Supporting Information: Impact of Drug Physicochemical Properties on Lipolysis-triggered Drug Supersaturation and Precipitation from Lipid-Based Formulations

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All solubility samples in dispersion and digestion media, as well as drug loaded IIIB-MC lipolysis samples were analyzed by an HPLC coupled to a diode array detector (1290 Infinity with a Zorbrax Eclipse XDB-C18 column 4.6 x 100 mm, Agilent Technologies, USA). The accuracy of the HPLC-analyzes was controlled by quality control samples, prepared from a separate stock solution and recovery samples with a known concentration of drug. Prior to analysis, diluted samples were centrifuged at 22 °C, 21,000 g for 10 min. The injection volume was consistently 20 ul. Compound-specific analytical conditions are found in Table S1.

Table S1. Compound-specific HPLC analytical conditions.

Compound	Mobile phase (% v/v)		Wavelength (nm)	Flow rate (ml/min)	t_r (min)
	Solvent A	Solvent B			
Cinnarizine	80% 25 mM NaAc buffer pH 5.0	20% ACN	253	1.0	2.4
Danazol	30% 25 mM NaAc buffer pH 5.0	70% ACN	286	1.0	2.5
Felodipine	20% 25 mM NaAc buffer pH 5.0	80% ACN:MeOH 1:1	360	1.0	2.0
Griseofulvin	40% H_2O	60% ACN	292	1.0	1.5
Haloperidol	40% 25 mM NaAc buffer pH 5.0	60% ACN:MeOH 1:1	248	0.8	1.9
Indomethacin	70% ACN:H_2O:FA 95:5:0.1	30% ACN:H_2O:FA 5:95:0.1	320	1.0	1.9
Ketoconazole	40% 10 mM PH buffer pH 8.5	60% ACN	297	0.8	2.3
Niclosamide	75% ACN:H_2O:FA 95:5:0.1	25% ACN:H_2O:FA 5:95:0.1	332	1.0	2.4

Abbreviations: Retention time (t_r)

Table S2. X-variables and Y-response used as input for PLS-DA of drug precipitation behavior from LBFs under digestive conditions.

Compound	Mw (g/mol)	A/B/N	Ionized at lipolysis	Tm (°C)	GF/nGF	Solid form
Carvedilol	406.5	B	n	115	GF	A
Cinnarizine	368.6	B	y	119	GF	A
Danazol	337.5	N	n	227	GF	C
Felodipine	384.3	N	n	143	GF	A
Fenofibrate	360.9	N	n	79	GF	C
Griseofulvin	352.8	N	n	217	nGF	C
Halofantrine	500.5	B	y	89	nd	A
Indomethacin	357.8	A	y	160	GF	A
Loratidine	382.9	B	n	134	GF	C
Niclosamide	327.1	A	n	231	nGF	C
Simvastatin	418.6	N	n	135	GF	A
Tolfenamic acid	261.7	A	y	213	nGF	C

Abbreviations: acid (A); base (B); neutral in the pH range 2–12 (N), No (n), Yes (y), not determined (nd), glass-former (GF), non-glassformer (nGF), amorphous (A), crystalline (C).

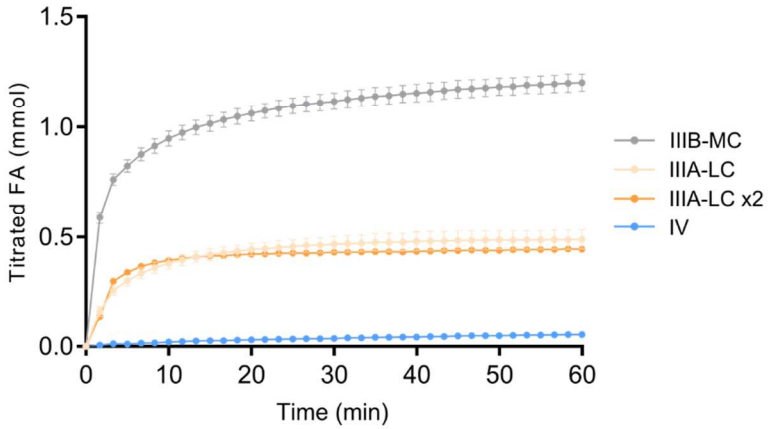

Figure S1. Liberated ionized free fatty acids (FFAs) during 60 minutes of *in vitro* digestion (37 °C) from LBFs; IIIA-LC, IIIB-MC and IV (n =3). The IIIA-LC was digested using 4.44 ml (IIIA-LC) and 8.88 ml (IIIA-LC x2) of the pancreatic extract (n = 1). The similar FFA release profiles shows that 4.44 ml of the pancreatic extract (~ 6,600 TBU/ml extract) was sufficient for achieving complete digestion. The values have been corrected for the level of FFA released by the lipolysis media.

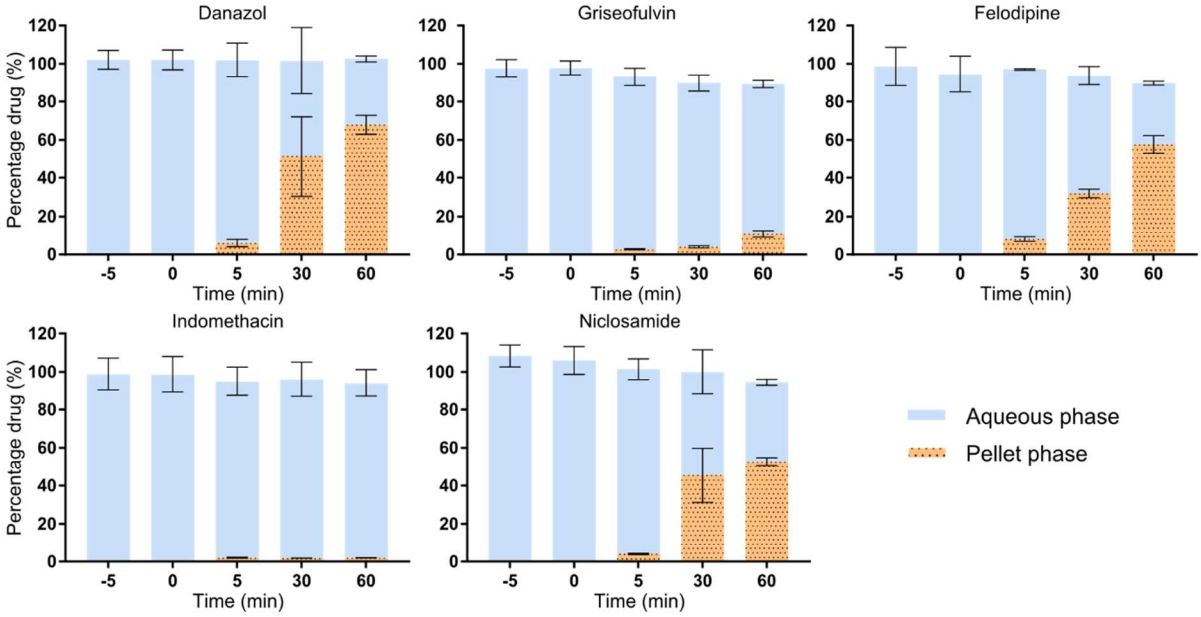

Figure S2. Percentage of drug in aqueous and pellet phase respectively (37 °C, pH 6.5), at 5 and 10 minutes of dispersion and 5, 30, and 60 minutes of digestion.