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Supplementary Material:

2.3.1. Quality target product profile

The quality target product profile (QTPP) is defined as "A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product". The target product profile forms the basis of design for development of the product. Product attributes defining the QTPP for nanostructured lipid carriers includes particle size, polydispersity index, entrapment efficiency and stabilization of nanoparticles (ionic or steric hindrance). Justification for selection of attributes and desired target levels for each product attribute have been tabulated in Table I.

Table I. Quality target product profile of ANLC

Product Attribute	Desired Target Attribute Level	Justification			
Particle Size (nm) (d=50%)	<200 nm	Based on the literature report, the particle size $<$ 200 nm have potential to cross blood brain barrier. Since brain is the desired target for action of asenapine, we have decided to make the nanoparticles in size of below 200 nm ^{2, 3} .			
Entrapment Efficiency (% Drug Loaded)	>60%	High drug entrapment permits lower total volume/excipient for administration of formulation. This minimizes the undue exposure of excipients to tissues which may occur due to lower entrapment efficiency or high volume dose.			
Polydispersity Index (PDI)	<0.3	Since polydisperse system have greater tendency to aggregation than monodisperse system a lower PDI is desired to target the achievement of a stable nanoparticulate system.			
Ionic/steric stabilization	Stable Nanosuspension	Since the lipids and surfactants screened for the formulation are non-ionic, the charge on particles was predicted to be near neutral range with some residual charge from other sources. This was confirmed during the initial trails and evaluation of formulation characteristics (Zeta Potential: -2 to -5.98 mV). It was concluded that the stability of nanosuspension will be achieved by steric hindrance.			

2.3.2. Critical material attributes and process parameter

Critical material attribute (CMA) and critical process parameters (CPP) are defined as "A material or process whose variability has an impact a critical quality attribute and therefore it should be monitored or controlled to ensure desired drug product quality". The Critical Quality Attribute (CQA) of drug product and their QTPP were contributed in selection of excipient and process parameters. For preparation of ANLC, critical material attributes of drug substance asenapine and excipients including solid lipid, liquid lipid and surfactant were accessed. Further, two critical process parameters: homogenization speed and sonication time, were included based on the selected method for preparation of NLC (high shear homogenization and sonication). The justifications for selection of materials and process parameters have been tabulated in Table II.

Table II. Critical material attributes and critical process characteristics of ANLC.

		Drug substance attribute			
Drug Si	ıbstance	Justification			
BCS Class	Class II	Asenapine is classified as a BCS Class II compound (low solubility, high permeability). Low solubility problem may be overcome by nanonization of particles.			
Sublingual bioavailability Oral bioavailability	35% <2%	The low sublingual bioavailability and high gastro instability of asenapine, makes it a suitable candidate for nanoparticulate lipid drug delivery system. The lipid coat over the particles prevents metabolism.			
Oral bloavallability	<276	Excipients attribute			
Exci	pient	Justification			
Selection of Solid Lipid	Glyceryl monostearate	Drug solubility was evaluated in stearic acid, glyceryl monostearate, Compritol 888 ato and Precirol ATO 5. Based on high solubility, Glyceryl monostearate was selected as solid lipid. (Data not shown)			
Selection of Liquid lipid	Oleic acid	The trial batches were prepared with fixed ratio of liquid lipid (oleic acid, caprylic/capric triglyceride and propylene glycol dicaprylate/dicaprate) to solid lipid (GMS). The minimum particle size with sufficiently stable colloidal dispersion was obtained with oleic acid. (Data not shown)			
Selection of Surfactant	Tween-80	Among screened surfactants having brain targeting ability (Tween 80 and Poloxamer 188), it was concluded that Tween 80 stabilized colloidal dispersion resulted in low particle size and had acceptable stability. (Data not shown)			
		Critical process parameters			
Pro	cess	Justification			
Homogenization speed	8000-16000 rpm	The homogenization speed ranges were selected based on instrument limitation and trial batches. The homogenization speed less than 8000 rpm leads to large particle size and polydisperse colloidal system. However, the upper range was set at 16000, since no significant difference in particle size was observed above 16000 rpm. (Data not shown)			
Sonication time	5-15 min	The time duration for sonication was selected based on the literature and trial batches. Moreover, longer duration of sonication was avoided due to leaching of drug from matrix and possible metal contamination ⁴ . (Data not shown)			

Table III. Composition of different batches and their response.

Batch No	Composition and process variables					Results		
	OA/ GMS (w/w)	ASM/ GMS (w/w)	Tween-80 (%w/v)	HS (rpm)	ST (minute)	PS (nm)	EE (%)	PDI
NLC -1	0.15	0.15	1.00	12000.00	10.00	274.65±4.51	75.72±1.83	0.293±0.015
NLC -2	0.10	0.20	1.00	12000.00	10.00	309.75±3.63	69.62±2.52	0.361±0.027
NLC -3	0.15	0.15	1.00	12000.00	10.00	275.63±5.46	74.83±1.58	0.293±0.023
NLC -4	0.15	0.10	1.50	12000.00	10.00	195.51±6.35	59.93±2.62	0.220±0.018
NLC -5	0.10	0.15	0.50	12000.00	10.00	298.46±2.23	67.19±3.23	0.415±0.038
NLC -6	0.15	0.15	1.00	8000.00	5.00	310.98±.3.71	87.22±1.71	0.373±0.022
NLC -7	0.15	0.20	0.50	12000.00	10.00	334.61±4.89	89.78±2.34	0.393±0.027
NLC -8	0.15	0.15	1.00	12000.00	10.00	275.61±2.35	74.14±2.61	0.296±0.011
NLC -9	0.15	0.15	1.00	16000.00	5.00	250.39±2.34	77.56±3.27	0.333±0.029
NLC -10	0.10	0.15	1.00	12000.00	5.00	297.27±5.25	69.72±1.54	0.293±0.021

NIC-11 0.15 0.20 1.00 12000.00 15.00 278.39±2.36 52.69±2.42 0.25500.023 NIC-13 0.15 0.20 1.00 12000.00 10.00 278.39±2.36 76.16±2.31 0.295±0.018 NIC-14 0.20 0.15 1.00 8000.00 10.00 274.52±2.02 91.94±2.12 0.255±0.018 NIC-15 0.15 0.15 0.50 8000.00 10.00 274.52±2.02 91.94±2.12 0.257±0.017 NIC-16 0.15 0.10 1.00 16000.00 10.00 275.52±4.66 60.35±1.14 0.248±0.021 NIC-17 0.20 0.20 1.00 12000.00 10.00 305.14±7.63 92.56±1.65 0.255±0.024 NIC-18 0.15 0.15 1.50 12000.00 5.00 230.15±6.42 76.78±2.57 0.303±0.014 NIC-19 0.15 0.15 1.50 12000.00 5.00 230.15±6.42 76.78±2.57 0.303±0.014 NIC-19 0.15 0.15 1.50 16000.00 10.00 262.32±4.68 52.42±2.46 0.310±0.026 NIC-20 0.15 0.15 1.50 16000.00 10.00 262.32±4.68 52.42±2.46 0.310±0.026 NIC-21 0.10 0.10 1.00 12000.00 10.00 262.32±4.68 52.42±2.46 0.310±0.028 NIC-22 0.10 0.15 1.00 12000.00 15.00 277.34±8.34 74.26±2.61 0.295±0.013 NIC-23 0.15 0.15 1.00 12000.00 10.00 277.34±8.34 74.26±2.61 0.295±0.013 NIC-24 0.15 0.15 0.10 1.00 8000.00 10.00 275.62±7.35 70.62±2.52 0.290±0.024 NIC-25 0.20 0.15 0.50 12000.00 10.00 275.62±7.35 70.62±2.52 0.290±0.024 NIC-27 0.20 0.15 1.50 12000.00 10.00 275.36±4.30 76.24±2.54 0.374±0.03 NIC-26 0.15 0.20 1.50 12000.00 10.00 275.62±7.35 70.62±2.52 0.290±0.024 NIC-27 0.20 0.15 1.50 12000.00 10.00 275.62±7.35 70.62±2.52 0.290±0.024 NIC-27 0.20 0.15 1.50 12000.00 10.00 275.62±7.35 70.62±2.52 0.290±0.024 NIC-28 0.15 0.20 1.50 12000.00 10.00 275.62±7.35 70.62±2.52 0.290±0.024 NIC-30 0.15 0.50 12000.00 10.00 275.62±7.35 70.62±2.52 0.290±0.024 NIC-31 0.15 0.20 1.50 12000.00 10.00 275.62±7.35 70.62±2.52 0.290±0.024 NIC-31 0.15 0.50 1.50 12000.00 10.00 275.62±7.35 70.62±2.52 0.290±0.024 NIC-32 0.20 0.15 1.50 12000.00 10.00 275.62±7.35 70.62±2.52 0.290±0.024 NIC-31 0.15 0.20 1.00 12000.00 10.00 275.62±7.35 70.62±2.52 0.290±0.024 NIC-32 0.20 0.15 1.50 12000.00 10.00 275.62±7.35 70.62±2.52 0.290±0.024 NIC-32 0.20 0.15 0.50 12000.00 10.00 275.62±7.25 92.27±1.75 0.305±0.022 NIC-33 0.15 0.15 0.00 150 0.00 12000.00 10.00 275.62±7	NIC 11	0.15	0.10	1.00	12000.00	15.00	105 2216 20	F2 6414 2F	0.106+0.013
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NIC-18			-	1.00	16000.00	10.00	215.21±4.66	60.35±1.14	0.248±0.021
NIC-19	NLC -17	0.20	0.20	1.00	12000.00	10.00	305.14±7.63	92.56±1.65	0.255±0.024
NIC - 20	NLC -18	0.15		1.50			230.15±6.42	76.78±2.57	0.303±0.014
NLC -21 0.10 0.10 1.00 12000.00 10.00 262.32±4.68 52.42±2.46 0.310±0.028 NLC -22 0.10 0.15 1.00 12000.00 15.00 211.35±7.56 74.97±3.25 0.271±0.022 NLC -23 0.15 0.15 1.00 12000.00 10.00 277.34±8.34 74.26±2.61 0.295±0.013 NLC -24 0.15 0.10 1.00 8000.00 10.00 275.62±7.35 70.62±2.52 0.290±0.024 NLC -25 0.20 0.15 0.50 12000.00 10.00 291.25±7.25 92.27±1.75 0.306±0.031 NLC -26 0.15 0.20 1.50 12000.00 10.00 245.36±4.40 76.24±2.74 0.275±0.023 NLC -27 0.20 0.15 1.50 12000.00 10.00 198.53±3.83 86.18±2.96 0.184±0.013 NLC -28 0.15 0.20 1.00 12000.00 5.00 331.32±2.52 91.36±1.71 0.374±0.032 NLC -30 0.15 0.20	NLC -19	0.15	0.15	1.50	8000.00	10.00	223.62±5.72	69.71±2.67	0.277±0.026
NLC -22 0.10 0.15 1.00 12000.00 15.00 211.35±7.56 74.97±3.25 0.271±0.022 NLC -23 0.15 0.15 1.00 12000.00 10.00 277.34±8.34 74.26±2.61 0.295±0.013 NLC -24 0.15 0.10 1.00 8000.00 10.00 275.62±7.35 70.62±2.52 0.290±0.024 NLC -25 0.20 0.15 0.50 12000.00 10.00 291.25±7.25 92.27±1.75 0.306±0.031 NLC -26 0.15 0.20 1.50 12000.00 10.00 245.36±4.40 76.24±2.74 0.275±0.023 NLC -27 0.20 0.15 1.50 12000.00 10.00 198.53±3.83 86.18±2.96 0.184±0.013 NLC -28 0.15 0.20 1.00 12000.00 10.00 284.21±3.61 75.82±4.38 0.343±0.012 NLC -30 0.15 0.20 1.00 16000.00 10.00 265.76±7.34 77.93±2.23 0.305±0.022 NLC -31 0.15 0.15	NLC -20	0.15	0.15	1.50	16000.00	10.00	165.62±6.36	59.74±3.60	0.237±0.012
NLC -23 0.15 0.15 1.00 12000.00 10.00 277.34±8.34 74.26±2.61 0.295±0.013 NLC -24 0.15 0.10 1.00 8000.00 10.00 275.62±7.35 70.62±2.52 0.290±0.024 NLC -25 0.20 0.15 0.50 12000.00 10.00 291.25±7.25 92.27±1.75 0.306±0.031 NLC -26 0.15 0.20 1.50 12000.00 10.00 245.36±4.40 76.24±2.74 0.275±0.023 NLC -27 0.20 0.15 1.50 12000.00 10.00 198.53±3.83 86.18±2.96 0.184±0.013 NLC -28 0.15 0.20 1.00 12000.00 5.00 331.32±2.52 91.36±1.71 0.374±0.032 NLC -29 0.15 0.10 0.50 12000.00 10.00 284.21±3.61 75.82±4.38 0.343±0.012 NLC -30 0.15 0.20 1.00 16000.00 10.00 265.746±3.34 77.93±2.23 0.305±0.022 NLC -31 0.15 0.15	NLC -21	0.10	0.10	1.00	12000.00	10.00	262.32±4.68	52.42±2.46	0.310±0.028
NIC -24 0.15 0.10 1.00 8000.00 10.00 275.62±7.35 70.62±2.52 0.290±0.024 NIC -25 0.20 0.15 0.50 12000.00 10.00 291.25±7.25 92.27±1.75 0.306±0.031 NIC -26 0.15 0.20 1.50 12000.00 10.00 245.36±4.40 76.24±2.74 0.275±0.023 NIC -27 0.20 0.15 1.50 12000.00 10.00 198.53±3.83 86.18±2.96 0.184±0.013 NIC -28 0.15 0.20 1.00 12000.00 5.00 331.32±2.52 91.36±1.71 0.374±0.032 NIC -29 0.15 0.10 0.50 12000.00 10.00 284.21±3.61 75.82±4.38 0.343±0.012 NIC -30 0.15 0.20 1.00 16000.00 10.00 265.76±7.34 77.93±2.23 0.305±0.022 NIC -31 0.15 0.15 1.00 12000.00 10.00 273.46±6.32 72.61±3.21 0.297±0.021 NIC -32 0.20 0.10	NLC -22	0.10	0.15	1.00	12000.00	15.00	211.35±7.56	74.97±3.25	0.271±0.022
NLC -25 0.20 0.15 0.50 12000.00 10.00 291.25±7.25 92.27±1.75 0.306±0.031 NLC -26 0.15 0.20 1.50 12000.00 10.00 245.36±4.40 76.24±2.74 0.275±0.023 NLC -27 0.20 0.15 1.50 12000.00 10.00 198.53±3.83 86.18±2.96 0.184±0.013 NLC -28 0.15 0.20 1.00 12000.00 5.00 331.32±2.52 91.36±1.71 0.374±0.032 NLC -29 0.15 0.10 0.50 12000.00 10.00 284.21±3.61 75.82±4.38 0.343±0.012 NLC -30 0.15 0.20 1.00 16000.00 10.00 265.76±7.34 77.93±2.23 0.305±0.022 NLC -31 0.15 0.15 1.00 12000.00 10.00 273.46±6.32 72.61±3.21 0.297±0.021 NLC -32 0.20 0.10 1.00 12000.00 10.00 224.97±6.30 62.28±2.36 0.252±0.025 NLC -33 0.15 0.15	NLC -23	0.15	0.15	1.00	12000.00	10.00	277.34±8.34	74.26±2.61	0.295±0.013
NLC -26 0.15 0.20 1.50 12000.00 10.00 245,36±4.40 76,24±2.74 0.275±0.023 NLC -27 0.20 0.15 1.50 12000.00 10.00 198.53±3.83 86.18±2.96 0.184±0.013 NLC -28 0.15 0.20 1.00 12000.00 5.00 331.32±2.52 91.36±1.71 0.374±0.032 NLC -29 0.15 0.10 0.50 12000.00 10.00 284.21±3.61 75.82±4.38 0.343±0.012 NLC -30 0.15 0.20 1.00 16000.00 10.00 265.76±7.34 77.93±2.23 0.305±0.022 NLC -31 0.15 0.15 1.00 12000.00 10.00 273.46±6.32 72.61±3.21 0.297±0.021 NLC -32 0.20 0.10 1.00 12000.00 10.00 251.25±9.46 87.13±3.67 0.203±0.024 NLC -33 0.15 0.15 1.00 8000.00 15.00 224.97±6.30 62.28±2.36 0.252±0.025 NLC -34 0.15 0.20	NLC -24	0.15	0.10	1.00	8000.00	10.00	275.62±7.35	70.62±2.52	0.290±0.024
NLC -27 0.20 0.15 1.50 12000.00 10.00 198.53±3.83 86.18±2.96 0.184±0.013 NLC -28 0.15 0.20 1.00 12000.00 5.00 331.32±2.52 91.36±1.71 0.374±0.032 NLC -29 0.15 0.10 0.50 12000.00 10.00 284.21±3.61 75.82±4.38 0.343±0.012 NLC -30 0.15 0.20 1.00 16000.00 10.00 265.76±7.34 77.93±2.23 0.305±0.022 NLC -31 0.15 0.15 1.00 12000.00 10.00 273.46±6.32 72.61±3.21 0.297±0.021 NLC -32 0.20 0.10 1.00 12000.00 10.00 251.25±9.46 87.13±3.67 0.203±0.024 NLC -33 0.15 0.15 1.00 8000.00 15.00 224.97±6.30 62.28±2.36 0.252±0.025 NLC -34 0.15 0.20 1.00 8000.00 10.00 325.63±4.75 87.86±3.83 0.345±0.032 NLC -35 0.20 0.15 <	NLC -25	0.20	0.15	0.50	12000.00	10.00	291.25±7.25	92.27±1.75	0.306±0.031
NLC -28 0.15 0.20 1.00 12000.00 5.00 331.32±2.52 91.36±1.71 0.374±0.032 NLC -29 0.15 0.10 0.50 12000.00 10.00 284.21±3.61 75.82±4.38 0.343±0.012 NLC -30 0.15 0.20 1.00 16000.00 10.00 265.76±7.34 77.93±2.23 0.305±0.022 NLC -31 0.15 0.15 1.00 12000.00 10.00 273.46±6.32 72.61±3.21 0.297±0.021 NLC -32 0.20 0.10 1.00 12000.00 10.00 251.25±9.46 87.13±3.67 0.203±0.024 NLC -33 0.15 0.15 1.00 8000.00 15.00 224.97±6.30 62.28±2.36 0.25±0.025 NLC -34 0.15 0.20 1.00 8000.00 10.00 325.63±4.75 87.86±3.83 0.345±0.022 NLC -35 0.20 0.15 1.00 12000.00 5.00 288.26±4.72 94.36±1.32 0.282±0.032 NLC -36 0.15 0.10 <td< td=""><td>NLC -26</td><td>0.15</td><td>0.20</td><td>1.50</td><td>12000.00</td><td>10.00</td><td>245.36±4.40</td><td>76.24±2.74</td><td>0.275±0.023</td></td<>	NLC -26	0.15	0.20	1.50	12000.00	10.00	245.36±4.40	76.24±2.74	0.275±0.023
NLC -29 0.15 0.10 0.50 12000.00 10.00 284.21±3.61 75.82±4.38 0.343±0.012 NLC -30 0.15 0.20 1.00 16000.00 10.00 265.76±7.34 77.93±2.23 0.305±0.022 NLC -31 0.15 0.15 1.00 12000.00 10.00 273.46±6.32 72.61±3.21 0.297±0.021 NLC -32 0.20 0.10 1.00 12000.00 10.00 251.25±9.46 87.13±3.67 0.203±0.024 NLC -33 0.15 0.15 1.00 8000.00 15.00 224.97±6.30 62.28±2.36 0.252±0.025 NLC -34 0.15 0.20 1.00 8000.00 10.00 325.63±4.75 87.86±3.83 0.345±0.032 NLC -35 0.20 0.15 1.00 12000.00 5.00 288.26±4.72 94.36±1.32 0.282±0.032 NLC -36 0.15 0.10 1.00 12000.00 5.00 280.45±9.43 77.15±4.86 0.317±0.031 NLC -37 0.10 0.15 <t< td=""><td>NLC -27</td><td>0.20</td><td>0.15</td><td>1.50</td><td>12000.00</td><td>10.00</td><td>198.53±3.83</td><td>86.18±2.96</td><td>0.184±0.013</td></t<>	NLC -27	0.20	0.15	1.50	12000.00	10.00	198.53±3.83	86.18±2.96	0.184±0.013
NLC -30 0.15 0.20 1.00 16000.00 10.00 265.76±7.34 77.93±2.23 0.305±0.022 NLC -31 0.15 0.15 1.00 12000.00 10.00 273.46±6.32 72.61±3.21 0.297±0.021 NLC -32 0.20 0.10 1.00 12000.00 10.00 251.25±9.46 87.13±3.67 0.203±0.024 NLC -33 0.15 0.15 1.00 8000.00 15.00 224.97±6.30 62.28±2.36 0.25±0.025 NLC -34 0.15 0.20 1.00 8000.00 10.00 325.63±4.75 87.86±3.83 0.345±0.032 NLC -35 0.20 0.15 1.00 12000.00 5.00 288.26±4.72 94.36±1.32 0.282±0.032 NLC -36 0.15 0.10 1.00 12000.00 5.00 280.45±9.43 77.15±4.86 0.317±0.031 NLC -37 0.10 0.15 1.50 12000.00 10.00 210.15±5.27 51.72±3.98 0.294±0.026 NLC -38 0.10 0.15 <td< td=""><td>NLC -28</td><td>0.15</td><td>0.20</td><td>1.00</td><td>12000.00</td><td>5.00</td><td>331.32±2.52</td><td>91.36±1.71</td><td>0.374±0.032</td></td<>	NLC -28	0.15	0.20	1.00	12000.00	5.00	331.32±2.52	91.36±1.71	0.374±0.032
NLC -31 0.15 0.15 1.00 12000.00 10.00 273.46±6.32 72.61±3.21 0.297±0.021 NLC -32 0.20 0.10 1.00 12000.00 10.00 251.25±9.46 87.13±3.67 0.203±0.024 NLC -33 0.15 0.15 1.00 8000.00 15.00 224.97±6.30 62.28±2.36 0.252±0.025 NLC -34 0.15 0.20 1.00 8000.00 10.00 325.63±4.75 87.86±3.83 0.345±0.032 NLC -35 0.20 0.15 1.00 12000.00 5.00 288.26±4.72 94.36±1.32 0.282±0.032 NLC -36 0.15 0.10 1.00 12000.00 5.00 280.45±9.43 77.15±4.86 0.317±0.031 NLC -37 0.10 0.15 1.50 12000.00 10.00 210.15±5.27 51.72±3.98 0.294±0.026 NLC -38 0.10 0.15 1.00 8000.00 10.00 290.52±8.21 62.78±4.92 0.368±0.014 NLC -40 0.20 0.15 <td< td=""><td>NLC -29</td><td>0.15</td><td>0.10</td><td>0.50</td><td>12000.00</td><td>10.00</td><td>284.21±3.61</td><td>75.82±4.38</td><td>0.343±0.012</td></td<>	NLC -29	0.15	0.10	0.50	12000.00	10.00	284.21±3.61	75.82±4.38	0.343±0.012
NLC -32 0.20 0.10 1.00 12000.00 10.00 251.25±9.46 87.13±3.67 0.203±0.024 NLC -33 0.15 0.15 1.00 8000.00 15.00 224.97±6.30 62.28±2.36 0.25±0.025 NLC -34 0.15 0.20 1.00 8000.00 10.00 325.63±4.75 87.86±3.83 0.345±0.032 NLC -35 0.20 0.15 1.00 12000.00 5.00 288.26±4.72 94.36±1.32 0.282±0.032 NLC -36 0.15 0.10 1.00 12000.00 5.00 280.45±9.43 77.15±4.86 0.317±0.031 NLC -37 0.10 0.15 1.50 12000.00 10.00 210.15±5.27 51.72±3.98 0.294±0.026 NLC -38 0.10 0.15 1.00 8000.00 10.00 290.52±8.21 62.78±4.92 0.368±0.014 NLC -39 0.15 0.15 0.50 12000.00 15.00 236.26±3.67 67.37±2.71 0.301±0.03 NLC -40 0.20 0.15 1	NLC -30	0.15	0.20	1.00	16000.00	10.00	265.76±7.34	77.93±2.23	0.305±0.022
NLC -33 0.15 0.15 1.00 8000.00 15.00 224.97±6.30 62.28±2.36 0.25±0.025 NLC -34 0.15 0.20 1.00 8000.00 10.00 325.63±4.75 87.86±3.83 0.345±0.032 NLC -35 0.20 0.15 1.00 12000.00 5.00 288.26±4.72 94.36±1.32 0.282±0.032 NLC -36 0.15 0.10 1.00 12000.00 5.00 280.45±9.43 77.15±4.86 0.317±0.031 NLC -37 0.10 0.15 1.50 12000.00 10.00 210.15±5.27 51.72±3.98 0.294±0.026 NLC -38 0.10 0.15 1.00 8000.00 10.00 290.52±8.21 62.78±4.92 0.368±0.014 NLC -39 0.15 0.15 0.50 12000.00 15.00 236.26±3.67 67.37±2.71 0.301±0.030 NLC -40 0.20 0.15 1.00 16000.00 10.00 226.86±4.44 86.62±3.72 0.213±0.021 NLC -41 0.15 0.15	NLC -31	0.15	0.15	1.00	12000.00	10.00	273.46±6.32	72.61±3.21	0.297±0.021
NLC -34 0.15 0.20 1.00 8000.00 10.00 325.63±4.75 87.86±3.83 0.345±0.032 NLC -35 0.20 0.15 1.00 12000.00 5.00 288.26±4.72 94.36±1.32 0.282±0.032 NLC -36 0.15 0.10 1.00 12000.00 5.00 280.45±9.43 77.15±4.86 0.317±0.031 NLC -37 0.10 0.15 1.50 12000.00 10.00 210.15±5.27 51.72±3.98 0.294±0.026 NLC -38 0.10 0.15 1.00 8000.00 10.00 290.52±8.21 62.78±4.92 0.368±0.014 NLC -39 0.15 0.15 0.50 12000.00 15.00 236.26±3.67 67.37±2.71 0.301±0.030 NLC -40 0.20 0.15 1.00 16000.00 10.00 226.86±4.44 86.62±3.72 0.213±0.021 NLC -41 0.15 0.15 1.50 12000.00 15.00 147.78±2.35 51.28±4.22 0.182±0.012 NLC -42 0.10 0.15 <t< td=""><td>NLC -32</td><td>0.20</td><td>0.10</td><td>1.00</td><td>12000.00</td><td>10.00</td><td>251.25±9.46</td><td>87.13±3.67</td><td>0.203±0.024</td></t<>	NLC -32	0.20	0.10	1.00	12000.00	10.00	251.25±9.46	87.13±3.67	0.203±0.024
NLC -35 0.20 0.15 1.00 12000.00 5.00 288.26±4.72 94.36±1.32 0.282±0.032 NLC -36 0.15 0.10 1.00 12000.00 5.00 280.45±9.43 77.15±4.86 0.317±0.031 NLC -37 0.10 0.15 1.50 12000.00 10.00 210.15±5.27 51.72±3.98 0.294±0.026 NLC -38 0.10 0.15 1.00 8000.00 10.00 290.52±8.21 62.78±4.92 0.368±0.014 NLC -39 0.15 0.15 0.50 12000.00 15.00 236.26±3.67 67.37±2.71 0.301±0.030 NLC -40 0.20 0.15 1.00 16000.00 10.00 226.86±4.44 86.62±3.72 0.213±0.021 NLC -41 0.15 0.15 1.50 12000.00 15.00 147.78±2.35 51.28±4.22 0.182±0.012 NLC -42 0.10 0.15 1.00 16000.00 10.00 230.24±3.56 51.23±3.14 0.324±0.019 NLC -43 0.15 0.15 <	NLC -33	0.15	0.15	1.00	8000.00	15.00	224.97±6.30	62.28±2.36	0.252±0.025
NLC -36 0.15 0.10 1.00 12000.00 5.00 280.45±9.43 77.15±4.86 0.317±0.031 NLC -37 0.10 0.15 1.50 12000.00 10.00 210.15±5.27 51.72±3.98 0.294±0.026 NLC -38 0.10 0.15 1.00 8000.00 10.00 290.52±8.21 62.78±4.92 0.368±0.014 NLC -39 0.15 0.15 0.50 12000.00 15.00 236.26±3.67 67.37±2.71 0.301±0.030 NLC -40 0.20 0.15 1.00 16000.00 10.00 226.86±4.44 86.62±3.72 0.213±0.021 NLC -41 0.15 0.15 1.50 12000.00 15.00 147.78±2.35 51.28±4.22 0.182±0.012 NLC -42 0.10 0.15 1.00 16000.00 10.00 230.24±3.56 51.23±3.14 0.324±0.019 NLC -43 0.15 0.15 1.00 16000.00 15.00 165.26±2.46 52.67±2.84 0.211±0.015 NLC -44 0.20 0.15	NLC -34	0.15	0.20	1.00	8000.00	10.00	325.63±4.75	87.86±3.83	0.345±0.032
NLC -37 0.10 0.15 1.50 12000.00 10.00 210.15±5.27 51.72±3.98 0.294±0.026 NLC -38 0.10 0.15 1.00 8000.00 10.00 290.52±8.21 62.78±4.92 0.368±0.014 NLC -39 0.15 0.15 0.50 12000.00 15.00 236.26±3.67 67.37±2.71 0.301±0.030 NLC -40 0.20 0.15 1.00 16000.00 10.00 226.86±4.44 86.62±3.72 0.213±0.021 NLC -41 0.15 0.15 1.50 12000.00 15.00 147.78±2.35 51.28±4.22 0.182±0.012 NLC -42 0.10 0.15 1.00 16000.00 10.00 230.24±3.56 51.23±3.14 0.324±0.019 NLC -43 0.15 0.15 1.00 16000.00 15.00 165.26±2.46 52.67±2.84 0.211±0.015 NLC -44 0.20 0.15 1.00 12000.00 15.00 201.62±4.72 79.16±2.92 0.163±0.012 NLC -45 0.15 0.15	NLC -35	0.20	0.15	1.00	12000.00	5.00	288.26±4.72	94.36±1.32	0.282±0.032
NLC -38 0.10 0.15 1.00 8000.00 10.00 290.52±8.21 62.78±4.92 0.368±0.014 NLC -39 0.15 0.15 0.50 12000.00 15.00 236.26±3.67 67.37±2.71 0.301±0.030 NLC -40 0.20 0.15 1.00 16000.00 10.00 226.86±4.44 86.62±3.72 0.213±0.021 NLC -41 0.15 0.15 1.50 12000.00 15.00 147.78±2.35 51.28±4.22 0.182±0.012 NLC -42 0.10 0.15 1.00 16000.00 10.00 230.24±3.56 51.23±3.14 0.324±0.019 NLC -43 0.15 0.15 1.00 16000.00 15.00 165.26±2.46 52.67±2.84 0.211±0.015 NLC -44 0.20 0.15 1.00 12000.00 15.00 201.62±4.72 79.16±2.92 0.163±0.012 NLC -45 0.15 0.15 0.50 12000.00 5.00 322.62±3.47 89.45±3.17 0.423±0.038	NLC -36	0.15	0.10	1.00	12000.00	5.00	280.45±9.43	77.15±4.86	0.317±0.031
NLC -39 0.15 0.15 0.50 12000.00 15.00 236.26±3.67 67.37±2.71 0.301±0.030 NLC -40 0.20 0.15 1.00 16000.00 10.00 226.86±4.44 86.62±3.72 0.213±0.021 NLC -41 0.15 0.15 1.50 12000.00 15.00 147.78±2.35 51.28±4.22 0.182±0.012 NLC -42 0.10 0.15 1.00 16000.00 10.00 230.24±3.56 51.23±3.14 0.324±0.019 NLC -43 0.15 0.15 1.00 16000.00 15.00 165.26±2.46 52.67±2.84 0.211±0.015 NLC -44 0.20 0.15 1.00 12000.00 15.00 201.62±4.72 79.16±2.92 0.163±0.012 NLC -45 0.15 0.15 0.50 12000.00 5.00 322.62±3.47 89.45±3.17 0.423±0.038	NLC -37	0.10	0.15	1.50	12000.00	10.00	210.15±5.27	51.72±3.98	0.294±0.026
NLC -40 0.20 0.15 1.00 16000.00 10.00 226.86±4.44 86.62±3.72 0.213±0.021 NLC -41 0.15 0.15 1.50 12000.00 15.00 147.78±2.35 51.28±4.22 0.182±0.012 NLC -42 0.10 0.15 1.00 16000.00 10.00 230.24±3.56 51.23±3.14 0.324±0.019 NLC -43 0.15 0.15 1.00 16000.00 15.00 165.26±2.46 52.67±2.84 0.211±0.015 NLC -44 0.20 0.15 1.00 12000.00 15.00 201.62±4.72 79.16±2.92 0.163±0.012 NLC -45 0.15 0.15 0.50 12000.00 5.00 322.62±3.47 89.45±3.17 0.423±0.038	NLC -38	0.10	0.15	1.00	8000.00	10.00	290.52±8.21	62.78±4.92	0.368±0.014
NLC -41 0.15 0.15 1.50 12000.00 15.00 147.78±2.35 51.28±4.22 0.182±0.012 NLC -42 0.10 0.15 1.00 16000.00 10.00 230.24±3.56 51.23±3.14 0.324±0.019 NLC -43 0.15 0.15 1.00 16000.00 15.00 165.26±2.46 52.67±2.84 0.211±0.015 NLC -44 0.20 0.15 1.00 12000.00 15.00 201.62±4.72 79.16±2.92 0.163±0.012 NLC -45 0.15 0.15 0.50 12000.00 5.00 322.62±3.47 89.45±3.17 0.423±0.038	NLC -39	0.15	0.15	0.50	12000.00	15.00	236.26±3.67	67.37±2.71	0.301±0.030
NLC -42 0.10 0.15 1.00 16000.00 10.00 230.24±3.56 51.23±3.14 0.324±0.019 NLC -43 0.15 0.15 1.00 16000.00 15.00 165.26±2.46 52.67±2.84 0.211±0.015 NLC -44 0.20 0.15 1.00 12000.00 15.00 201.62±4.72 79.16±2.92 0.163±0.012 NLC -45 0.15 0.15 0.50 12000.00 5.00 322.62±3.47 89.45±3.17 0.423±0.038	NLC -40	0.20	0.15	1.00	16000.00	10.00	226.86±4.44	86.62±3.72	0.213±0.021
NLC -43 0.15 0.15 1.00 16000.00 15.00 165.26±2.46 52.67±2.84 0.211±0.015 NLC -44 0.20 0.15 1.00 12000.00 15.00 201.62±4.72 79.16±2.92 0.163±0.012 NLC -45 0.15 0.15 0.50 12000.00 5.00 322.62±3.47 89.45±3.17 0.423±0.038	NLC -41	0.15	0.15	1.50	12000.00	15.00	147.78±2.35	51.28±4.22	0.182±0.012
NLC -44 0.20 0.15 1.00 12000.00 15.00 201.62±4.72 79.16±2.92 0.163±0.012 NLC -45 0.15 0.15 0.50 12000.00 5.00 322.62±3.47 89.45±3.17 0.423±0.038	NLC -42	0.10	0.15	1.00	16000.00	10.00	230.24±3.56	51.23±3.14	0.324±0.019
NLC -45 0.15 0.15 0.50 12000.00 5.00 322.62±3.47 89.45±3.17 0.423±0.038	NLC -43	0.15	0.15	1.00	16000.00	15.00	165.26±2.46	52.67±2.84	0.211±0.015
	NLC -44	0.20	0.15	1.00	12000.00	15.00	201.62±4.72	79.16±2.92	0.163±0.012
NLC -46 0.15 0.15 0.50 16000.00 10.00 253.25±3.78 75.26±2.29 0.353±0.033	NLC -45	0.15	0.15	0.50	12000.00	5.00	322.62±3.47	89.45±3.17	0.423±0.038
	NLC -46	0.15	0.15	0.50	16000.00	10.00	253.25±3.78	75.26±2.29	0.353±0.033

HS: Homogenization speed, ST: Sonication time, PS: Particle size, EE: Entrapment efficiency, PDI: Polydispersity index, mean±SD, n=3.

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