SUPPORTING INFORMATION

Novel lignin nanoparticles for oral drug delivery

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Thermal and Fourier Transform Infrared Spectroscopy (FTIR) analysis

The thermal behavior of the nanoparticles in formulations was studied using differential scanning calorimetry (DSC 8000, PerkinElmer, Shelton, CT, USA). The analysis was performed in conventional (heating only) mode. Samples were equilibrated at 0 °C with a modulation of +/− 1 °C every 60 seconds and isothermal heating for 5 minutes. A heating ramp of 10 °C/min to 400 °C was used. Analyses of the scans, including the determination of glass transition (Tg), were performed using TA Instruments Universal Analysis software (TA Instruments, New Castle, DE, USA).

In order to examine chemical crosslinking interaction between citric acid and lignin nanoparticles, Fourier-Transform Infrared Spectroscopy (FTIR) was used. The IR spectra of citric acid, lignin, and crosslinked lignin nanoparticles were recorded using a FTIR spectrophotometer (ALPHA II ATR-FTIR, Bruker, USA).

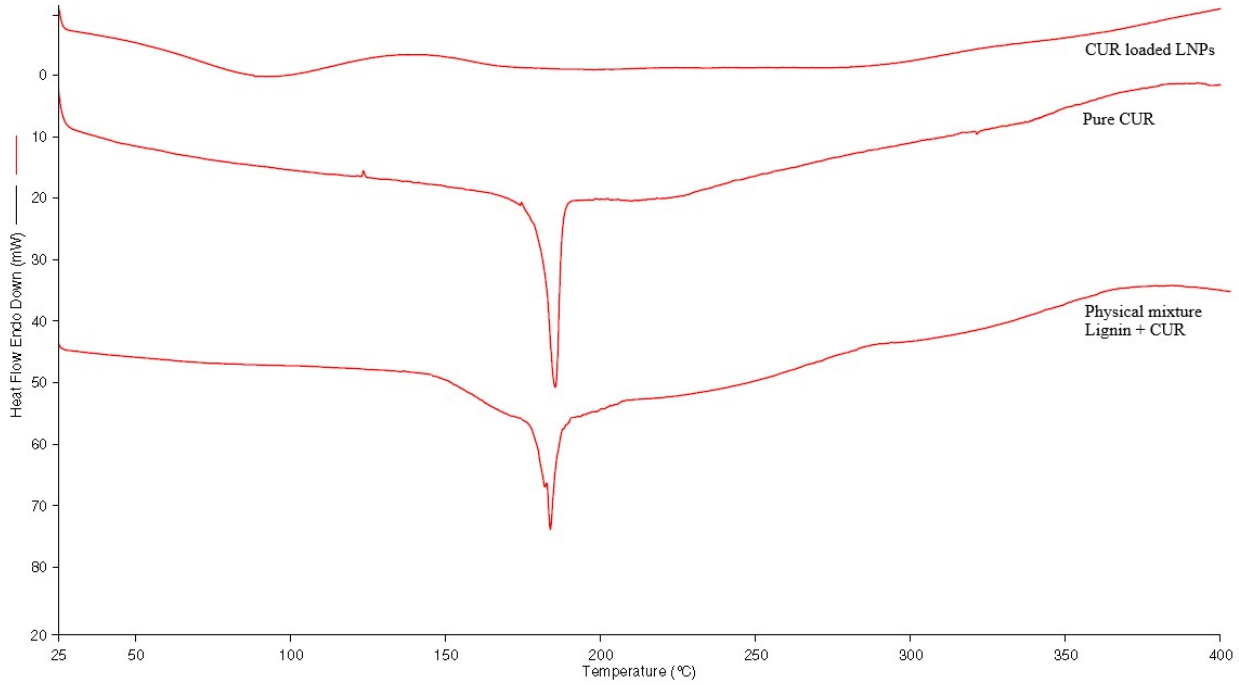


Figure S1. Differential scanning calorimetry analysis of pure curcumin, physical mixture of lignin and curcumin, and curcumin-loaded lignin nanoparticles. CUR, curcumin; LNPs, lignin nanoparticles.

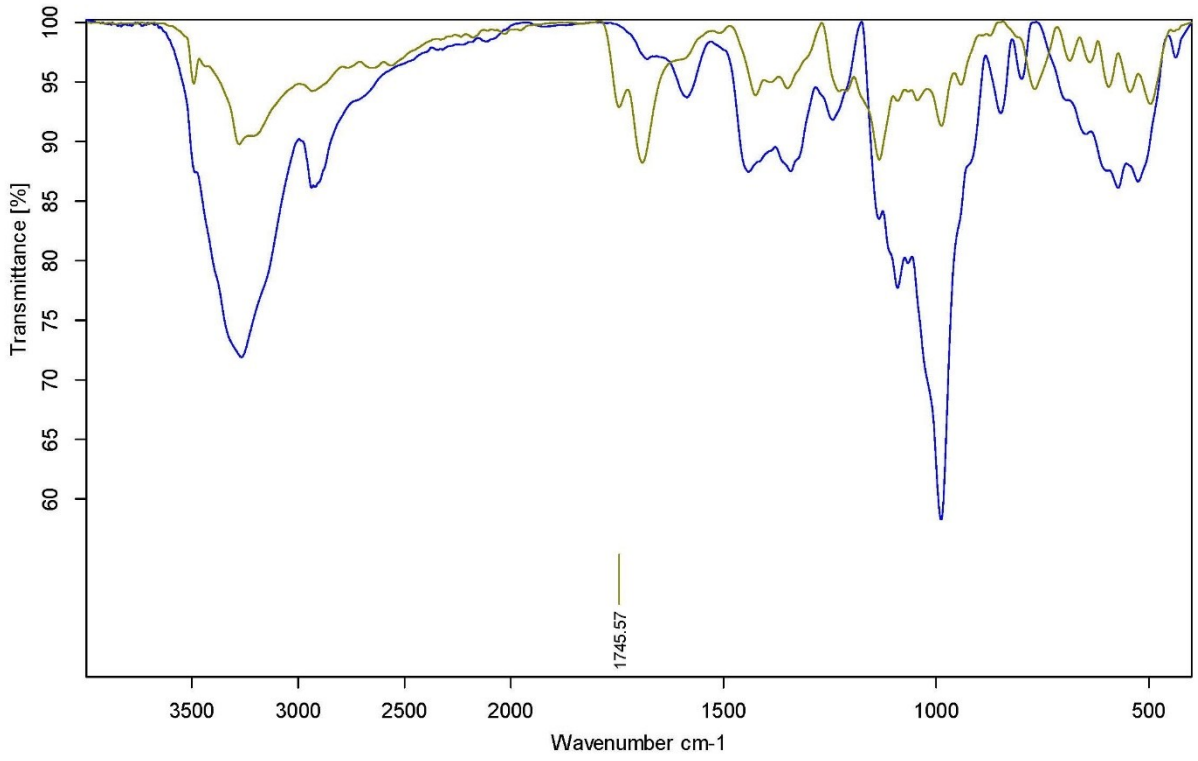
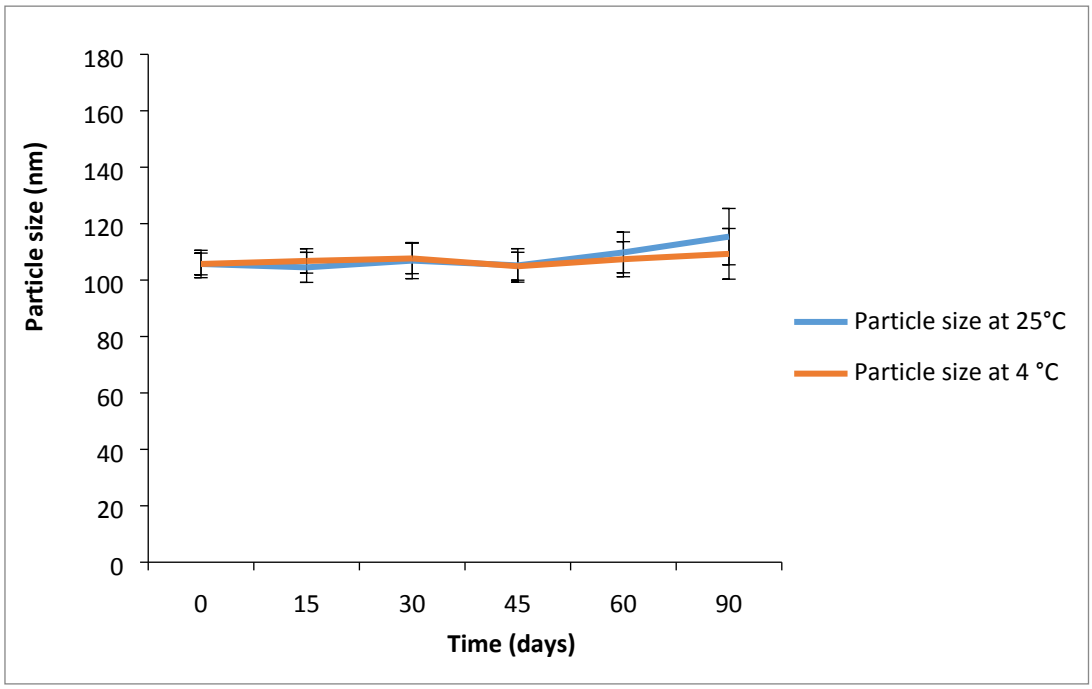
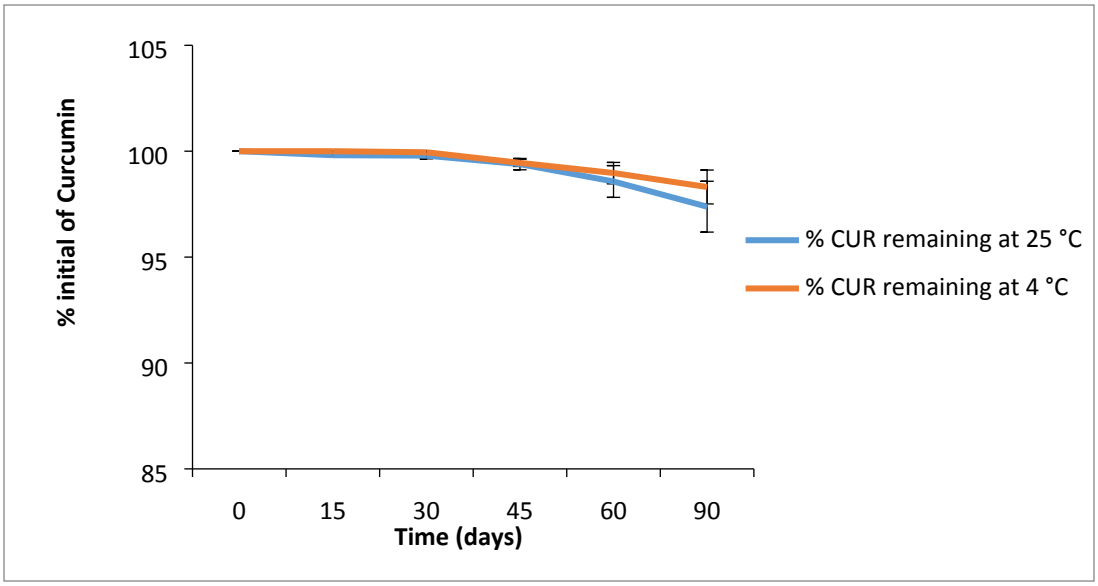


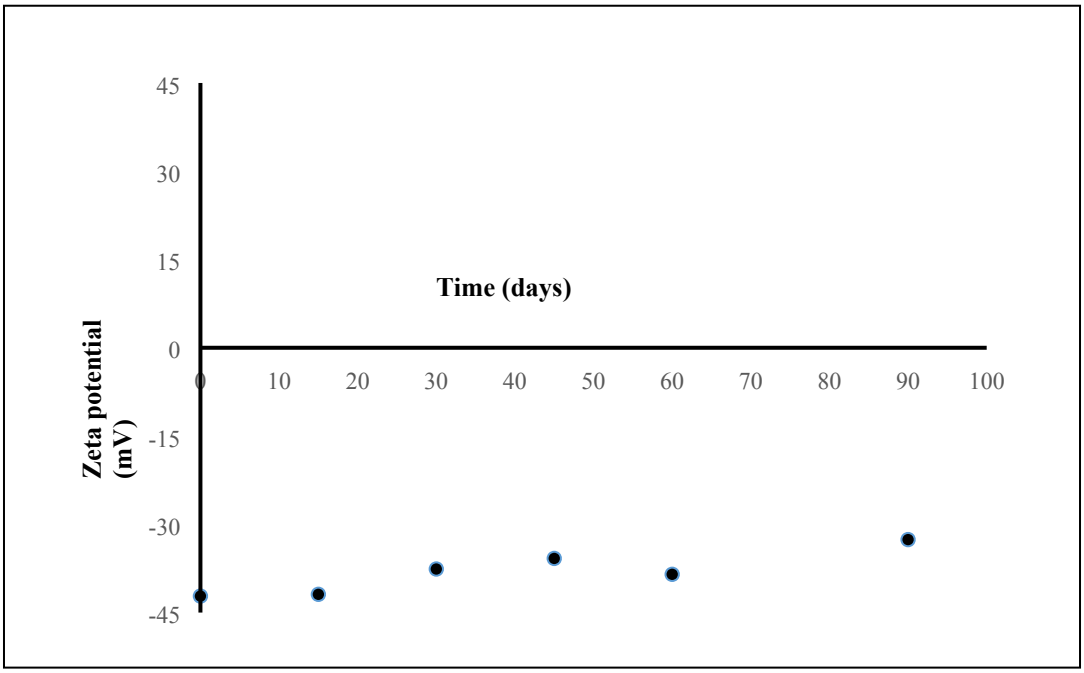
Figure S2. Fourier-transform infrared spectroscopy spectra of lignin powder (blue line) and citric acid crosslinked lignin nanoparticles (green line).

Stability of Curcumin in nanocarriers

The stability of CUR loaded LG NPs were evaluated. Briefly, 5 mg of CUR loaded nanoparticles was incubated in a constant climate chamber (Binder, Germany) at 25°C/60%±5% RH for three months (according to ICH guidelines). Around 1 mg of free curcumin was used as a control. At predetermined time points, the particle size, PDI and zeta potential were measured using the particle sizer (Malvern instrument). Curcumin content in the particles was determined using HPLC.







Figures S3. Solid state stability of free curcumin and curcumin loaded nanoparticles. Nanoparticles were kept in constant climate chamber for 3 months at 4°C or room temperature and 60% relative humidity. Each value represents mean ±SD (n=3).

Curcumin in nanoparticles was chemically stable compared to free curcumin in the solid state when tested for three months. Around 65% of curcumin degraded in free-form within hours, while more than 90% curcumin remained stable after encapsulation in nanoparticles (Fig. S3). The particle size of CUR loaded LG NPs increased slightly after three months, while there was no change in the zeta potential or dispersity index (Fig. S3). Particles with zeta potential values around ±30 mV is reported to be stable for overcoming particle aggregation (Bhattacharjee 2016). Overall, the stability studied indicate that the lignin based nanoparticles can enhance the chemical stability of curcumin.

Influence of pH and Ionic Strength on LNPs stability

To determine the effect of pH on nanoparticle size and zeta potential, the nanoparticles were dispersed in different solutions varying in pH from 2 to 10. The pH was adjusted using 0.1 M HCl or 0.1 M NaOH. Similarly, the effect of salt concentrations (0–200 mM NaCl) on particle size and zeta potential of the nanoparticles was also determined.

Table S1. Influence of pH on mean size and polydispersity index of lignin nanoparticles.

pH	Particle size (nm)	PDI
2	116.7 ± 12.03	0.110 ± 0.018
3	106.1 ± 10.32	0.104 ± 0.015
4	99.7 ± 11.23	0.108 ± 0.048
5	91.6 ± 9.23	0.103 ± 0.024
6	85.8 ± 8.91	0.105 ± 0.019
7	83.5 ± 7.10	0.097 ± 0.012
8	82.7 ± 5.31	0.093 ± 0.011
9	80.4 ± 7.82	0.102 ± 0.016

PDI, polydispersity index.

Table S2. Effect of ionic strength on particle characteristics of lignin nanoparticles.

Ionic strength (mM, NaCl)	Particle size (nm)	PDI	Zeta potential (mV)
0	82.3 ± 7.10	0.108 ± 0.05	-41.3 ± 3.5
10	85.16 ± 8.72	0.085 ± 0.025	-39.25 ± 4.6
20	93.34± 10.55	0.105 ± 0.015	-35.8 ± 3.41
50	91.33± 14.30	0.109 ± 0.016	-32.15 ± 2.90
100	83.30± 9.54	0.112 ± 0.018	-25.05 ± 3.81
150	92.86± 9.56	0.108 ± 0.021	-18.6 ± 5.49
200	91.10± 6.36	0.092 ± 0.018	-16.15 ± 4.21

PDI, polydispersity index.

Non-linear fit of NR release kinetics using different models

Table S3. Curcumin release kinetics using different models.

Release medium	R^2				
	Zero Order	First Order	Korsmeyer-Peppas	Hixson-Crowell	Higuchi
SGF	0.967	0.856	0.991	0.845	0.974
SIF	0.868	0.901	0.985	0.856	0.913

SGF: Simulated Gastric Fluid, SIF: Simulated Intestinal Fluid; R^2 was calculated from SigmaPlot software (SigmaPlot 2001, SPSS Inc., USA).