SUPPORTING INFORMATION

Sugar-induced self-assembly of curcumin-based dual drug nanocapsules with high drug loading

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Experimental Section

Materials

D-fructose (99%, Aldrich), curcumin (>75%, Aldrich), Dopamine hydrochloride (98%, Aldrich), DMSO (Aldrich), DMSO-d_6 (Aldrich), tris(hydroxymethyl)aminomethane base (>99.9%, Aldrich), Ellipticine (> 98%, AdooQ Bioscience), Paclitaxel (> 95%, Aldrich), Doxorubicin hydrochloride (98%, Aldrich), Gemcitabine HCl (Selleckchem), Erastin (98%, Focus Biomolecules), Sulfasalazine (98%, Aldrich), Albendazole (≥ 98%, Aldrich), 2-(5-Norborene-2,3-dicarboximido)-1,1,3,3-tetramethyluronium tetrafluoroborate (TNTU, TCI chemicals), were used as received.

Procedures

Preparation of PDA-Fructose-Curcumin hollow nanoparticles (PDA-Fru-CCM)

A typical procedure to prepare PDA-Fru-CCM nanoparticles is described as follows: To a solution of fructose (10 mg) in milliQ water (1 mL) at room temperature, curcumin/DMSO solution (20 μL, 2.5 mg/mL) was added dropwise. The fructose solution turned from colourless to yellow. After five minutes, dopamine hydrochloride aqueous solution (10 μL, from 10 mg/mL stock solution) and 10 μL Tris base aqueous solution (from 6 mg/mL stock solution) were added to the curcumin/fructose solution sequentially. Then, the vial was covered with foil and left for polymerisation. After 48 hours, the reaction solution was dialysed against milliQ water (molecular weight cut off 3500 Da) with water changes around every 24 hours for 2 days before characterisation.

Table S1. Preparation of PDA-Fru-CCM nanoparticles with varying dopamine polymerisation time, and reagent concentrations used.

Sample name	Polymerisation time (h)	[CCM] (μg/mL)	[Fru] (mg/mL)	[Dopamine] (μg/mL)	[Tris] (μg/mL)
Fru-CCM	N/A	80	10	0	0
PCF3	3	80	10	100	60
PCF24	24	80	10	100	60
PCF48	48	80	10	100	60
PCF72	72	80	10	100	60
PCF144	144	80	10	100	60

Preparation of drug loaded nanoparticles

A typical procedure to prepare drug loaded PDA-Fru-CCM nanoparticles is described as follows: Curcumin in DMSO (20 μL, from 2.5 mg/mL stock solution) and albendazole (5 μL, from 1 mg/mL) was dissolved together at room temperature to achieve desired mole ratio of 0.1:1 albendazole: curcumin. Refer to Table S4 and S5 for moles ratios and concentrations of drug to curcumin prepared. To a solution of fructose (10 mg) in water (1 mL) at room temperature, the albendazole/ curcumin in DMSO solution was slowly added dropwise and gently mixed. After 5 minutes, dopamine hydrochloride aqueous solution (10 μL, from 10 mg/mL stock solution) and Tris base aqueous solution (10 μL, from 6 mg/mL stock solution) were added to the fructose/ albendazole/ curcumin solution. The vial was covered with foil to avoid exposure to light and left for polymerisation. After 24 hours, the reaction solution was dialysed against water (1 L), and water changed every 24 hours twice.

Preparation of deprotonated doxorubicin (DOX)

Doxorubicin hydrochloride (1 mg) was dissolved in DMSO (1mL) to give a final concentration of 1mg/mL. To the doxorubicin/DMSO solution, 10 μL of triethylamine (TEA) base was added directly and left for 5 minutes at room temperature for deprotonation.

Release of Curcumin from PDA-Fru-CCM

Purified PDA-Fru-CCM (6 mL, refer to Table S1 for concentration of components) were placed in a tubular dialysis membrane (molecular weight cut off 3500 Da) and the sample was dialyzed against pH 7.4 buffer solution (250 mL) at 37 °C. Aliquots of 0.3 mL were taken in regular

time intervals from the dialysate over 168 h. In addition, samples were taken from the inside of the tubular membrane to confirm that the amount of CCM inside and outside the membrane add up to the initial CCM amount. The aliquots in water were diluted with DMSO to achieve 10 times dilution and the amount of released curcumin was quantified using UV-Vis spectroscopy. The concentration of curcumin released from the nanoparticles was expressed as a % of the amount curcumin released (the solution inside the dialysis membrane) and that in the initial sample. The percentage of curcumin released were measured at absorption at 425 nm and calculated using the equation:

$$\text{Release (\%)} = \frac{\text{Released amount of curcumin}}{\text{Total amount of curcumin}} \text{ x } 100$$

The *total amount of curcumin* is the concentration of CCM originally placed into the tubular membrane. This amount is determined by the concentration of drug used to prepare the solution and corrected considering that a small amount was lost during the purification process.

The release study was performed at acidic as well as physiological pH PBS solution (pH 7.4)/ acetate buffer solution (pH 4.5)

UV-Vis spectroscopy at 425 nm was also used to determine the drug loading content. The nanoparticles were immersed into a known amount of DMSO and the mixture was incubated until DMSO turned yellow. A small sample was taken and analyzed by UV-Vis spectroscopy and the absorption was compared to a standard curve of CCM in DMSO. The test needs to be repeated after a set time to ensure that all CCM has been leached out and the maximum CCM intensity was achieved.

Cell Culture

2D cell models were used to test cytotoxicity and cell viability of curcumin drug and PDA-Fru-CCM drug carriers. The cell line used was MCF-7 breast cancer cells cultured with DMEM media supplemented with 10% FBS, sodium pyruvate and antibiotics (100 U Penicillin and 100 μg streptomycin). Cells were grown in a ventilated tissue culture flask at 37 °C under 5% CO_2 humidified atmosphere and passaged when monolayers reached 80% confluence. The cells were seeded at a density of 4,000 cells per well in 96-well plates containing 200 μL of grown medium and incubated for a further 24 hours. All samples were sterilised under UV-light for 20 minutes before incubation with cancer cell line.

Sulforhodamine B (SRB) Assay

The established by the U.S. National Cancer Institute for rapid, sensitive, and inexpensive screening of antitumor drugs in microplates was employed to screen the cytotoxicity and antitumor activities of polymers and polymeric platinum drugs, respectively. Human breast cancer cells (MCF-7) diluted in 100 μL of DMEM medium were seeded into the wells with 2000 cells/well. The microtiter plates were left for 24 h at 37 °C and then exposed to various doses of capsules for 72 h. Cell cultures were fixed with TCA (10%, w/v) and incubated at 4 °C for 1 h. The wells were then washed five times with water to remove TCA, growth medium, and low molecular weight metabolites. Plates were air-dried and then stored until use. TCA-fixed cells were stained for 30 min with 0.4% (w/v) SRB dissolved in 1% (v/v) acetic acid. At the end of the staining period, SRB was removed, and cultures were quickly rinsed five times with 1% (v/v) acetic acid to remove unbound dye. Subsequently, the cultured plates were air-dried until no conspicuous moisture was visible before bound dye was shaken in 100 μL of 10 mM tris base for 5 min. The absorbance at 440 nm of each well was measured using microtiter plate reader scanning spectrophotometer (Biotech).

Preparation of binary drug mixtures for DSC analysis

A typical procedure to prepare binary drug mixtures is described as follows: Sulfasalazine (1.08 mg, 2.71*10^-6 mol) and curcumin (10 mg, 2.71*10^-5 mol) were weighed and vortexed for 5 minutes to achieve a desired homogenous mixture with a molar ratio of 0.1:1 sulfasalazine to curcumin.

Analysis Techniques

Dynamic light scattering (DLS)

The hydrodynamic diameter D_h was determined using a Malvern Zetaplus particle size analyser (laser, angle = 173°). The ζ potential determinations were based on electrophoretic mobility of the nanoparticles in the aqueous medium, which was performed using folded capillary cells in automatic mode. Different pH values were obtained and controlled by an autotitrator MPT-2 that utilised HCl acid (0.025 M) and NaOH base (0.025 M) additives with stirring to reach the desired pH.

Transmission electron microscopy (TEM)

The TEM micrographs were obtained using a JEOL1400 transmission electron microscope comprising of a dispersive X-ray analyser and a Gatan CCD facilitating the acquisition of digital images. The measurement was conducted at an accelerating voltage of 80 kV. The samples were prepared by casting the micellar solution onto a copper grid. For the measurement of fructose-curcumin hollow particles, the grids were dried by air and then negatively stained with uranyl acetate. No staining was conducted for the measurement of PDA-Curcumin-fructose hollow nanoparticles.

Differential Scanning Calorimetry (DSC)

DSC curves of solid drugs and binary mixtures were measured using a DSC 204 F1 Phoenix connected to NETZSCH-Proteus -80 software for analysis. Baseline correction at 20 to 280°C were performed to ensure flat baseline before sample analysis. Solid samples were weighed, and binary mixtures were mixed by vortex and placed in aluminium crucible pans. The crucible pans are sealed pressed with inserts at pressures up to 20 bar. Sample pan and reference pan (no sample) were inserted to DSC cell and covered by an automatically controlled cover before purged by branching gas channels. Temperature ramp was set at 10K/min from 20 to 269°C and endothermic and exothermic peaks were recorded.

Fluorescence Spectroscopy

The fluorescence spectra of CCM/fructose solutions were measured with Cary Eclipse spectrophotometer equipped with a xenon flash lamp. Fructose (10 mg) was dissolved in milliQ water (2 mL) and CCM/DMSO solution (8 μL, 2.5 mg/mL) was added dropwise with gentle stirring for a starting curcumin (10 μg/mL) and fructose (50 mg/mL) solution. The sample was placed in a 1 cm path length, four-sided quartz cuvette and the fluorescence spectra recorded between 450 to 800 nm at λex = 429 nm with entrance and exit slit width of 10 mm at room temperature.

Nuclear magnetic resonance (NMR)

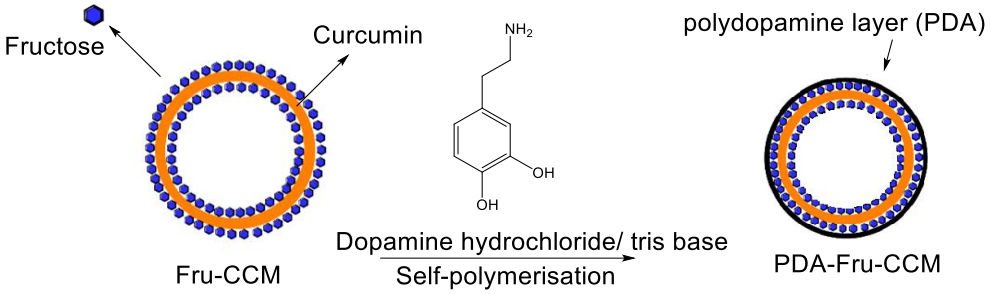
NMR spectra were acquired on a Bruker Advance III (400 MHz) spectrometer, using $CDCl_3$ as the solvent. All chemical shifts are stated in ppm (δ) relative to $CDCl_3$ (δ =7.26 ppm)

Computational details

All calculations were performed using the quantum chemistry software Orca (version 4.2.1)[2-4] and density functional theory (DFT).[5,6] We used the revPBE functional[7] and the D3BJ approximation to account for dispersion corrections.[8,9] This functional is a good choice for our study for two reasons. First, it has a moderate computational cost thus allowing us to explore many possible conformations for the molecules and complexes of interest. Second, thorough DFT benchmark studies have identified this functional and dispersion correction as a robust approach to model intermolecular interactions and have shown that they can even outperform typical hybrid functionals.[10,11] The def2-SVP basis set[12] was used to perform geometry optimizations and the def2-TZVPPD was used to refine the energy.[12,13] Locating the global energy minimum for the systems under investigation (i.e., complexes of large organic molecules in which numerous intermolecular and intramolecular weak interactions are possible) can be a difficult task. To help with this aspect, we sampled up to 150 conformations for each molecule and complex using molecular dynamics (MD) simulations at 400 K with the LAMMPS software.[14] For this simulations we used the Universal Force Field (UFF)[15] and CHELPG charges calculated in Orca with the DFT functional and basis set mentioned above. The sampled conformations from the MD simulations were optimized in Orca according to the computational protocol described above. The lowest energy minimum located with this procedure was confirmed by performing a frequency calculation to verify the absence of imaginary frequencies. The energy of this structure was then used to calculate binding energies of complexes according to the general equation:

$$\Delta E_b = E_{A+B} - E_A - E_B$$

where ΔE_b is the binding energy, E_{A+B} is the energy of the complex formed by two molecules A and B, E_A and E_B are the energies of the individual species binding together to form the complex. Enthalpic and entropic corrections at room temperature were computed from the vibrational frequencies by employing the ideal gas, the rigid rotor and harmonic oscillator approximations. Binding energies were corrected for the basis set superposition error.



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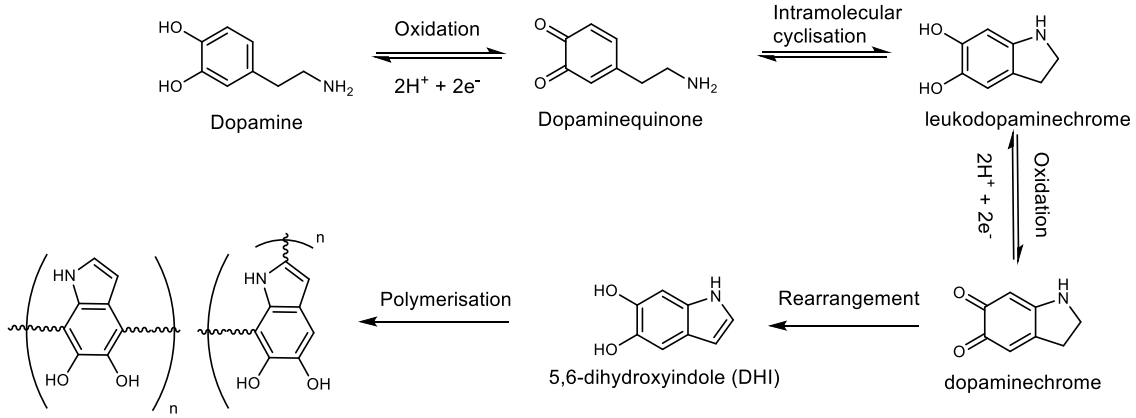
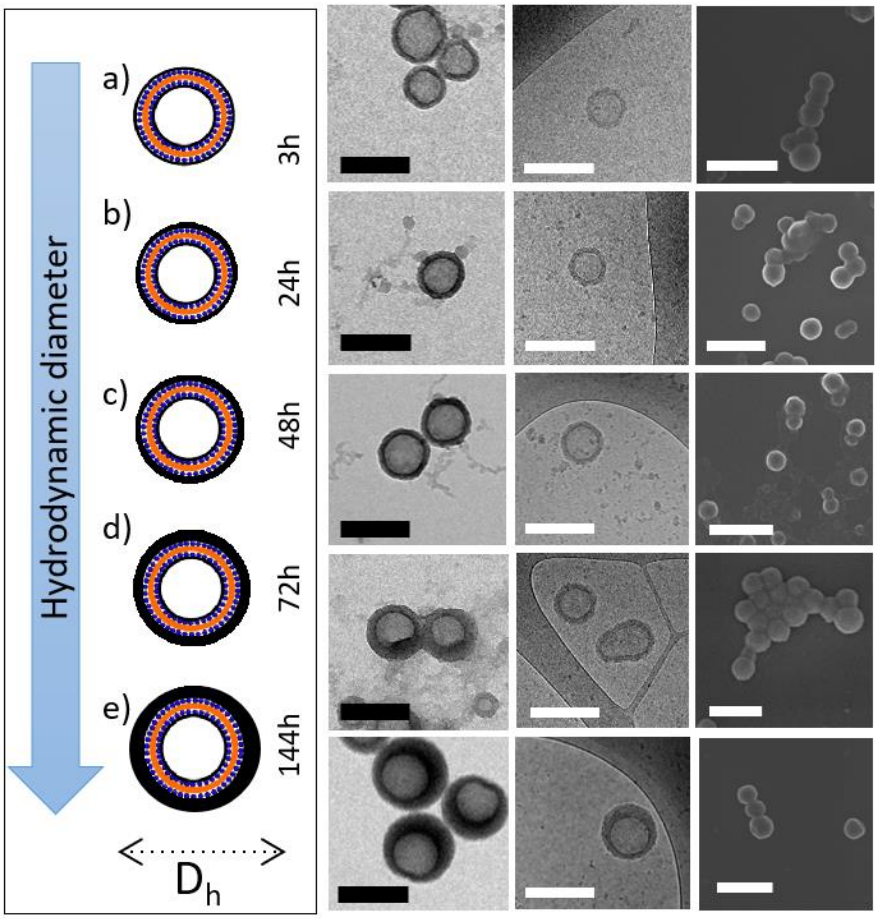


Scheme S1. (A) Scheme of one-pot template polymerisation where fructose-curcumin nanoparticle (Fru-CCM) template yield polydopamine (PDA) coated curcumin-fructose particles (PDA-Fru-CCM) after dopamine polymerisation, and (B) Proposed reaction mechanism of self-oxidation, polymerisation of dopamine and structures for PDA.



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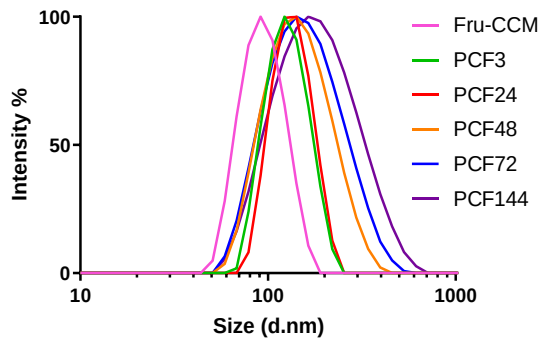

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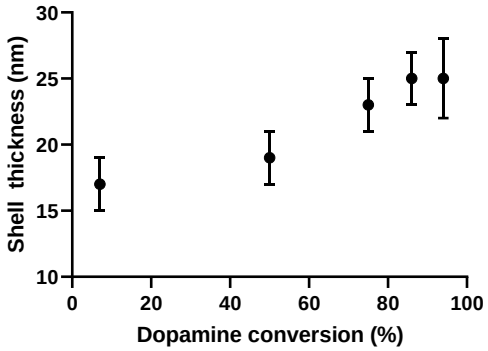


Figure S1. (A) Comparative illustration of PDA-Fru-CCM capsules (PCF) prepared at various polymerisation time going across with respective (B) Dry-state TEM (scale bar 200 nm) and (C) Cryo-TEM (scale bar 200 nm) (D) SEM (scale bar 400 nm) (E) Normalised DLS curve of PCF nanoparticle size dependent on dopamine deposition time denoted in hours after PCF in legend e.g. PCF3 refers to PCF with 3 hours dopamine deposition time (F) Dopamine conversion (%) versus PDA shell thickness formed as determined by cryo-TEM.

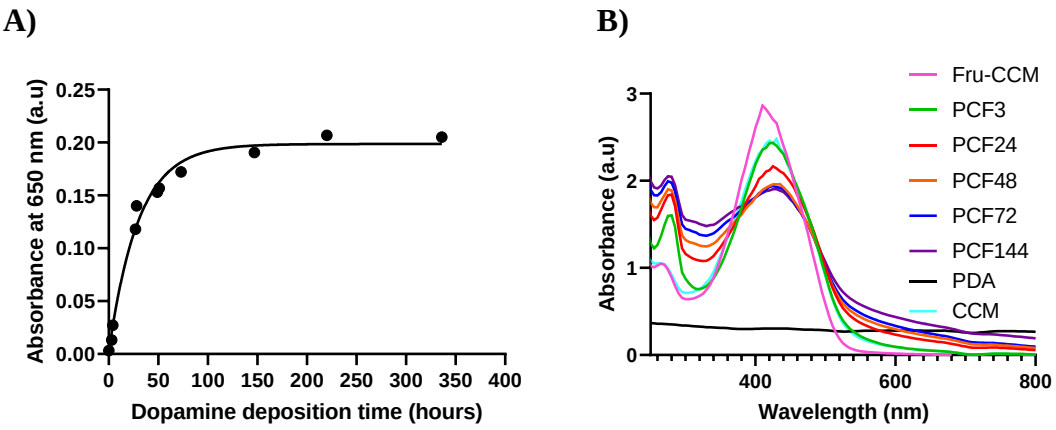


Figure S2. (A) UV-Vis curve of dopamine consumption, PDA absorption intensity at 650 nm monitored over time. Dopamine solutions prepared with [dopamine] = 100 mg/mL, and [tris] = 60 mg/mL. Samples are prepared in 1-fold dilutions in water for spectroscopy analysis, (B) UV-Vis curve of PDA-Fru-CCM with varying dopamine deposition time (solutions are in 1 fold dilutions), PDA is bulk polymerisation of dopamine in aqueous solution where [bulk PDA]= 250 µg /mL, and [pure CCM] = 30 µg/mL (the concentrations have been adjusted to suit UV-Vis analysis).

Table S1. Dopamine % conversion and concentration composing PDA-Fru-CCM nanoparticles. Samples named as PCF followed by the number of hours of dopamine polymerisation, [Dopamine]= 100 µg/mL, [CCM] = 80 µg/mL

Sample	Reaction time (h)	Dopamine (%)	Dopamine (µg/mL)
PCF3	3	7	7
PCF24	24	50	50
PCF48	48	75	75
PCF72	72	86	86
PCF144	144	94	94

Table S2. Curcumin concentration encapsulated in PDA-Fru-CCM nanoparticles prepared using [CCM] = 80 μg/mL. The amount of CCM lost during purification was measured by dissolving dialysis tubing with entrapped CCM in DMSO overnight. Dissolved CCM analysed at absorption maxima of 425 nm and compared to CCM calibration curve to determine CCM content remaining in nanoparticles.

Sample	[CCM] μg/mL	DLE
PCF3	74.9 ± 0.1	
PCF24	75.9 ± 0.1	
PCF48	77.9 ± 0.1	93-97%
PCF72	77.9 ± 0.1	
PCF144	78.1 ± 0.1	

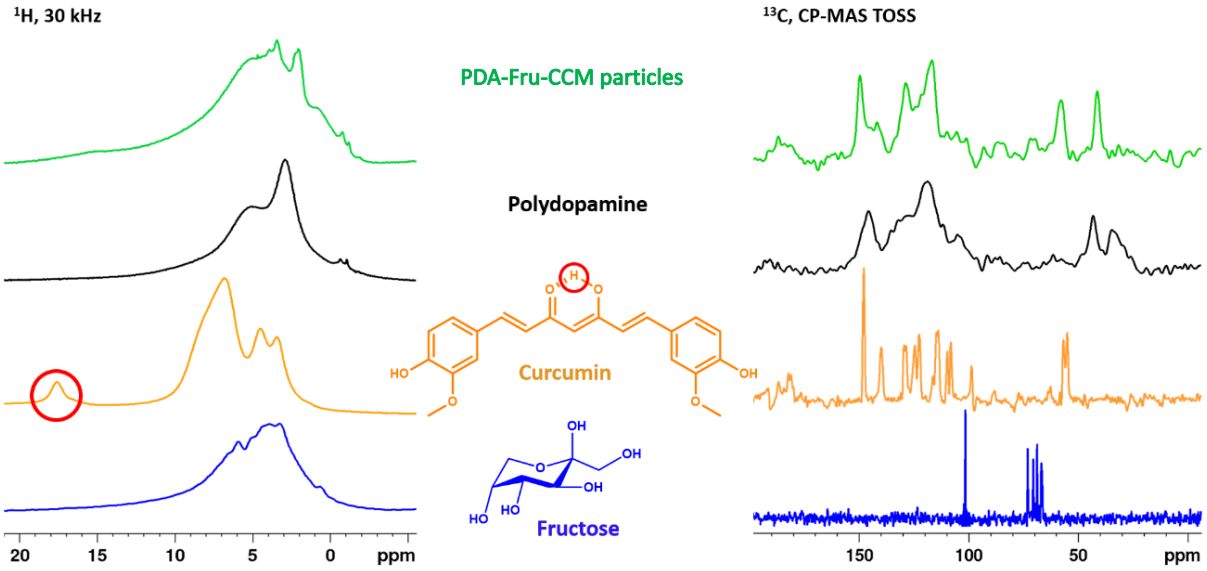


Figure S3. Solid-state ^{1}H and ^{13}C NMR spectra of (from top to bottom): PDA-Fru-CCM (PCF24) particles (24-hour deposition time), bulk PDA, curcumin (CCM), and fructose (Fru). PCF24 prepared with [Fru]= 10 mg/mL, [CCM]= 60 μg/mL, [Dopamine]= 100 μg/mL, [Tris]= 60 μg/mL.

Table S3. Drug loading content of PDA-Fru-CCM nanoparticles depending on the dopamine polymerization time. Samples named as PCF followed by the number of hours of dopamine polymerisation. [CCM] = 80 μg/mL; [DA] = 100 μg/mL

Sample	**[CCM] (μg/mL)**	**PDA (μg/mL)**	**CCM drug loading content**
PCF3	74.9 ± 0.1	7	91%
PCF24	75.9 ± 0.1	50	60%
PCF48	77.9 ± 0.1	75	51%
PCF72	77.9 ± 0.1	86	48%
PCF144	78.1 ± 0.1	94	45%

Table S4. DLS measurements on entrapment of hydrophilic drug and slightly hydrophobic drug in Fru-CCM nanocapsules in aqueous solution, where Fru= fructose, CCM= curcumin.

Drug	[Fru] mg/mL	[CCM] μg/mL	[Drug] μg/mL	Drug/CCM ratio	D_h (nm)	PDI	Morphology
Gemcitabine	10	50	4	0.1	6450	1.00	Precipitate
	10	50	8	0.2	7506	1.00	Precipitate
	10	50	18	0.5	4912	1.00	Precipitate
Doxorubicin	10	50	4.4	0.1	1242	0.55	Precipitate
	10	50	8.9	0.2	1749	0.41	Precipitate
	10	50	21.3	0.5	1778	0.46	Precipitate
	10	50	44.3	1	734.8	1.00	Precipitate

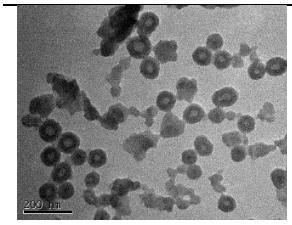
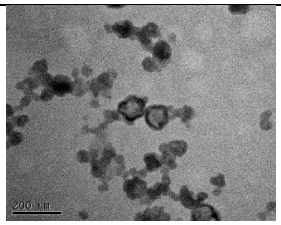
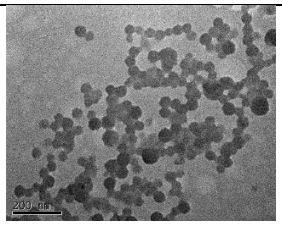
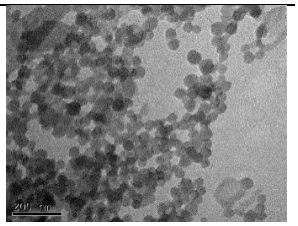
Table S5. Concentrations used for co-assembly, DLS measurements in aqueous solution before PDA coating and morphology analysis by TEM after PDA coating for 24 hours.

Drug	[Fru] mg/mL	[CCM] µg/mL	[Drug] µg/mL	Drug/ CCM ratio	D_h (nm)	PDI	Morphology
Albendazole	10	50	5	0.1	176	0.05	Hollow
	10	50	10	0.2	190	0.06	Hollow
	10	50	20	0.5	171	0.122	Solid
	10	50	40	1.0	192	0.172	Solid
Warfarin	10	50	4	0.1	179	0.029	None
	10	50	8	0.2	169	0.048	None
	10	50	21	0.5	182	0.002	None
	10	50	40	1	199	0.026	None
Ellipticine	10	50	4	0.1	219	0.138	Hollow
	10	50	8	0.2	240	0.205	Hollow
	10	50	35	1	264	0.195	Hollow/ Solid
	10	50	100	1.5	205	0.103	Solid
Sulfasalazine	10	50	5	0.1	186	0.11	Hollow
	10	50	10	0.2	169	0.024	Hollow
	10	50	25	0.5	173	0.02	Hollow
	10	50	52	1	181	0.036	Hollow
Erastin	10	50	5	0.01	105	0.108	Hollow
	10	50	10	0.1	100	0.078	Hollow
	10	50	25	0.3	95.3	0.049	Hollow/ Solid
	10	50	50	0.7	121	0.058	Solid
Paclitaxel	10	50	10	0.1	128	0.066	Hollow
	10	50	25	0.2	103	0.08	Hollow
	10	50	55	0.5	114	0.064	Hollow
	10	50	115	1	126	0.286	Solid/ Precipitate

Hollow particles

Solid nanospheres

Albendazole/ CCM

0.1	0.2	0.5	1.0
			

Ellipticine/ CCM

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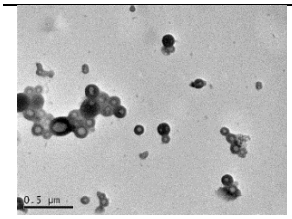
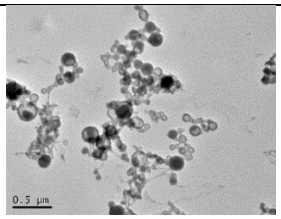
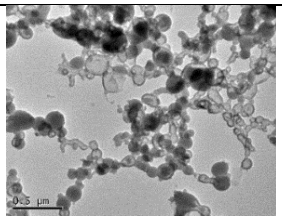
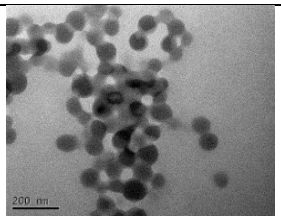
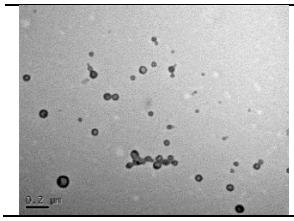
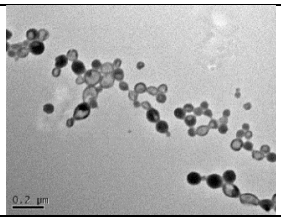
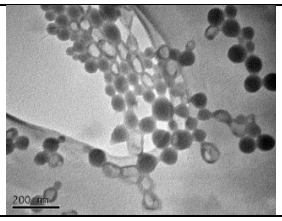
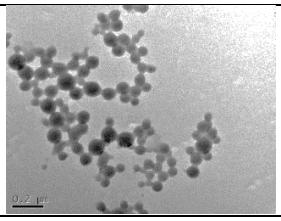
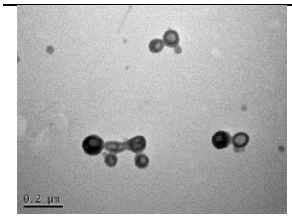
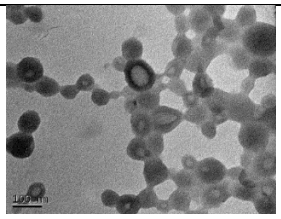
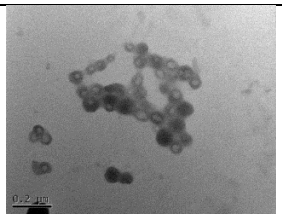
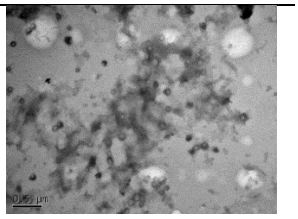
			

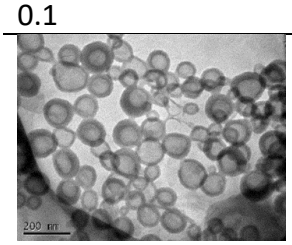
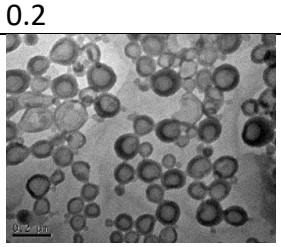
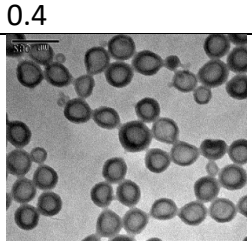
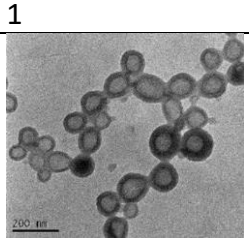
Erastin/ CCM

0.01	0.1	0.3	0.7
			

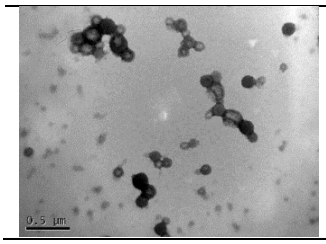
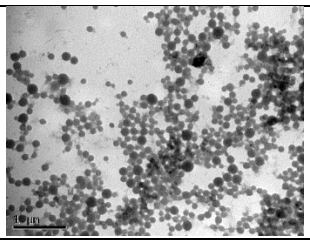
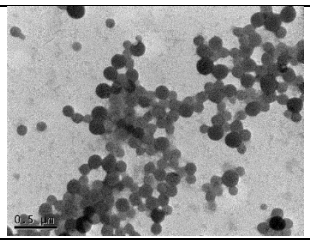
Paclitaxel/ CCM

0.1	0.2	0.4	1
			

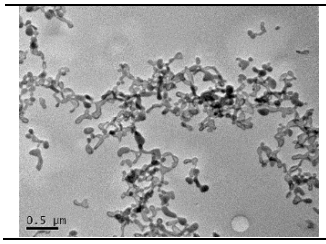
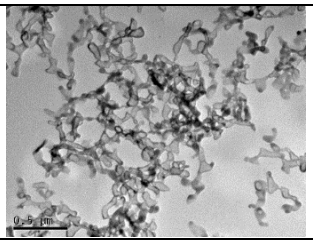
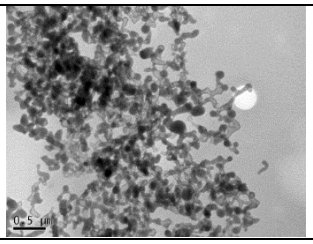
Sulfasalazine/ CCM

0.1	0.2	0.4	1
			

Compound J3

0.1	0.5	1.0
		

Compound C4

0.1	0.5	1.0
		

Compound C12

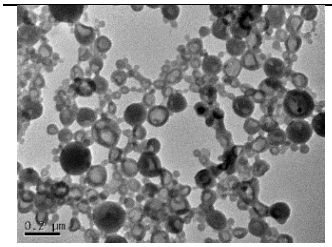
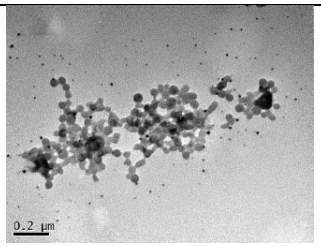
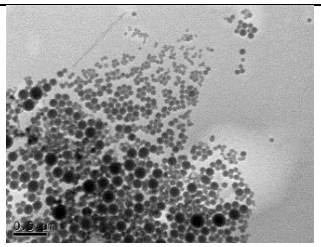
0.1	0.5	1.0
		

Figure S4. Schematic illustration of drug loaded PDA-Fru-CCM hollow particles prepared with low to high drug: CCM molar ratios for encapsulation and their corresponding TEM micrographs (no staining) with albendazole, ellipticine, erastin, sulfasalazine, paclitaxel and the compounds J3, C4, C12.

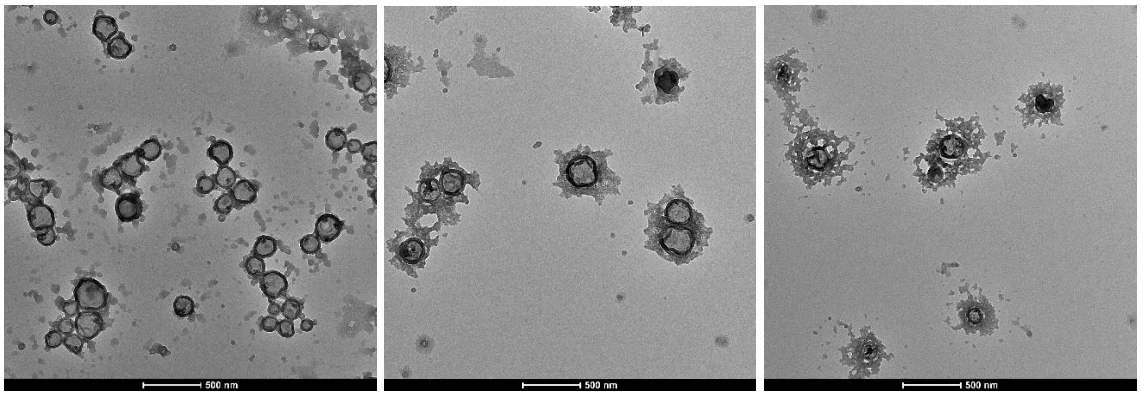


Figure S5. TEM images of high sulfasalazine (sulf) loading in PDA-Fru-CCM, prepared with (A) 1.2:1 Sulf:CCM, (B) 1.5:1 Sulf:CCM and (C) 2:1 Sulf:CCM drug ratios.

Table S6. Concentrations used for co-assembly of CCM and albendazole with a constant overall drug concentration of 50 µg/mL

	1	**2**	**3**	**4**	**5**
Fructose (mg/mL)	10	10	10	10	10
Curcumin (µg/mL)	50	40	30	20	10
Albendazole (µg/mL)	0	10	20	30	40
Before PDA coating DLS diameter (nm) and PDI	152.2 ± 0.5	144.7 ± 0.6	111.9 ± 5.1	134.8 ± 99	79.3 ± 21.5
	0.05 ± 0.01	0.05 ± 0.01	0.09 ± 0.01	0.90 ± 0.04	0.98 ± 0.02
After PDA coating DLS diameter (nm) and PDI	182.4± 1.4	157.6 ± 2.7	128.5 ± 5.7	126.9 ± 91	90.3 ± 0.5
	0.06 ± 0.02	0.07 ± 0.02	0.15 ± 0.02	0.22 ± 0.02	0.27 ± 0.01

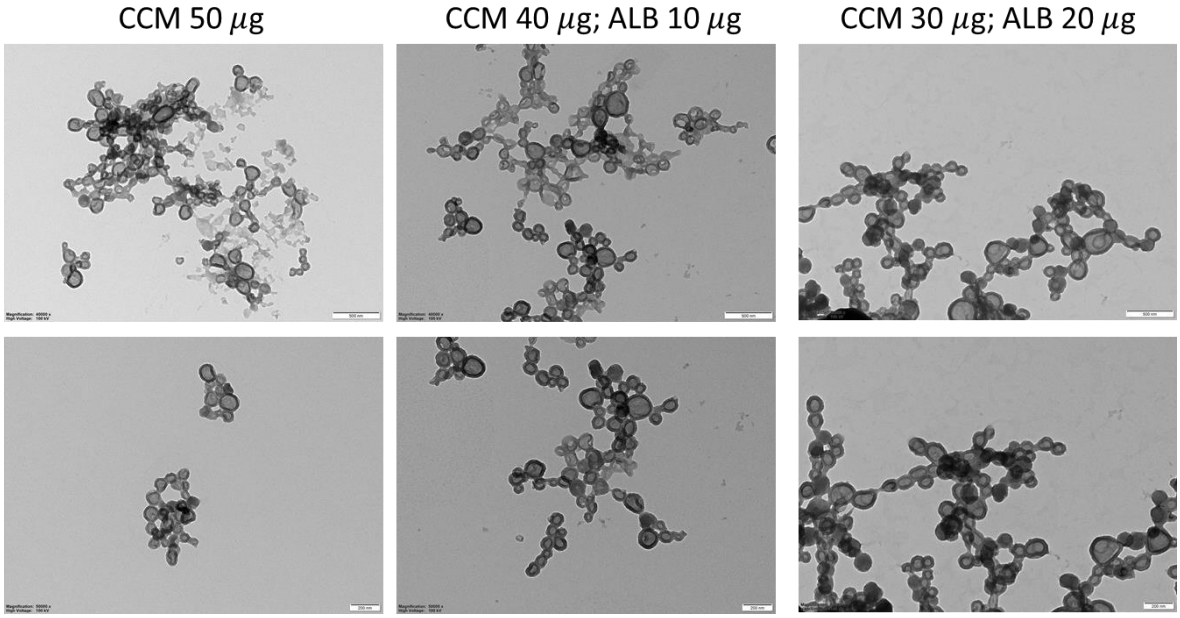


Figure S6. TEM analysis of sample **1-3** (Table S6) after PDA coating; no particles were found in sample 4 and 5

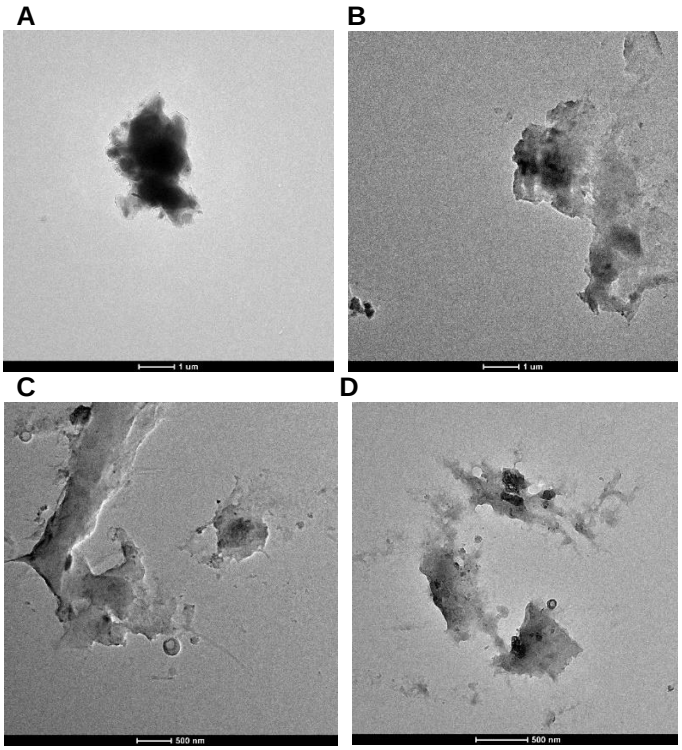
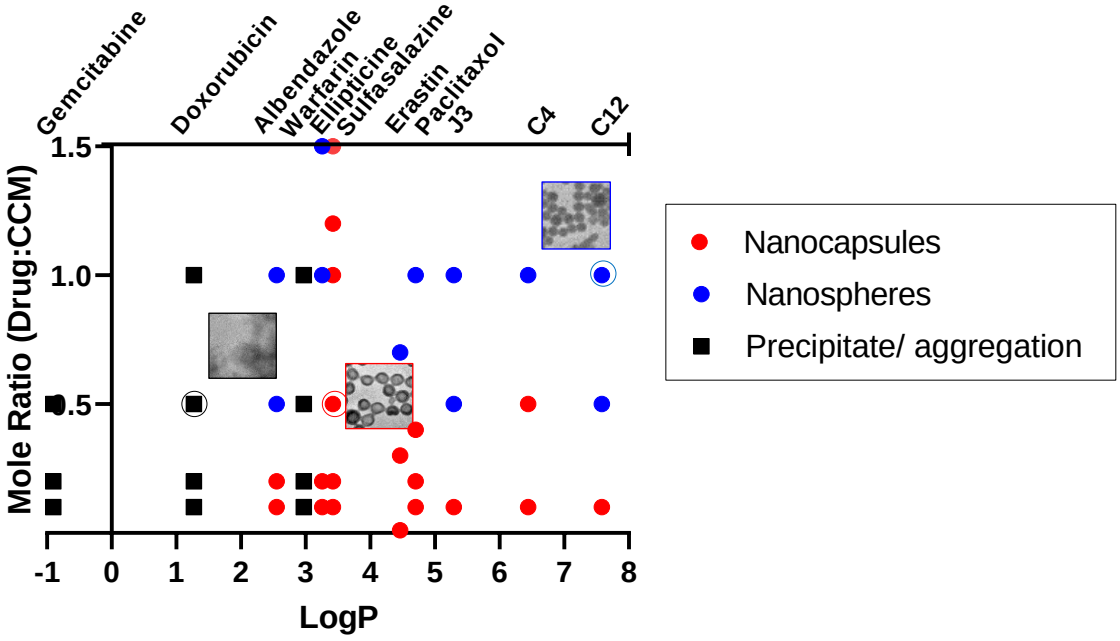


Figure S7. TEM micrographs of PDA-warfarin-CCM prepared at warfarin:CCM mole ratios A) 0.1, (B) 0.2, (C) 0.5, and (D) 1.0. Scale bar is 1μm in (A) and (B), and 500 nm in (C) and (D).

Table S7. Concentrations used for co-assembly of CCM and warfarin with a constant overall drug concentration of 50 μg/mL

Sample	**1**	**2**	**3**	**4**	**5**
Curcumin (μg/mL)	50	40	30	20	10
Warfarin (μg/mL)	0	10	20	30	40
Before coating DLS diameter (nm) and PDI	152.2 ± 0.5	711.6 ± 78	444.8 ± 67.8	512.8 ± 17.3	423.8 ± 92.6
	0.05 ± 0.01	0.27 ± 0.04	0.22 ± 0.17	0.24 ± 0.03	0.25 ± 0.02

A)



B)

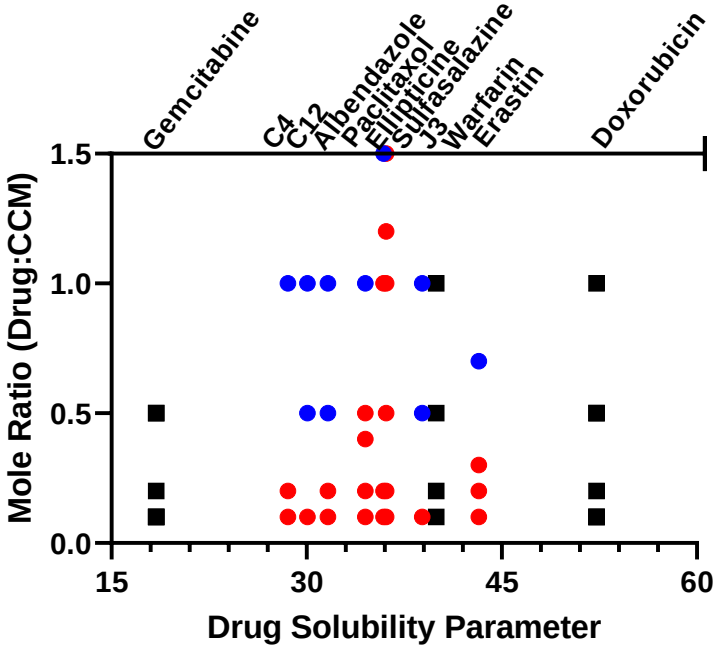


Figure S8. A) Phase diagram of various drugs with different LogP values in co-assembly with curcumin at different mole ratios and their subsequent nanoparticle morphology formed; B) Hansen Solubility Parameters and their different drug:CCM mole ratios. Morphology denoted by legend (red circle: nanocapsules, blue circle: nanospheres, black square: precipitate/ aggregation)

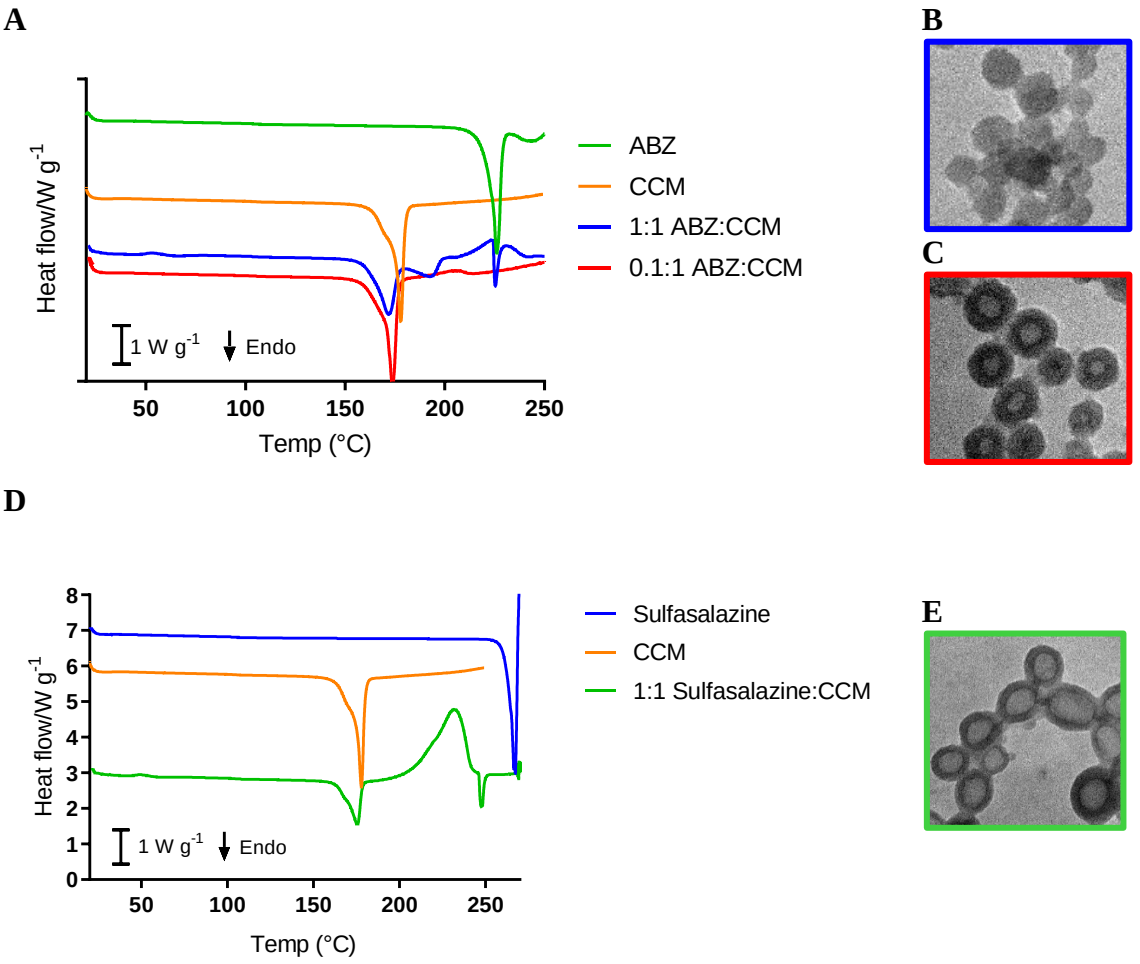


Figure S9. (A) DSC of albendazole (ABZ) and curcumin (CCM) system with molar ratios within ranges of nanoparticle and nanocapsule formation. TEM micrographs of PDA-Fru-CCM-ABZ at (B) 1:1 ratio of CCM and ABZ and (C) 1: 0.1 CCM to ABZ, (D) DSC of sulfasalazine and CCM system with molar ratio corresponding to nanocapsule formation with (E) TEM micrograph of PDA-Fru-CCM-Sulfasalazine at 1:1 ratio of Sulfasalazine and CCM.

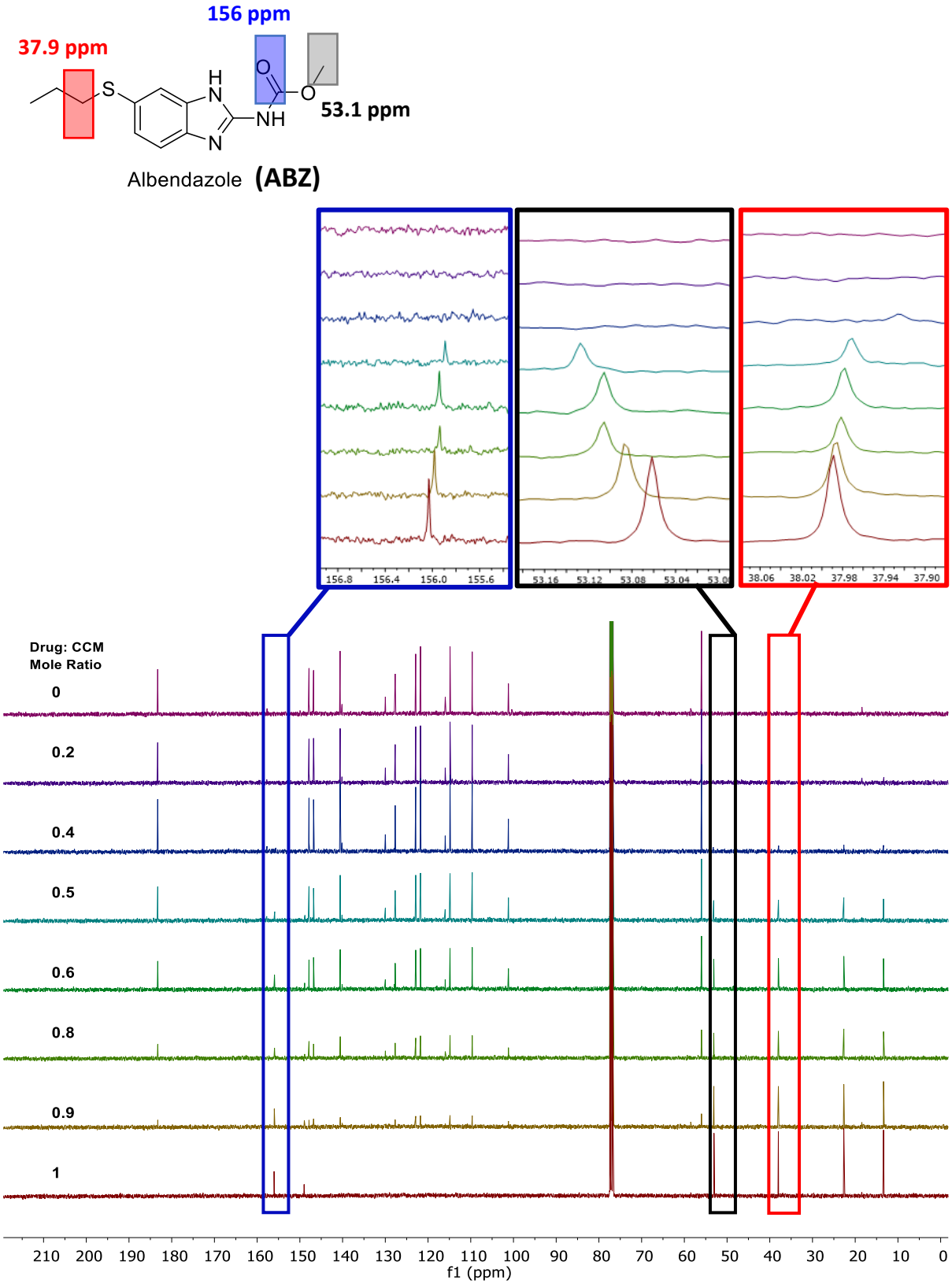


Figure S10. ^{13}C NMR (400 MHz, $CDCl_3$) stacked spectrum of drug (Albendazole, ABZ) and Curcumin (CCM) at differing mole ratios. Solutions prepared with 25 mg/mL stock solutions of albendazole and CCM in $CDCl_3$ and combined to give a total of 1.0 $x10^{-4}$ moles for desired drug:CCM mole ratio. Peak shifts highlighted in boxes where blue box: C=O at 156 ppm, black box: $-CH_3$ at 53.1 ppm and red box: $-CH_2$ at 37.9 ppm.

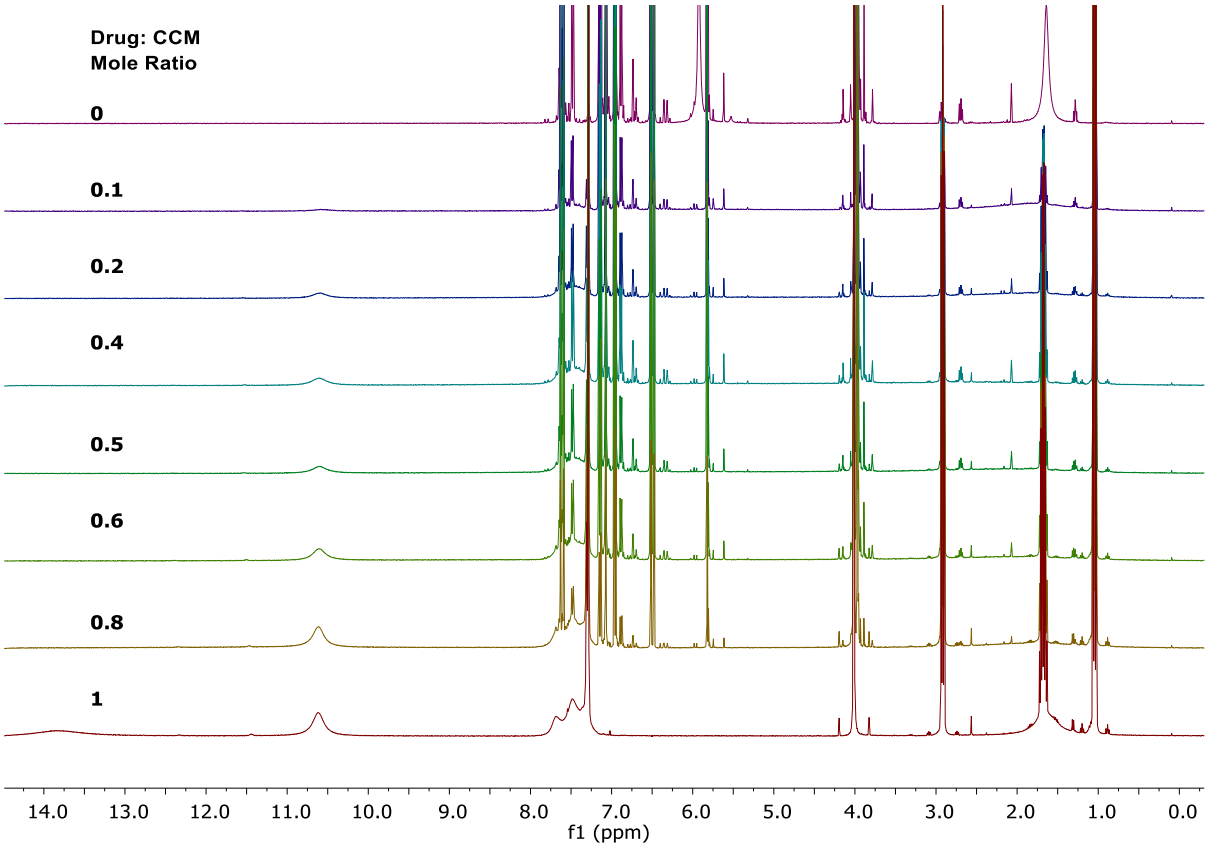


Figure S11. ^{1}H NMR (400 MHz, $CDCl_3$) stacked spectrum of drug (Albendazole, ABZ) and Curcumin at differing mole ratios. Solutions prepared with 25 mg/mL stock solutions of albendazole and CCM in $CDCl_3$ and combined to give a total of 1.0 x10^{-4} moles for desired drug:CCM mole ratio.

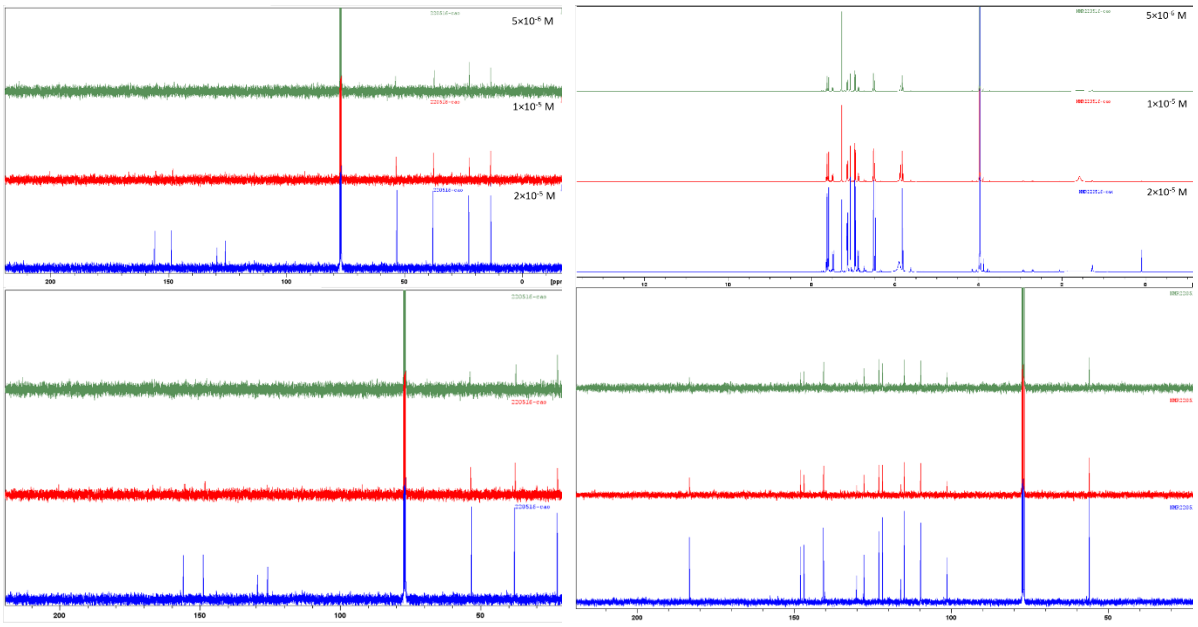


Figure S12. ^{1}H (top) and ^{13}C (bottom) NMR spectrum of albendazole (left) and curcumin (right) in $CDCl_3$ at different concentrations

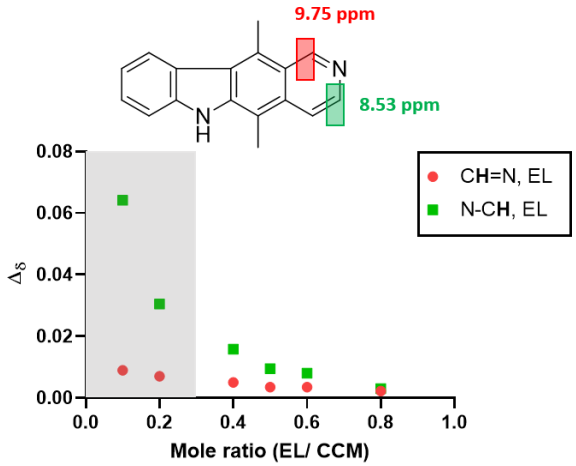


Figure S13. Job Plot of ^{1}H NMR peak shifts at predetermined mole ratio of ellipticine (EL) to CCM in $CDCl_3$. Grey area denotes range of nanocapsule formation.

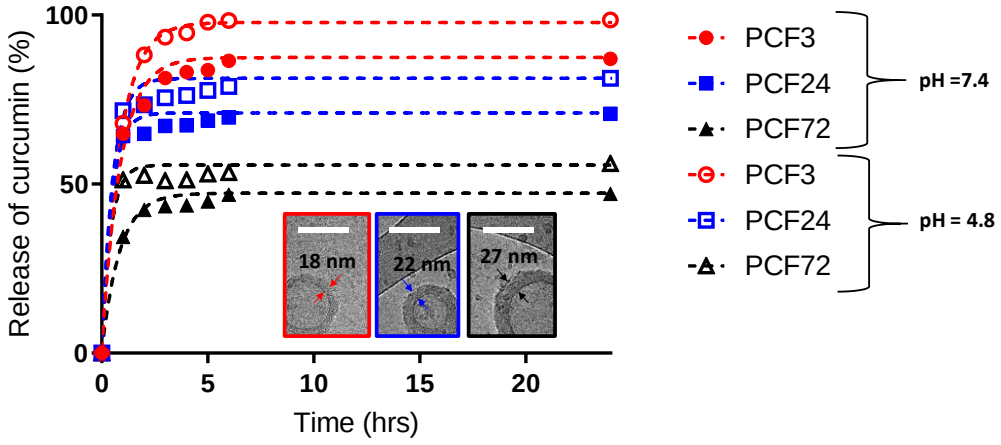


Figure S 14. The release of curcumin from PDA-Fru-CCM nanocapsules in both PBS pH 7.4 and pH 4.5 (10 mM) over 24 hours.

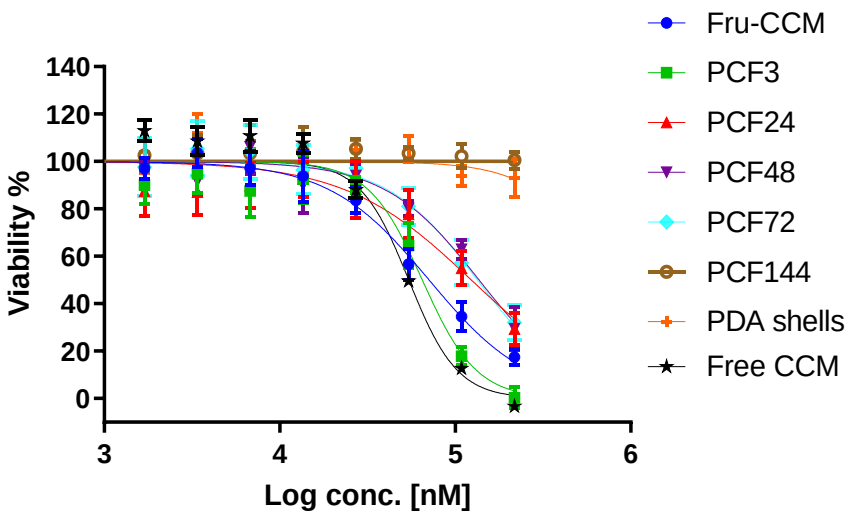


Figure S15. Dose response curve of MCF-7 cell line treated with a range of PDA-Fru-CCM nanoparticles with varying PDA shell achieved at different dopamine polymerisation times, indicated as PCFX, where X = 3,24,48, 72, and 144 hours.

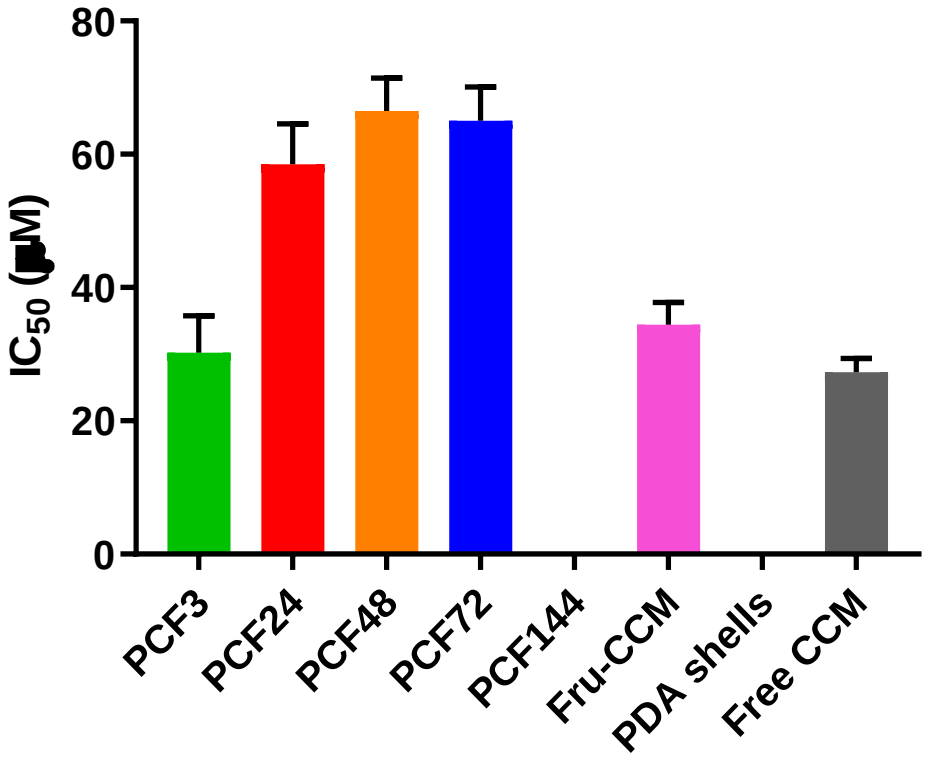


Figure S16. Half-maximal inhibitory concentration (IC_{50}) graph of PDA-Fru-CCM particles prepared with different dopamine polymerisation times (see Table S1), Fru-CCM (before PDA coating), CCM (80 μg/mL, control) and PDA shells (PDA capsules after Fru-CCM template removal by washing), tested against MCF-7 breast cancer cells measured by SRB assay.

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