Supporting Information for publication

PEO-b-PCL/Tween 80/Cyclodextrin systems: from bioinspired fabrication to possible nasal administration of Ropinirole Hydrochloride

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The synthetic procedure of the PEO-b-PCL block copolymers

Block copolymer synthesis: In a typical synthesis of PEO-b-PCL (copolymer PEO-b-PCL_1), monomethoxy-PEO of 5,000 g/mol molar mass was utilized as the macromolecular initiator (and first block) in the presence of stannous octoate as the catalyst ($SnOct_2$). At first, PEO homopolymer (2 g) was dissolved in toluene (20 mL) and transferred to a spherical flask. Toluene was evaporated partially in a rotary evaporator (one-fourth of the toluene initial volume remaining), leaving the dried polymer as a concentrated toluene solution. ε-caprolactone monomer (0.5 g, distilled over CaH_2 in a vacuum line) was added to the flask under a nitrogen atmosphere, and then two drops of $SnOct_2$ solution (as received) were added through a rubber septum. The flask was then immersed in an oil bath at 130 °C and left for CL polymerization for 3 hours. Afterwards, the contents were allowed to cool at room temperature, the mixture was diluted with 15 mL of $CHCl_3$, and the polymer was precipitated in hexane. The solvents were decanted, and the obtained solid was dried in a vacuum oven for 48 hours at room temperature.

Table S1. The molecular characteristics of the PEO-b-PCL block copolymers

Copolymer	M_w [a] (g/mol)	M_w/M_n [a]	%wt PCL[b]	M_w [c] (g/mol, corrected)
PEO-b-PCL_1	11,100	1.04	15	5,900
PEO-b-PCL_2	12,500	1.18	30	7,100
PEO-b-PCL_3	14,400	1.42	53	10,600

[a] by SEC in THF

[b] by ^{1}H-NMR in $CDCl_3$

[c] corrected by using composition from NMR and PEO block molecular weight

Table S2. Molecular characteristics of the utilized compounds.

Compound	**Molecular weight** (g/mol)
PEO-b-PCL$_1$	5,900 (15% wt PCL)
PEO-b-PCL$_2$	7,100 (30% wt PCL)
PEO-b-PCL$_3$	10,600 (53% wt PCL)
Tween 80	1,310
β-CD	1,135
Methyl-β-CD	1,303.3
Hydroxy-propyl-β-CD	1,541.54
Ropinirole hydrochloride	296.83

Table S3. Calorimetric heating parameters of pure compounds and their mixtures in the solid state. These calorimetric parameters correspond to the thermograms in Figures 2, S1, and S2.

Sample	$T_{onset,m}$ (°C)[a]	T_m (°C)[b]	$\Delta T_{1/2,m}$ (°C)[c]	ΔH_m (KJ mol^{-1})[d]	$T_{onset,s}$ (°C)	T_s (°C)	$\Delta T_{1/2,s}$ (°C)	ΔH_s (KJ mol^{-1})	$T_{onset,t}$ (°C)	T_t (°C)	$\Delta T_{1/2,t}$ (°C)	ΔH_t (KJ mol^{-1})
PEO-b-PCL_1	54.56	57.50	3.18	-34.61	191.67	195.33	4.25	9.28	35.51	42.17	5.31	0.44
PEO-b-PCL_2	56.36	62.50	10.55	-34.26	192.31	194.17	81.29	70.83	37.03	49.00	10.81	5.81
PEO-b-PCL_3	52.56	58.00	6.31	-40.37	179.33	186.83	7.95	7.74	38.85	44.00	4.13	0.81
Tw80	25.43	59.50	39.05	-2.07	–	–	–	–	–	–	–	–
PEO-b-PCL_1/Tw80	49.07	55.00	5.51	-40.24	–	–	–	–	–	–	–	–
PEO-b-PCL_2/Tw80	48.14	53.67	11.05	-20.09	54.47	63.50	9.27	12.01	–	–	–	–
PEO-b-PCL_3/Tw80	48.03	54.33	5.16	-33.50	–	–	–	–	–	–	–	–
MβCD	145.13	179.50	17.63	-1.29	68.20	75.33	6.91	-0.02	–	–	–	–
PEO-b-PCL_1/MβCD	52.84	56.00	3.87	-38.85	188.25	195.67	7.96	6.97	–	–	–	–
PEO-b-PCL_2/MβCD	46.66	53.00	5.80	-25.54	194.46	199.00	5.81	6.96	–	–	–	–
PEO-b-PCL_3/MβCD	50.36	56.33	5.17	-37.54	176.66	184.50	9.24	13.37	270.41	272.33	4.86	-1.18
HPβCD	142.17	147.33	20.30	-5.70	–	–	–	–	–	–	–	–
PEO-b-PCL_1/HPβCD	52.03	55.17	3.39	-30.32	189.86	194.00	5.57	17.84	262.59	264.33	4.14	-3.03
PEO-b-PCL_2/HPβCD	46.29	53.00	6.05	-21.33	189.96	195.50	6.78	9.24	261.24	263.50	6.16	-1.49
PEO-b-PCL_3/HPβCD	49.71	56.17	6.21	-39.71	–	–	–	–	–	–	–	–
Tw80/MβCD	123.78	147.50	27.10	0.50	184.83	187.00	6.65	-1.07	–	–	–	–
PEO-b-PCL_1/Tw80/MβCD	48.84	53.17	3.65	-24.88	161.00	181.67	40.29	3.81	111.73	147.33	24.25	-0.68
PEO-b-PCL_2/Tw80/MβCD	17.29	51.33	6.34	-26.28	180.89	188.17	14.42	1.60	126.96	132.17	18.41	-0.81
PEO-b-PCL_3/Tw80/MβCD	46.43	54.33	6.25	-37.58	166.70	176.17	10.08	4.52	–	–	–	–
Tw80/HPβCD	121.29	132.33	16.19	-0.74	–	–	–	–	–	–	–	–
PEO-b-PCL_1/Tw80/HPβCD	51.43	55.83	4.05	-36.04	155.15	180.67	25.55	-1.38	–	–	–	–
PEO-b-PCL_2/Tw80/HPβCD	55.64	60.00	4.14	-22.13	179.08	188.17	9.98	5.23	226.60	228.83	5.12	-2.06
PEO-b-PCL_3/Tw80/HPβCD	46.80	54.67	6.26	-34.34	174.59	183.33	9.46	10.88	205.11	207.50	5.67	-2.35

[a]T_{onset}: the temperature at which the thermal event starts.

[b]T: the temperature at which heat capacity at constant pressure is at its maximum.

[c]$\Delta T_{1/2}$: half width at the half peak height of the transition.

[d]ΔH: transition enthalpy normalized per mol of each system. m: main transition; s: secondary; t: trinary transition.

Table S4. The physicochemical characteristics of ternary systems in **A.** Water-HPLC grade, **B.** FBS/PBS mixture (10:90), and **C.** buffer solution (pH=5.6 at the temperature of 34 °C).

A. Dispersed in Water-HPLC grade

Colloidal dispersions	w/w	$R_{h\ (Cumulant)}$ (nm)[1]	PDI[2]	Number of peaks	$R_{h\ (Contin)}$ (nm)[3]	Weight of Peak (%)
(PEO-b-PCL_1/Tw80)/MβCD	80:20	87	0.3_6	2	1) 12 2) 116	1) 7% 2) 93%
(PEO-b-PCL_2/Tw80)/MβCD	80:20	69	0.4_7	2	1) 13 2) 120	1) 14% 2) 85%
(PEO-b-PCL_3/Tw80)/MβCD	80:20	39	0.4_3	2	1) 19 2) 96	1) 38% 2) 62%
(PEO-b-PCL_1/Tw80)/HPβCD	80:20	91	0.3_6	2	1) 10 2) 99	1) 5% 2) 95%
(PEO-b-PCL_2/Tw80)/HPβCD	80:20	81	0.5_1	2	1) 12 2) 120	1) 15% 2) 85%
(PEO-b-PCL_3/Tw80)/HPβCD	80:20	37	0.4_7	2	1) 17 2) 88	1) 40% 2) 60%

B. Dispersed in FBS/PBS mixture

Colloidal dispersions	w/w	$R_{h\ (Cumulant)}$ (nm)[1]	PDI[2]	Number of peaks	$R_{h\ (Contin)}$ (nm)[3]	Weight of Peak (%)
(PEO-b-PCL_1/Tw80)/MβCD	80:20	73	0.5_2	3	1) 4 2) 17 3) 137	1) 12% 2) 22% 3) 66%
(PEO-b-PCL_2/Tw80)/MβCD	80:20	67	0.4_8	3	1) 3 2) 10 3) 192	1) 5% 2) 24% 3) 71%
(PEO-b-PCL_3/Tw80)/MβCD	80:20	40	0.5_2	3	1) 3 2) 12 3) 83	1) 7% 2) 27% 3) 65%
(PEO-b-PCL_1/Tw80)/HPβCD	80:20	48	0.5_4	3	1) 3 2) 12 3)175	1) 8% 2) 23% 3) 68%
(PEO-b-PCL_2/Tw80)/HPβCD	80:20	166	0.4_6	3	1) 3 2) 12 3)123	1) 9% 2) 24% 3) 67%
(PEO-b-PCL_3/Tw80)/HPβCD	80:20	41	0.5_1	3	1) 3 2) 11 3)78	1) 6% 2) 26% 3) 67%

C. Dispersed in buffer solution pH=5.6 at 34 °C						
Colloidal dispersions	**w/w**	**$R_{h\ (Cumulant)}$ (nm)[1]**	**PDI[2]**	**Number of peaks**	**$R_{h\ (Contin)}$ (nm)[3]**	**Weight of Peak (%)**
(PEO-b-PCL_1/Tw80)/MβCD	80:20	87	0.3_6	2	1) 12 2) 120	1) 8% 2) 92%
(PEO-b-PCL_2/Tw80)/MβCD	80:20	67	0.4_8	2	1) 14 2) 122	1) 16% 2) 83%
(PEO-b-PCL_3/Tw80)/MβCD	80:20	38	0.4_1	2	1) 22 2) 119	1) 49% 2) 51%
(PEO-b-PCL_1/Tw80)/HPβCD	80:20	90	0.3_3	2	1) 14 2) 117	1) 6% 2) 94%
(PEO-b-PCL_2/Tw80)/HPβCD	80:20	70	0.4_9	2	1) 14 2) 136	1) 17% 2) 82%
(PEO-b-PCL_3/Tw80)/HPβCD	80:20	37	0.4_2	2	1) 22 2) 129	1) 52% 2) 48%

[1] R_h indicates the average hydrodynamic radius of three replicates of each sample obtained by the Cumulant method

[2] PDI indicates the average polydispersity index

[3] R_h indicates the average hydrodynamic radius of three replicates of each sample obtained by the Contin method

Table S5. The physicochemical characteristics of ternary systems and RH-loaded ternary systems, using water-HPLC grade as a dispersion medium.

Dispersed in Water-HPLC grade						
Colloidal dispersions	**w/w**	**$R_{h\ (Cumulant)}$ (nm)[1]**	**PDI[2]**	**Number of peaks**	**R_h (Contin) (nm)[3]**	**Weight of Peak (%)**
(PEO-b-PCL_1/Tw80)/MβCD	80:20	87	0.3_6	2	1) 12 2) 116	1) 7% 2) 93%
(PEO-b-PCL_1/Tw80/MβCD)/RH	10:1	38	0.4_9	2	1) 9 2) 75	1) 20% 2) 80%
(PEO-b-PCL_1/Tw80/MβCD)/RH	10:5	72	0.5_1	2	1) 9 2) 102	1) 20% 2) 80%
(PEO-b-PCL_1/Tw80)/HPβCD	80:20	91	0.3_6	2	1) 10 2) 99	1) 5% 2) 95%
(PEO-b-PCL_1/Tw80/HPβCD)/RH	10:1	47	0.5_0	2	1) 10 2) 68	1) 20% 2) 80%
(PEO-b-PCL_1/Tw80/HPβCD)/RH	10:5	51	0.5_3	2 not separated curves	1^{st} peak ~12 nm 2^{nd} peak ~ 110 nm	
(PEO-b-PCL_2/Tw80)/MβCD	80:20	69	0.4_7	2	1) 13 2) 120	1) 14% 2) 85%
(PEO-b-PCL_2/Tw80/MβCD)/RH	10:1	22	0.4_3	2	1) 14 2) 97	1) 55% 2) 45%
(PEO-b-PCL_2/Tw80/MβCD)/RH	10:5	21	0.4_5	2	1) 14 2) 150	1) 61% 2) 39%
(PEO-b-PCL_2/Tw80)/HPβCD	80:20	70	0.4_9	2	1) 14 2) 136	1) 17% 2) 82%
(PEO-b-PCL_2/Tw80/HPβCD)/RH	10:1	20	0.4_2	1	18	100%
(PEO-b-PCL_2/Tw80/HPβCD)/RH	10:5	23	0.4_3	1	30	100%
(PEO-b-PCL_3/Tw80)/MβCD	80:20	39	0.4_3	2	1) 19 2) 96	1) 38% 2) 62%
(PEO-b-PCL_3/Tw80/MβCD)/RH	10:1	26	0.1_5	1	25	100%
(PEO-b-PCL_3/Tw80/MβCD)/RH	10:5	27	0.2_0	1	25	100%

(PEO-b-PCL_3/Tw80)/HPβCD	80:20	37	0.4_7	2	1) 17 2) 88	1) 40% 2) 60%
(PEO-b-PCL_3/Tw80/HPβCD)/RH	10:1	29	0.3_7	2	1) 22 2) 221	1) 71% 2) 29%
(PEO-b-PCL_3/Tw80/HPβCD)/RH	10:5	25	0.1_8	1	23	100%

[1] R_h indicates the average hydrodynamic radius of three replicates of each sample obtained by the Cumulant method

[2] PDI indicates the average polydispersity index

[3] R_h indicates the average hydrodynamic radius of three replicates of each sample obtained by the Contin method

Table S6. Regression analysis of the amount of RH permeated per unit area vs. time (up to 120 min) for formulations F1-F12 and RH solution (0.5 mg/mL). Flux (J) (mean ± SD, n=3) and R-square (mean ± SD, n=3) values are presented.

Formulation (F)	J (μg/cm²/min)	R-square
F1	0.00052 ± 0.00009	0.87162 ± 0.00916
F2	0.00058 ± 0.00008	0.91827 ± 0.00798
F3	0.00053 ± 0.00007	0.92526 ± 0.00700
F4	0.00059 ± 0.00007	0.93570 ± 0.00722
F5	0.00053 ± 0.00007	0.92321 ± 0.00706
F6	0.00057 ± 0.00007	0.92699 ± 0.00745
F7	0.00051 ± 0.00005	0.94937 ± 0.00541
F8	0.00061 ± 0.00008	0.91191 ± 0.00875
F9	0.00043 ± 0.00006	0.92526 ± 0.00570
F10	0.00053 ± 0.00006	0.93590 ± 0.00646
F11	0.00042 ± 0.00007	0.88415 ± 0.00699
F12	0.00059 ± 0.00006	0.94367 ± 0.00666
RH solution (0.5 mg/mL)	0.00060 ± 0.00008	0.91575 ± 0.00845

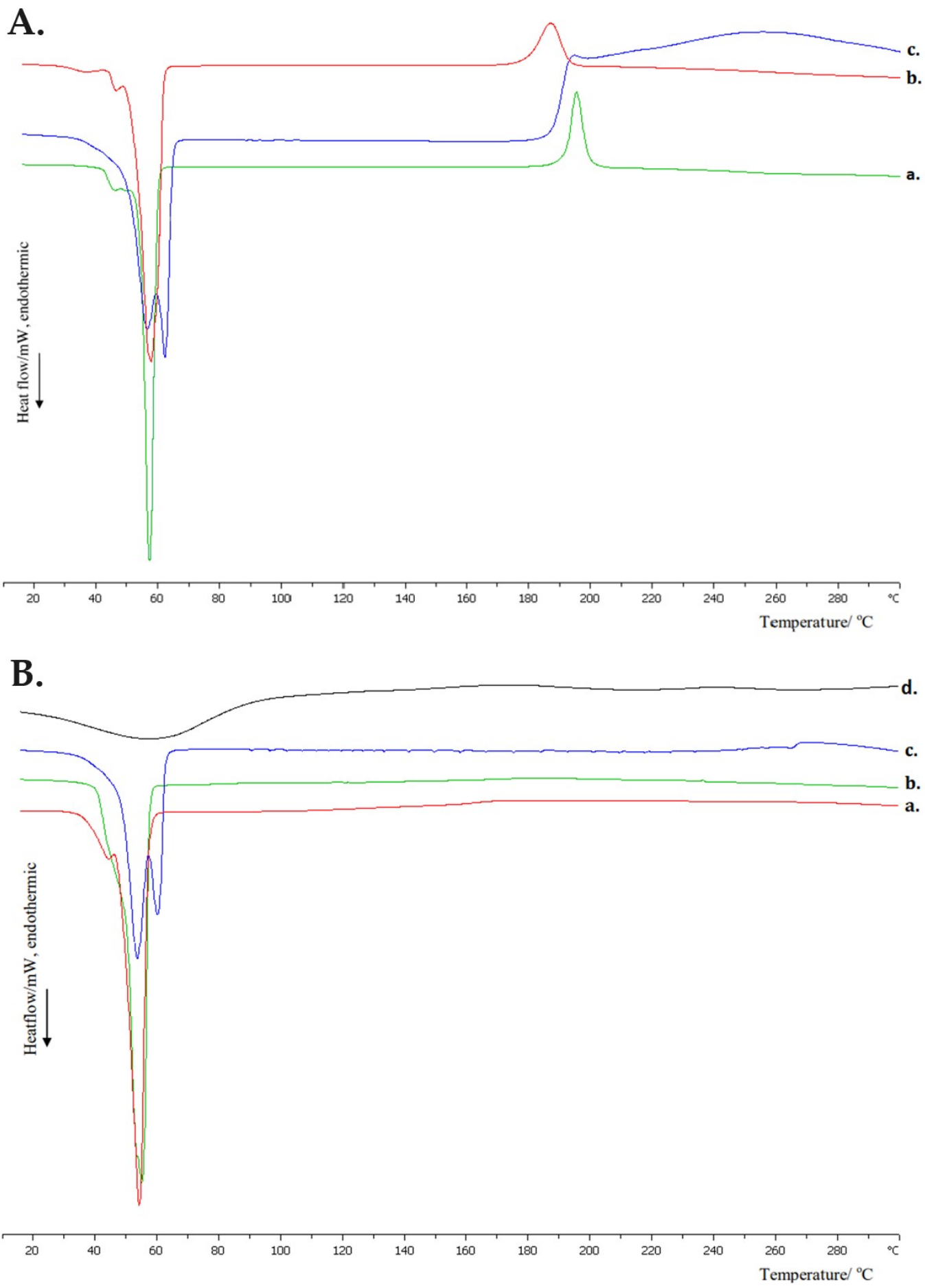

Figure S1. DSC thermograms. The heating curves of **A. a.** PEO-b-PCL_2, b. PEO-b-PCL_3, **c.** PEO-b-PCL_1, and **B. a.** PEO-b-PCL_3/Tw80, **b.** PEO-b-PCL_1/Tw80, **c.** PEO-b-PCL_2/Tw80, **d.** Tw80.

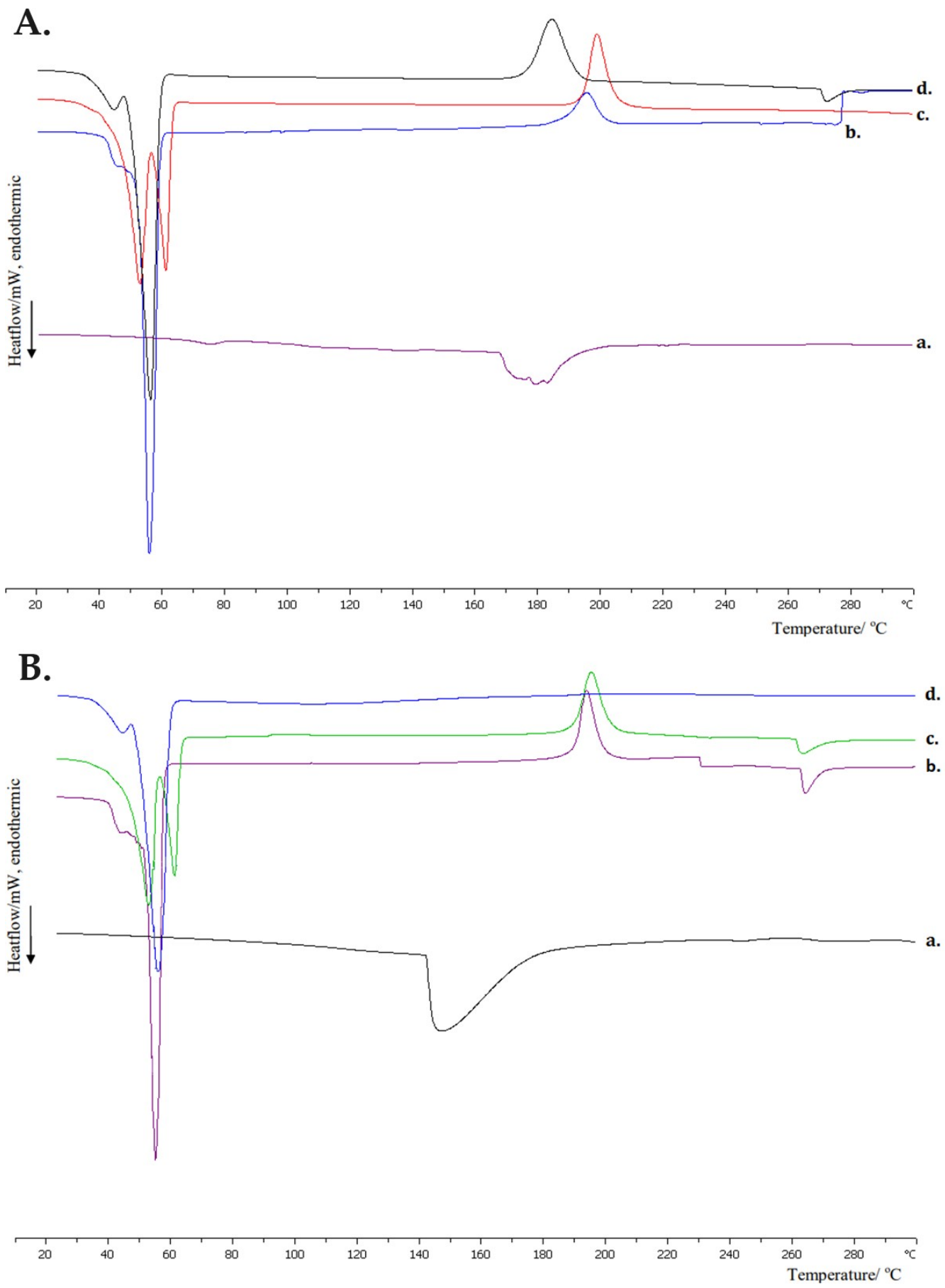

Figure S2. DSC thermograms. The heating curves of **A. a.** MβCD, **b.** PEO-b-PCL_1/MβCD, **c.** PEO-b-PCL_2/MβCD, **d.** PEO-b-PCL_3/MβCD, and **B. a.** HPβCD, **b.** PEO-b-PCL_1/HPβCD, **c.** PEO-b-PCL_2/HPβCD, **d.** PEO-b-PCL_3/HPβCD.

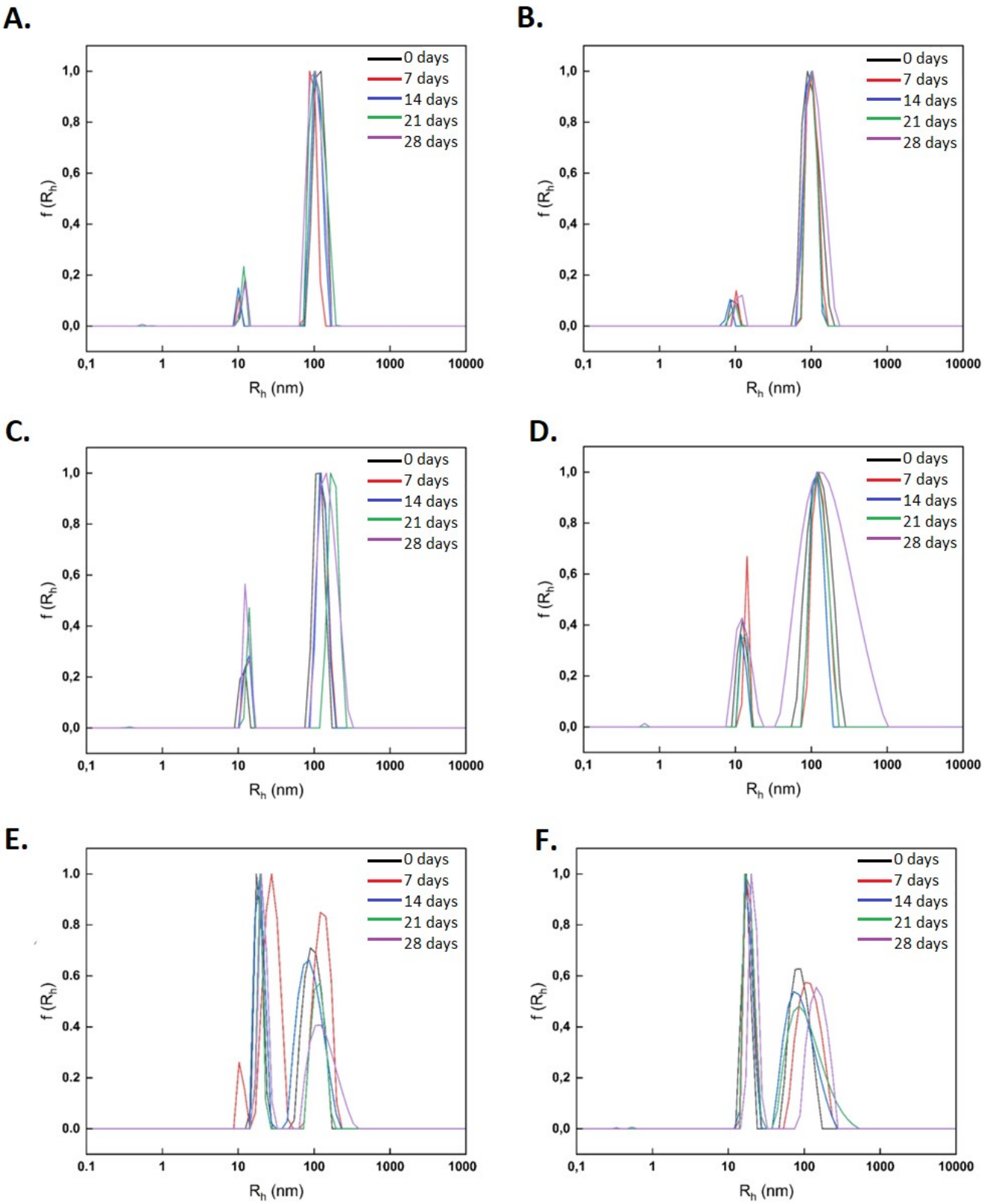

Figure S3. Stability assessment of ternary systems **A.** PEO-b-PCL_1/Tw80/MβCD, **B.** PEO-b-PCL_1/Tw80/HPβCD, **C.** PEO-b-PCL_2/Tw80/MβCD, **D.** PEO-b-PCL_2/Tw80/HPβCD, **E.** PEO-b-PCL_3/Tw80/MβCD, **F.** PEO-b-PCL_3/Tw80/HPβCD systems through R_h measurements during the 28-day period.

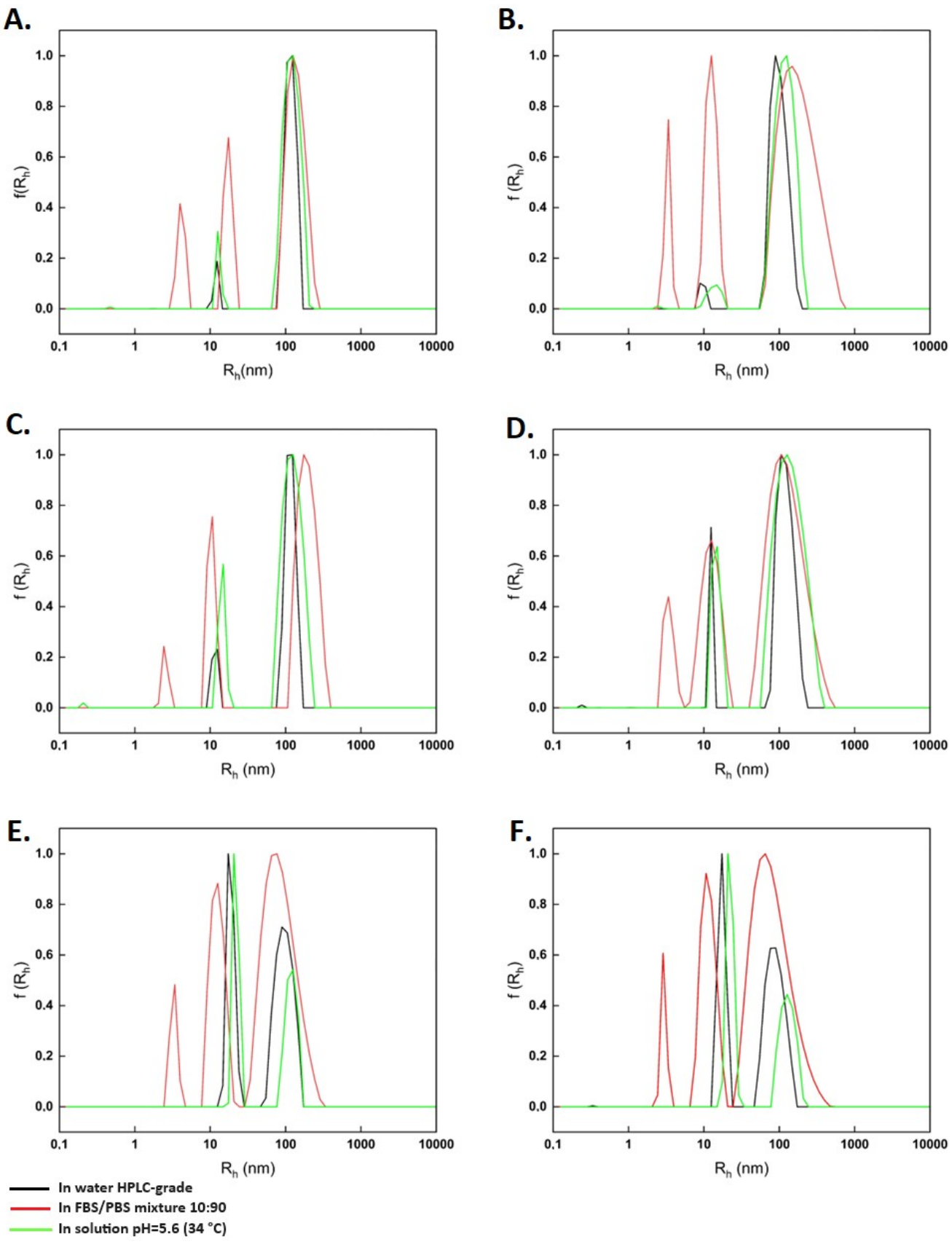

Figure S4. Size distribution for the **A.** PEO-b-PCL_1/Tw80/MβCD, **B.** PEO-b-PCL_1/Tw80/HPβCD, **C.** PEO-b-PCL_2/Tw80/MβCD, **D.** PEO-b-PCL_2/Tw80/HPβCD, **E.** PEO-b-PCL_3/Tw80/MβCD, **F.** PEO-b-PCL_3/Tw80/HPβCD systems in different dispersion media using the thin-film hydration method (t=0 days).

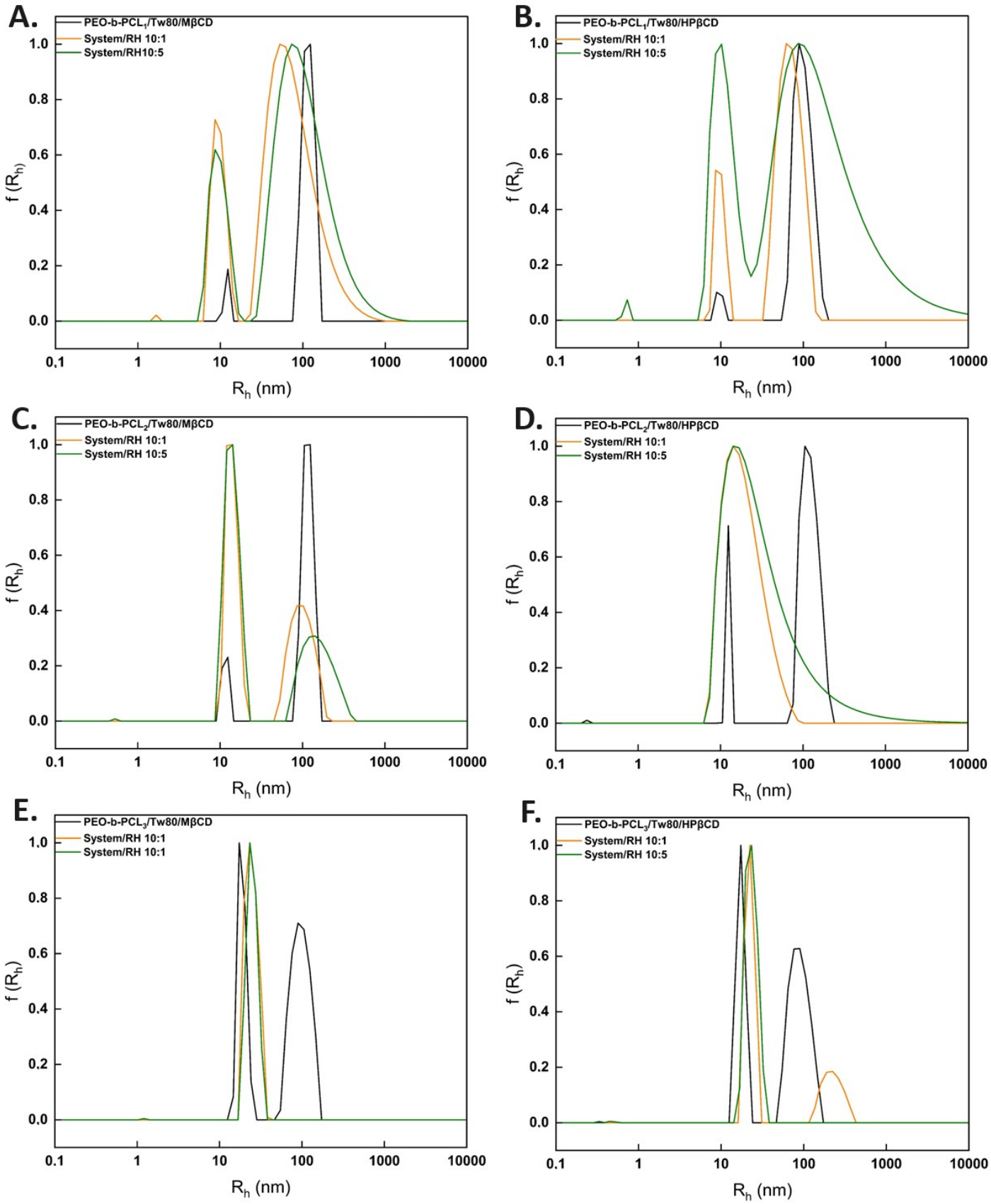

Figure S5. Size distribution for the colloidal dispersions of **A.** PEO-b-PCL_1/Tw80/MβCD and PEO-b-PCL_1/Tw80/MβCD/RH, **B.** PEO-b-PCL_1/Tw80/HPβCD and PEO-b-PCL_1/Tw80/HPβCD/RH, **C.** PEO-b-PCL_2/Tw80/MβCD and PEO-b-PCL_2/Tw80/MβCD/RH, **D.** PEO-b-PCL_2/Tw80/HPβCD and PEO-b-PCL_2/Tw80/HPβCD/RH, **E.** PEO-b-PCL_3/Tw80/MβCD and PEO-b-PCL_3/Tw80/MβCD/RH, **F.** PEO-b-PCL_3/Tw80/HPβCD and PEO-b-PCL_3/Tw80/HPβCD/RH in weight ratios of 10:1 and 10:5 in aqueous solutions using the thin-film hydration method (t=0 days).

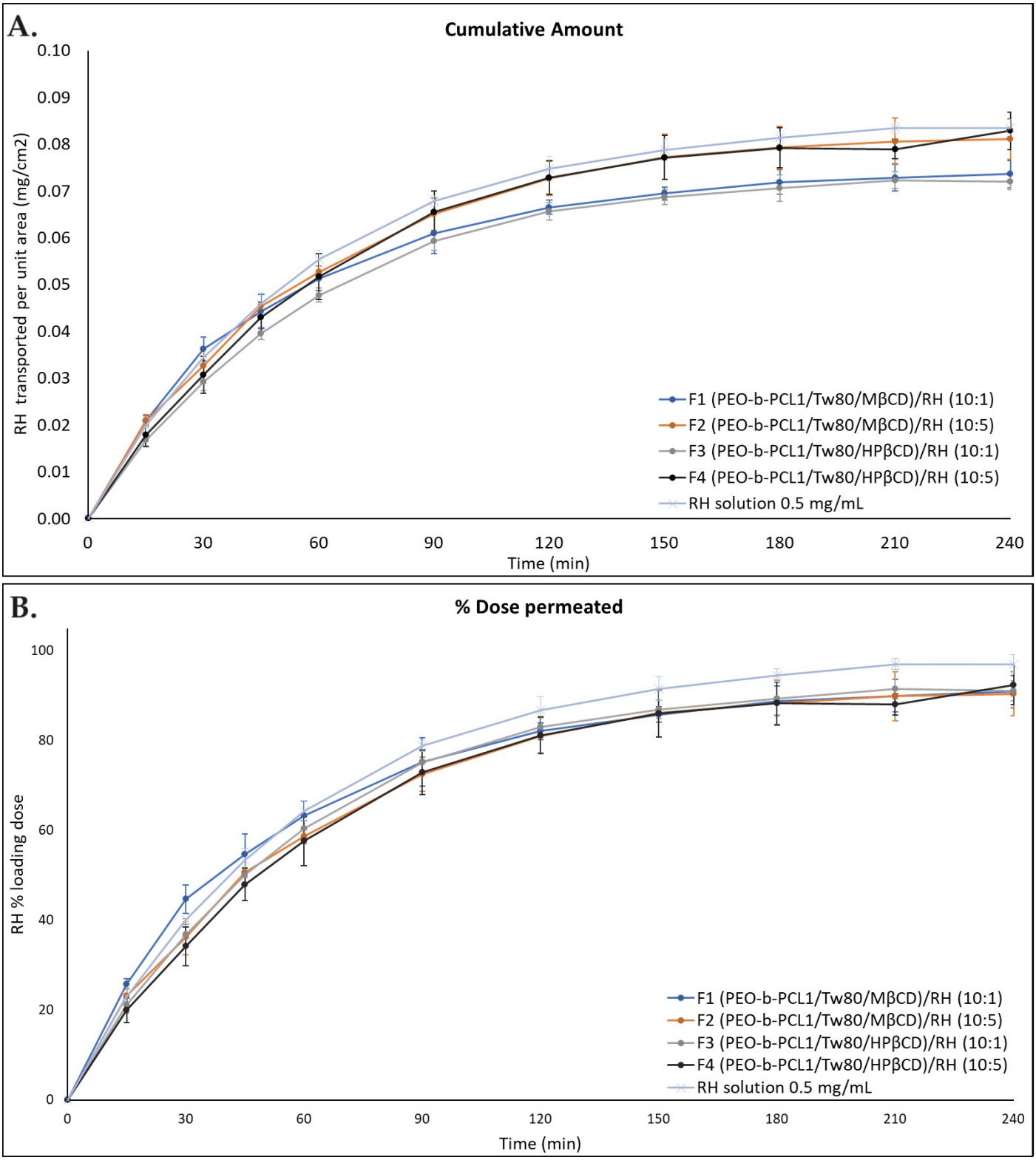

Figure S6. Permeation profiles through regenerated cellulose membranes for the colloidal dispersion of RH-loaded PEO-b-PCL_1 hybrid systems at the weight ratios of 10:1 and 10:5 at the buffer solution pH=5.6, compared to the RH solution (0.5 mg/mL, pH=5.6) expressed as **A.** quantity permeated per unit area (mean ± SD, n=3) and **B.** % loading dose permeated for the tested formulation (mean ± SD, n=3).

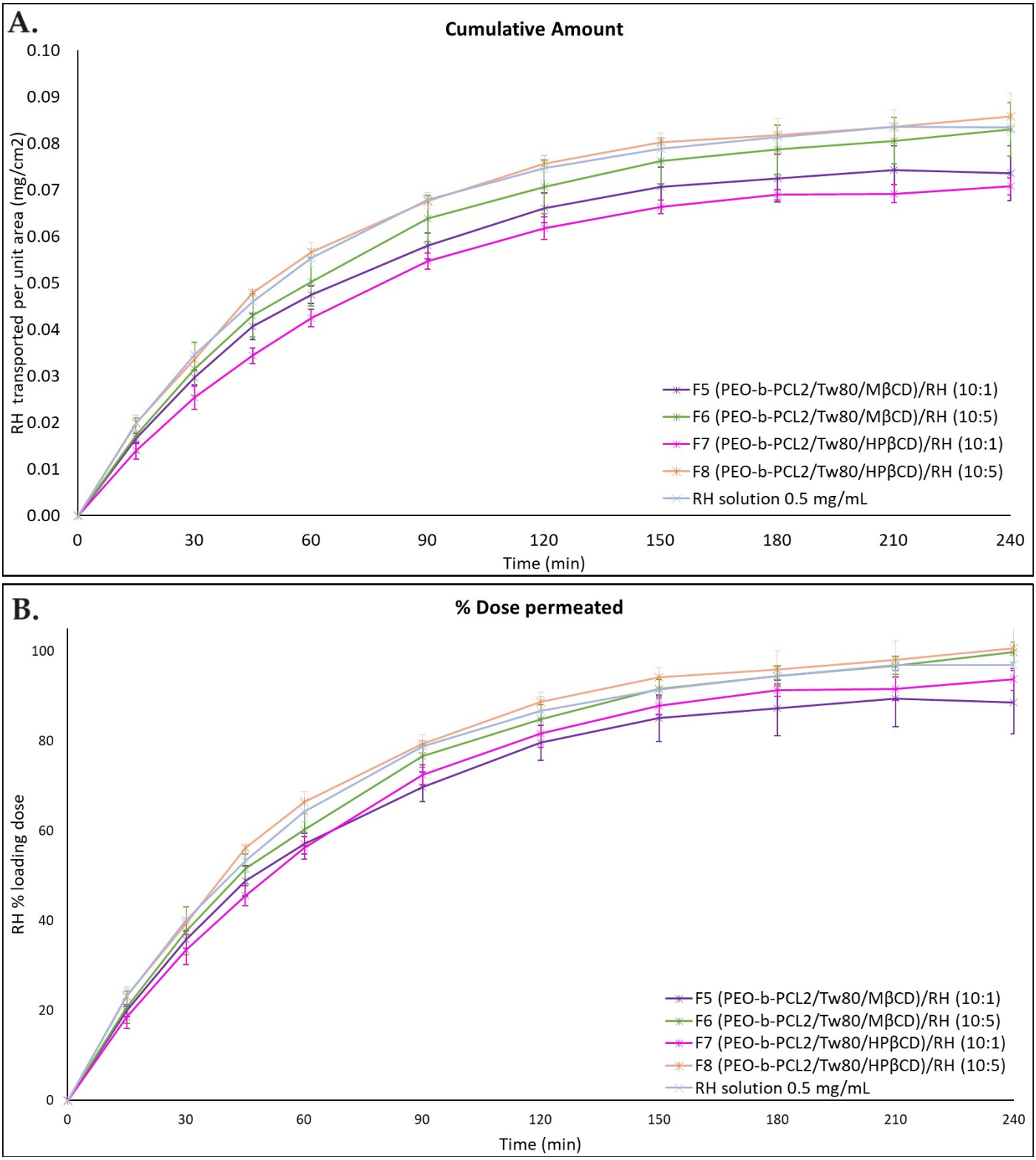

Figure S7. Permeation profiles through regenerated cellulose membranes for the colloidal dispersion of RH-loaded PEO-b-PCL_2 hybrid systems at the weight ratios of 10:1 and 10:5 at the buffer solution pH=5.6, compared to the RH solution (0.5 mg/mL, pH=5.6) expressed as **A.** quantity permeated per unit area (mean ± SD, n=3) and **B.** % loading dose permeated for the tested formulation (mean ± SD, n=3).

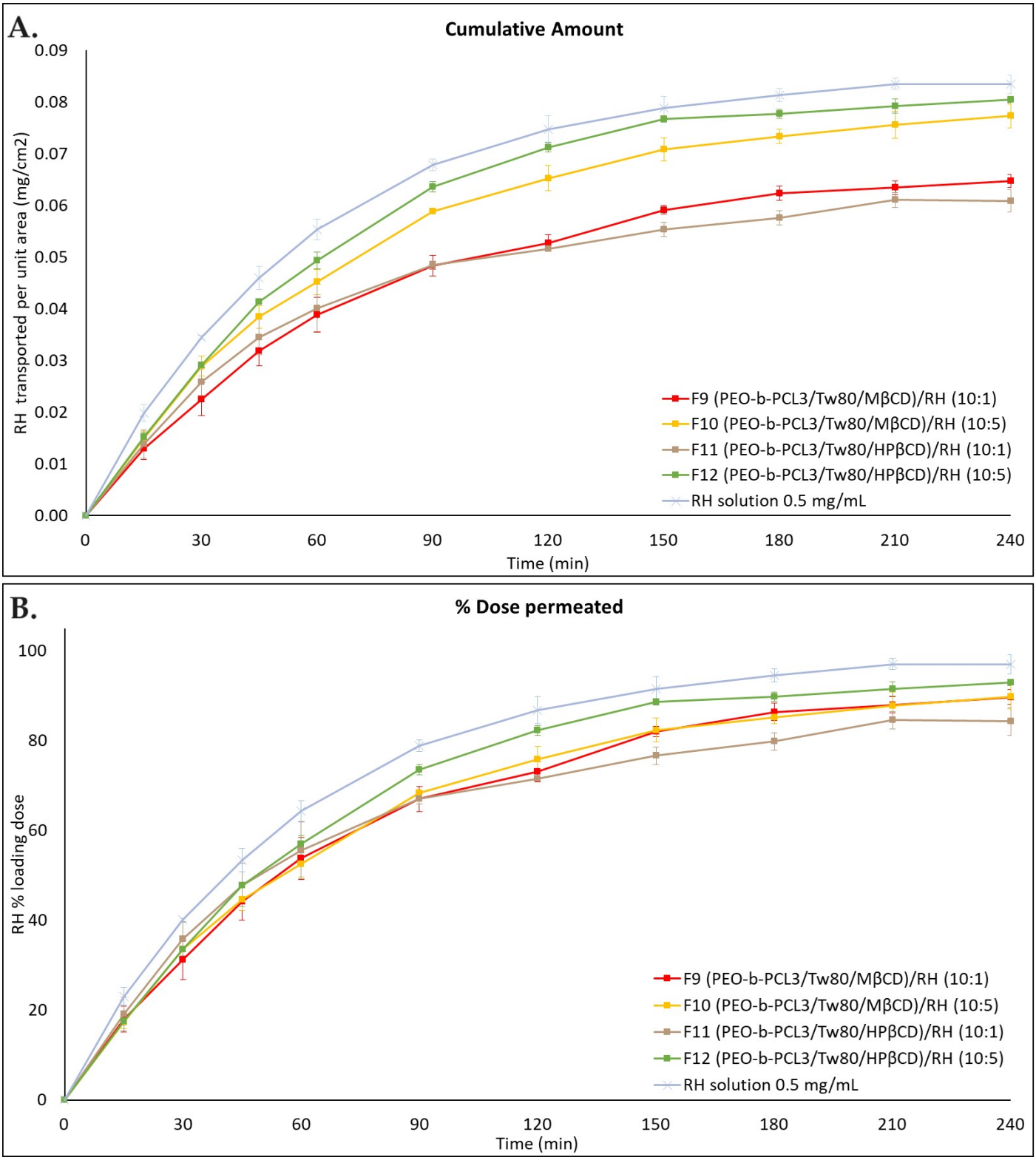

Figure S8. Permeation profiles through regenerated cellulose membranes for the colloidal dispersion of RH-loaded PEO-b-PCL_3 hybrid systems at the weight ratios of 10:1 and 10:5 at the buffer solution pH=5.6, compared to the RH solution (0.5 mg/mL, pH=5.6) expressed as **A.** quantity permeated per unit area (mean ± SD, n=3) and **B.** % loading dose permeated for the tested formulation (mean ± SD, n=3).