Optimization of modified poly (glycerol adipate) polymer nanoparticles for pulmonary drug delivery

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Introduction

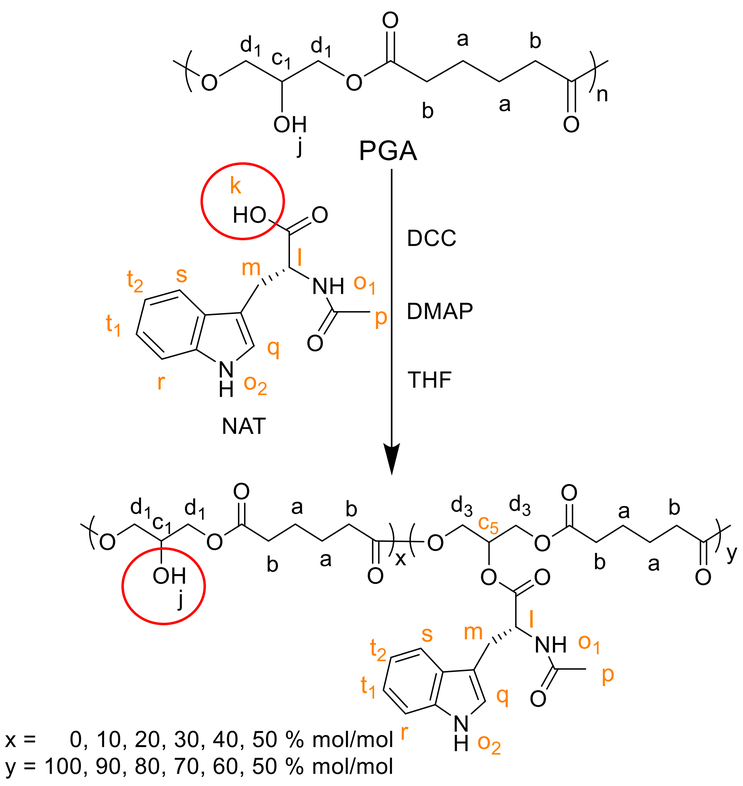
- Pulmonary drug delivery has attracted great interest especially in localized treatment of lung diseases.
- Nanoparticles can provide vast benefits in overcoming some of that route challenges.
- However, few polymers have shown suitability for the inhaled route. In contrast, Poly (glycerol adipate) (PGA) has emerged as a green enzyme synthesized polyester polymer with various unique advantages for that route of delivery.

Aims

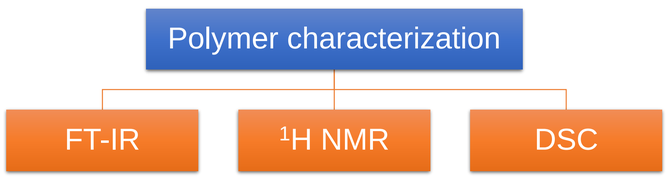
- Test the aptness of PGA polymer for pulmonary drug delivery application.
- Modification of PGA polymer to obtain solid polymers with glass transition temperature (T_g) > 40°C.
- Formulation of modified polymers into stable nanoparticle formulations.

Methodology

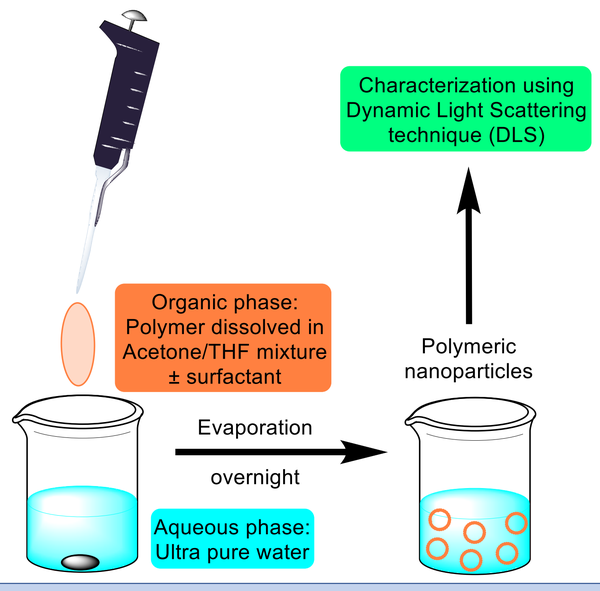
Modification of PGA polymer with *N*-acetyl tryptophan (NAT) using simple Steglich esterification reaction



Characterization of PGA and modified PGA-NAT polymers



Formulation of PGA-NAT polymeric nanoparticles (NPs) using nanoprecipitation technique and characterization using Dynamic Light Scattering (DLS)



Results (Polymers characterization)

Fourier-transform infrared spectroscopy (FT-IR) confirming the successful coupling reaction

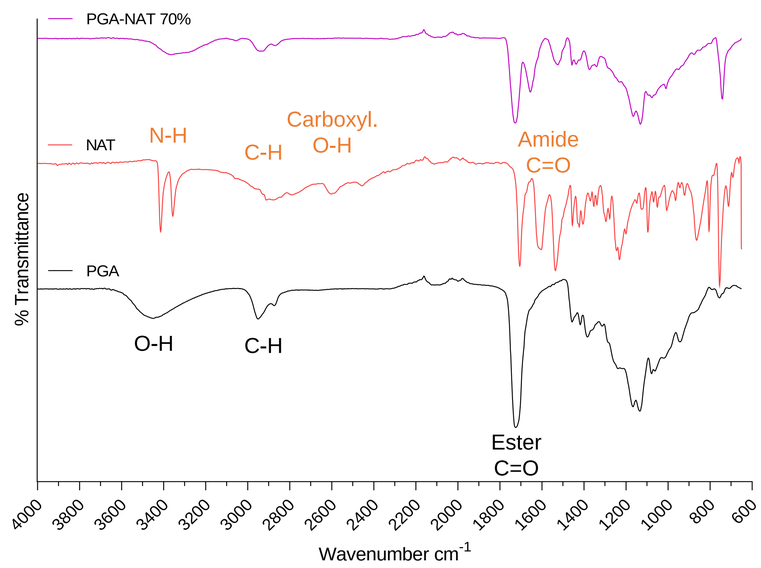


Figure 1: FT-IR spectra showing characteristic peaks of: (Black) PGA (free O-H broad peak, C-H stretching and strong ester C=O peaks), (Red) NAT (aromatic & aliphatic N-H stretching, C-H stretching, carboxylic O-H, carboxylic and amide C=O peaks) and (Purple) PGA-NAT 70% substituted polymer (PGA free O-H peak decrease & overlap with NAT N-H peaks, disappearance of NAT carboxylic O-H peak, C-H stretching, ester and amide C=O peaks).

^{1}H Nuclear Magnetic Resonance (^{1}H NMR) analysis confirming the successful coupling reaction

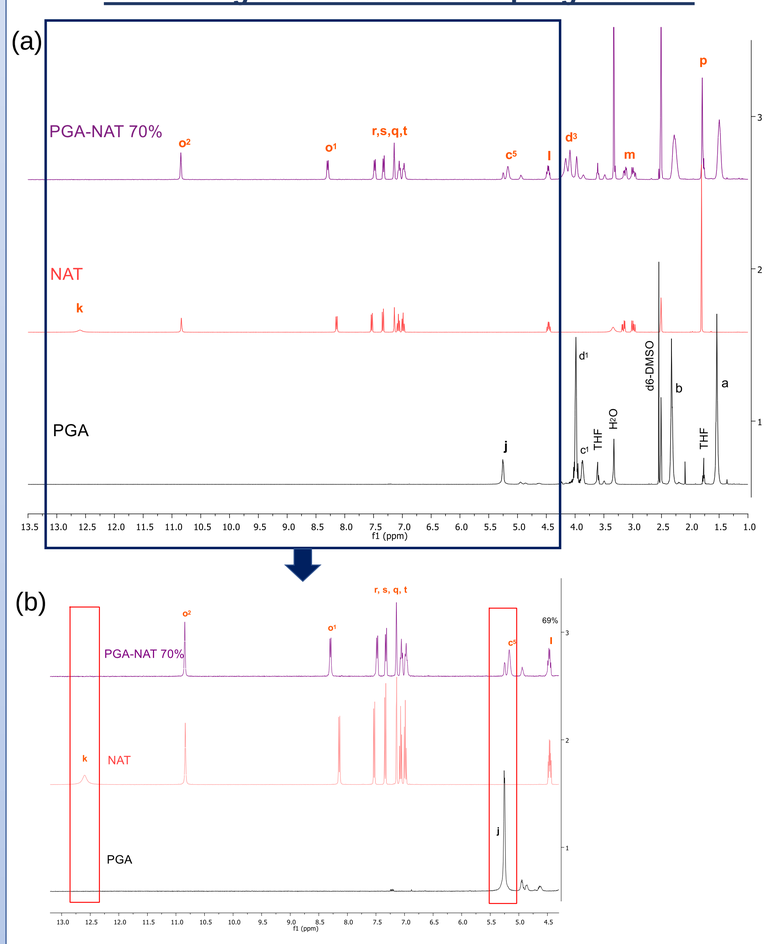


Figure 2: ^{1}H NMR analysis (a) complete spectra showing characteristic proton peaks of: (Black) PGA (a – j peaks), (Red) NAT (k – t peaks) and (Purple) PGA-NAT 70% substituted polymer (a – t peaks). (b) spectra inset between 13.2 and 4.3 ppm showing decrease in area of PGA free hydroxyl group proton (j) and disappearance of NAT free carboxylic group proton (k) upon modification.

Differential Scanning Calorimetry (DSC) analysis showing proper control of Glass transition temperatures (T_g) of modified polymers with their NAT % substitution

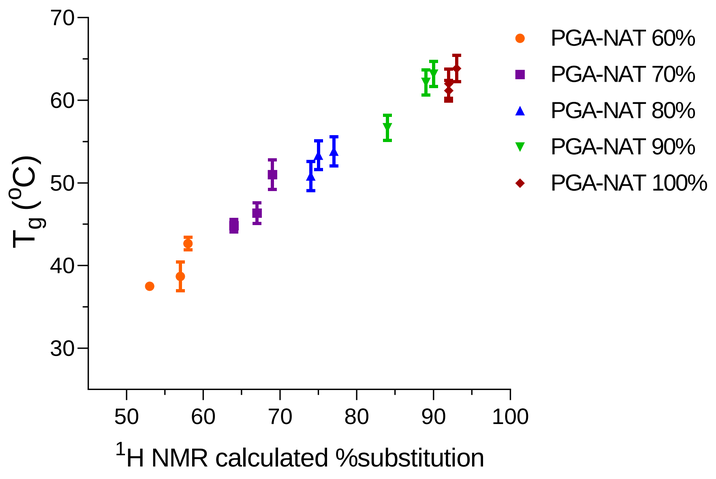


Figure 3: DSC analysis showing Glass transition temperatures (T_g) values (40 – 63°C) for the PGA-NAT modified polymers prepared at different % substitution (60 – 100%). Three different modified polymer batches were prepared at each % substitution and characterized to demonstrate reproducibility of results (n = 3).

References

1. Swainson SME, Styliari ID, Taresco V, Garnett MC. Poly (glycerol adipate) (PGA), an Enzymatically Synthesized Functionalizable Polyester and Versatile Drug Delivery Carrier: A Literature Update. Polymers. 2019;11(10):11.
2. Taresco V, Suksiriworapong J, Styliari ID, Argent RH, Swainson Sadie ME, Booth J, et al. New N-acyl amino acid-functionalized biodegradable polyesters for pharmaceutical and biomedical applications. RSC Advances. 2016;6(111):109401-5.
3. Loira-Pastoriza C, Todoroff J, Vanbever R. Delivery strategies for sustained drug release in the lungs. Advanced Drug Delivery Reviews. 2014;75:81-91.

Results (Nanoparticle characterization)

DLS characterization of highly substituted polymers nanoparticles colloidally stabilised with surfactants

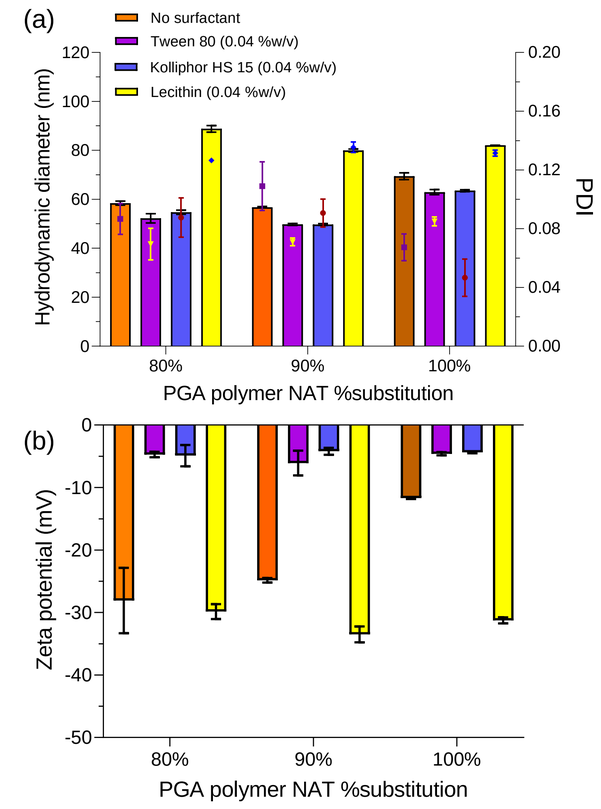


Figure 4: DLS analysis of highly substituted PGA-NAT polymers nanoparticles prepared using 0.04 %w/v of surfactants (Tween 80, Kolliphor HS 15 or Lecithin powder) with respect to (a) Bar chart: hydrodynamic diameter (nm) and Data point chart: polydispersity index (PDI), and (b) zeta potential (mV) (n = 3 ± S.D.).

Storage stability characterization of the surfactant-stabilised PGA-NAT 80% polymeric nanoparticles

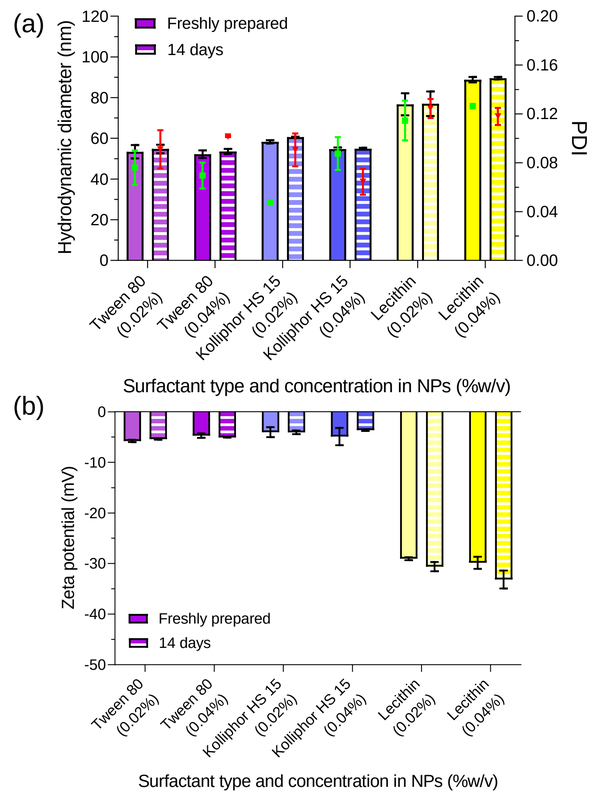


Figure 5: DLS analysis of PGA-NAT 80% substituted polymer nanoparticles prepared using different concentrations of surfactants upon storage at 4°C for 14 days with respect to (a) Bar chart: hydrodynamic diameter (nm) and Data point chart: polydispersity index (PDI), and (b) zeta potential (mV) (n = 3 ± S.D.).

Conclusions

- ✓ A library of PGA-NAT modified polymers was successfully synthesised and characterised.
- ✓ The T_g of parent PGA polymer was elevated from -33°C to > 40°C in a controlled manner by varying the % substitution.
- ✓ All polymers were self-assembled into nanoparticles that could be colloidally stabilised with surfactants compatible with pulmonary delivery.

Future work

- Test the enzymatic degradability of PGA-NAT NPs and evaluate their safety on lung cell lines.
- Spray-drying of optimized nanoparticles formulations into inhalable powders and testing of their *in-vitro* aerosolization behaviour upon delivery using dry powder inhalers (DPIs).

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