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Quantifying the hygroscopic properties of cyclodextrin containing aerosol for drug delivery to the lungs

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Supplementary Information

AIOMFAC functional group assignments

The 2-hydroxypropyl-β-cyclodextrin (2-HP-β-CD) ring contains seven repeat units, with a chemical formula of $(C_9H_{16}O_6)_7$, (Cambridge Bioscience, CAS 128446-35-5, molecular weight *M* = 1541.6 g/mol). The molecule was assigned functional groups according to A. Zuend et al., *Atmos. Chem. Phys.* 2015, **15**, 447-493. For modelling of 2HP-β-CD, the molecule was therefore assigned as 7 repeat units comprised of 3 x CH[OH], 3 x OH, 1 x CH(standard), 2 x CHO(ether), 1 x CH_2O(ether), 1 x CH_3 (alc) and 1 x CH_2 (standard). One glucopyranose unit can be described as 2 x CHO (ether), 1 x CH (standard), 2 x CH[OH], 1 x CH_2[OH], 3 x OH. As such α-, β-, and γ-CD can be modelled using 6, 7 and 8 glucopyranose repeat units, respectively.

Extrapolation of dynamic vapour sorption data

The measurements obtained from the DVS for each RH step were fitted to an exponential growth or decay curve for the adsorption and desorption sections of the humidity isotherms, respectively. Exponential fits were used according to $Mass_{stablised}(t) = a + b\exp(ct)$, where coefficients *a*, *b* and *c* were optimised to fit the experimental data using a least squares fit error analysis. The equilibration mass was obtained by extrapolation of the exponential curve at each step and was subsequently used as the initial mass for the proceeding RH step. For the initial stabilisation of the sample mass at RH = 0%, the M_0 value was taken as the lowest recorded mass value and assumed to be equal to M_{dry}. Examples of the exponential fitting and extrapolation are shown in figures S.1 and S.2.

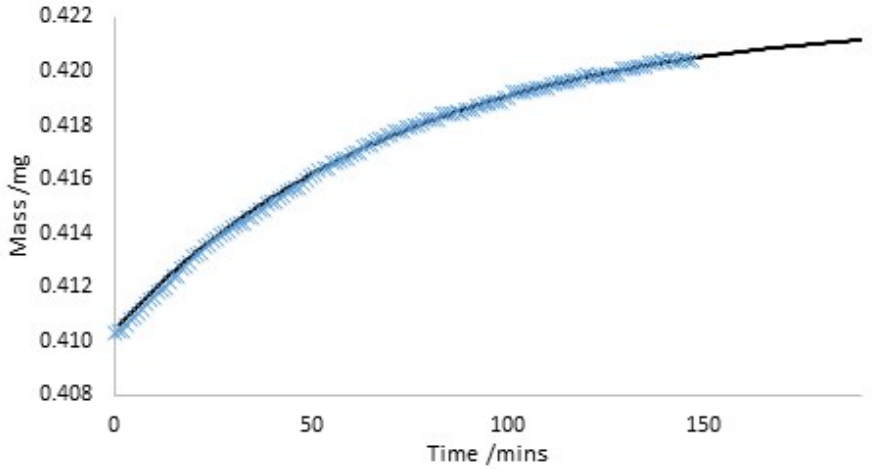

Figure S.1. DVS measurements are shown as blue crosses and fitted to an exponential curve to allow extrapolation to a stable mass (black line) DVS data for stabilisation of the sample mass at from room atmosphere to the environment chamber at RH = 0.4 %. Exponential curve fitting coefficients are a = 0.0117, b = -0.0115 and c = -0.0140.

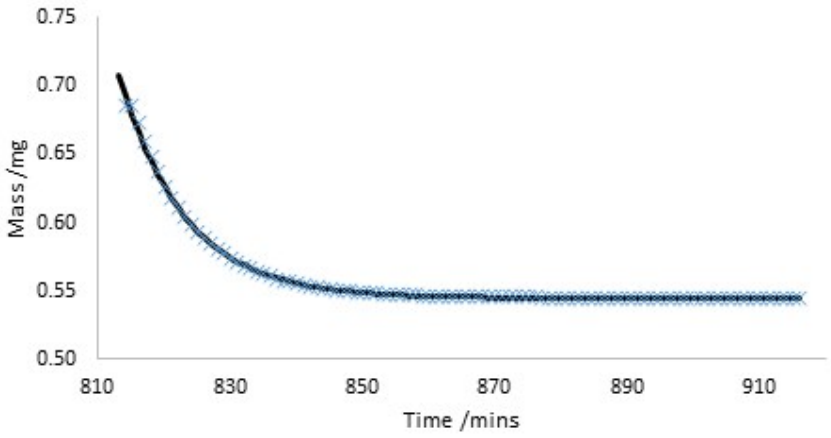

Figure S.2. Measured (blue crosses) and extrapolated (black line) DVS data for the first desorption RH step from 98% to 90%. Exponential curve fitting coefficients are a = 0.1810, b = -0.1007 and c = -0.1373.

Refractive index and density measurements

Density data was recorded using a Metler Toledo Densito 30PX densitometer and RI data recorded using a Metler Toledo Refracto 30PX Abbe refractometer. To calculate the temperature correction coefficients for density (γ_ρ) and RI (γ_n) an aqueous solution of 200 mg/mL of 2-HP-β-CD was cooled in an ice bath and RI and density measurements recorded as $\rho(T=8.6\ ^oC) = 1.0099\ g/cm^3$ and $n(T = 9.1\ ^oC) = 1.3376$. The solution was then gently

warmed on a hot-plate and the RI and density measurements recorded as $\rho(T=28.8\ ^oC) = 1.0061\ g/cm^3$ and $n(T = 27.8\ ^oC) = 1.3307$.

Temperature correction factors γ_ρ and γ_n were then determined according to the manufacturers handbook using $\gamma_\rho = [(\rho_{Low}/\rho_{High}) - 1]/(T_{High} - T_{Low})$ and $\gamma_n = (n_{Low} - n_{High})/(T_{High} - T_{Low})$. The density temperature correction factor was determined to be $\gamma_\rho = 0.187 \times 10^{-3}\ 1/^oC$ and was programmed into the densitometer and all density data corrected to a temperature of 25 °C. Refractometer measurements were recorded at the measured room temperature, and corrected to 25 °C post-measurement using the formula $n(25\ ^oC) = n(T) + \gamma_n(T - 25)$, where the temperature correction factor was determined to be $\gamma_n = 0.369 \times 10^{-3}\ 1/^oC$.

The table below lists the raw RI and density measurements. The RI Temperature (T_n) column indicates the temperature recorded by the refractometer for each solution and corresponds to the RI measurement, n_T.

MFS	Density at 25 °C /g.cm^{-3}	n_T	T_n / °C
0.3762	1.1231	1.3972	17.3
0.3537	1.1087	1.3848	17.5
0.3433	1.1042	1.3835	17.5
0.3333	1.0991	1.3799	17.7
0.3238	1.0919	1.3770	17.7
0.3144	1.0893	1.3760	17.7
0.3053	1.0843	1.3730	17.7
0.2965	1.0788	1.3702	17.7
0.2878	1.0757	1.3689	17.9
0.2792	1.0716	-	-
0.2708	1.0682	1.3654	17.5
0.2626	1.0644	1.3636	17.5
0.2548	1.0607	1.3621	17.5
0.2471	1.0566	1.3601	17.6
0.2398	1.0544	1.3593	17.8
0.2326	1.0516	1.3577	17.9
0.2257	1.0489	1.3568	18.0
0.2188	1.0462	1.3563	18.0
0.2121	1.0439	1.3544	18.0
0.2057	1.0418	1.3537	17.9
0.1994	1.0399	1.3527	17.9
0.1932	1.0377	1.3518	17.8
0.1872	1.0364	-	-
0.1814	1.0344	1.3503	17.9
0.1759	1.0338	1.3502	18.1
0.1703	1.0328	1.3493	18.1
0.1650	1.0316	1.3489	18.0
0.1599	1.0306	1.3484	17.5
0.1549	1.0296	1.3482	17.7
0.1501	1.0286	1.3475	18.4
0.1455	1.0277	1.3470	18.4
0.1410	1.0268	1.3465	18.4
0.1368	1.0258	1.3462	18.5
0.1326	1.0246	1.3455	18.4
0.1287	1.0237	1.3452	18.5
0.1250	1.0225	1.3446	18.4

0.1213	1.0215	1.3444	18.5
0.1145	1.0198	1.3434	18.4
0.1080	1.0182	1.3428	18.4
0.1019	1.0166	1.3421	18.5
0.0962	1.0153	1.3412	18.6
0.0908	1.0142	1.3407	18.6
0.0857	1.0129	1.3402	18.7
0.0810	1.0117	1.3395	18.8
0.0765	1.0101	1.3389	18.8
0.0723	1.0091	1.3384	18.7
0.0683	1.0084	1.3382	18.7
0.0645	1.0078	1.3379	18.7
0.0609	1.0071	1.3377	18.3
0.0576	1.0064	1.3372	18.4
0.0544	1.0059	1.3371	18.5
0.0514	1.0053	1.3366	18.7
0.0486	1.0048	1.3365	18.8
0.0000	0.9991	1.3335	16.9

Optical tweezers measurements

Optical tweezers measurements providing droplet properties of RI and dispersion in RI were determined through analysis of the morphology dependent resonances present in Raman spectra. The table below shows the droplet RI and dispersion in RI (μ) when equilibrated to the given RH value, along with standard deviations for each measurement.

Droplet	RH/ %	RI @ λ = 650 nm	σ_{RI}	μ /x10^{-6} m^{-1}	σ_{μ} /x10^{-6} m^{-1}
A	98	1.472	0.021	1.11	0.04
	91	1.489	0.014	1.10	0.10
	82	1.499	0.027	1.16	0.06
	72	1.502	0.015	1.23	0.05
	62	1.502	0.009	1.15	0.12
	51	1.506	0.005	1.21	0.12
	41	1.504	0.006	1.14	0.07
B	99	1.465	0.023	1.10	0.04
	82	1.496	0.019	1.15	0.05
	62	1.508	0.010	1.21	0.13
	41	1.512	0.014	1.19	0.10
	21	1.511	0.010	1.17	0.10
C	95	1.478	0.028	1.12	0.06
	88	1.493	0.029	1.15	0.08
	79	1.502	0.014	1.10	0.09
	69	1.505	0.016	1.00	0.14
	59	1.505	0.01	1.13	0.13
	50	1.507	0.008	1.23	0.30
	41	1.507	0.006	1.18	0.06
	30	1.508	0.009	1.14	0.07
D	97	1.467	0.010	1.07	0.09
	96	1.472	0.022	1.14	0.20
	95	1.478	0.030	1.04	0.10
E	91	1.486	0.011	1.00	0.16
	81	1.492	0.021	1.14	0.15
	70	1.507	0.013	1.07	0.50
	60	1.502	0.014	1.10	0.06