Supporting Information

Mechanistic study on the formation of Arbutin polymorphs and solvates

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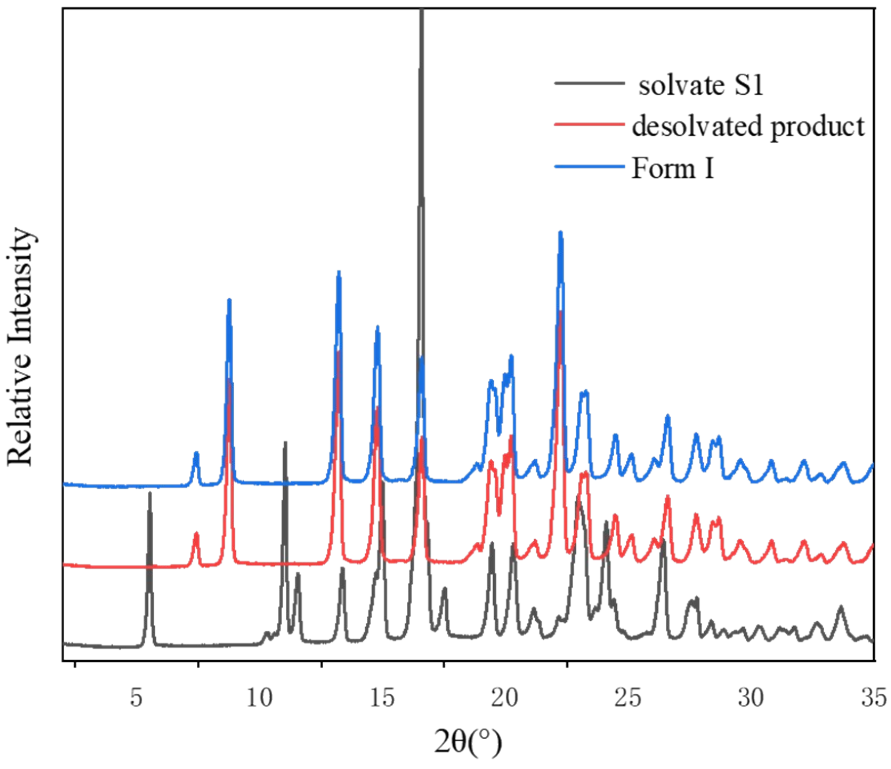
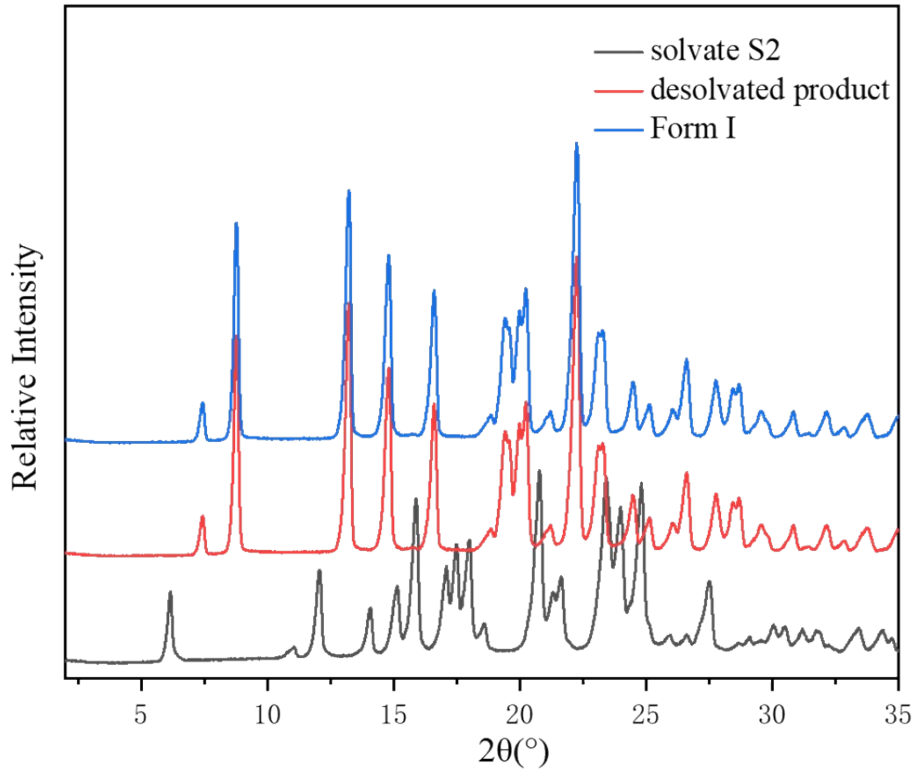
TableS1. Solvents used for screening and the results of obtained crystal forms

Solvent	Results
methanol	Form I
ethanol	Form I
n-propanol	Form I
isopropanol	Form I
sec-Butanol	Form I
isobutanol	Form I
glycol	Form I
n-Pentanol	Form I
Acetone	Form I
2-butanone	Form I
Acetonitrile	Form I
methyl acetate	Form I
ethyl acetate	Form I

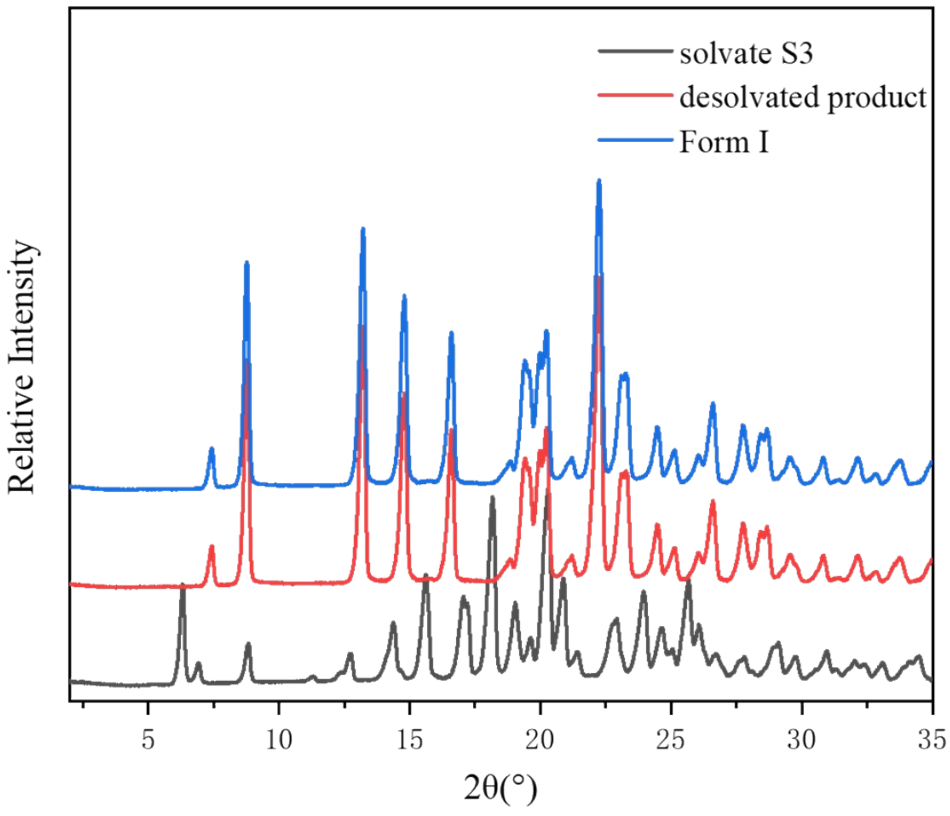
butyl acetate	Form I
1,4-dioxane	Form I
dichloromethane	Form I
trichloromethane	Form I
pyridine	Form I
tetrahydrofuran	Form I
formamide	Form I
DMSO	-
DMF	Solvate
DMA	Solvate
NMP	Solvate
Water	Solvate
NMP + methanol	Solvate



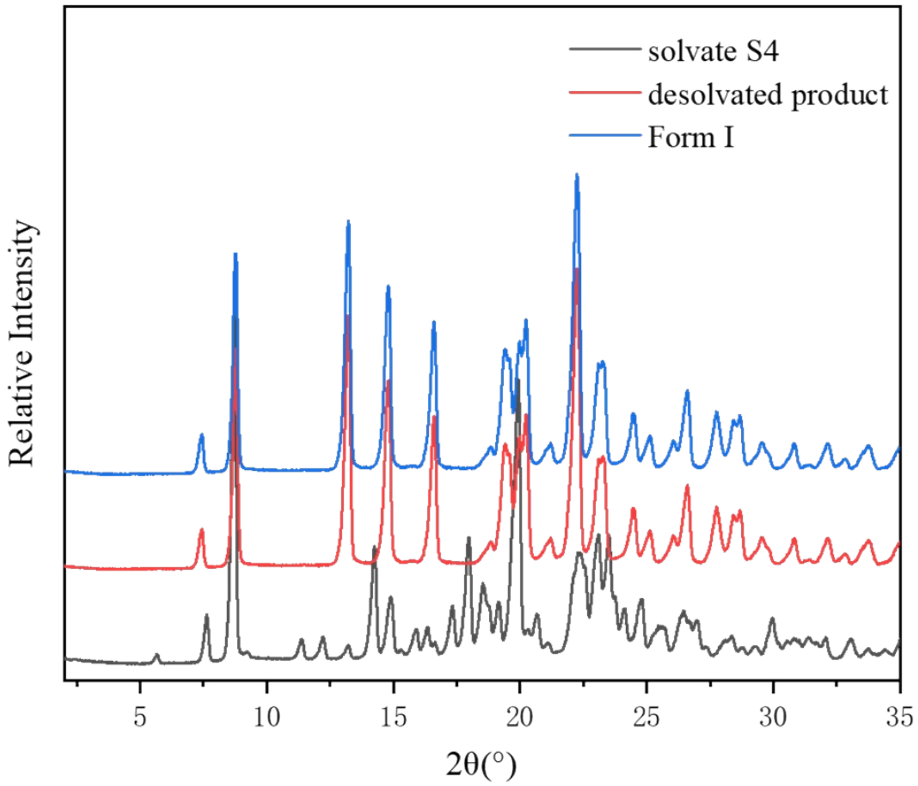
(a)


solvate S2
desolvated product
Form I
Relative Intensity
5
10
15
20
25
30
35
2θ(°)

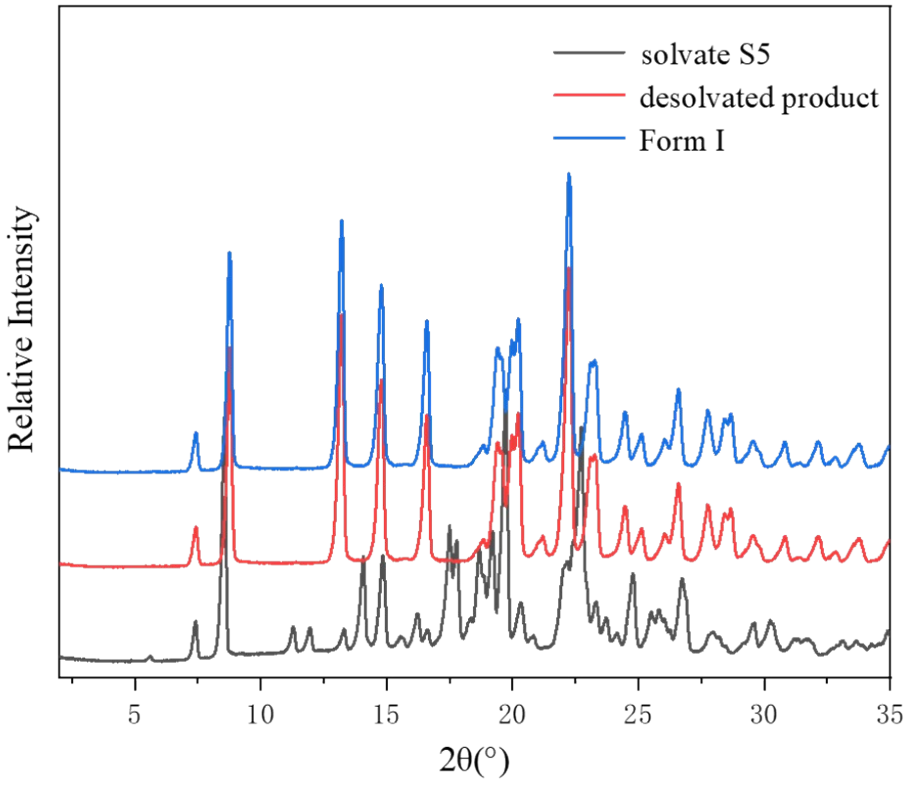
(b)


solvate S3
desolvated product
Form I
Relative Intensity
5
10
15
20
25
30
35
2θ(°)

(c)


solvate S4
desolvated product
Form I
Relative Intensity
5
10
15
20
25
30
35
2θ(°)

(d)


solvate S5
desolvated product
Form I
Relative Intensity
5
10
15
20
25
30
35
2θ(°)

(e)

Figure S1. Comparison of desolvated products, (a) solvate S1, (b) solvate S2, (c) solvate S3, (d) solvate S4, (e) solvate S5.

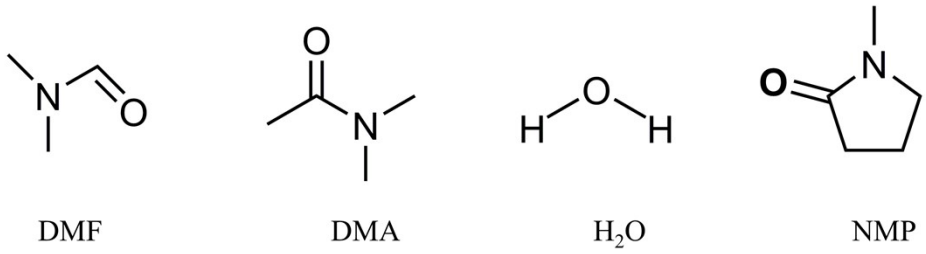


Figure S2. Molecular structures of the solvents.

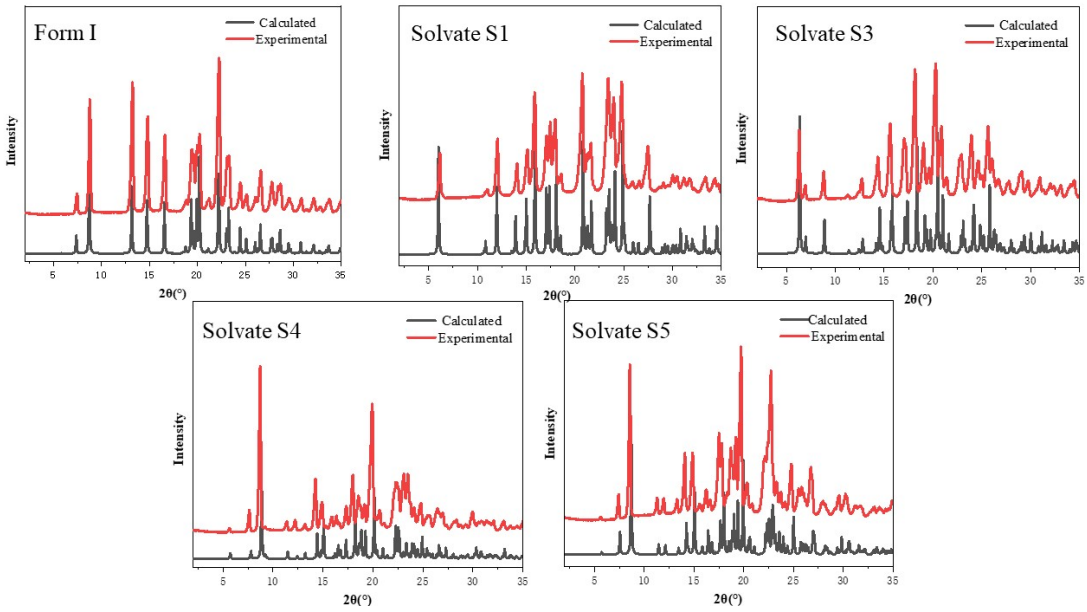


Figure S3. The calculated and experimented PXRD of arbuin different solid forms.

Table S2. Torsion Angles (τ, deg) for Various Conformers of ARB (τ_1

$(C_4O_2C_7C_{11})$, $\tau_2(C_4O_2C_7O_3)$, $\tau_3(O_3C_8C_{12}O_4)$, $\tau_4(O_1C_1C_2C_3)$, $\tau_5(O_1C_1C_6C_5)$)

	Form I(A)	Form I(B)	Form I(C)	Form I(D)	solvate S1(E)	solvate S3(F)	solvate S3(G)	solvate S4(H)	solvate S4(I)	solvate S5(J)	solvate S5(K)
τ_1	150.61	155.94	156.80	150.45	157.04	152.18	148.54	166.36	168.61	161.67	170.23
τ_2	-90.13	-84.77	-84.52	-90.76	-85.05	-89.67	-94.23	-77.53	-73.65	-81.85	-72.53
τ_3	-68.54	-66.18	-66.01	-70.05	58.47	-60.16	-63.58	-61.34	-68.38	-63.47	-68.53
τ_4	179.19	178.46	-179.37	178.19	178.49	179.02	177.84	-178.63	-176.87	-179.10	-177.40
τ_5	-178.11	-177.27	-179.16	-176.88	-177.98	-177.64	-176.69	179.23	177.91	179.95	178.23

Table S3. Hydrogen bonds in crystal structures of various solid forms of arbutin.

	D-H…A	D-H	H…A	D…A	D-H…A	Symmetric code
Form I	O1-H1…O6A	0.82	1.931	2.711	158.66	x-1, y+1, z
	O4-H4…O5	0.82	2.109	2.827	146.11	x, y+1, z
	O5-H5…O4A	0.82	1.92	2.739	175.97	-x+1, y-1/2, -z+1
	O6-H6…O1A	0.82	1.899	2.715	173.75	
	O7-H7…O7B	0.82	1.967	2.749	159.1	x, y-1, z
	C3-H3…O3	0.93	2.625	3.119	113.81	
	O1A-H1A…O6	0.82	2.044	2.771	147.65	x, y+1, z
	O4A-H4A…O5A	0.82	2.042	2.773	148.31	x, y+1, z
	O5A-H5AA…O4	0.82	1.904	2.71	167.47	-x+1, y-1/2, -z+1
	O6A-H6AA…O1	0.82	2.01	2.815	167.04	x+1, y, z
	O7A-H7AA…O7D	0.82	2.009	2.768	153.71	-x+1, y-1/2, -z
	O1B-H1B…O6D	0.82	1.925	2.727	165.75	-x+1, y+3/2, -z
	O4B-H4B…O5B	0.82	2.11	2.854	150.76	x, y+1, z
	O5B-H5B…O4B	0.82	1.92	2.736	174.02	-x, y-1/2, -z
	O6B-H6B…O1D	0.82	2.027	2.814	160.72	-x, y-1/2, -z
	O7B-H7B… O7	0.82	2.119	2.764	135.44	
	C2B-H2B…O4D	0.93	2.654	3.546	161	
	C3B-H3B…O3B	0.93	2.605	3.109	114.54	
	O1D-H1D…O6B	0.82	1.921	2.722	165.15	-x, y-1/2, -z
	O4D-H4D…O5D	0.82	2.045	2.759	145.27	x, y+1, z
	O5D-H5D…O4D	0.82	1.904	2.72	173.74	-x+1, y-1/2, -z
	O6D-H6D…O1B	0.82	2.009	2.817	168.67	-x+1, y-1/2, -z
	O7D-H7D…O7A	0.82	2.321	2.767	114.72	-x+1, y-1/2, -z
Solvate S1	O1-H1…O9	0.84	1.815	2.637	165.67	x-1, y-1, z
	O4-H4…O8	0.84	1.952	2.771	164.79	
	O5-H5…O7	0.84	1.896	2.718	165.69	-x, y+1/2, -z-1
	O6-H6…O4	0.84	1.956	2.784	168.09	x+1, y, z
	O7-H7…O8	0.84	1.82	2.653	171.41	x+1, y, z
	C3-H3…O3	0.95	2.47	3.051	119.42	
	C7-H7A…O6	1	2.595	3.461	144.86	-x, y-1/2, -z-1
	C10-H10…O6	1	2.624	3.482	143.96	-x, y-1/2, -z-1
	C15-H15B…O1	0.98	2.495	3.457	166.72	-x-2, y+1/2, -z-2
	C16-H16…O5	0.95	2.427	3.367	170.14	-x, y+1/2, -z-1

	C17-H17B…O2	0.98	2.497	3.443	162.23	
Solvate S3	O1-H1…O8^a	0.82	1.971	2.786	171.97	-x, y-1/2, -z+3/2
	O1-H1…O9^b	0.82	1.725	2.538	170.56	-x, y-1/2, -z+3/2
	O4-H4…O3A	0.82	1.946	2.766	176.94	
	O5-H5…O6A	0.82	1.989	2.804	172.2	x+1/2, -y+3/2, -z+1
	O6-H6…O5	0.82	1.91	2.718	168.63	x-1/2, -y+1/2, -z+1
	O7-H7…O6	0.82	1.938	2.752	171.36	x-1/2, -y+1/2, -z+1
	C2-H2…O8^a	0.93	2.62	3.305	130.85	-x, y-1/2, -z+3/2
	C3-H3…O3	0.93	2.565	3.126	119.2	
	C7-H7A…O1A	0.98	2.501	3.398	152.1	-x+1, y-1/2, -z+3/2
	C12-H12B…O2	0.97	2.559	3.184	122.18	x+1, y, z
	O1A-H1A…O10	0.82	2.003	2.78	157.88	-x+1, y-1/2, -z+3/2
	O4A-H4A…O3	0.82	2.046	2.861	172.48	
	O5A-H5AA…O4	0.82	1.881	2.678	163.94	x-1/2, -y+3/2, -z+1
	O6A-H6AA…O4A	0.82	1.99	2.804	172.07	x+1/2, -y+3/2, -z+1
	O7A-H7AA…O5A	0.82	1.969	2.785	173.47	x+1, y, z
	C7A-H7AB…O1	0.98	2.52	3.43	154.32	-x, y+1/2, -z+3/2
	C12A-H12D…O2A	0.97	2.545	3.152	120.69	x-1, y, z
	O10-H10B…O7A	0.85	1.944	2.741	155.52	
	O10-H10C…O8^a	0.85	2.019	2.862	171.5	x+1, y, z
	O10-H10C…O9^b	0.85	2.059	2.902	171.79	x+1, y, z
Solvate S4	O1-H1…O4A	0.84	1.936	2.757	165.52	-x+3/2, -y+1, z+1/2
	O4-H4…O7A	0.848	1.898	2.737	169.7	x-1, y, z
	O5-H5…O6A	0.847	2.109	2.869	149.12	x-1, y, z
	O5-H5…O7A	0.847	2.403	3.063	135.12	x-1, y, z
	O6-H6…O8	0.84	1.882	2.635	148.45	-x+1/2, -y+1, z-1/2
	O7-H7…O5	0.851	2.001	2.764	148.96	x+1, y, z
	C2-H2…O7	0.95	2.641	3.482	147.74	x-1/2, -y+3/2, -z+1
	C6-H6A…O4A	0.95	2.416	3.132	131.94	-x+3/2, -y+1, z+1/2
	C9-H9…O7A	1	2.565	3.212	122.23	x-1, y, z
	C10-H10…O1	1	2.542	3.529	169.05	x-1/2, -y+3/2, -z+1
	O1A-H1A…O4	0.84	1.922	2.756	171.84	x+1/2, -y+1/2, -z+1
	O4A-H4A…O7	0.84	1.898	2.73	170.53	-x+1, y-1/2, -z+1/2
	O5A-H5AA…O8	0.84	1.944	2.737	156.94	-x+1/2, -y+1, z-1/2
	O6A-H6AA…O6	0.84	1.901	2.731	169.58	
	O7A-H7AA…O5A	0.84	1.884	2.667	154.48	x+1, y, z
	C2A-H2A…O4	0.95	2.494	3.205	131.68	x+1/2, -y+1/2, -z+1
	C3A-H3A…O3A	0.95	2.419	3.013	120.38	
	C11A-H11A…O5A	1	2.629	3.142	111.89	x+1, y, z
Solvate S5	O1-H1…O4A	0.84	1.938	2.752	162.99	x+1/2, -y+1/2, -z+1
	O4-H4…O7A	0.84	1.94	2.769	168.72	-x+1, y-1/2, -z+1/2
	O5-H5…O8^a	0.84	1.838	2.63	156.57	
	O5-H5…O8A^b	0.84	2.15	2.924	153.16	
	O6-H6…O6A	0.84	1.885	2.723	175.53	
	O7-H7…O5	0.84	1.865	2.662	157.8	x+1, y, z
	C2-H2…O4A	0.95	2.45	3.17	132.47	x+1/2, -y+1/2, -z+1
	C3-H3…O3	0.95	2.442	3.038	120.62	
	C11-H11…O5	1	2.606	3.124	112.19	x+1, y, z
	O1A-H1A…O4	0.84	1.926	2.755	168.96	-x+3/2, -y+1, z+1/2
	O4A-H4A…O7	0.84	1.933	2.756	166.1	x-1, y, z
	O5A-H5AA…O6	0.851	2.157	2.889	144.1	x-1, y, z

	O5A-H5AA…O7	0.851	2.301	2.999	139.45	x-1, y, z
	O6A-H6AA…O8^a	0.84	1.938	2.674	145.73	
	O6A-H6AA…O8A^b	0.84	1.823	2.604	153.78	
	O7A-H7AA…O5A	0.845	1.982	2.793	160.44	x+1, y, z
	C2A-H2A…O7A	0.95	2.528	3.329	142.05	x-1/2, -y+3/2, -z+1
	C6A-H6AB…O4	0.95	2.464	3.167	130.79	-x+3/2, -y+1, z+1/2
	C9A-H9A…O7	1	2.532	3.174	121.69	x-1, y, z
	C10A-H10A…O1A	1	2.599	3.595	173.9	x-1/2, -y+3/2, -z+1
	C17^a-H17A^a…O5A	0.98	2.607	3.253	123.63	
	C15A^b-H15C^b..O5A	0.99	2.635	3.429	137.34	

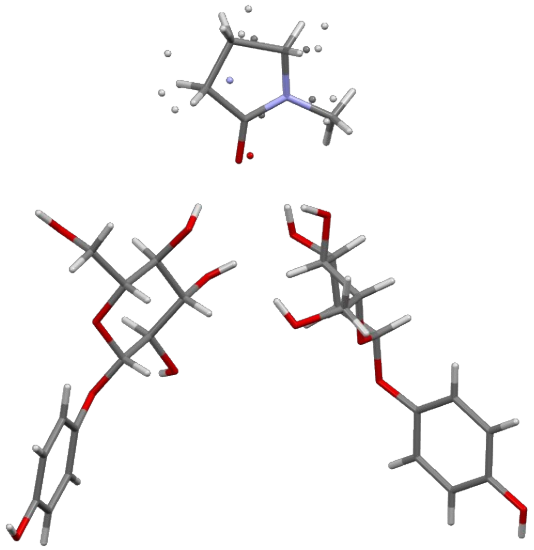


Figure S4. The disorder packing arrangements of solvate S5

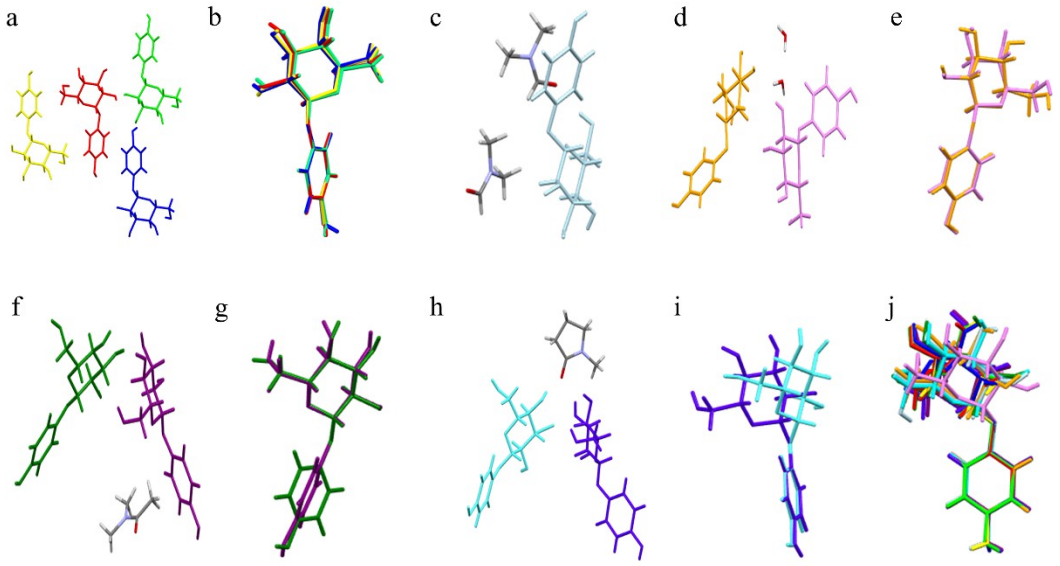


Figure S5. a) asymmetric unit of Form I, b) overlay diagram of different conformers in Form I, c) asymmetric unit of Solvate S1, d) asymmetric unit of Solvate S3, e) overlay diagram of different conformers in Solvate S3, f) asymmetric unit of Solvate S4, g) overlay diagram of different conformers in Solvate S4, h) asymmetric unit of Solvate S5, i) overlay diagram of different conformers in Solvate S5, j) overlay diagram of different conformers of all different solid forms of arbutin.

	Form I.cif 0	solvate S1.cif 1	solvate S3.cif 2	solvate S4.cif 3	solvate S5.cif 4
0: Form I.cif	0.0000	38.6960	37.1419	32.4862	33.6135
1: solvate S1.cif	38.6960	0.0000	33.4074	37.2288	36.1969
2: solvate S3.cif	37.1419	33.4074	0.0000	28.8572	27.2125
3: solvate S4.cif	32.4862	37.2288	28.8572	0.0000	0.3125
4: solvate S5.cif	33.6135	36.1969	27.2125	0.3125	0.0000

Figure S6. The three-dimensional stacking similarity index of arbutin solid

forms.

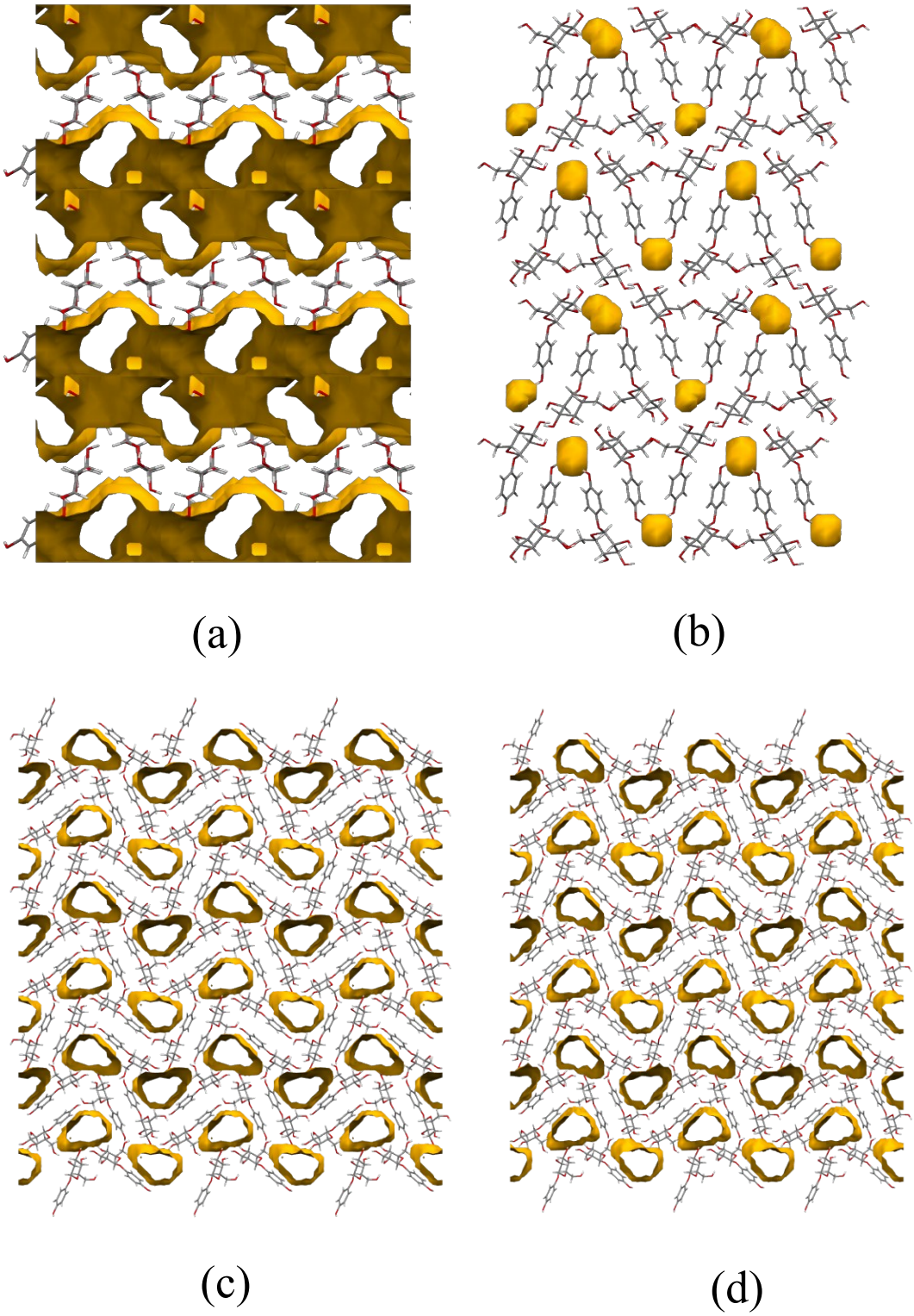


Figure S7. Void maps in the crystal structures of solvates: (a) Solvate S1, (b) Solvate S3, (c) Solvate S4, and (d) Solvate S5

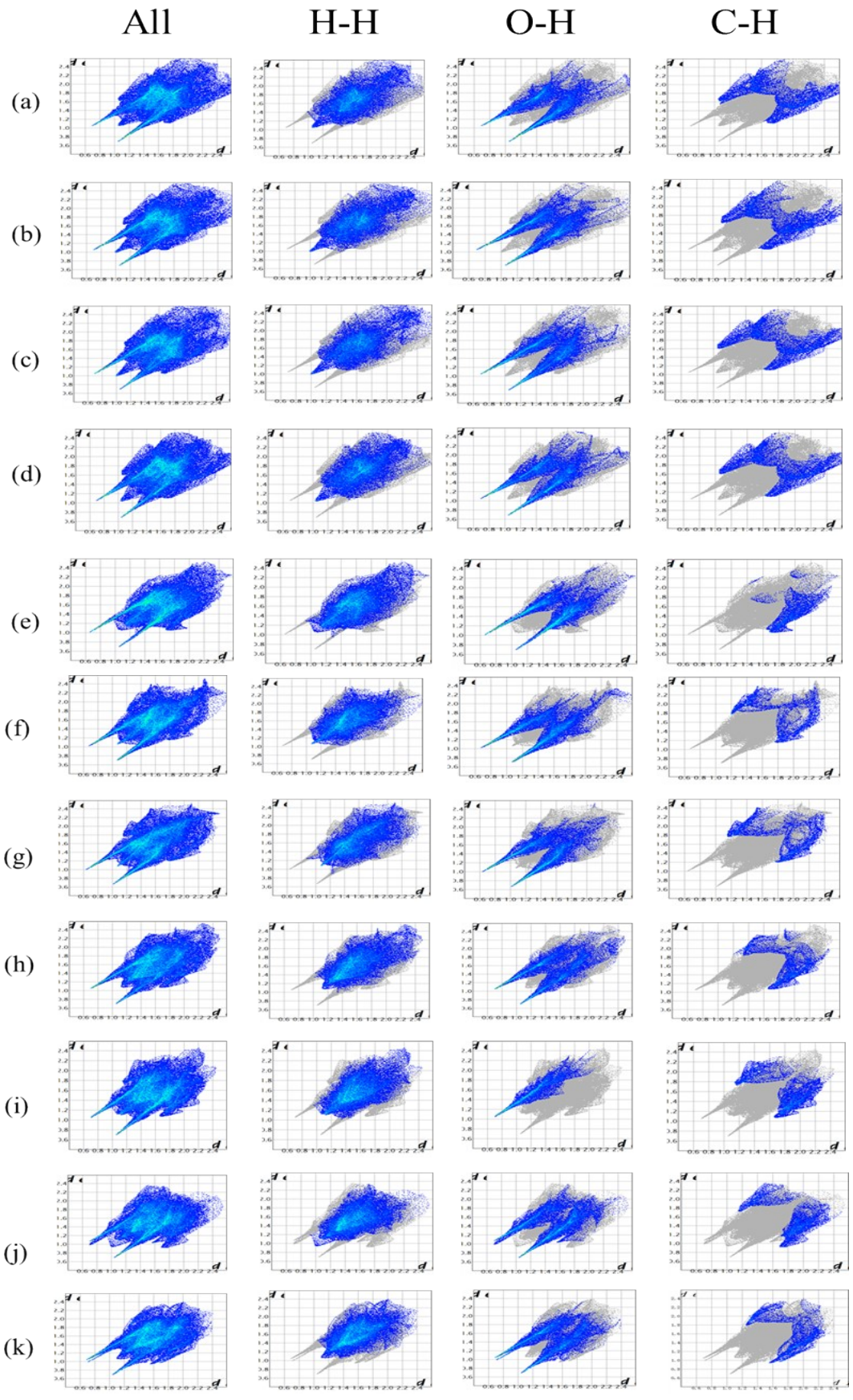


Figure S8. 2D fingerprint plots of arbutin in: (a)Form I(A), (b) Form I(B),

(c) Form I(C), (d) Form I(D), (e) solvate S1(E), (f) solvate S3(F), (g) solvate S3(G), (h) solvate S4(H), (i) solvate S4(I), (j) solvate S5(J), and (k) solvate S5(K).

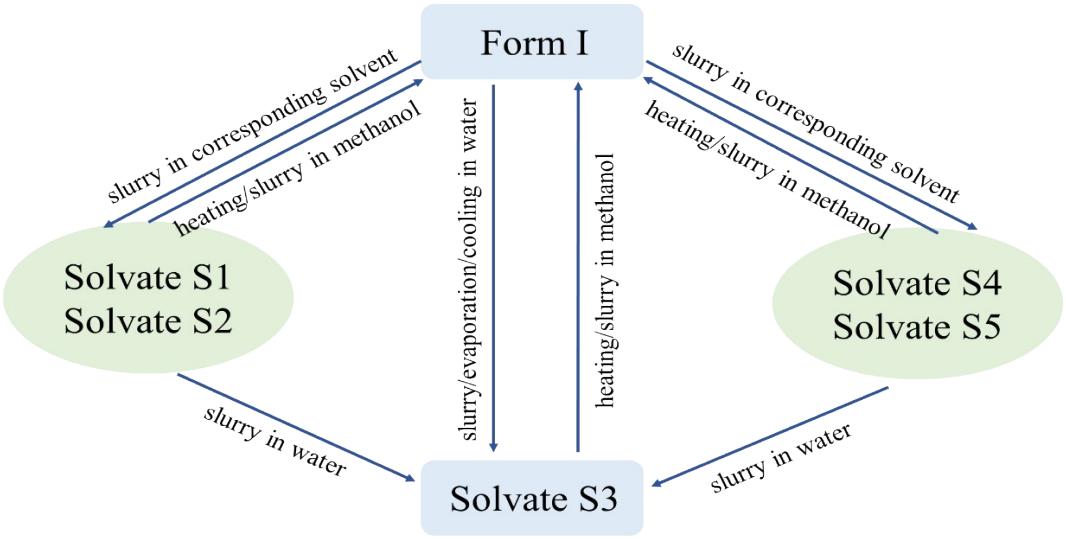


Figure S9. Interconversion between different solid forms of arbutin.

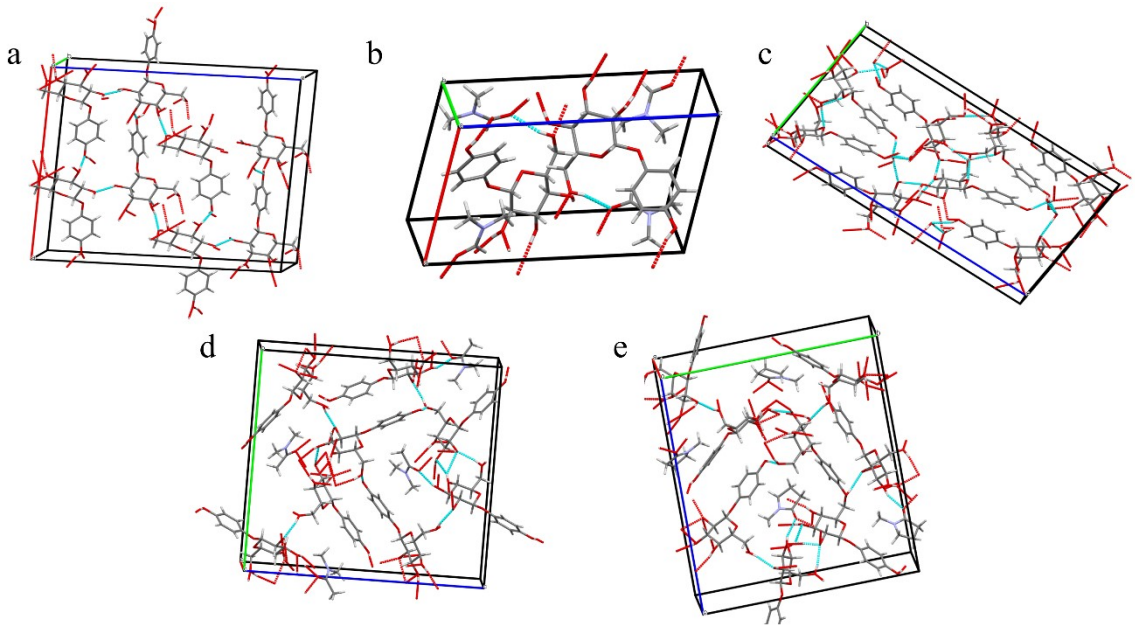


Figure S10. Hydrogen bond interactions in the cell of (a)Form I, (b) solvate S1, (c) solvate S3, (d) solvate S4, (e) solvate S5

Table S4. Contacts lists in the unit cell

	Atom 1	Atom 2	Length	Length-VsW
Form I	O5	H4	2.109	-0.611
	O1	H6AA	2.010	-0.710
	H1	O6A	1.931	-0.789
	O6	H1A	2.044	-0.676
	H6	O1A	1.899	-0.821
	H5	O4A	1.920	-0.800
	O4	H5AA	1.903	-0.817
	H7	O7B	1.967	-0.753
	O7	H7B	2.119	-0.601
	O5A	H4A	2.042	-0.678
	H7AA	O7D	2.009	-0.711
	O5B	H4B	2.110	-0.610
	H5B	O4B	1.921	-0.799
	H6B	O1D	2.027	-0.693
	O6B	H1D	1.921	-0.799
	O1B	H6D	2.009	-0.711
	H1B	O6D	1.925	-0.795
	O5D	H4D	2.045	-0.675
	H5D	O4D	1.904	-0.816
solvate S1	O4	H6	1.956	-0.764
	O7	H5	1.896	-0.824
	H4	O8	1.952	-0.768
	H7	O8	1.820	-0.900
	H1	O9	1.815	-0.905
solvate S3	H6	O5	1.910	-0.810
	H7	O6	1.938	-0.782
	O3	H4A	2.046	-0.674
	H4	O3A	1.947	-0.773
	O4	H5AA	1.880	-0.840
	H5	O6A	1.989	-0.731
	O7	H8B	2.200	-0.520
	H1	O8	1.719	-0.749
	O5A	H7AA	1.969	-0.751
	O4A	H6AA	1.990	-0.730
	O7A	H10B	1.944	-0.776
	H1A	O10	2.003	-0.717
	O1A	H8B	2.463	-0.257
	H10C	O8	2.019	-0.701

solvate S4	O5	H7	1.995	-0.725
	H4	O7A	1.891	-0.829
	H5	O6A	2.105	-0.615
	H5	O7A	2.405	-0.315
	O6	H6AA	1.901	-0.819
	H1	O4A	1.935	-0.785
	O7	H4A	1.898	-0.822
	O4	H1A	1.922	-0.789
	H6	O8	1.882	-0.838
	O5A	H7AA	1.884	-0.836
	H5AA	O8	1.944	-0.776
solvate S5	O5	H7	1.865	-0.855
	H6	O6A	1.885	-0.835
	O6	H5AA	2.158	-0.562
	O7	O4A	1.933	-0.787
	O7	H5AA	2.302	-0.418
	O4	H1A	1.926	-0.794
	H4	O7A	1.940	-0.780
	H1	O4A	1.938	-0.782
	H5	O8	1.837	-0.883
	O5A	H7AA	1.981	-0.739
	H6AA	O8	1.938	-0.782

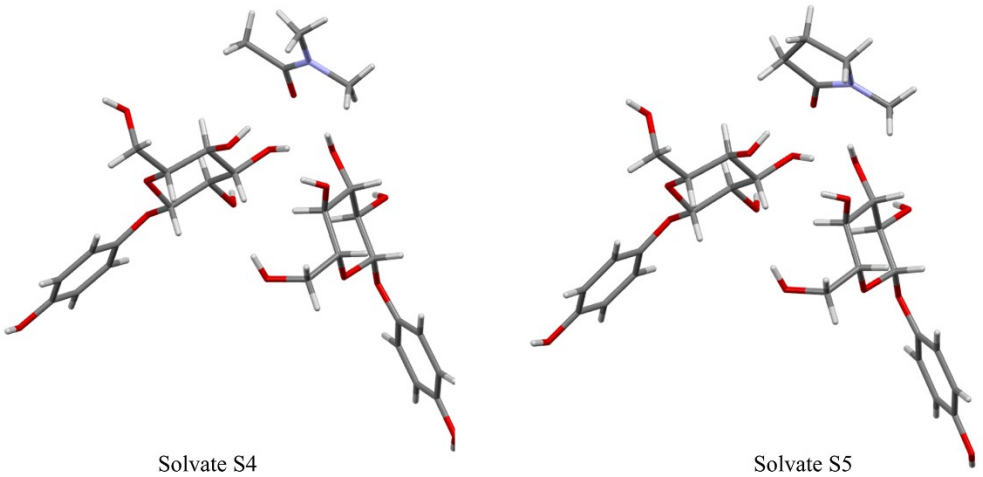


Figure S11. A comparison of the solvate S4 and S5 asymmetric units.

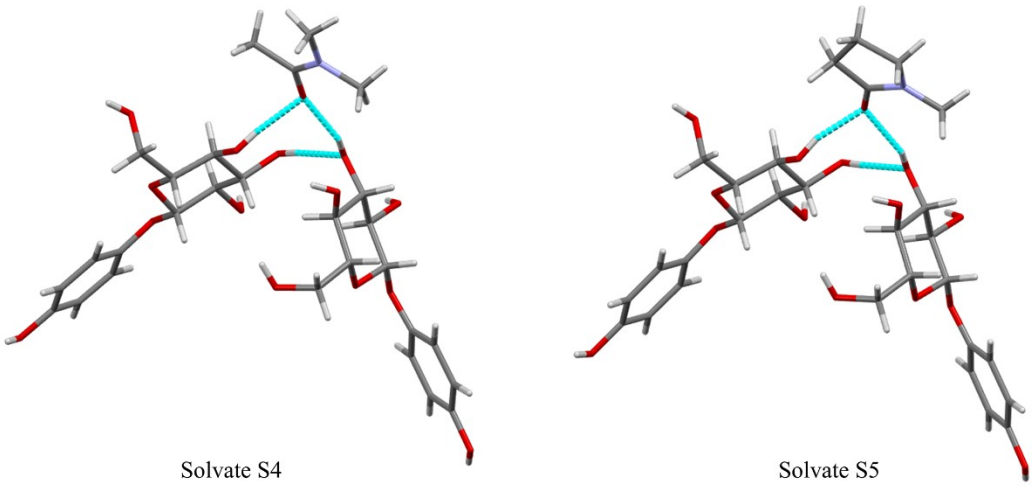


Figure S12. A comparison of the solvate S4 and S5 asymmetric units (with hydrogen bond interaction forces).

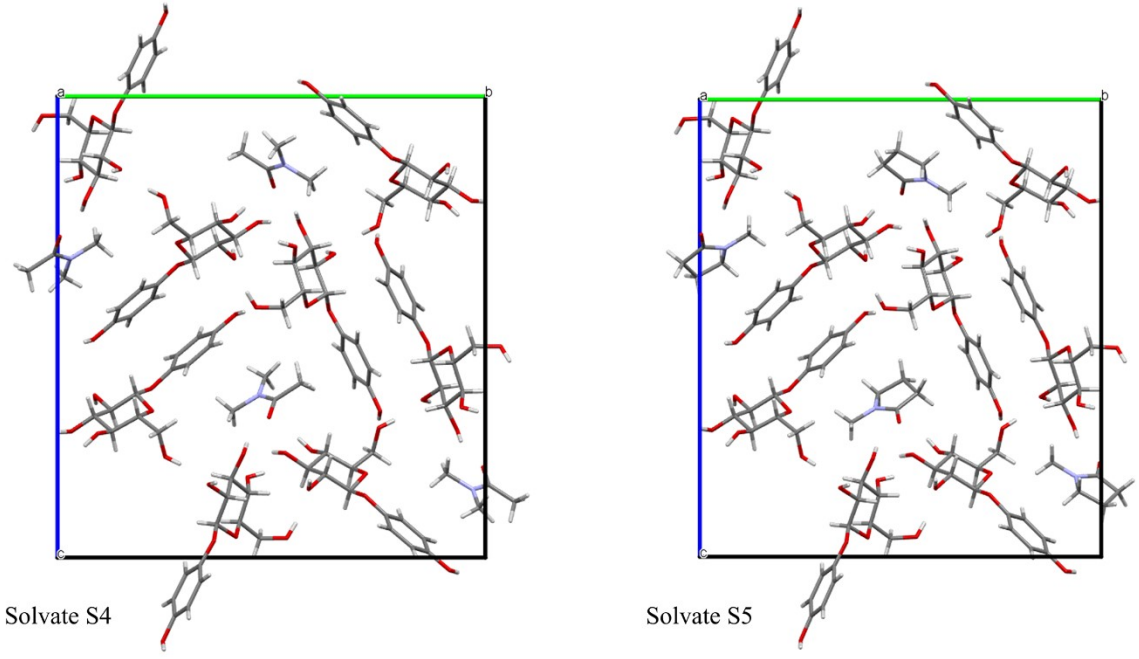


Figure S13. A comparison of the solvate S4 and S5 packing arrangements.

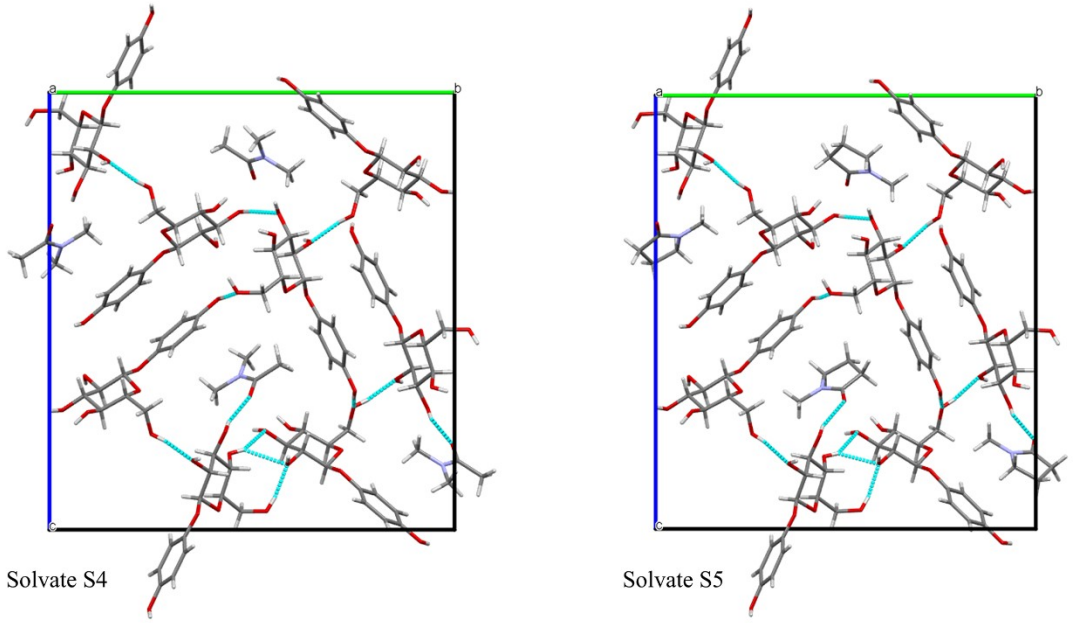


Figure S14. A comparison of the solvate S4 and S5 packing arrangements. (with hydrogen bond interaction forces).

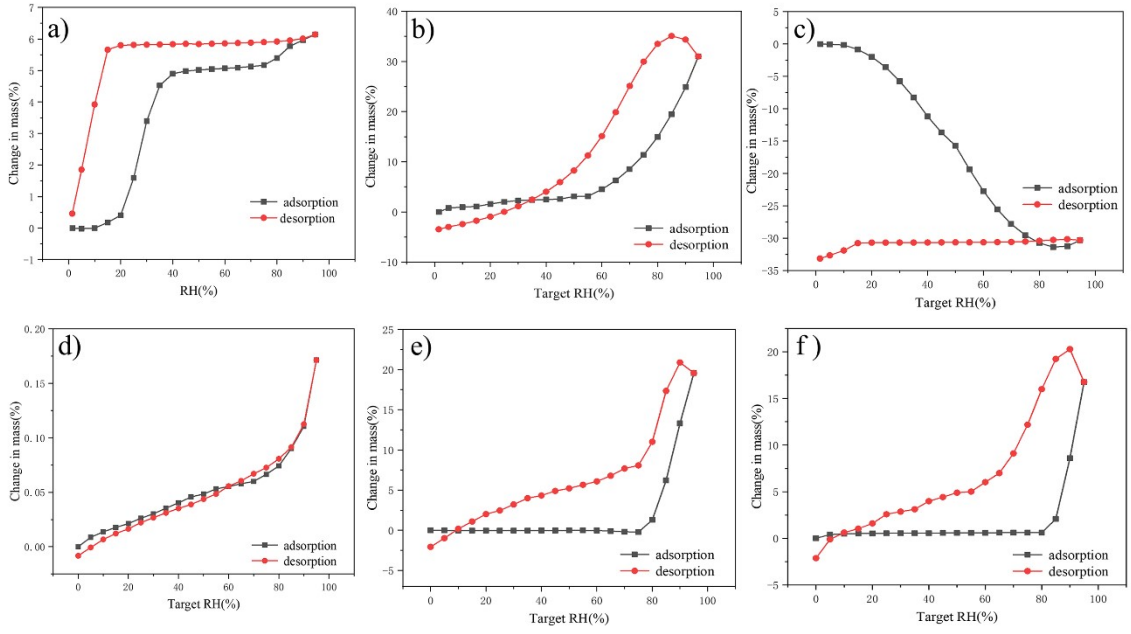


Figure S15. DVS diagrams of different solid forms of arbutin: (a) Form I, (b) solvate S1, (c) solvate S2, (d) solvate S3, (e) solvate S4, (f) solvate S5.