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Tuning HIV drug release from a nanogel-based in situ forming implant by changing nanogel size

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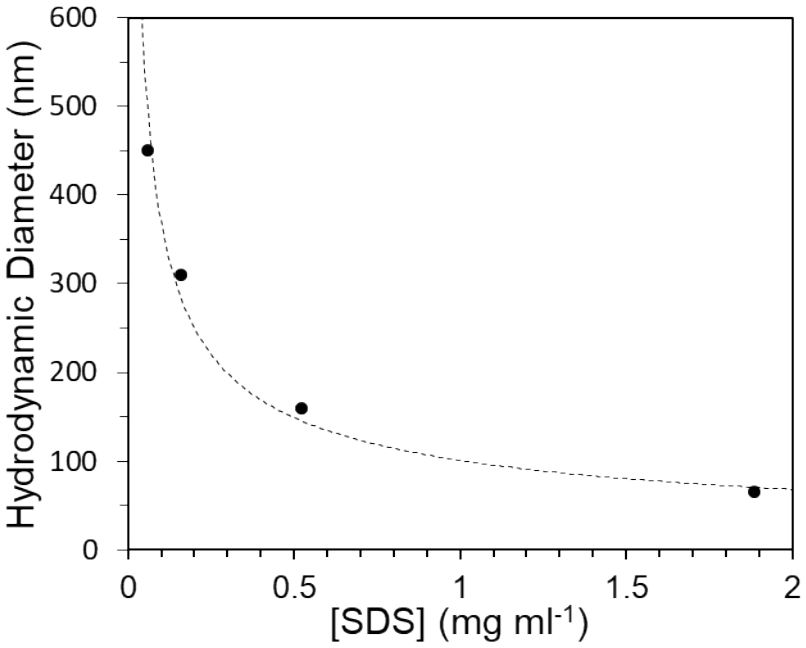

Figure S1 The effect of the concentration of sodium dodecyl sulphate (SDS) used in synthesis on the mean hydrodynamic diameter of PolyNIPAm nanogels.

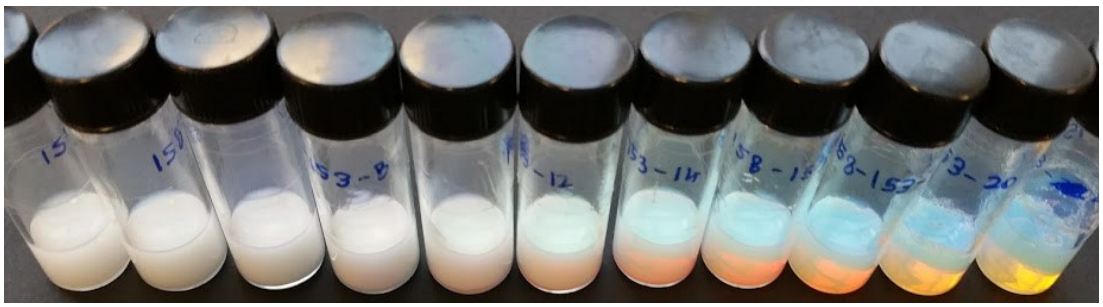

Figure S2 Tyndall scattering in PNA160. Sample dispersed from 2 to 22 wt% increasing in 2wt% increments from right to left.

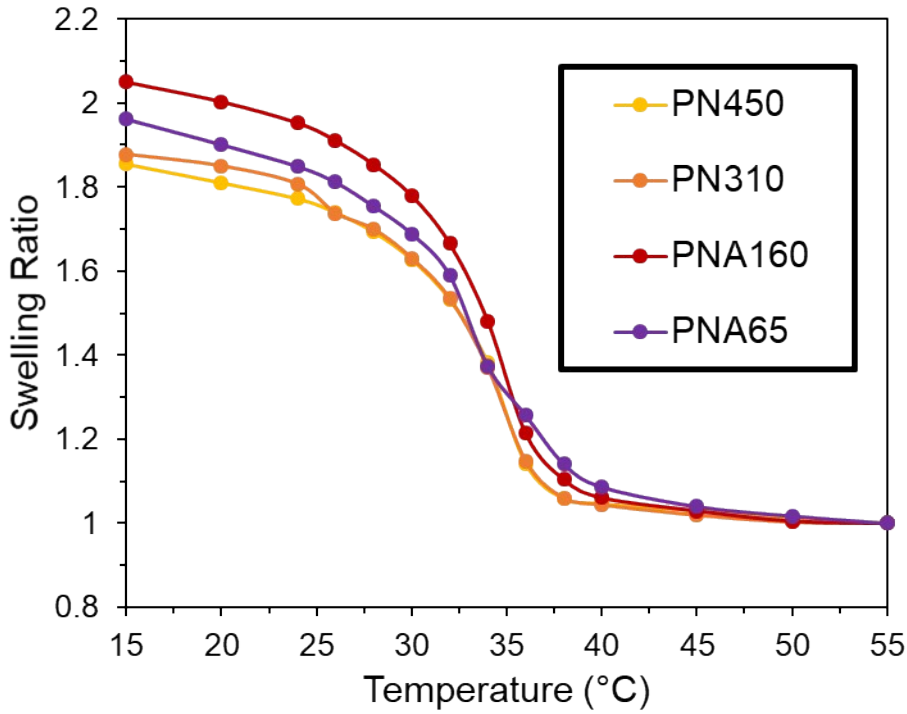

Figure S3 Swelling ratio vs temperature of different sized nanogels. Swelling ratio equals hydrodynamic diameter at given temperature divided by hydrodynamic diameter at 55 °C.

The zeta potential of the four samples was measured using laser Doppler electrophoresis below and above the VPTT (25 °C and 40 °C respectively) as shown in (figure 3). The zeta potential at 25 °C was similar for all the samples with the values ranging between -11.7 and -18.1 mV. When the nanogels were heated to a temperature of 40 °C all the samples become more charged with zeta potential values between -19.6 and -36.9, with a clear trend for samples with larger mean diameters having greater surface charge. The larger nanogels also have a much higher turbidity (figure 1b). Andersson and Maunu showed that a similar substantial zeta potential increase and higher turbidity was seen for polyNIPAm nanogels with a hydrodynamic diameter of 194 and 400 nm, but not for smaller nanogels synthesised with a higher SDS concentration.[50]

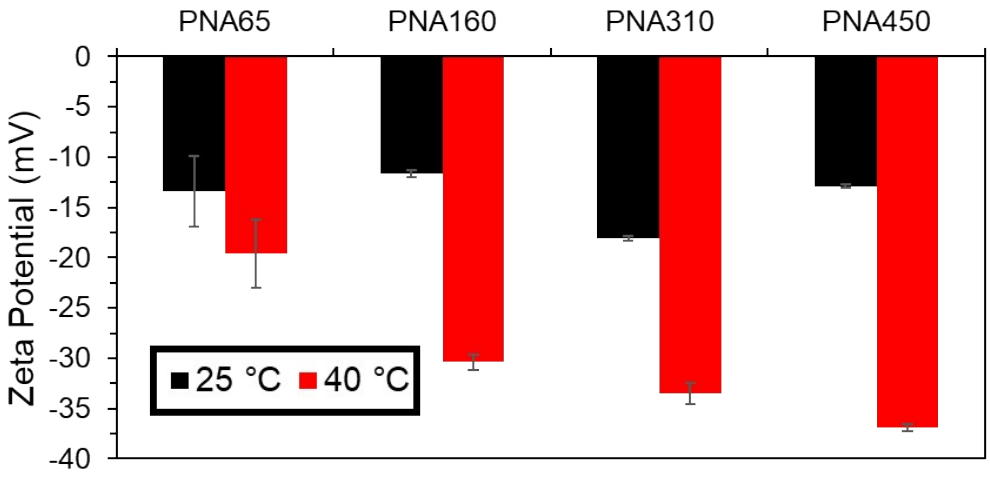

Figure S4. Zeta Potential of nanogels at 25 °C and 40 °C, measured using Laser Doppler Electrophoresis with 1 mg ml^{-1} aqueous dispersions with 10 mM NaCl at pH 7.

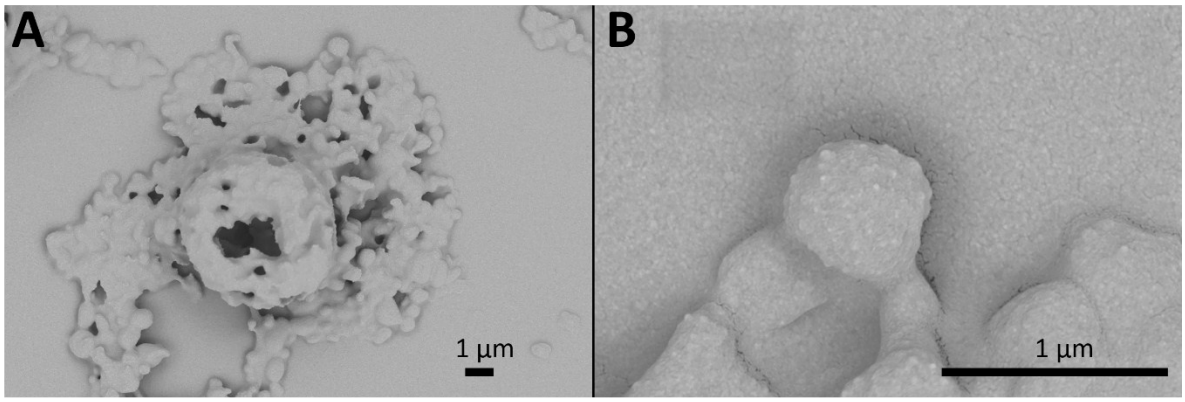

Figure S5. SEM analysis of the lopinavir SDNs alone at two magnifications A) x10,000 and (B) x75,000.

Drug Release Saturation Study

To ensure the saturation limit of drug in release media was avoided, a saturation study was conducted on the nanogel predicted to give the greatest release rate, and at the highest SDN loading tested, PNA-450-66 (article table 3). PNA450 was expected to show the greatest permeability and hence drug release rate, owing to it being the largest nanogel, and so containing the largest pores between nanogels. In the saturation study 1 ml of release media was removed from 200 ml of PBS at each sampling interval. It can be seen that the cumulative amount of drug released over time begins to plateau after approximately 30 hours, (figure S4). According to the European Pharmacopeia 8.0 (5.17.1) and United States Pharmacopeia (USP37/NF32),[1,2] sink conditions are reached when the volume of release media is at least

three times saturation volume. Using the saturation study, a sampling interval of 24 hrs was selected for a 15 day *in vitro* study of drug release from aggregate depots, as a compromise between realistic experimental parameters, and avoiding a saturation limit on the rate of drug release.

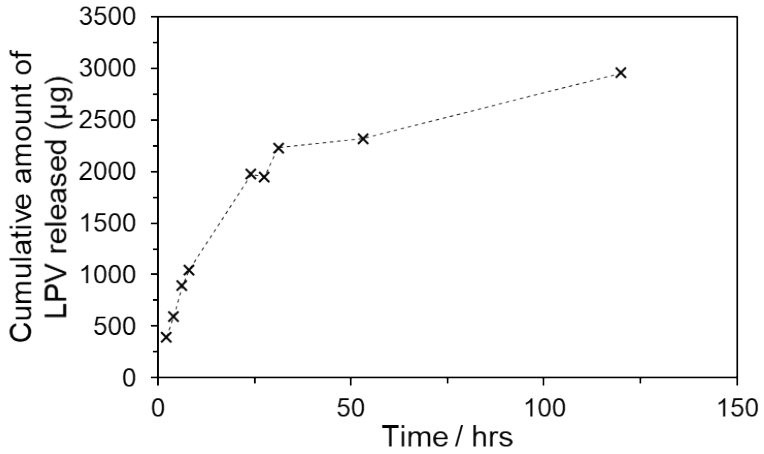

Figure S6. Cumulative release of Lopinavir drug from PNA450-66 (article table 3) into 200 ml of PBS. All samples were analysed in duplicate and in all cases the standard deviation of measurements was less than 1.7 µg drug release, therefore error bars are not shown.

Table S1 Correlation coefficient (R_c) and dissolution constant (k) values.

Formulation	k	R_c
PNA65-33	2.08	0.9942
PNA65-50	3.17	0.9988
PNA65-66	5.97	0.9872
PNA160-33	4.13	0.9995
PNA160-50	14.69	0.9972
PNA160-66	15.15	0.9837
PNA310-33	5.56	0.9950
PNA310-50	12.80	0.9813
PNA310-66	11.82	0.9949
PNA450-33	8.88	0.9971
PNA450-50	8.31	0.9964
PNA450-66	12.14	0.9964

Estimation of potential clinical release rates

The fastest drug release of all the samples, PNA160-66 displayed release rates of over ~45 µg hr-1 over the 300 hours of the experiment. The release rate was for a volume of 0.5 mL of the implant. If the total volume of the implant was increased to 15 mL (x30) and assuming that

the release rate is independent of the volume of the implant, then the total release rate would be 45 µg hr-1 x 30 = 1350 µg hr-1 or 1.35 mg hr-1.

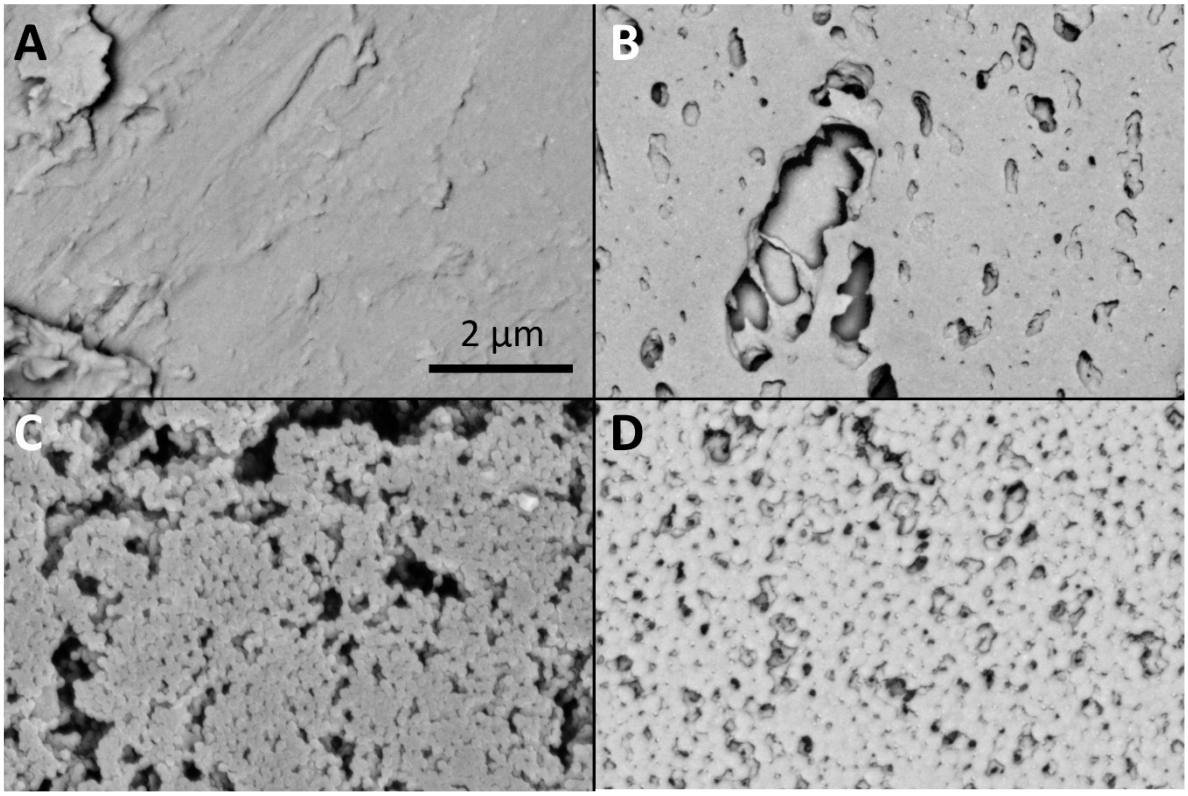

Figure S7. SEM characterisation of aggregates of the four different nanogels samples formed at 12 wt% in PBS at 37 °C and air dried. A) PNA65, (B) PNA160, (C) PNA310, (D) PNA 450.

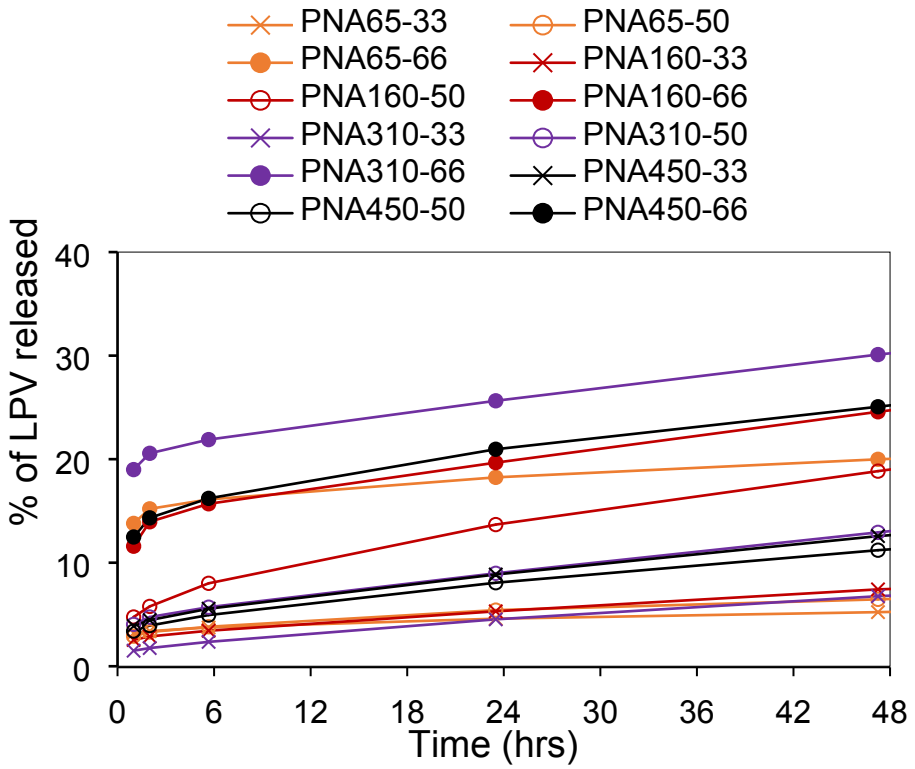

Figure S8. Cumulative % release of LPV drug from aggregated nanogel discs over first 48 hours. Burst release complete within 1st hour, with no further dramatic rise in total cumulative release. All samples were analysed in duplicate, the mean relative standard deviation for all samples was 1.9% and the maximum relative standard deviation for a sample was 11.2%.

References

1 P. Liu, O. De Wulf, J. Laru, T. Heikkilä, B. van Veen, J. Kiesvaara, J. Hirvonen, L. Peltonen and T. Laaksonen, *AAPS PharmSciTech*, 2013, **14**, 748–756.

2 S. A. Abouelmagd, B. Sun, A. C. Chang, Y. J. Ku and Y. Yeo, *Mol. Pharm.*, 2015, **12**, 997–1003.