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Article

Supplementary Materials: Assessment of the Inter-Batch Variability of Microstructure Parameters in Topical Semisolids and Impact on the Demonstration of Equivalence

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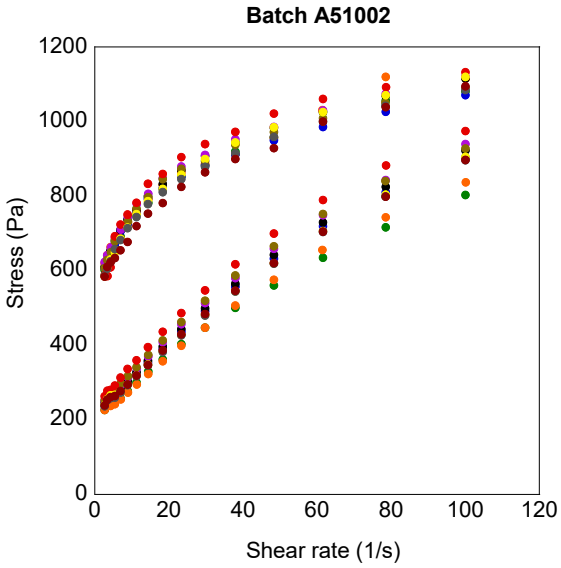
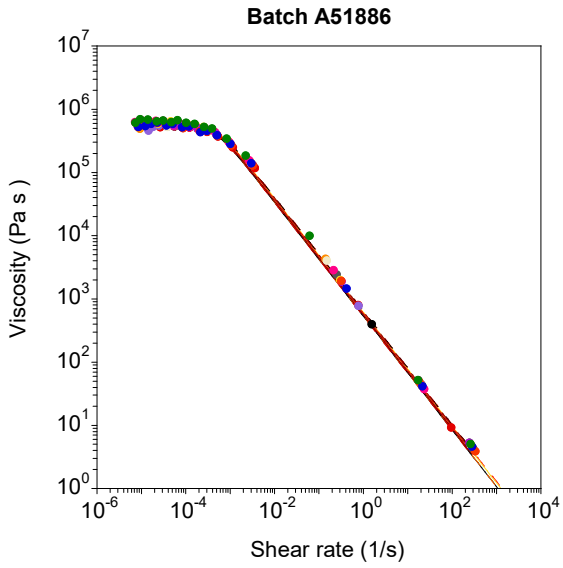
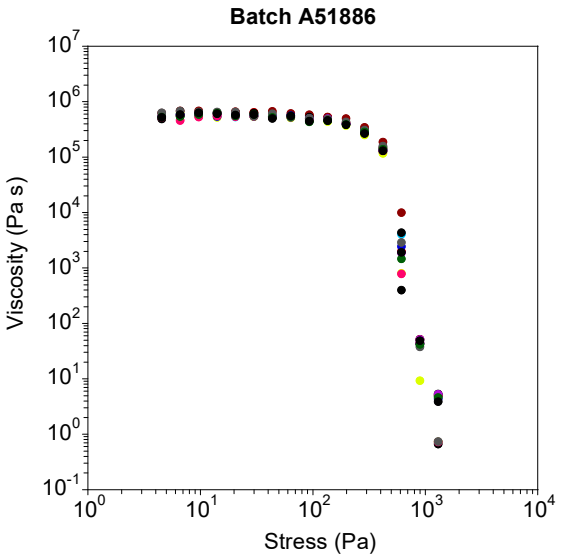


(**A**)



(**B**)



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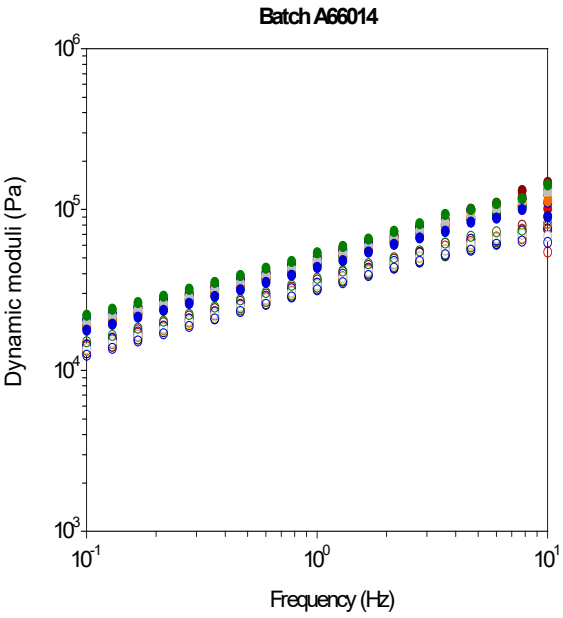
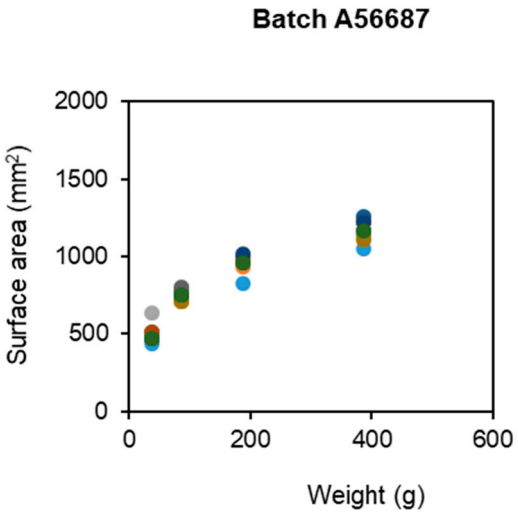


(**D**)



(**E**)

Figure S1. Representative rheograms of evaluated batches. (**A**) Hysteresis cycle. (**B**) Viscosity *versus* shear rate fitted to Carreau model. (**C**) Viscosity versus shear stress. (**D**) Elastic modulus G′ (closed symbols) and viscous modulus G′′ (open symbols) *versus* frequency. (**E**) Surface area *versus* weight (spreadability assay).

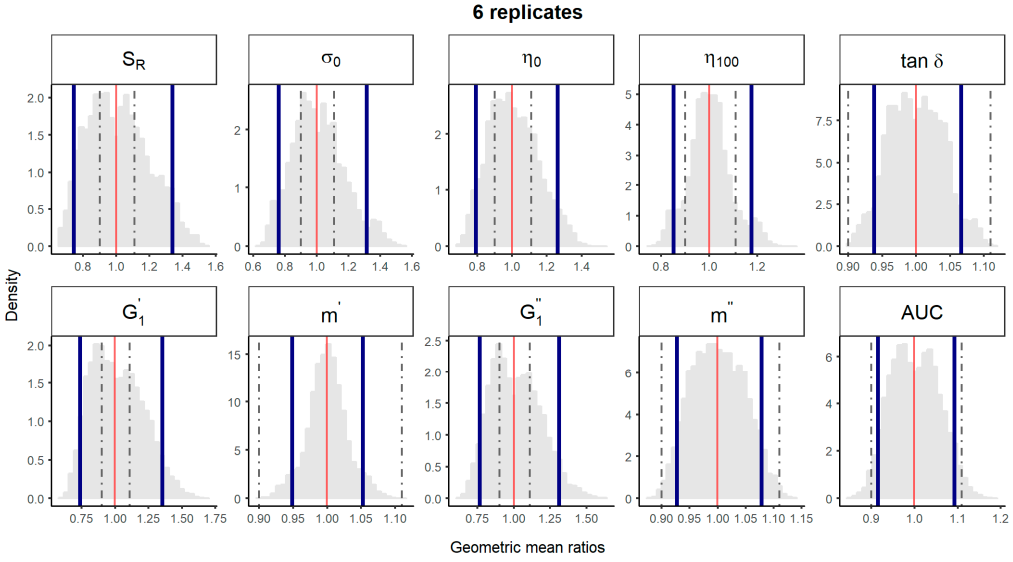


Figure S2. Bootstrap analysis of rheological parameters using 6 replicates - 1 reference batch *versus* 1 reference batch. 10,000 geometric mean ratios (light grey area) resulting from the bootstrap analysis of "1 reference batch *versus* 1 test batch" for each rheological parameter. Data of 10 batches and 6 replicate each were used. Median (red line) and non-parametric 90% CI (blue lines) of the probability distribution. Dashed lines represent the acceptance limits for equivalence (90–111.11%) stated in the EMA guideline [4]. S_R, relative thixotropic area; σ_0, yield stress; η_0, zero-shear viscosity; η_{100}, viscosity at 100 s^{-1}; *tan* δ, loss tangent at 1 Hz; G_1', calculated elastic modulus; G_1'', calculated viscous modulus; m' and m" are the parameters obtained when fitting G' and G'', respectively, *versus* frequency; *AUC*, area under the weight *versus* surface curve (spreadability).

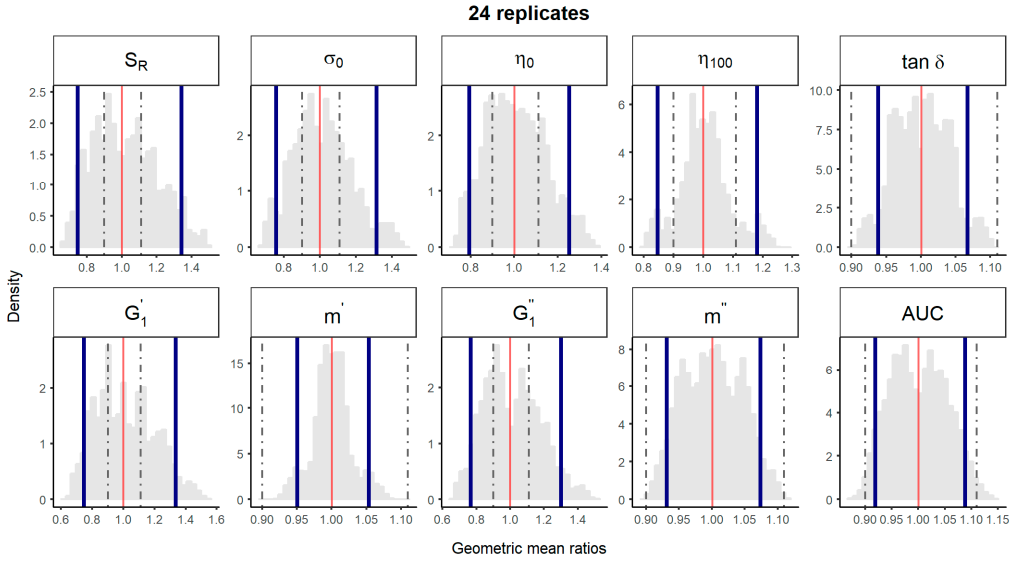


Figure S3. Bootstrap analysis of rheological parameters using 24 replicates - 1 reference batch *versus* 1 reference batch. 10,000 geometric mean ratios (light grey area) resulting from the bootstrap analysis of "1 reference batch *versus* 1 test batch" for each rheological parameter. Data of 10 batches and 24 replicate each were used. Median (red line) and non-parametric 90% CI (blue lines) of the probability distribution. Dashed lines represent the acceptance limits for equivalence (90–111.11%) stated in the EMA guideline [4]. .S_R, relative thixotropic area; σ_0, yield stress; η_0, zero-shear viscosity; η_{100}, viscosity at 100 s^{-1}; *tan* δ, loss tangent at 1 Hz; G_1', calculated elastic modulus; G_1'', calculated viscous modulus; *m'* and m" are the parameters obtained when fitting *G'* and *G''*, respectively, *versus* frequency; *AUC*, area under the weight *versus* surface curve (spreadability).

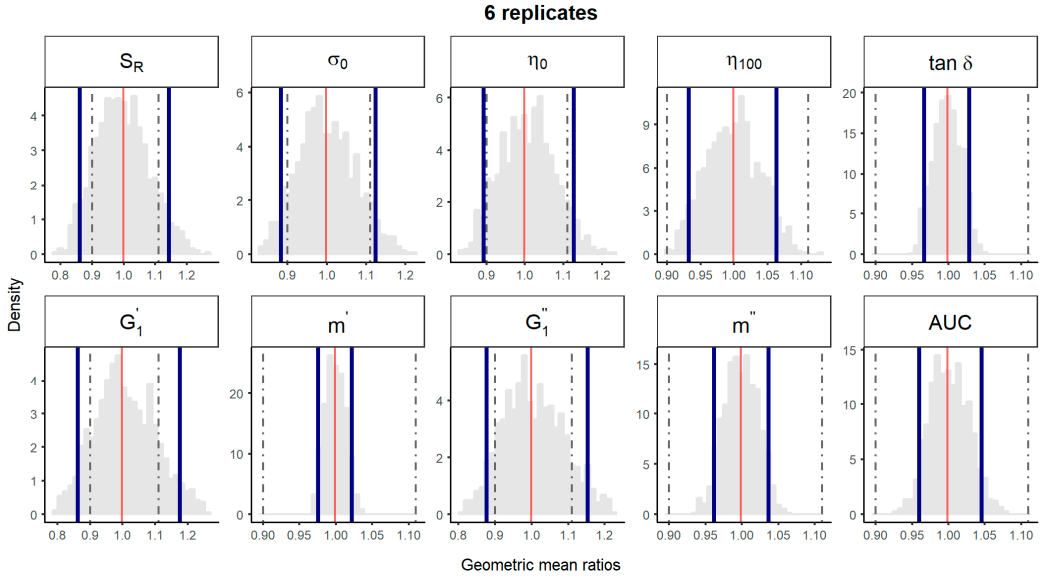


Figure S4. Bootstrap analysis of rheological parameters using 6 replicates – 5 reference batches *versus* 5 references batches.10,000 geometric mean ratios (light grey area) resulting from the bootstrap analysis of "5 reference batches *versus* 5 test batches" for each rheological parameter. Data of 10 batches and 6 replicate each were used. Median (solid red line) and non-parametric 90% CI (solid blue lines) of the probability distribution. Dashed lines represent the acceptance limits for equivalence (90–111.11%) stated in the EMA guideline [4]. .S_R, relative thixotropic area; σ_0, yield stress; η_0, zero-shear viscosity; η_{100}, viscosity at 100 s^{-1}; *tan* δ, loss tangent at 1 Hz; G_1', calculated elastic modulus; G_1'', calculated viscous modulus; *m'* and m" are the parameters obtained when fitting *G'* and *G''*, respectively, *versus* frequency; *AUC*, area under the weight *versus* surface curve (spreadability).

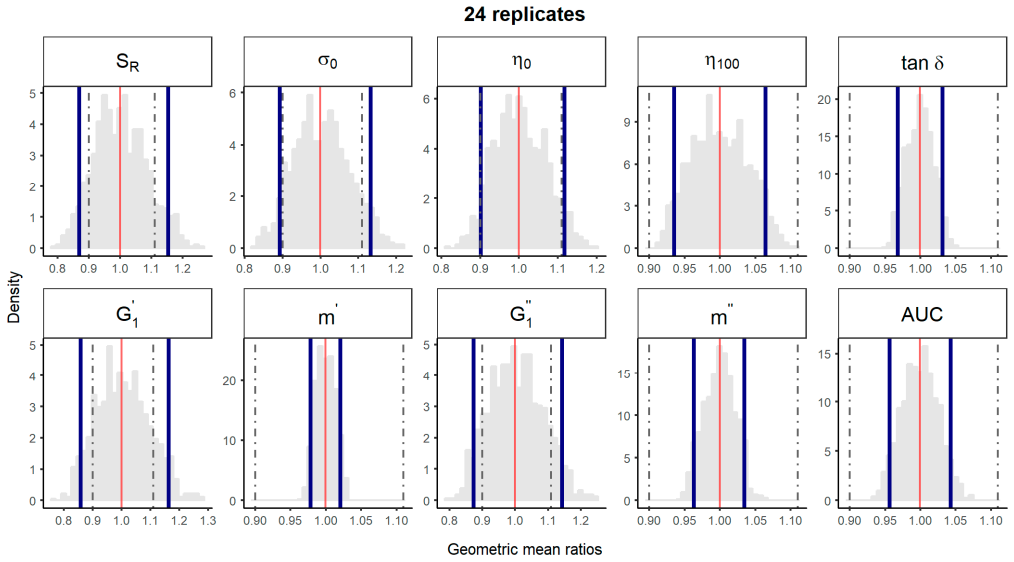


Figure S5. Bootstrap analysis of rheological parameters using 24 replicates – 5 reference batches *versus* 5 references batches. 10,000 geometric mean ratios (light grey area) resulting from the bootstrap analysis of "5 reference batches *versus* 5 test batches" for each rheological parameter. Data of 10 batches and 24 replicate each were used. Median (solid red line) and non-parametric 90% CI (solid blue lines) of the probability distribution. Dashed lines represent the acceptance limits for equivalence (90–111.11%) stated in the EMA guideline [11]. .S_R, relative thixotropic area; σ_0, yield stress; η_0, zero-shear viscosity; η_{100}, viscosity at 100 s^{-1}; *tan δ*, loss tangent at 1 Hz; G_1', calculated elastic modulus; G_1'', calculated viscous modulus; m' and m" are the parameters obtained when fitting G' and G'', respectively, *versus* frequency; *AUC*, area under the weight *versus* surface curve (spreadability).

Table S1. Raw Data.

Id Batch	Id Replicate	S_R	σ_0	η_0	η_{100}	*tan δ*	G_1'	m'	G_1''	m"	AUC
1	1	34.16	489	518980	9.15	0.731	39190	0.372	27080	0.377	351207
1	2	33.22	520	542830	9.12	0.711	56684	0.372	38284	0.371	350348
1	3	33.52	514	585390	10.09	0.718	47526	0.377	31626	0.326	344349
1	4	34.51	527	489920	10.28	0.718	37195	0.366	26149	0.377	338155
1	5	35.72	520	572010	9.37	0.713	44185	0.37	30857	0.386	339765
1	6	30.76	526	589330	10.19	0.728	47647	0.37	32830	0.378	331616
1	7	31.41	522	536160	10.12	0.722	47984	0.376	33804	0.392	334989
1	8	32.87	521	603160	9.38	0.713	43664	0.379	30544	0.386	324047
1	9	34.07	503	498130	9.12	0.700	42414	0.371	29128	0.382	327655
1	10	32.99	521	589440	10.16	0.712	43711	0.371	30485	0.385	337423
1	11	40.76	513	614890	9.32	0.734	43244	0.378	29769	0.387	349499
1	12	41.01	523	602020	10.25	0.699	40195	0.354	28254	0.373	336609
2	1	36.62	647	651010	10.7	0.717	50107	0.37	34997	0.372	349243
2	2	36.33	580	557290	10.09	0.727	46522	0.375	32596	0.379	343108
2	3	36.92	570	568770	10.08	0.727	47926	0.386	33313	0.382	346195
2	4	38.01	603	572200	10.08	0.730	46260	0.358	32850	0.36	337585
2	5	36.34	623	621070	10.07	0.721	51402	0.382	36089	0.382	330959
2	6	40.56	527	570330	10.49	0.729	55454	0.367	38519	0.364	326359
2	7	38.21	535	575350	9.09	0.727	45241	0.394	32022	0.393	326831
2	8	39.08	602	573150	9.44	0.728	41757	0.377	29425	0.385	330267
2	9	38.83	545	525590	10.39	0.737	40144	0.373	27907	0.376	333060
2	10	40.18	551	551160	10.21	0.712	42864	0.387	30695	0.399	334027
2	11	41.29	625	557810	9.45	0.731	44930	0.376	32425	0.386	330350
2	12	37.69	614	579980	9.62	0.718	46663	0.386	32642	0.388	324548

Table S1. *Cont.*

Id Batch	Id Replicate	S_R	σ_0	η_0	η_{100}	$tan\ \delta$	G_1'	m'	G_1''	m''	AUC
3	1	28.28	555	666380	9.40	0.697	63266	0.371	40127	0.347	358830
3	2	30.60	555	568810	9.30	0.679	56462	0.368	37441	0.354	312198
3	3	28.50	615	573030	9.60	0.670	60576	0.366	39666	0.357	309027
3	4	31.35	570	784310	9.20	0.665	56605	0.375	38396	0.364	329339
3	5	30.18	557	592620	9.30	0.681	55698	0.364	37578	0.357	317912
3	6	28.17	514	729850	9.80	0.691	52792	0.362	35112	0.354	299676
3	7	29.15	601	681870	8.70	0.666	55461	0.359	38600	0.371	315850
3	8	29.52	564	657560	9.20	0.683	58345	0.362	38274	0.349	338096
3	9	28.91	524	703110	8.70	0.693	63830	0.367	42659	0.359	323709
3	10	29.15	610	680950	9.10	0.701	58515	0.368	37149	0.347	318245
3	11	29.73	578	591990	8.80	0.706	62104	0.363	39793	0.348	332073
3	12	30.01	547	645580	8.90	0.673	55899	0.361	36216	0.351	336643
4	1	27.31	464	559370	10.80	0.684	51203	0.362	34183	0.353	336761
4	2	29.83	369	594390	10.50	0.694	50946	0.365	33480	0.351	350132
4	3	28.05	441	557160	10.70	0.689	46430	0.366	31335	0.36	351894
4	4	27.67	398	546600	10.80	0.680	52069	0.372	33950	0.353	348860
4	5	27.25	390	587910	11.10	0.683	41137	0.37	28258	0.368	362384
4	6	26.47	403	558380	11.40	0.707	41079	0.357	27376	0.345	355492
4	7	32.18	445	593020	9.20	0.699	45334	0.363	30485	0.365	352674
4	8	31.95	404	549970	9.23	0.705	45942	0.371	30449	0.365	339765
4	9	31.70	398	585680	9.37	0.694	48813	0.372	32695	0.364	345901
4	10	31.71	399	601150	9.13	0.708	44034	0.382	30089	0.38	335165
4	11	30.94	402	594720	9.15	0.700	39846	0.371	26763	0.361	338616
4	12	31.26	403	557420	8.90	0.698	44010	0.368	29414	0.364	340697
5	1	28.03	514	601980	10.09	0.688	56027	0.352	38709	0.355	338366
5	2	26.96	555	601660	10.32	0.695	54921	0.379	36293	0.361	338042
5	3	27.09	584	595860	9.80	0.685	61309	0.369	41659	0.372	307937
5	4	25.06	525	565910	9.96	0.685	58235	0.368	39670	0.364	326831
5	5	32.13	537	593330	9.83	0.683	51497	0.367	35288	0.367	336800
5	6	28.50	544	568850	9.98	0.704	59227	0.38	39859	0.364	334822
5	7	34.26	502	741600	10.20	0.691	64754	0.376	43624	0.364	340707
5	8	32.54	545	667510	9.90	0.692	55627	0.35	37803	0.31	330517
5	9	34.04	565	675450	9.72	0.702	65003	0.366	43283	0.356	320896
5	10	35.90	547	712980	9.19	0.692	62557	0.371	43213	0.374	328907
5	11	44.15	554	622860	9.99	0.681	59564	0.371	39078	0.36	333433
5	12	33.18	565	665950	9.82	0.695	60235	0.361	39406	0.35	315693
6	1	30.04	441	640110	10.47	0.727	43810	0.371	30704	0.38	350372
6	2	31.29	514	638680	10.32	0.698	47596	0.374	32972	0.374	348502
6	3	31.57	458	585650	10.14	0.707	47665	0.379	32527	0.377	336643
6	4	33.04	469	542150	9.94	0.726	49500	0.369	33425	0.385	351055
6	5	31.32	500	530220	9.73	0.713	54661	0.367	33320	0.369	353293
6	6	31.61	489	541410	9.98	0.727	48100	0.371	37127	0.374	337585
6	7	44.37	498	640720	10.09	0.712	44566	0.379	30486	0.378	354648
6	8	32.04	457	542990	10.02	0.705	47337	0.357	32852	0.371	351379
6	9	31.59	500	621160	9.53	0.707	46528	0.375	31815	0.375	351899
6	10	44.56	476	688780	9.46	0.694	49733	0.362	33636	0.359	353489
6	11	36.67	444	599560	9.58	0.711	53170	0.379	35900	0.369	354049
6	12	41.92	510	520290	9.86	0.712	50375	0.363	34744	0.366	349719
7	1	27.09	517	839980	8.59	0.662	55026	0.357	42111	0.341	356484
7	2	25.18	560	779980	8.05	0.665	53687	0.334	34631	0.340	347010
7	3	28.45	578	712780	8.40	0.655	61096	0.360	35784	0.343	352714
7	4	26.02	545	717580	8.41	0.671	57763	0.353	38367	0.353	365147
7	5	25.99	546	739780	8.41	0.675	59618	0.355	37601	0.352	347010
7	6	25.78	540	644530	8.60	0.654	62899	0.335	37530	0.342	354977

Table S1. *Cont.*

Id Batch	Id Replicate	S_R	σ_0	η_0	η_{100}	$tan\ \delta$	G'_1	m'	G''_1	m"	AUC
7	7	28.76	555	755085	8.35	0.674	57388	0.347	36956	0.340	365663
7	8	28.24	548	737850	8.45	0.651	66661	0.358	43183	0.350	354471
7	9	26.83	565	744070	8.11	0.670	58266	0.361	36958	0.345	356160
7	10	30.11	571	702410	8.27	0.658	52788	0.355	33678	0.351	358005
7	11	26.40	532	745450	8.27	0.657	52738	0.358	33404	0.342	362688
7	12	28.35	512	820940	8.26	0.654	58888	0.358	39453	0.364	357259
8	1	31.55	527	725070	10.26	0.725	51834	0.368	35138	0.366	346504
8	2	34.25	489	602700	10.75	0.729	51640	0.372	35496	0.375	379991
8	3	36.60	515	651890	10.56	0.721	53050	0.38	36615	0.383	368372
8	4	36.64	502	603320	10.39	0.717	60185	0.379	34367	0.381	374145
8	5	36.37	498	640210	10.20	0.712	53122	0.385	41454	0.385	360440
8	6	37.29	515	611540	10.35	0.711	60185	0.379	37234	0.391	361466
8	7	37.89	485	703600	9.75	0.710	51267	0.383	34832	0.382	367268
8	8	38.16	510	659460	10.51	0.711	46415	0.369	32514	0.377	355963
8	9	38.40	520	690680	10.27	0.728	55331	0.38	37644	0.374	357136
8	10	38.88	490	635190	10.16	0.721	57526	0.376	39720	0.382	357652
8	11	38.18	504	641910	9.58	0.715	48860	0.376	31845	0.358	368696
8	12	37.74	515	631690	9.87	0.719	50549	0.37	35413	0.381	358786
9	1	34.88	430	488890	9.84	0.699	49940	0.369	33428	0.364	364445
9	2	33.89	476	674650	9.06	0.709	52849	0.376	35678	0.362	358854
9	3	33.99	500	643240	8.70	0.707	60845	0.376	40396	0.361	342195
9	4	33.13	485	579900	9.35	0.710	51443	0.381	35174	0.38	355143
9	5	35.25	437	577110	9.74	0.705	53090	0.369	36146	0.365	340501
9	6	35.94	459	548750	9.66	0.703	48207	0.375	32457	0.363	338567
9	7	36.17	455	618640	9.61	0.707	54285	0.368	35691	0.352	350171
9	8	34.87	501	651940	9.75	0.712	52379	0.368	35047	0.36	352714
9	9	35.26	436	630620	9.51	0.698	56733	0.375	37206	0.354	348070
9	10	35.17	448	606220	9.68	0.694	48380	0.371	33156	0.365	332721
9	11	35.69	464	604360	9.63	0.707	51249	0.381	34791	0.368	352714
9	12	36.29	476	668510	9.79	0.705	49231	0.364	33491	0.362	348365
10	1	40.08	584	768370	9.60	0.697	63833	0.367	43117	0.357	292922
10	2	40.45	564	718070	9.40	0.696	66955	0.386	43289	0.36	328043
10	3	40.15	559	718980	9.70	0.700	65966	0.375	42766	0.344	350392
10	4	39.62	560	726270	9.90	0.694	70941	0.377	46480	0.352	336785
10	5	40.19	579	724360	9.30	0.679	60911	0.373	40928	0.363	330959
10	6	39.17	580	738550	9.50	0.690	67503	0.363	48626	0.376	326600
10	7	40.59	564	693890	9.60	0.681	60021	0.369	41153	0.362	341689
10	8	39.74	564	782160	9.70	0.692	62167	0.367	40556	0.350	342219
10	9	40.15	558	693920	9.10	0.708	65875	0.374	43604	0.360	332829
10	10	40.11	559	621020	9.40	0.678	66925	0.378	43265	0.360	319556
10	11	39.62	571	663060	9.20	0.674	62487	0.371	42478	0.370	343608
10	12	39.52	563	615410	9.30	0.679	76270	0.364	49457	0.343	329118
Mean		33.80	519	630067	9.63	0.700	53255	0.369	35829	0.365	342224
SD		4.82	57	74229	0.67	0.020	7741	0.010	4723	0.015	15438
CV (%)		14.3	11.0	11.8	7.0	2.9	14.6	2.6	13.2	4.1	4.5

S_R, relative thixotropic area; σ_0, yield stress; η_0, zero-shear viscosity; η_{100}, viscosity at 100 s^{-1}; $tan\ \delta$, loss tangent at 1 Hz; G'_1, calculated elastic modulus; G''_1, calculated viscous modulus; m' and m" are the parameters obtained when fitting G' and G'', respectively, *versus* frequency; *AUC*, area under the weight *versus* surface curve (spreadability).