The development of an in situ forming dexamethasone implant to treat diabetic retinopathy

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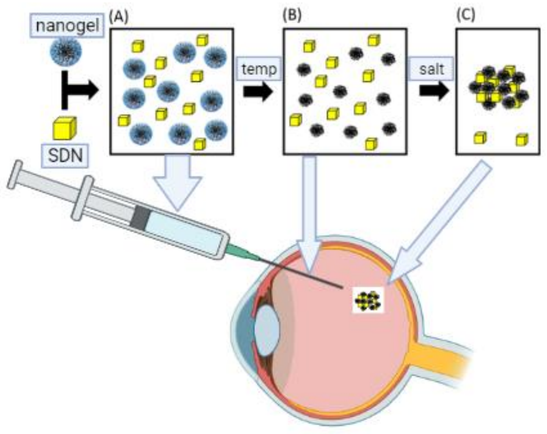
Introduction

Intraocular drug delivery devices are a useful way of reducing costs in the long term and improving patient outcomes through the reduction of complications. Drug release is an important property that could have an impact on the efficacy of the treatment. An injectable implant that solidifies upon contact with a physiologically relevant environment could be an alternative to current treatments, which in some cases involve surgical interventions for insertion.

Figure 1: *A nanocomposite material contains solid drug nanoparticles (SDNs) and hydrogel. The salt concentration in the eye and the temperature causes the gel like consistency of the material to become a drug depot which can allow for sustained release over time [2]. Image has been adapted [2].*

Aims

1) Synthesis and screening of dexamethasone solid drug nanoparticles (SDNs)
2) Synthesis of 65nm, 310nm and 450nm n-isopropylacrylamide (NIPAm) nanogels
3) Investigate if controlled drug release can be achieved using a nanocomposite consisting of a NIPAm nanogel and dexamethasone SDNs.



Methods

Figure 2: *Dispersion polymerisation technique was used to synthesise three different NIPAm nanogels. In dispersion polymerisation: a) monomers are in solution with the surfactant and crosslinker; b) initiation stage after one hour of homogenising the solution by addition of initiator; c) Nucleation occurs; and d) polymerisation begins.*

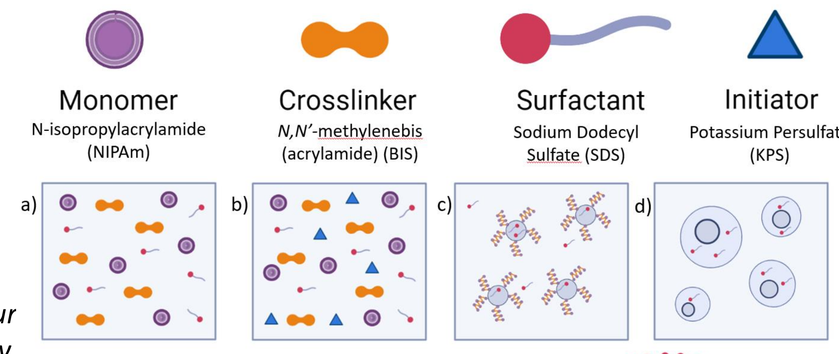
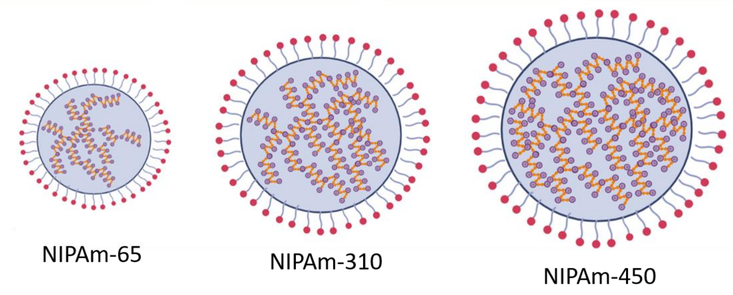
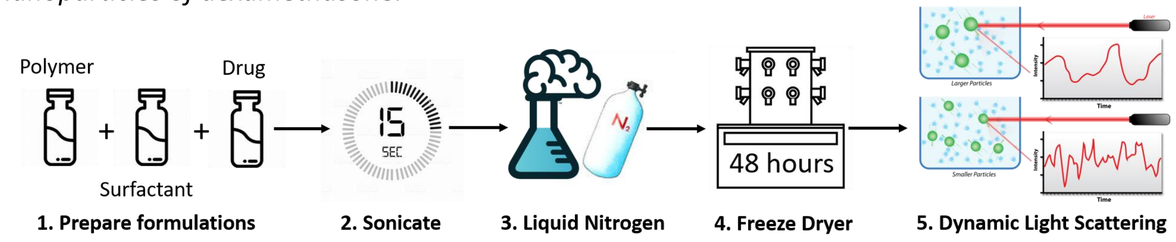


Figure 3: *Emulsion templated freeze drying (ETFD) technique was used to synthesise solid drug nanoparticles of dexamethasone.*





Results

Dynamic Light Scattering shows consistent reproducibility of nanoparticles

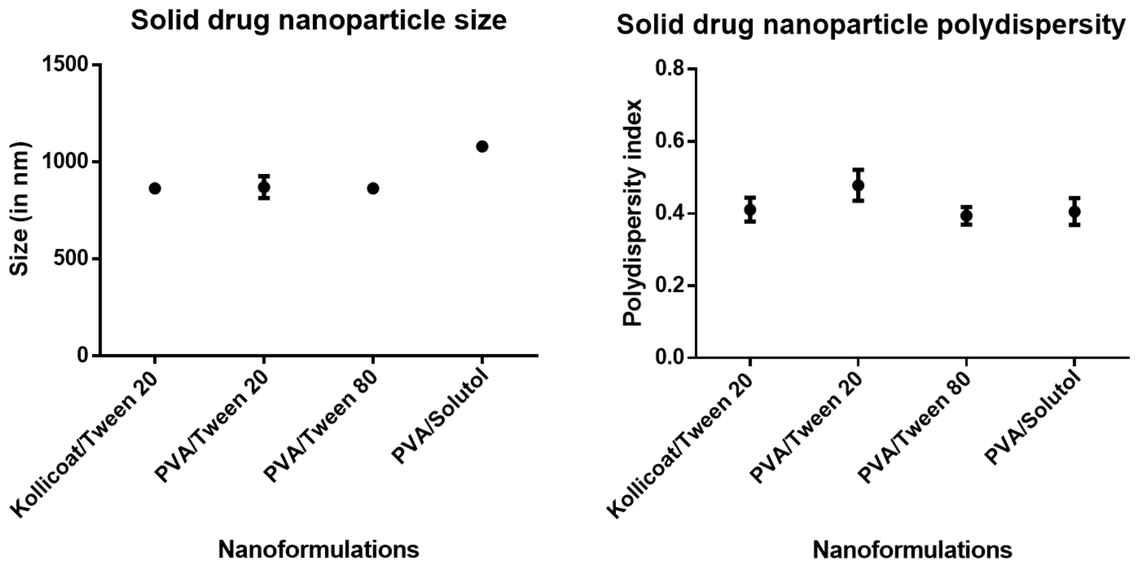
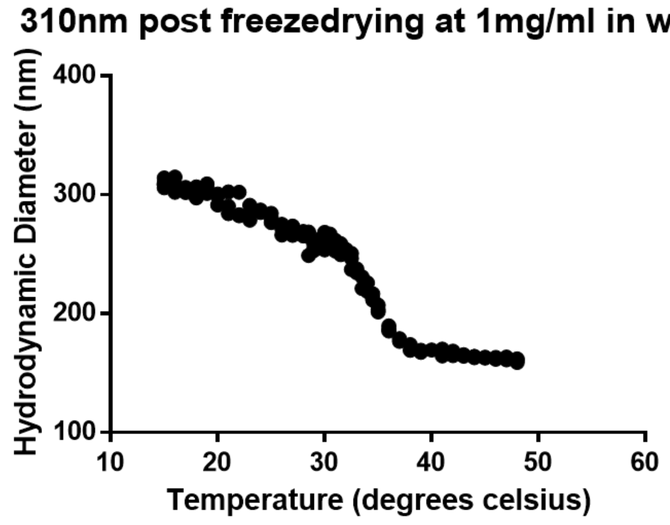
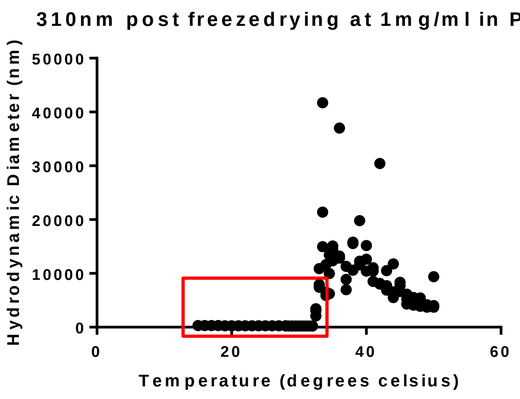


Figure 4 *The dynamic light scattering analysis has shown consistent reproducibility between each batch. All samples satisfied a polydispersity index (PDI) of 0.7 or below in line with ISO 22412 particle size analysis (DLS) [1].*

NIPAm gels show aggregation behavior in the presence of salt





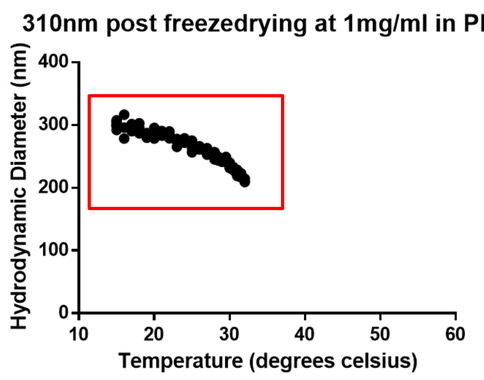


Figure 5 *Aggregation occurs in the presence of salt at 32.5°C. which indicates they have good potential for forming an in situ forming implant at a physiologically relevant temperature. Whilst this example is specifically for the NIPAm-310 nanogel, similar behaviour was noted with the 65nm and 450nm nanogels. Upon injecting into a vitreous environment, a drug depot should form which releases drug over time.*

PVA/Tween 20 when combined with 310nm nanogel shows potential for controlled drug release

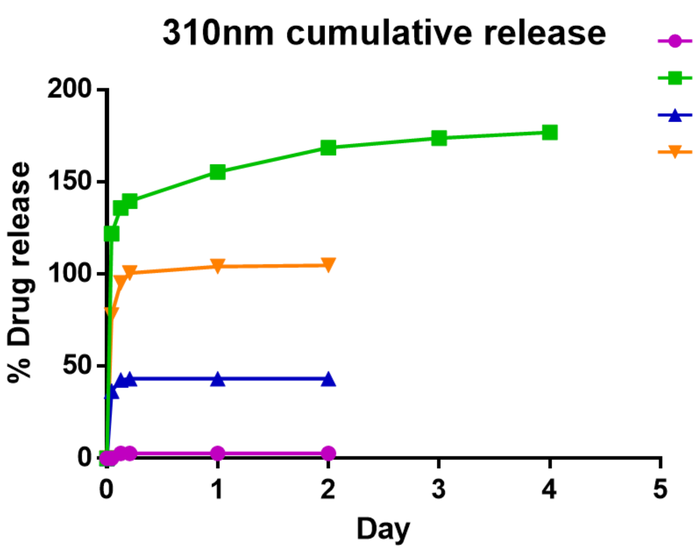


Figure 6 *Cumulative drug release was plotted after testing the four nanoformulations with the three different NIPAm nanogels. PVA/Tween 20 nanoformulation showed slower drug release compared to the other nanoformulations that were combined with the 310nm nanogel. The % drug release obtained in this case for that nanoformulation was over >100% indicating that the amount of drug loaded in the nanoparticles in some cases may be much higher than expected.*

Conclusions

- These are the first examples of dexamethasone solid drug nanoparticles (SDNs) using the ETFD technique
- The stability testing of the nanoformulations narrowed the SDNs to four nanoformulations
- Whilst there is reproducibility between batches of nanoparticles, the amount of drug loaded may differ occasionally
- Aggregation occurs when the nanogels are in the presence of salt indicating good potential for forming an in situ implant
- Further testing will be required to evaluate the potential of PVA/Tween 20 nanocomposite as an in situ forming implant

References

[1] ISO (ISO/TC 24/SC 4 Particle characterization). (2017).
[2] Town, A. R., Giardiello, M., Gurjar, R., Siccardi, M., Briggs, M. E., Akhtar, R., & McDonald, T. O. (2017).

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