pharmaceutics

MDPI

Supplement

Improved Manufacturability and In Vivo Comparative Pharmacokinetics of Dapagliflozin Co-Crystals in Beagle Dogs and Human Volunteers

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Table S1. Coformers used in the co-crystal screen with DAP.

Adenine.	**Gentisic acid**	**D,L-mandelic acid**	**Sorbic acid**
Adipic acid	L-glutamic acid	D-mannitol	Sorbitol
4-aminobenzoic acid	D-glucose	Monosodium glutamate	Succinic acid
Ammonium chloride	Glutamine	Mucic (galacteric) acid	Sucralose
Arginine	Glutaric acid	Nicotinamide	Sucrose
L-ascorbic acid	Glycine	Oxalic acid	L-tartaric acid
Asparagine	Glycolic acid	L-proline	Thiamine hydrochloride
Aspartame	Hippuric acid	Propyl gallate	L-threonine
Benzoic acid	Histidine	L-pyroglutamic acid	Tromethamine hydrochloride
Betaine hydrochloride	1-hydroxy-2-naphthoic acid	Riboflavin	L-tryptophan
(+)-camphoric acid	L-lactic acid	Saccharin	Urea
Capric acid	L-leucine	Salicylic acid	L-valine
Choline chloride	L-lysine	Sebacic acid	Vanillin
Cinnamic acid	Maleic acid	L-serine	Xylitol
Citric acid	L-malic acid	Sodium chloride	Zinc chloride
Cyclamic acid	Malonic acid	Sodium lauryl sulfate	

Table S2. Composition for dissolution media.

Composition	pH 1.2	pH 4.0	pH 6.8
Sodium chloride (mM)	34.2	-	-
Hydrochloric acid conc. (mM)	82.4	-	-
Sodium acetate trihydrate (mM)	-	9.0	-
Acetic acid glacial (mM)	-	41.0	-
Potassium dihydrogen phosphate (mM)	-	-	50.0
Sodium hydroxide (mM)	-	-	23.5

Table S3. Results of DAP content and impurity of DAP, DAP-PH and DAP co-crystal in 3 conditions; 1) 60 °C, closed 2) 25 °C, 90 % RH, open 3) 40 °C, 75 % RH, open; after 4 week.

Conditions	API Type	Time Points (week)	DAP Contents (%)	Contents of Total DAP Impurities (%) *
60 °C, closed	DAP	0	99.4 ± 1.0	0.1 ± 0.1
		4	98.1 ± 1.0	0.2 ± 0.1
	DAP-PH	0	99.6 ± 1.0	0.1 ± 0.1
		4	99.4 ± 1.1	0.1 ± 0.1

Pharmaceutics **2021**, *13*, 70. https://doi.org/10.3390/pharmaceutics13010070

	DAP co-crystal	0	99.3 ± 1.0	0.1 ± 0.1
		4	99.1 ± 1.1	0.1 ± 0.1
25 °C, 90 % RH	DAP	0	99.5 ± 1.0	0.1 ± 0.1
		4	99.1 ± 1.0	0.1 ± 0.1
	DAP-PH	0	99.4 ± 1.0	0.1 ± 0.1
		4	99.6 ± 1.2	0.1 ± 0.1
	DAP co-crystal	0	99.7 ± 1.0	0.1 ± 0.1
		4	99.9 ± 1.2	0.1 ± 0.1
40 °C, 75 % RH	DAP	0	99.4 ± 0.8	0.1 ± 0.0
		4	99.0 ± 1.0	0.2 ± 0.1
	DAP-PH	0	99.6 ± 1.2	0.1 ± 0.1
		4	99.4 ± 1.1	0.1 ± 0.1
	DAP co-crystal	0	99.7 ± 1.3	0.1 ± 0.1
		4	99.6 ± 1.1	0.1 ± 0.1

* mean ± standard deviation (*n* = 3)

Table S4. Particle size distribution of DAP co-crystal before and after milling process.

.	**D 10**	**D 50**	**D 90**
Before milling (μm)	3.5 ± 1.6	83.4 ± 5.9	229.5 ± 11.9
After milling (μm)	1.3 ± 0.2	4.8 ± 0.6	15.5 ± 1.1

Table S5. Detailed information on manufacturability of DC formulations.

Characterization	**DC-D1**	**DC-D2**	**DC-D3**	**DC-D4**	**DC-D5**
Carr`s index (%)	33.2 ± 0.8	34.4 ± 1.0	34.6 ± 0.8	31.1 ± 1.0	30.5 ± 0.9
Contents uniformity (%)	12.3	11.0	10.7	11.0	10.4
Manufacturing troubleshooting	Mass deviation	Mass deviation	Mass deviation	Mass deviation	Mass deviation

Table S6. Manufacturing parameters screening for roller compaction process.

Parameter	**Screen Range**	**Optimum Production Range**
Roll rotation speed (RPM)	2.0~8.0	5.0
Screw feeder speed (RPM)	1.0~10.0	7.0
Roll pressure (MPa)	1.0~6.0	3.5~6.0

Table S7. Flowability and contents uniformity test of roller compaction (RC) formulation.

Characterization	**RC-T1**	**RC-T2**	**RC-T3**	**RC-T4**	**RC-T5**
Carr`s index (%)	27.2 ± 1.3	25.1 ± 1.1	18.0 ± 0.9	18.3 ± 0.7	19.1 ± 0.8
Contents uniformity (%)	6.4	5.4	3.3	3.2	3.4
Manufacturing trouble	Discontinuous manufacturing	-	-	-	-

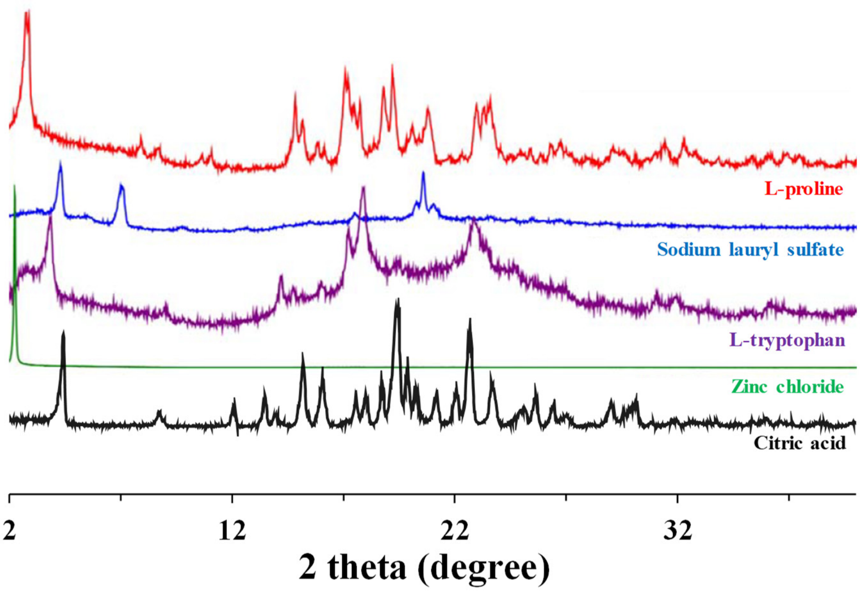

Figure S1. Overlay XRD results of citric acid(black), zinc chloride (green), L-tryptophan (purple), sodium lauryl sulfate (blue) and L-proline (red).

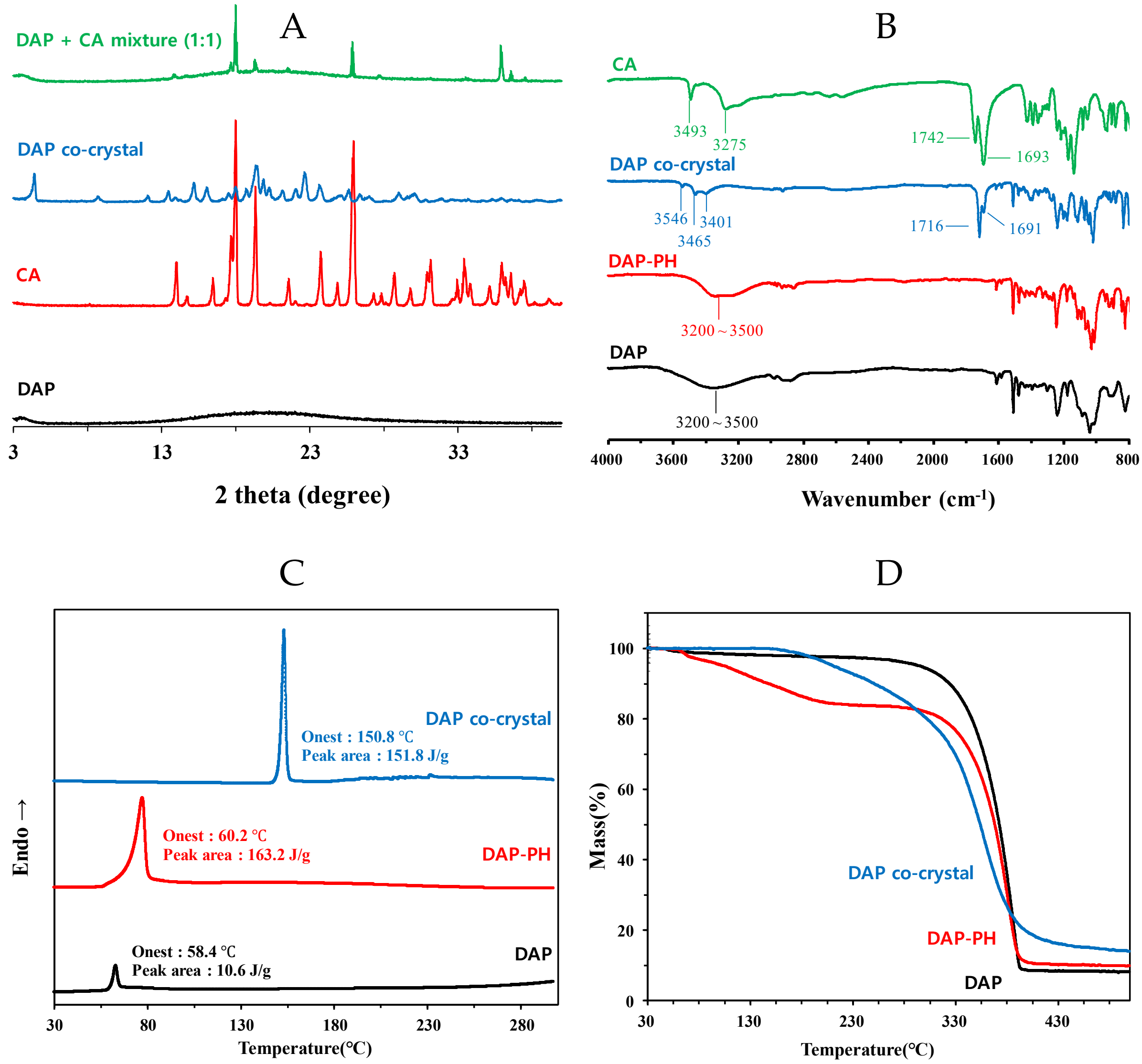

Figure S2. (**A**) XRD patterns of DAP (black), CA (red), DAP co-crystal (blue) and DAP: CA (1:1) physical mixture (green). (**B**) FTIR spectra of DAP (black), DAP-PH (red), DAP co-crystal (blue) and CA (green). (**C**) DSC thermograms of DAP (black), DAP-PH (red) and DAP co-crystal (blue). (**D**) TGA thermograms of DAP (black), DAP-PH (red) and DAP co-crystal (blue).

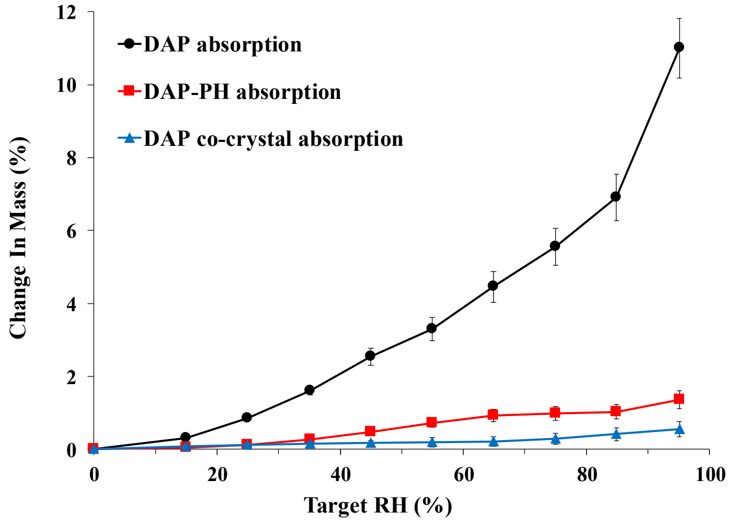

Figure S3. Water sorption isotherms for DAP (blank), DAP-PH (red) and DAP co-crystal (blue).

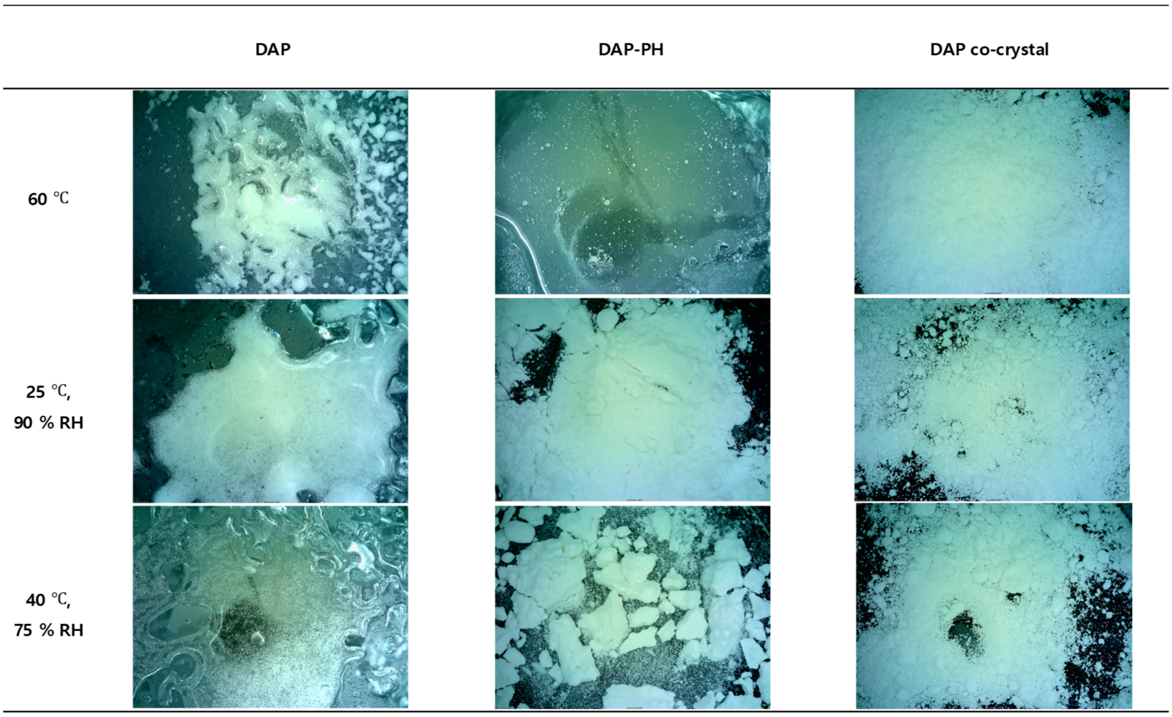

Figure S4. Appearance test of DAP, DAP-PH, and DAP co-crystal in 3 conditions; (1) 60 °C, closed (2) 25 °C, 90 % RH, open (3) 40 °C, 75 % RH, open; after 1 week.