

Effects of the Polymer Glass Transition on the Stability of Nanoparticle Dispersions

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Materials & Methods

Polymers - The following polymers were formulated into nanoparticles (NPs) in this study to obtain a broad sampling of glass transition temperatures (T_g 's):

Table S1. List of polymers studied with associated properties and suppliers.

Polymer	Abbrev.	T_g (°C)	M_n (g/mol)	M_w (g/mol)	Supplier
Poly(1,4-butadiene)	PB	-102	18000	18720	Polymer Source
Poly(<i>cis</i> -isoprene)	PI	-69	-	35000	Sigma-Aldrich
Poly(<i>n</i> -nonyl methacrylate)	PnNonMA	-36	17500	24500	Polymer Source
Poly(<i>n</i> -hexyl methacrylate)	PnHexMA	-7	15000	21000	Polymer Source
Poly(<i>n</i> -butyl methacrylate)	PnBuMA	20	14100	15500	Polymer Standards Service
Poly(<i>n</i> -propyl methacrylate)	PnPrMA	43	13400	14200	Polymer Standards Service
Poly(<i>iso</i> -butyl methacrylate)	PiBuMA	57	23000	31000	Polymer Source
Poly(styrene)	PS	100	-	35000	Sigma-Aldrich
Poly(<i>t</i> -butyl methacrylate)	PtBuMA	118	16200	17000	Polymer Source
Poly(bromostyrene)	PBrS	138	24000	33600	Polymer Source
Poly(4-vinylphenol)	P4HS	157	-	11000	Sigma-Aldrich

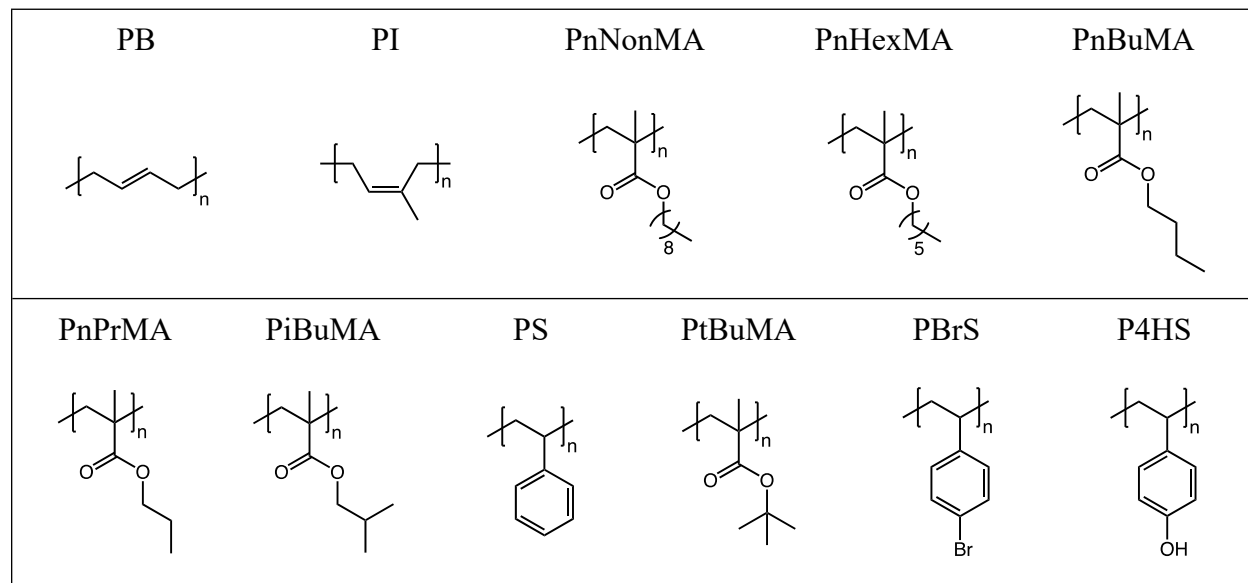


Figure S1. Chemical structures of polymers studied.

NP Preparation - Flash nanoprecipitation (FNP), a rapid and scalable colloid fabrication platform, was used to produce NPs of these polymers. First, polymers were dissolved in tetrahydrofuran (THF, HPLC Grade, Fisher Scientific) at 5 mg/mL under gentle stirring for 3 hr.

Using a confined impingement jet (CIJ) mixer, 0.5 mL of a polymer solution was impinged against 0.5 mL of DI H₂O (filtered *via* Milli-Q IQ 7000 Ultrapure system) and the effluent was flown into a stirred 4 mL reservoir of H₂O to yield an overall 10-fold dilution of the original inlet solution. Following FNP, dispersions were subjected to rotary evaporation (Büchi Rotavapor R-300) to remove the remaining 10 vol% THF fraction. As H₂O may have also been removed during evaporation and to avoid discrepancies between precipitation efficiencies among polymers, thermal gravimetric analysis (TA Q50) was used to measure final NP dispersion concentrations in which 100 µL of NP dispersion was carefully pipetted onto a tared platinum pan and heated to 100°C for 15 min., followed by 120°C for 30 min. to ensure complete drying. From the remaining sample mass measured, the mass concentration of the NP dispersion was calculated and used for subsequent experiments.

Salting Experiments – The addition of potassium chloride (KCl), tetrabutylphosphonium bromide (TBPB), or tetraphenylphosphonium bromide (TPPB) to NP dispersions was conducted in a manner to minimize mixing time and avoid heterogeneity of salt concentrations which could lead to premature aggregation. Samples of NP stock dispersions were first diluted with appropriate volumes of H₂O in 1.5 mL centrifuge tubes. Holding the tubes over a vortex mixer (Fisherbrand), appropriate volumes of salt stock solutions were quickly injected into the samples, which were immediately capped and vortexed for 5 seconds at 3000 rpm (~1 sec). In experiments with logarithmic salting series (TBPB and TPPB), stock solutions were created with 10² order of magnitude spacing to minimize volumetric pipetting error across samples. Salted dispersions were allowed to sit for 24 hours at room temperature after which particle size and zeta potential measurements were conducted using dynamic light scattering (DLS) and

continuously-monitored phase-analysis light scattering (cmPALS), respectively (Anton Paar Litesizer 500).

Supporting Results

FNP of Polymers – In using FNP to produce colloids of hydrophobic polymers without the presence of added stabilizing agents (*e.g.* amphiphilic polymers, polyelectrolytes, ionomers), the mechanism of hydrophobic anion adsorption which stabilizes the precipitating polymer aggregates during rapid mixing is not fully understood. Therefore, to find candidate polymers for the present study, FNP was performed for a wide variety of available polymers (5 mg/mL THF inlet solution) and particle size (initial and 4 days) and zeta potential was measured (Figure S2 and S3).

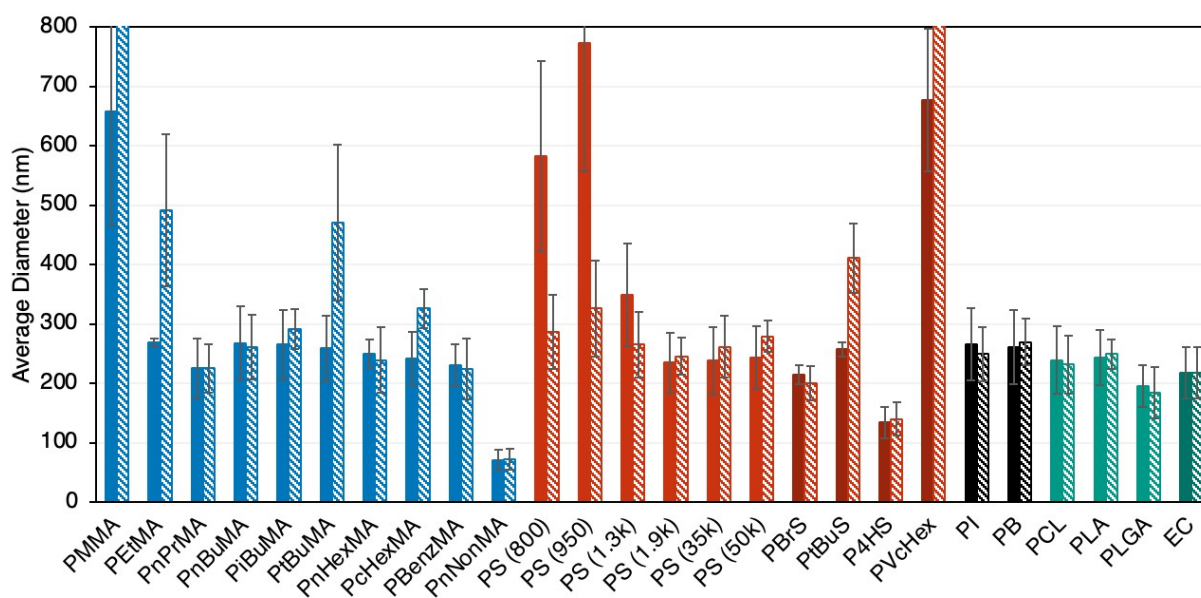


Figure S2. Particle size of polymeric NPs produced by FNP at $c_{\text{inlet}} = 5$ mg/mL for initial (solid) and 4 days (dashed) time points. Colors correspond to chemical classes: methacrylates (blue), styrenics (red), polydienes (black), and polyesters and ethyl cellulose (green).

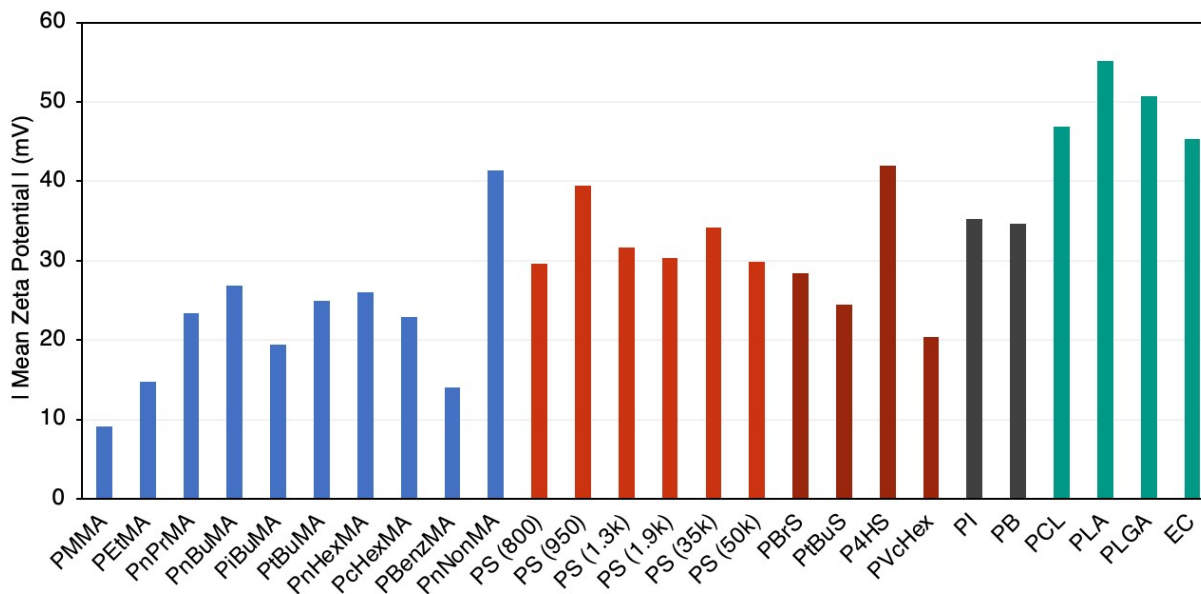


Figure S3. Mean zeta potential magnitudes of negatively charged polymeric NPs.

Trends were observed within each chemical class of polymers. Poly(alkyl methacrylates) require a minimum carbon number (C3 or higher) to become adequately stabilized as evidenced by the low zeta potential and poor size stability of poly(methyl methacrylate) (PMMA) and poly(ethyl methacrylate) (PEtMA) with visibly large aggregates forming after precipitation. It is posited that inadequately hydrophobic surface of NPs formed from these polymers hinders the hydrophobic adsorption of naturally-present anions. As alkyl group carbon number increases, zeta potential is shown to plateau around -25 ± 8 mV while poly(benzyl methacrylate) (PBenzMA) and poly(*n*-nonyl methacrylate) (PnNonMA) exhibit depressed and elevated surface potentials respectively.

Poly(styrenics) showed trends for both molecular weight as well as functionalization. Oligomers (800 Da, 950 Da) were unable to form particles while for molecular weights greater than 1.3k, stable NPs were formed. It is important to note that the measured reduction in size for PS (800 Da) and PS (950 Da) was an artefact of bulk aggregation which depleted large aggregates from the dispersion that had previously obscured a small NP fraction. From these results, PS (35

kDa) was chosen as a representative molecular weight. Among the functionalities tested, the *tert*-butyl group (PtBuS) was found to have a destabilizing effect while the addition of a hydroxyl group (P4HS) enhanced the zeta potential and reduced particle size. Lastly, poly(vinyl cyclohexane) (PVcHex), or hydrogenated PS, was found to have poor stability, suggesting the necessity for some degree of polarity or polarizability for hydrophobic polymer to be naturally stabilized.

Polydienes (PI, PB) exhibited similar zeta and size measurements while polyesters showed enhanced zeta potentials. While useful for consideration in formulations such as biodegradable drug delivery vehicles, the presence of carboxylate end groups resulting from chain hydrolysis restricted their use in the current study as their NP surface were not purely hydrophobic.

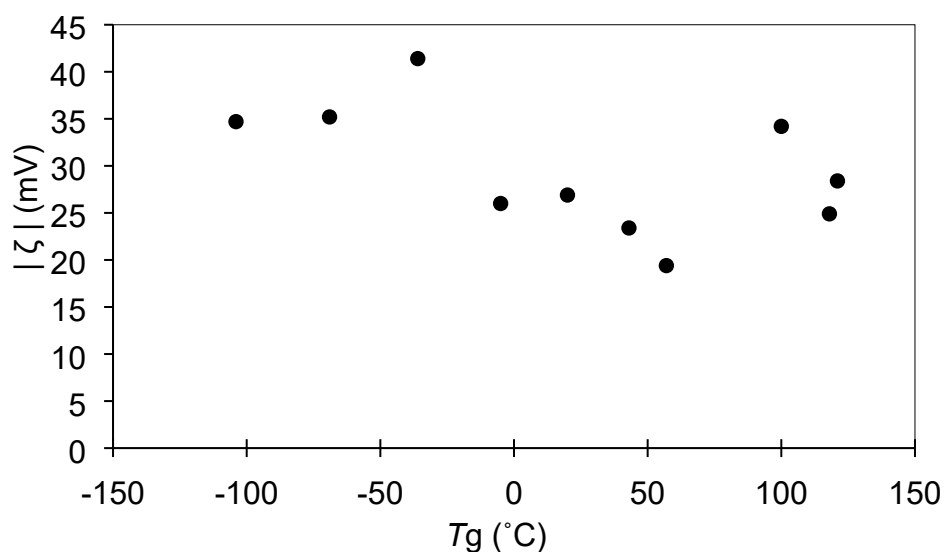


Figure S4. Plot of mean zeta potential magnitude of polymeric NPs vs. corresponding polymer T_g for polymers used in this study showing negligible correlation.

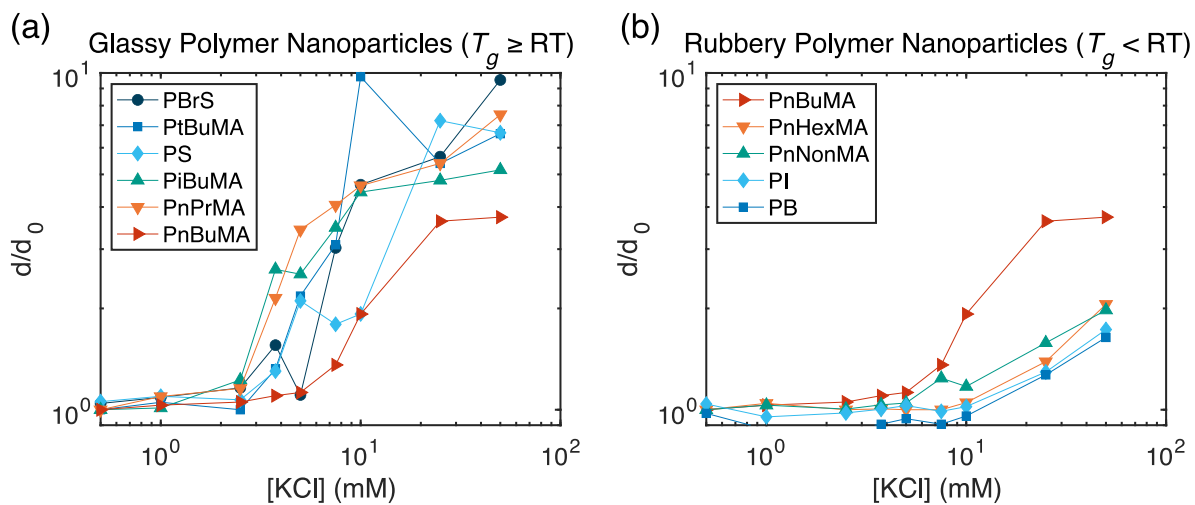


Figure S5. Effect of [KCl] on particle size for (a) glassy and (b) rubbery polymeric NPs. DLS measurements were conducted 24 hr after addition of KCl to NP dispersions.

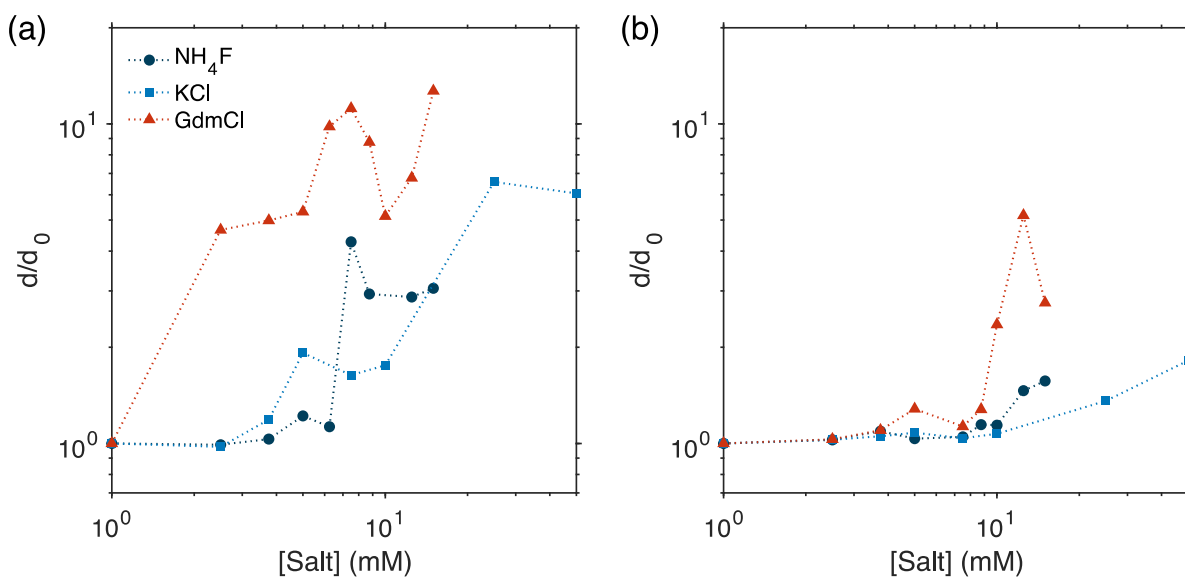


Figure S6. Comparison of size stability for (a) PS and (b) PI NPs in the presence of GdmCl, KCl, NH_4F .