Electronic Supplementary Material (ESI) for Nanoscale.

Enhanced Blood Brain Barrier Permeability and Glioblastoma Cell Targeting via Thermoresponsive Lipid Nanoparticles

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Preparation of Thermoresponsive Lipid Mixtures (TLM)

TLM were prepared by the addition of liquid fatty acids, oleic acid or linoleic acid, to solid lipids (stearic acid, palmitic acid, myristic acid and lauric acid) in defined ratios. The melting point of lipid mixtures was plotted against liquid content and straight line equations were derived as shown in Figure S1. These equations were rearranged and the liquid content required for TLM (x) was calculated by placing the value of the required melting point (y) at 39.

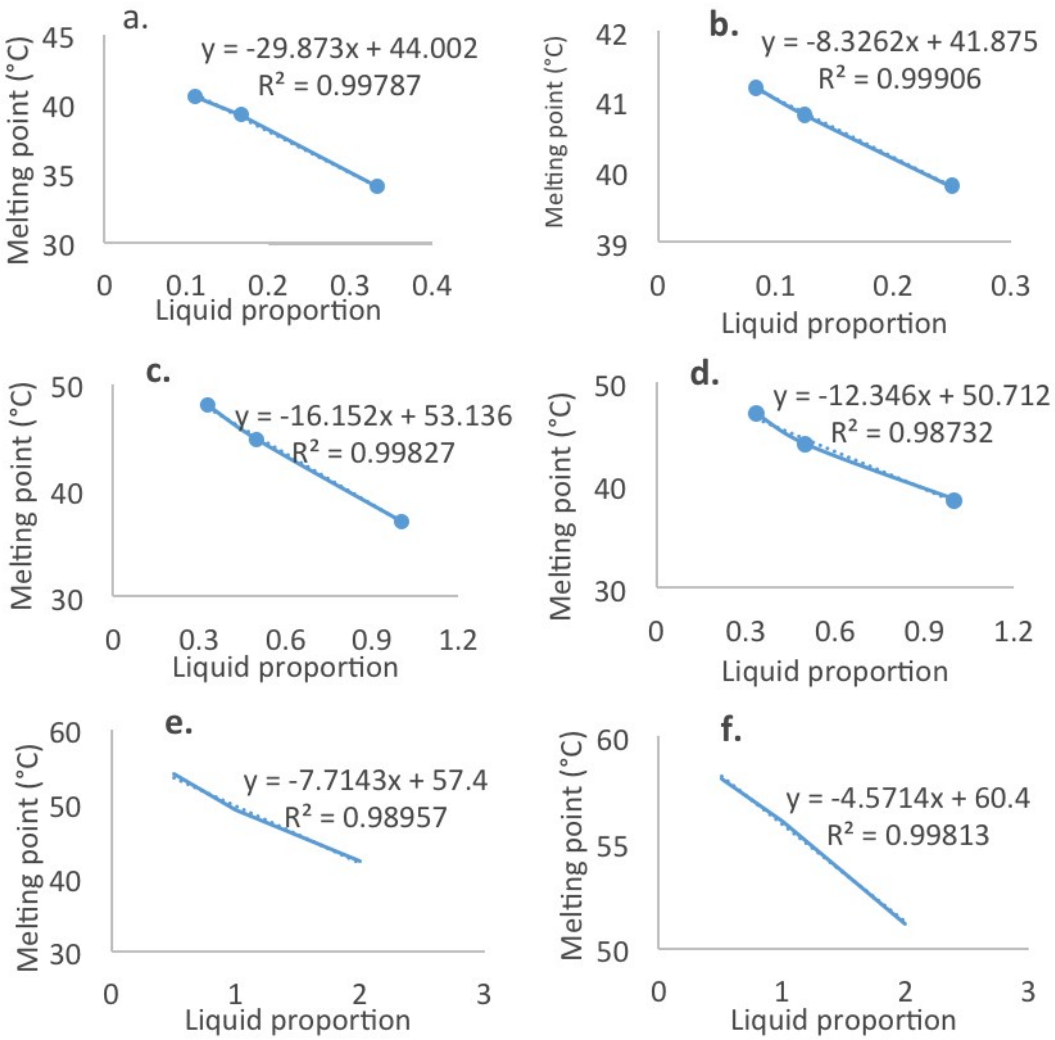

Figure S1: Graph between liquid content and melting points of, (a) lauric acid and oleic acid, (b) lauric acid and linoleic acid, (c) myristic acid and oleic acid, (d) myristic acid and linoleic acid, (e) palmitic acid and oleic acid, and (f) stearic acid and oleic acid.

FTIR studies

FTIR studies were completed to evaluate the compatibility of paclitaxel with TL and surfactants. Most paclitaxel peaks were superimposed by the peaks of lipid and surfactants (Figure S2). However, the aliphatic secondary amine stretch was at 3500-3300 cm^{-1} while the asymmetrical and symmetrical methyl stretches were present at 3000-2800 cm^{-1} (Coates, 2000). The lower intensity of the paclitaxel peaks in TLN is due to the lower amount of the drug present as compared to the lipids and surfactants.

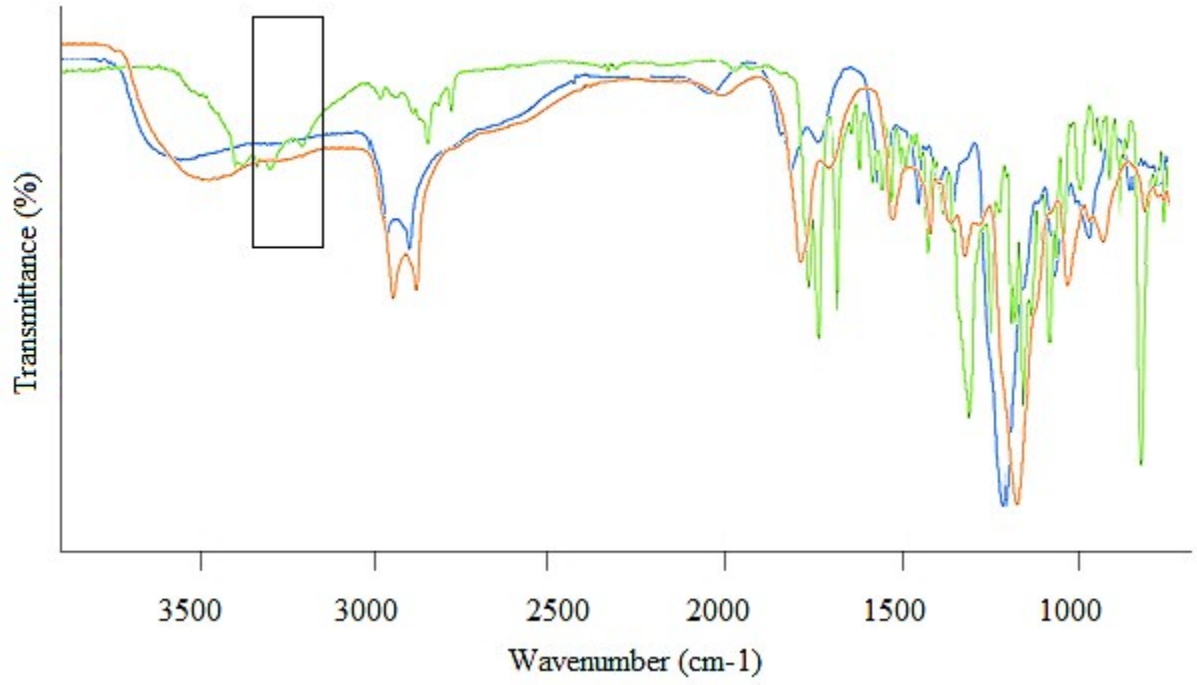

Figure S2: FTIR spectra of paclitaxel (green), TLN2 (blue) and TLN4 (red). Characteristic peaks of paclitaxel are shown in TLN by black box.

Dissolution kinetics analysis

Dissolution kinetics analysis was completed by fitting drug release profiles in different kinetic models (Table S1). The order of drug release was evaluated by data fitting to zero order and first order models. The mechanism of drug release was evaluated by data fitting to the Higuchi, Korsmeyer-Peppas, Hixon-Crowell and Weibull models. An R^2 value close to 1 would indicate a perfect fit.

It was found that R^2 values were higher for a zero order model which indicated drug release independent of the amount of drug in the TLN. The drug release mechanism was found to be anomalous at 37°C because data showed a good fit to both the Higuchi and Hixon-Crowell models. Similarly, the release exponent (n) in the Korsmeyer-Peppas model was between 0.5-1. On the other hand, the drug was released at 39°C by a diffusion controlled mechanism as indicated by the release exponent less than 0.5 and a good fit to the Higuchi model as compared to other models.

Table S1. Dissolution kinetic analysis of drug release profiles for the prediction of order, rate and mechanism of drug release.

Formulation	Zero order		First order		Korsmeyer-Peppas model			Higuchi model		Hixon-Crowell model		Weibull model	
	R^2	K_0	R^2	K	R^2	K	n	R^2	K_H	R^2	K_s	R^2	B
At 37 °C													
TLN1	0.9854	1.8133	0.8887	0.0726	0.9916	1.7840	0.7728	0.9800	7.6086	0.9978	0.0804	0.8808	0.0389
TLN2	0.9334	2.3173	0.7708	0.0591	0.9854	2.8341	0.5980	0.9961	10.1184	0.9833	0.08663	0.7613	0.0557
TLN3	0.9444	2.6749	0.8094	0.0681	0.9969	2.3246	0.6724	0.9981	11.5076	0.9948	0.0829	0.8028	0.0649
TLN4	0.9554	1.5450	0.8715	0.0551	0.9865	2.6828	0.6185	0.9821	7.8633	0.9809	0.0654	0.8650	0.0388
TLN5	0.9392	2.5562	0.8121	0.0570	0.9946	2.7482	0.6095	0.9965	9.8740	0.9851	0.0723	0.8034	0.0525
TLN6	0.9493	1.8452	0.8949	0.0460	0.9916	3.6148	0.5079	0.9867	8.5946	0.9770	0.0602	0.8888	0.0426
TLN7	0.9137	2.55	0.8349	0.045	0.9946	3.8318	0.49	0.9972	12.06	0.9776	0.06	0.8294	0.06
TLN8	0.9723	2.7267	0.8270	0.0522	0.9931	3.3757	0.5331	0.9914	11.1726	0.9791	0.0692	0.8203	0.0605
TLN9	0.9540	2.4186	0.8583	0.0564	0.9975	2.8356	0.5974	0.9972	10.4057	0.9928	0.0650	0.8520	0.0547
OM	0.9851	21.7500	0.9221	0.3018	0.9981	2.3017	0.4822	0.9997	42.3477	0.9358	0.1523	0.9717	0.9283
At 39 °C													
TLN1	0..9751	13.3330	0.9286	0.1939	0.9982	1.9714	0.4221	0.9975	46.5665	0.9543	0.1968	0.9278	0.8196
TLN2	0.9749	18.0000	0.9390	0.2350	0.9956	1.7031	0.4135	0.9931	57.0577	0.9946	0.2382	0.9536	1.0916

TLN3	0.9687	7.3619	0.9055	0.1191	0.9961	2.7662	0.4092	0.9950	33.9690	0.8543	0.1211	0.9041	0.4474
TLN4	O.9537	9.5143	0.8895	0.1405	0.9973	2.5759	0.4007	0.9933	36.2398	0.9807	0.1430	0.8882	0.4858
TLN5	0.9505	10.8480	0.8847	0.1744	0.9937	2.2257	0.4241	0.9906	40.2138	0.9954	0.1774	0.8834	0.5744
TLN6	0.9343	9.3751	0.8647	0.1545	0.9879	2.4367	0.3619	0.9788	38.7619	0.9863	0.1572	0.8635	0.5416
TLN7	0.9166	11.9290	0.8403	0.1877	0.9775	2.1758	0.4398	0.9711	41.9033	0.9329	0.1909	0.8389	0.6418
TLN8	0.9412	9.0625	0.8422	0.1593	0.9781	2.4151	0.3680	0.9708	36.7512	0.9747	0.1623	0.8408	0.4945
TLN9	0.9320	7.7881	0.8337	0.1456	0.9789	3.2325	0.3735	0.9807	33.0545	0.9842	0.1956	0.8315	0.3677