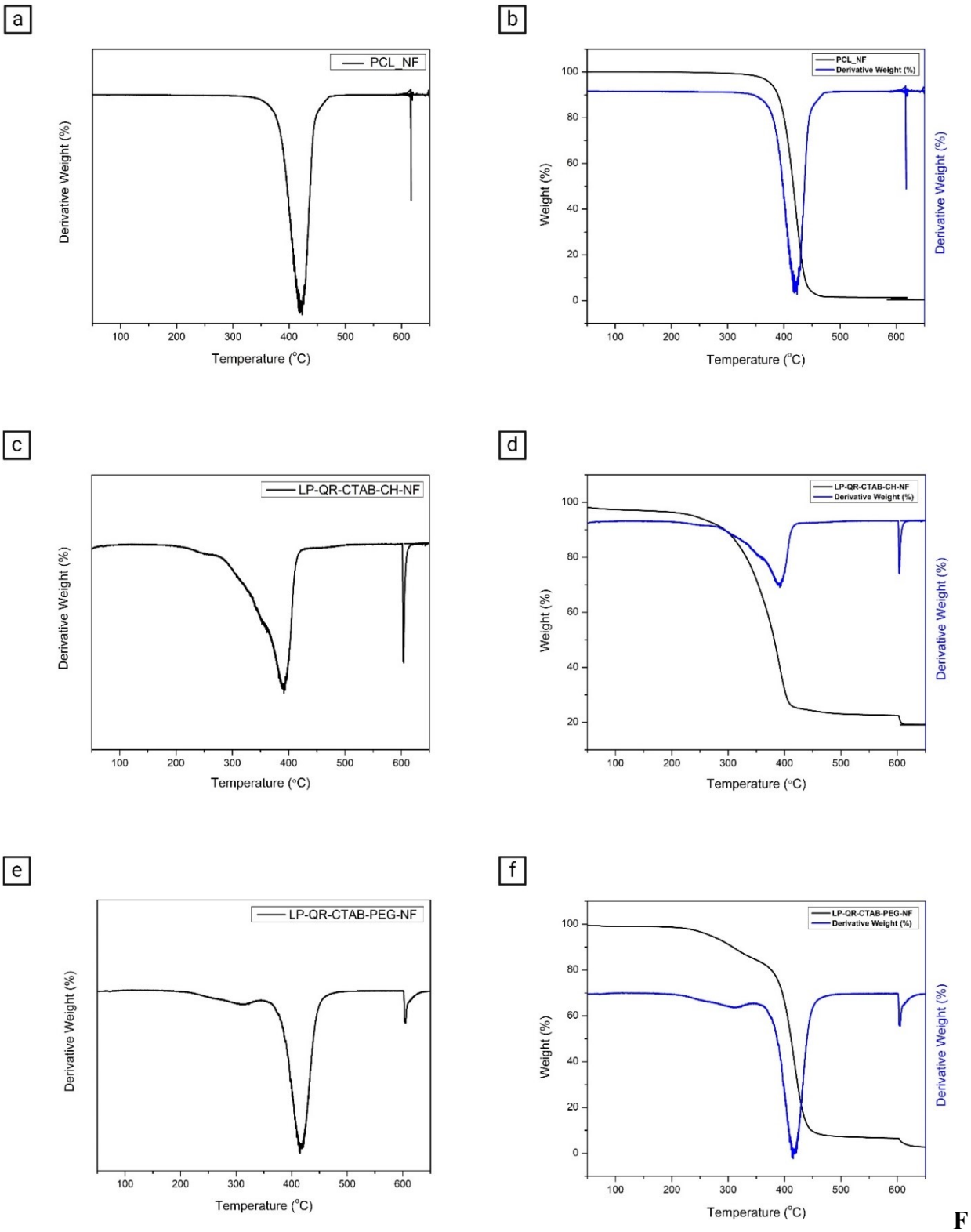

Fig. S5 TGA and weight derivative curves of PCL-NF **(a,b)**; LP-QR-CTAB-CH-NF **(c,d)**; and

LP-QR-CTAB-PEG-NF **(e,f)**.

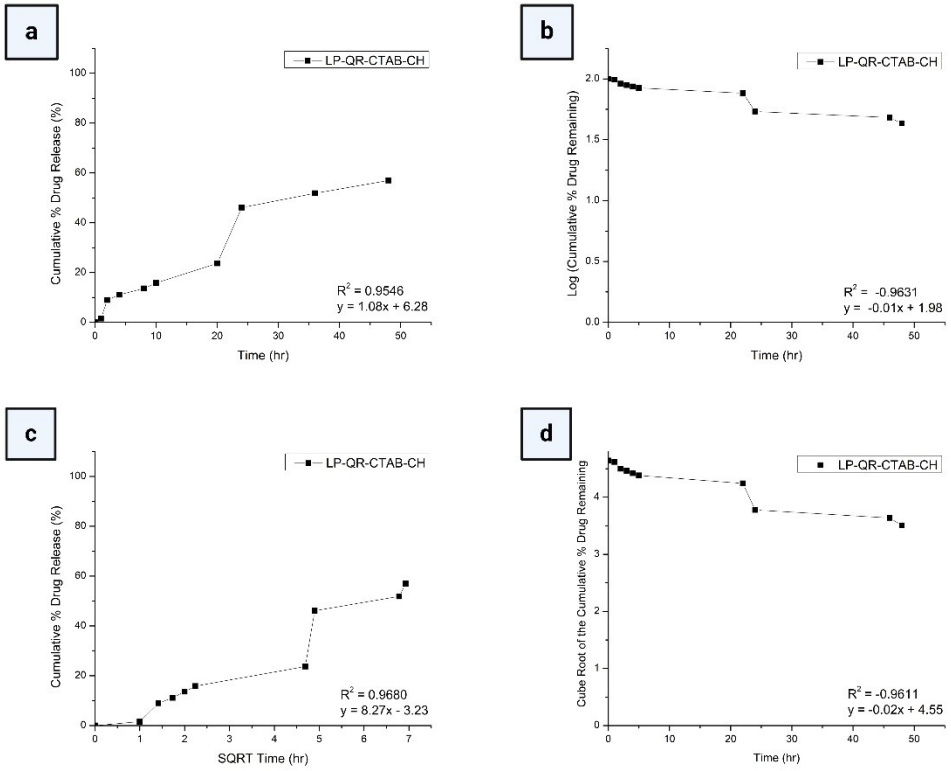

Fig. S6 Drug release kinetic models of LP-QR-CTAB-CH liposome. (a) Zero-order release, (b) first-order release, (c) Higuchi release, and (d) Hixon-Crowell release.

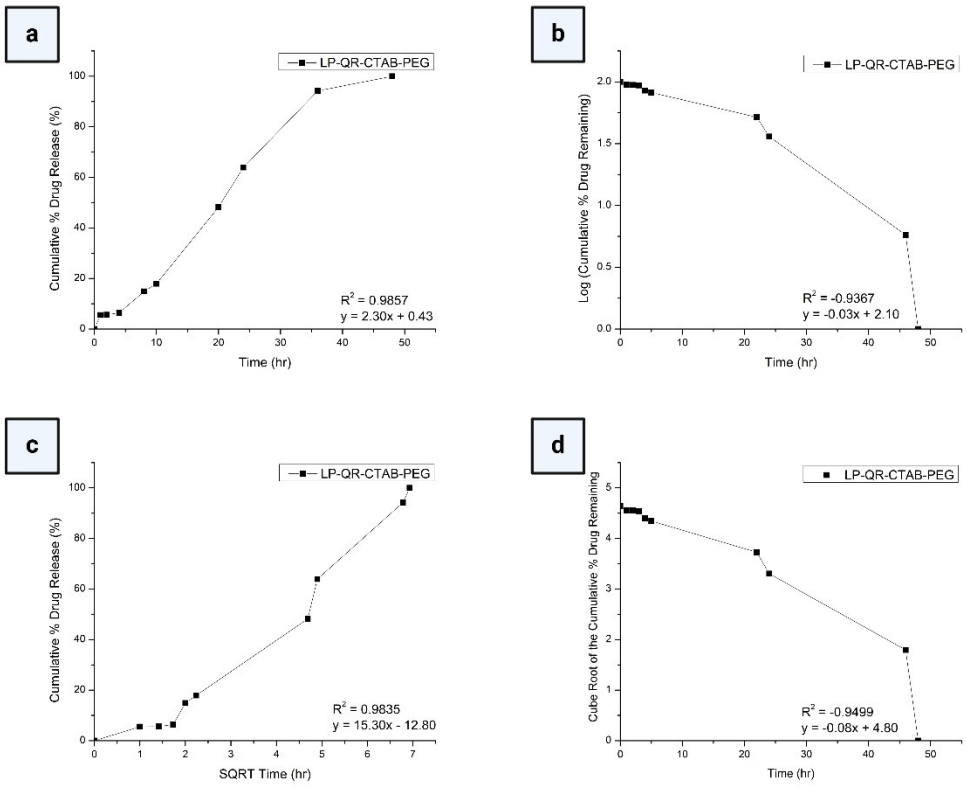

Fig. S7 Drug release kinetic models of LP-QR-CTAB-PEG liposome. (a) Zero-order release, (b) first-order release, (c) Higuchi release, and (d) Hixon-Crowell release.

Supplementary Tables

Table S1. Liposome and forcespun nanofiber formulations and their compositions (mg/mL).

Formula Code	Formula Composition					
	Quercetin (mg)	**Phospholipid (mg)**	**Cholesterol (mg)**	**CTAB (mg)**	**Coating Polymer (mg)**	**Nanofiber Polymer (mg)**
	Surface-Coated Liposomes					
LP-QR-CTAB-CH	10	38	19	5.7	Chitosan, 0.5	_____
LP-QR-CTAB-PEG	10	38	19	5.7	PEG, 40	_____
	Nanofiber-Loaded Surface-Coated Liposomes					
LP-QR-CTAB-CH-NF	10	38	19	5.7	Chitosan, 0.5	PCL, 200
LP-QR-CTAB-PEG-NF	10	38	19	5.7	PEG, 40	PCL, 200

Table S2. Preparation of quercetin calibration standards.

Standard: 0.1 gm of quercetin in 100 mL of methanol			
Dilution (mL/25mL)	**DF**	**Conc (mg/mL)**	**Absorbance**
0.2	125	0.08	0.640524268
0.4	62.5	0.16	1.142894506
0.6	41.7	0.24	1.685053229
0.8	31.3	0.32	2.33641839
1	25	0.4	2.783970118
Slope	6.85		
Intercept	0.07		
R^2	0.9973		
Regression equation	$y = 6.85x + 0.07$		

Table S3. Physicochemical characteristics of the coated liposomes at initial and after 3 months of storage.

Formula Code	PS (nm)	PDI	Zeta Potential (mV)	Viscosity (cP)	EE (%)	LC (%)	Cumulative % Drug Release (%, 48 hours)
Initial							
LP-QR-CTAB-CH	552.62 ± 25.12	0.48 ± 0.06	30.18 ± 1.36	11.94 ± 3.79	96.82 ± 0.007	9.381 ± 0.01	59.96 ± 5.74
LP-QR-CTAB-PEG	469.08 ± 48.75	0.55 ± 0.06	14.57 ± 0.95	12.79 ± 6.79	96.39 ± 0.002	8.794 ± 0.003	99.84 ± 4.98
3 Months of storage							
LP-QR-CTAB-CH	622.20 ± 9.49	0.52 ± 0.12	26.45 ± 1.88	11.87 ± 2.24	———	———	———
LP-QR-CTAB-PEG	613.78 ± 122.98	0.50 ± 0.46	10.08 ± 0.83	12.34 ± 5.81	———	———	———

Table S4. Formulation and optimization of forcespun microfibers.

Polymer name	Polymer Concentration (%)	Co-polymer name	Co-polymer Concentration (%)	Polymer to co-polymer ratio (v/v)	Solvent name	Co-solvent name	Fiber yield and quality
PVA (hydrophilic)	10	_____	_____	_____	Purified water	_____	No fiber
	10	_____	_____	_____	DMSO	_____	No fiber
	10	Chitosan	1	50:50	Purified water	TFA	No fiber
	15	_____	_____	_____	Purified water	_____	No fiber
	15	_____	_____	_____	DMSO	_____	No fiber
	20	_____	_____	_____	Purified water	_____	No fiber
	20	_____	_____	_____	DMSO		No fiber
PCL (hydrophobic)	10	_____	_____	_____	THF	DMF	Low yield
	10	_____	_____	_____	Chloroform	Methanol	Low yield
	15	_____	_____	_____	THF	DMF	Low yield
	15	_____	_____	_____	Chloroform	Methanol	Moderate yield
	15	Chitosan	1	50:50	TFA	_____	No fiber
	17.5	_____	_____	_____	THF	DMF	Low yield
	17.5	_____	_____	_____	Chloroform	Methanol	Moderate yield
	20	_____	_____	_____	THF	DMF	Low yield
	20	_____	_____	_____	Chloroform	Methanol	High yield
	20	Chitosan	1	50:50	TFA	_____	No fiber

Table S5. Linear fit and coefficient of determination (R^2) of the LP-QR-CTAB-CH and LP-QR-CTAB-PEG liposomes in different kinetic models.

Formula code	Zero-order release kinetics		First-order release kinetics		Higuchi square release model		Hixon-Crowell release model		Korsmeyer-Peppas model	
	Linear fit	R^2	Linear fit	R^2	Linear fit	R^2	Linear fit	R^2	Linear fit	R^2
LP-QR-CTAB-CH	y = 1.08x + 6.28	0.9546	y = -0.01x + 1.98	-0.9631	y = 8.27x – 3.23	0.9680	y = -0.02x + 4.55	-0.9611	y = 0.73x + 0.56	0.930
LP-QR-CTAB-PEG	y = 2.30x + 0.43	0.9857	y = -0.03x + 2.10	-0.9367	y = 15.30x – 12.80	0.9835	y = -0.08x + 4.80	-0.9499	y = 0.83x + 0.60	0.981

Table S6. Drug release rate parameters of the Korsmeyer-Peppas kinetic model for LP-QR-CTAB-CH and LP-QR-CTAB-PEG liposomes.

Formula code	Linear fit	R^2	K	SSD	*n*
LP-QR-CTAB-CH	y = 0.73x + 0.56	0.930	5.587	233.044	0.585
LP-QR-CTAB-PEG	y = 0.83x + 0.60	0.981	4.465	105.248	0.802

Coefficient of determination (R^2); rate constant (K); sum of the squared difference (SSD); release exponent (*n*).

n **$\leq$ 0.45: Fickian diffusion (Case-I transport); 0.45 < *n* < 0.89: anomalous (non-Fickian) diffusion; *n* $\simeq$ 0.89: zero-order release (Case-II transport); *n* > 0.89: super Case-II transport.**

References

1 Jain, A.; Jain, S.K. In vitro release kinetics model fitting of liposomes: An insight. *Chem. Phys. Lipids* 2016, **201**, 28–40.

2 Hwang, K.J.; Luk, K.F.; Beaumier, P.L. Hepatic uptake and degradation of unilamellar sphingomyelin/cholesterol liposomes: a kinetic study. *PNAS* 1980, **77**, 4030–4034.

3 Higuchi, T. Rate of release of medicaments from ointment bases containing drugs in suspension. *J. Pharm. Sci.* 1961, **50**, 874–875.

4 Hixon, A.W.; Crowell, J.H. Dependence of reaction velocity upon surface and agitation. *Ind. Eng. Chem.* 1931, **23**, 923–931.

5 Korsmeyers, R.W.; Gumy, R.; Doelker, E.M.; Buri, P.; Peppas, N.A. Mechanism of solute release from porous hydrophilic polymers. *Int. J. Pharm.* 1983, **15**, 25–35.