Supplementary materials

A Novel Drug-Drug Coamorphous System without Molecular Interactions: Improve the Physicochemical Properties of Tadalafil and Repaglinide

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Fig. S1

Fig. S2

Fig. S3
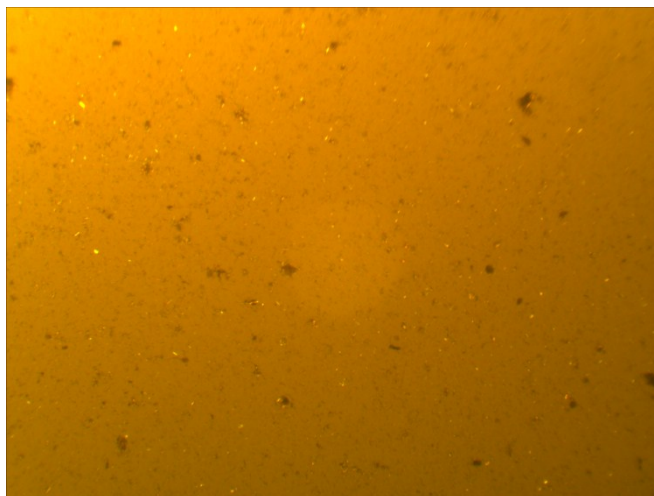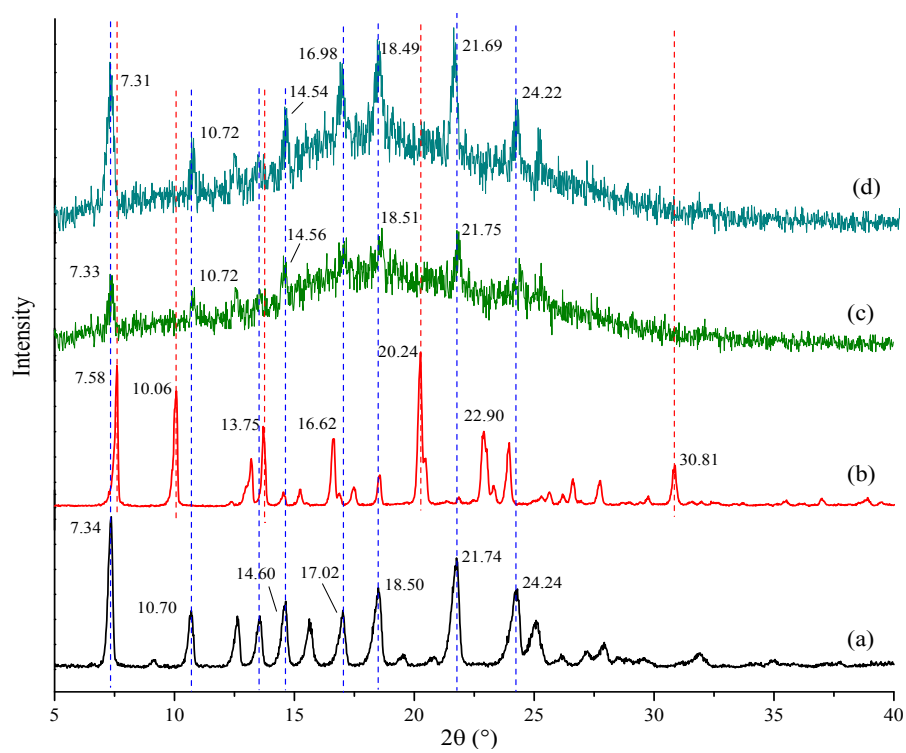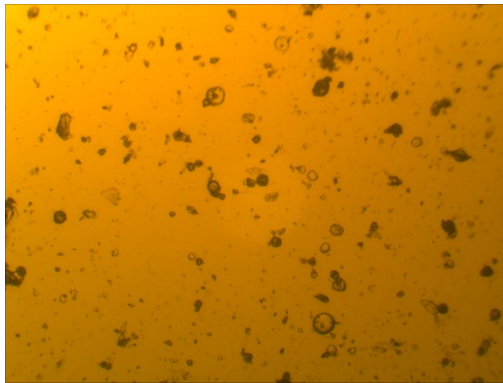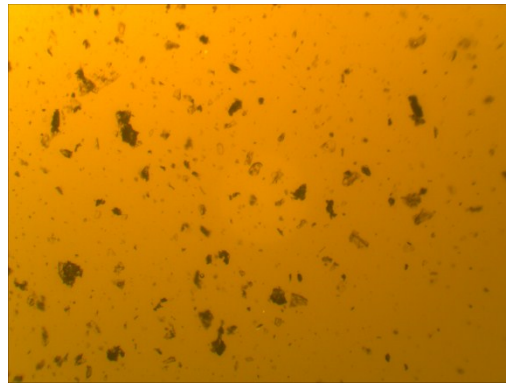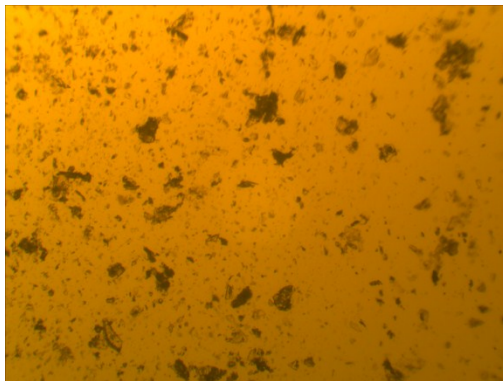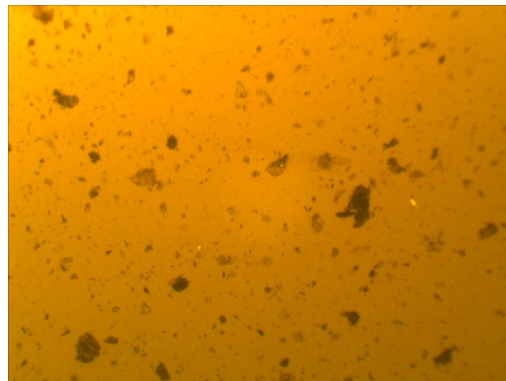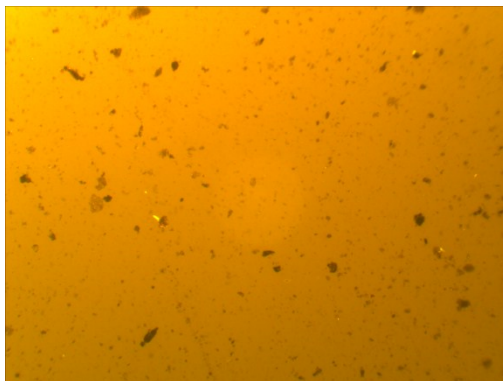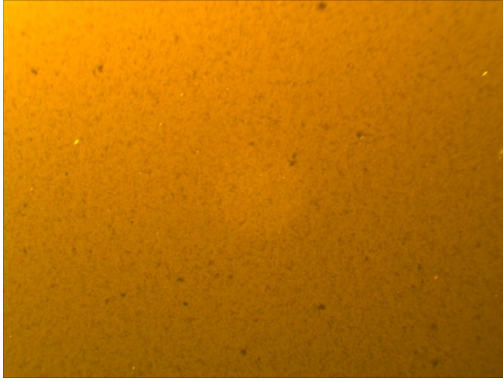

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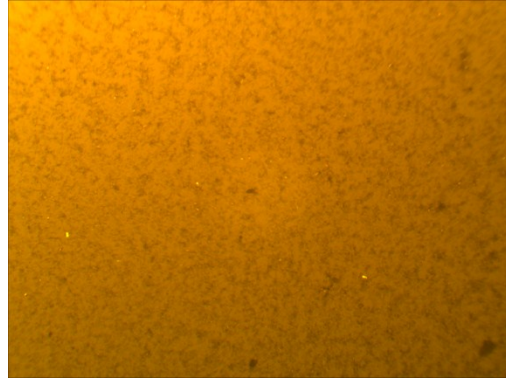60 min
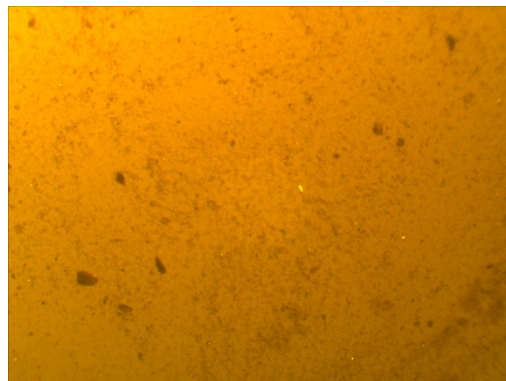
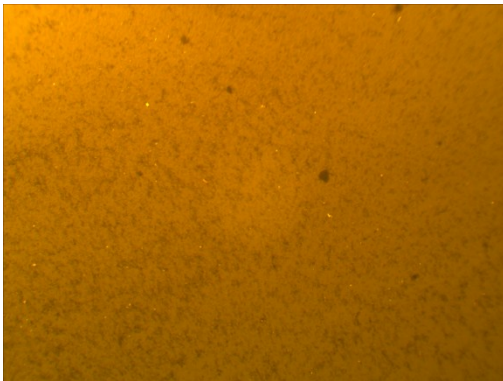120 min

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Table S1 Calculation of HSPs and molar volume for tadalafil according to the Hoftyzer-Van Krevelen method.

Group	Frequency	F_{d_i} (J$^{1/2}$ cm$^{3/2}$ mol^{-1})	F_{p_i} (J$^{1/2}$ cm$^{3/2}$ mol^{-1})	$F_{p_i}^2$	E_{h_i} (J/mol)	V_m (cm^3/mol)
CH3	1	420	0	0	0	33.5
-CH$_2$-	3	810	0	0	0	48.3
>CH-	2	160	0	0	0	-2
=CH-	3	600	0	0	0	40.5
=C<	5	350	0	0	0	-27.5
Phenylene (O, M, P)	1	1270	110	12100	0	52.4
-O-	2	200	800	640000	6000	7.6
-CO-	2	580	1540	2371600	4000	21.6
-NH-	1	160	210	44100	3100	4.5
>N-	2	40	1600	2560000	10000	-18
Ring closure 5 or more atoms	3	570	0	0	0	48
Ring closure 3 or 4 atoms	2	380				36
Conjugation in ring for each double bond	4					-8.8
Total		5160		5627800	23100	236.1

$$\delta_d = \frac{\sum_i F_{d_i}}{\sum_i V_i} \qquad 21.86 \; MP_a^{0.5}$$

$$\delta_p = \frac{\left(\sum_i F_{p_i}^2\right)^{0.5}}{\sum_i V_i} \qquad 10.05 \; MP_a^{0.5}$$

$$\delta_h = \left(\frac{\sum_i F_{h_i}}{\sum_i V_i}\right)^{0.5} \qquad 9.89 \; MP_a^{0.5}$$

$$\delta_t = \left(\delta_d^2 + \delta_p^2 + \delta_h^2\right)^{0.5} \qquad 26.01 \; MP_a^{0.5}$$

Table S2 Calculation of HSPs and molar volume for repaglinide according to the Hoftyzer-Van Krevelen method.

Group	Frequency	F_{d_i} (J$^{1/2}$ cm$^{3/2}$ mol^{-1})	F_{p_i} (J$^{1/2}$ cm$^{3/2}$ mol^{-1})	$F_{p_i}^2$	E_{h_i} (J/mol)	V_m (cm^3/mol)
-CH$_3$	3	1260	0	0	0	100.5
-CH$_2$-	8	2160	0	0	0	128.8
>CH-	2	160	0	0	0	-2
=CH-	3	600	0	0	0	40.5
=C<	3	210	0	0	0	-16.5
Phenylene (O, M, P)	1	1270	110	12100	0	52.4
-O-	1	100	400	160000	3000	3.8
-CO-	2	580	1540	2371600	4000	21.6
-NH-	1	160	210	44100	3100	4.5
-N<	1	20	800	640000	5000	-9
OH	1	210	0	0	0	48
Ring closure 5 or more atoms	3	570	0	0	0	48
Conjugation in ring for each double bond	4					-8.8
Total		7300		3477800	35100	373.8

$$\delta_d = \frac{\sum_i F_{d_i}}{\sum_i V_i} \qquad 19.53 \; MP_a^{0.5}$$

$$\delta_p = \frac{\left(\sum_i F_{p_i}^2\right)^{0.5}}{\sum_i V_i} \qquad 4.99 \; MP_a^{0.5}$$

$$\delta_h = \left(\frac{\sum_i F_{h_i}}{\sum_i V_i}\right)^{0.5} \qquad 9.69 \; MP_a^{0.5}$$

$$\delta_t = \left(\delta_d^2 + \delta_p^2 + \delta_h^2\right)^{0.5} \qquad 22.36 \; MP_a^{0.5}$$

Table S3 Resonance assignments of chemical shifts in Ss ^{13}C NMR spectra of tadalafil in crystalline, amorphous, amorphous

physical mixture and coamorphous system

Carbon Number	Chemical shift (ppm)			
	Crystalline tadalafil	Amorphous tadalafil	Amorphous physical mixture	Coamorphous system
29	167.74	167.06	167.45	167.45
27	164.70			
5	148.19	147.08	147.05	147.08
4	146.67			
15, 17	139.09	136.59	136.59	136.59
7	135.38	134.02	133.03	133.63
18	126.62	126.11	126.05	126.31
20	122.75	119.58	120.17	120.37
9	119.21			
21	118.03			
19	116.01			
22	115.84			
8	110.78	110.68	110.88	111.08
6	107.92	107.12	107.12	107.12
14	105.73			
2	101.35	100.79	100.39	100.98
10, 12	56.86	56.08	55.29	55.69
24	50.29	51.73	51.93	52.13
28	32.42	32.74	32.54	32.94
13	24.50	23.64	24.83	25.22

Table S4 Resonance assignments of chemical shifts in Ss ^{13}C NMR spectra of repaglinide in crystalline, amorphous, amorphous physical mixture and coamorphous system

Carbon Number	Chemical shift (ppm)			
	Crystalline repaglinide	Amorphous repaglinide	Amorphous physical mixture	Coamorphous system
15	169.60	170.59	170.22	170.03
31	167.30			
23	159.29	157.88	157.76	157.76
7	152.62	152.35	152.22	152.23
21	143.64	142.13	141.54	141.74
25	136.84	132.96	133.03	133.63
9	134.90			
8	130.29			
11	126.65	127.24	126.50	126.31
10	125.44	124.63	-	-
26	122.04	121.54	-	-
24	119.25			
12	116.70	115.68	-	-
22	114.88			
29	61.74	65.64	65.58	65.18
2, 6	58.47	55.01	55.29	55.69
13	52.76			
20	47.91	46.18	45.99	45.79
17	44.99			
3, 5	26.56	25.27	24.83	25.22
4, 18	24.25			
19, 27	19.52			
30	13.94	14.73	14.35	14.15

Table S5 Area under the curve (AUC, μg·min·ml^{-1}) of tadalafil and repaglinide in dissolution of crystalline, physical mixture and coamorphous system

Drug	System	Water	PBS 6.8
Tadalafil	Crystalline	1188.28	1278.08
	Physical mixture	1246.57	1364.22
	Coamorphous system	2377.51	1826.72
Repaglinide	Crystalline	2730.97	9736.38
	Physical mixture	2601.45	8174.68
	Coamorphous system	7678.31	37064.96

Protocol of Principal component analysis (PCA) by SPSS

(1) Open the SPSS software and import the original data (i.e. wavenumber-transmittance for FTIR original data).

(2) Open the "Factor analysis" module: Analysis-Dimensionality reduction-Factor analysis.

(3) Open the "Factor analysis" interface and put the original variables that need to participate in the analysis into the "Variables" box.

(4) Click "Descriptives" button, open the "Factor analysis: Descriptives" dialog box: choose "KMO and Bartlett's test of sphericity" in the "Correlation Matrix" module, click "Continue" button.

(5) Click "Extraction" button, open the "Factor analysis: Extraction" dialog box: choose "Principal components" in the "Method" module and set the "Eigenvalues" in the "Extract" module according to your demand, click "Continue" button.

(6) The values of parameters on other modules such as "Scores" and "Options" are default and you can adjust them to satisfy your analysis requirement.

(7) After parameters are set, click "OK" button in the "Factor analysis" interface to perform factor analysis. The principal components (PCs) of original data are extracted and listed in the table of "Total Variance Explained".

(8) Two principal components (PCs) are chosen to plot using the eigenvalues of the selected PCs, which could explain 95% of the variance in the original data.

(9) The score plot of the PCA analysis is obtained.