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

Ramy Said-Elbahr[1, 2], Vincenzo Taresco[3], Giuseppe Mantovani[1], Snow Stolnik[1], Cynthia Bosquillon[1]

[1] University of Nottingham, School of Pharmacy, University Park, Nottingham, NG7 2RD, United Kingdom
[2] Ain Shams University, Faculty of Pharmacy, Abbassia, Cairo, 11566, Egypt
[3] University of Nottingham, School of Chemistry, University Park, Nottingham, NG7 2RD, United Kingdom

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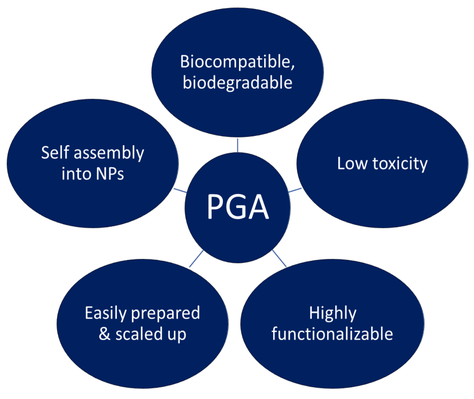
Introduction

- Pulmonary drug delivery is largely used for localized treatment of lung diseases but suffers from various limitations, some of which could be overcome by use of polymeric nanoparticles.
- Few polymers have been deemed compatible with the inhaled route. In contrast, Poly (glycerol adipate) (PGA) can offer several advantages over traditional polymers for pulmonary drug delivery purposes.



Aims

- Test the aptness of PGA polymers for pulmonary drug delivery application.
- Modification of PGA polymer (T_g= -33°C) to obtain solid polymers with glass transition temperature (T_g) > 40°C and thus, enable future spray-drying of their nanoparticle formulations into micron-sized inhalable powders.
- Formulation of modified polymers into stable nanoparticles and assessing their enzymatic degradability.

Methodology

- Modification of PGA with *N*-acetyl tryptophan (NAT) using simple Steglich esterification reaction
- Polymers were characterised with ^{1}H NMR and DSC to monitor the effect of NAT % substitution on the T_g values.
- PGA polymers were formulated into nanoparticles by nanoprecipitation using different surfactants and characterized using Dynamic Light Scattering (DLS) and Transmission Electron Microscopy (TEM).
- PGA-NAT nanoparticles were incubated with Lipase enzyme and change in polymer molecular weight was monitored with Size Exclusion Chromatography (SEC).

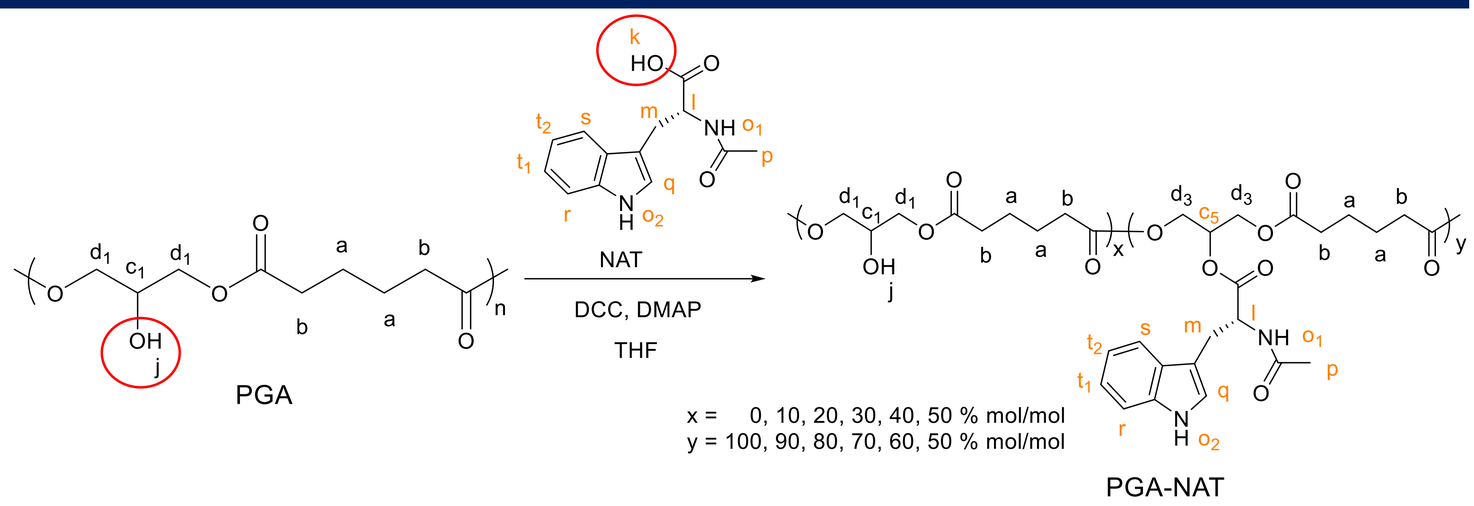


Figure 1: Coupling scheme of PGA and NAT in anhydrous THF using DCC as the coupling agent and DMAP as the organo-catalyst

Results

Confirmation of successful coupling reaction

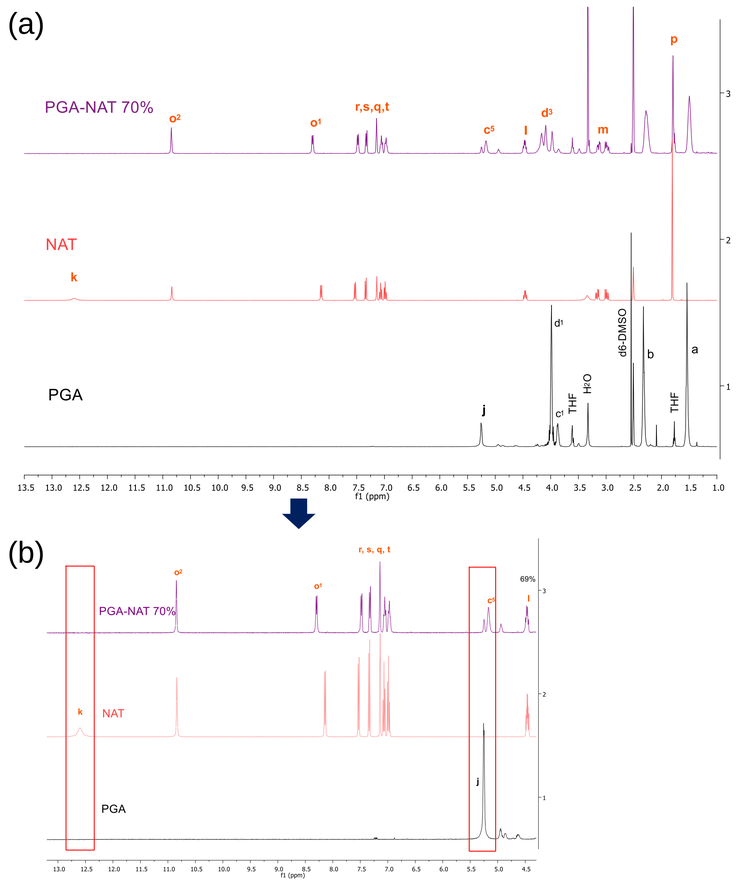


Figure 2: **^{1}H NMR** analysis (a) complete spectra showing characteristic proton peaks of: (Black) PGA (a – j peaks), (Red) NAT (k – t peaks) and (Purple) PGA-NAT 70% substituted polymer (a – t peaks), and (b) spectra inset between 13.2 and 4.3 ppm showing **decrease** in area of **PGA free hydroxyl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

Effect of surfactants on nanoparticles colloidal properties

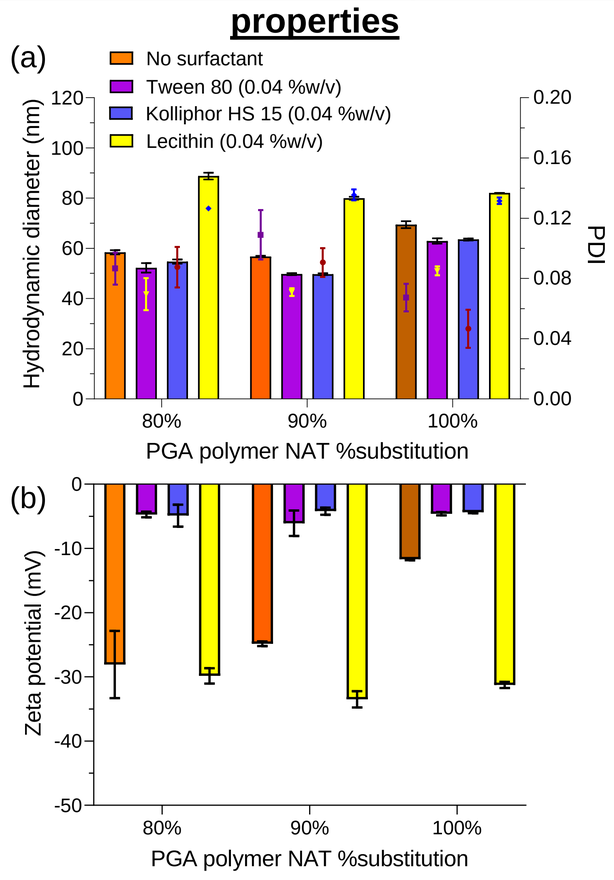


Figure 4: **DLS** analysis of **highly** substituted PGA-NAT polymers (**80 - 100%**) nanoparticles (1 mg/ml) prepared using 0.04 %w/v of surfactants (**Tween 80, Kolliphor HS 15 or Lecithin powder**) with respect to (a) **Bar chart**: hydrodynamic diameter (nm) and **Data point chart**: polydispersity index (PDI), and (b) zeta potential (mV) (n = 3 ± S.D.).

Enzymatic degradability of PGA-NAT nanoparticles

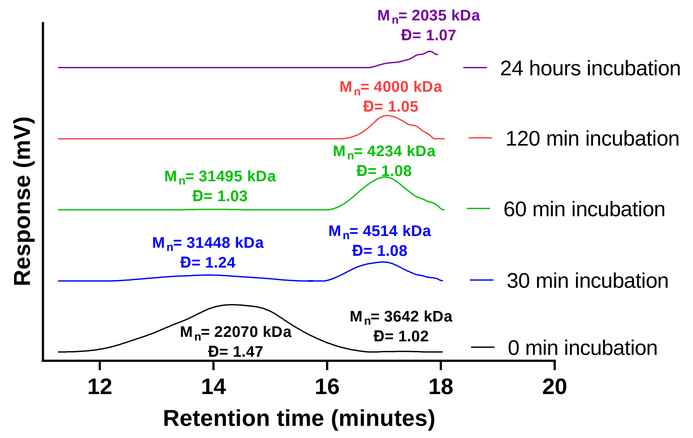


Figure 6: **SEC** of Tween 80-stabilised PGA-NAT 80% substituted polymer nanoparticles incubated with Porcine Pancreatic **Lipase** enzyme in PBS (pH 7.4) at ratio (**0.5 mg enzyme / mg polymer**) for: (Black) 0 minutes, (Blue) 30 minutes, (Green) 60 minutes, (Red) 120 minutes and (Purple) 24 hours. **M_n** represents the **number average molecular weight** and **Đ** represents **polydispersity**. Analysis was carried out using DMF + 0.1% LiBr as the mobile phase and results were selected between the higher and lower detection limits.

Glass transition temperatures (T_g) of modified polymers depends on their NAT % substitution

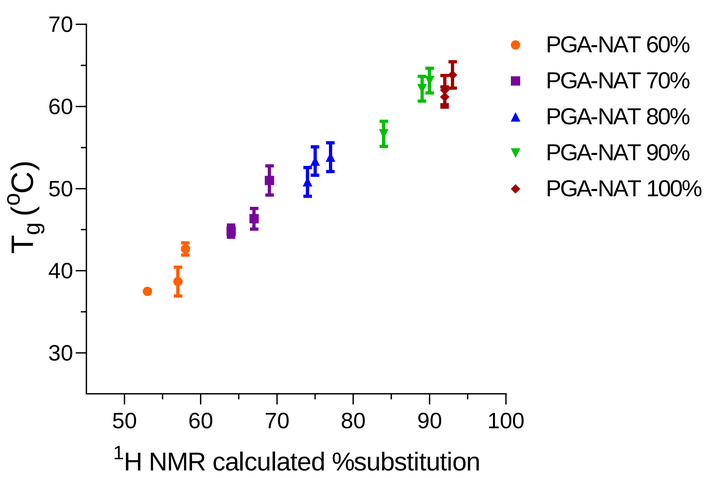


Figure 3: **DSC** analysis showing Glass transition temperatures (T_g) values (**40 – 63°C**) for the PGA-NAT modified polymers prepared at different % substitution (60 – 100%). Three different modified polymer batches were prepared at each % substitution and characterized to demonstrate **reproducibility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

Morphology of the surfactant-stabilised PGA-NAT nanoparticle formulation

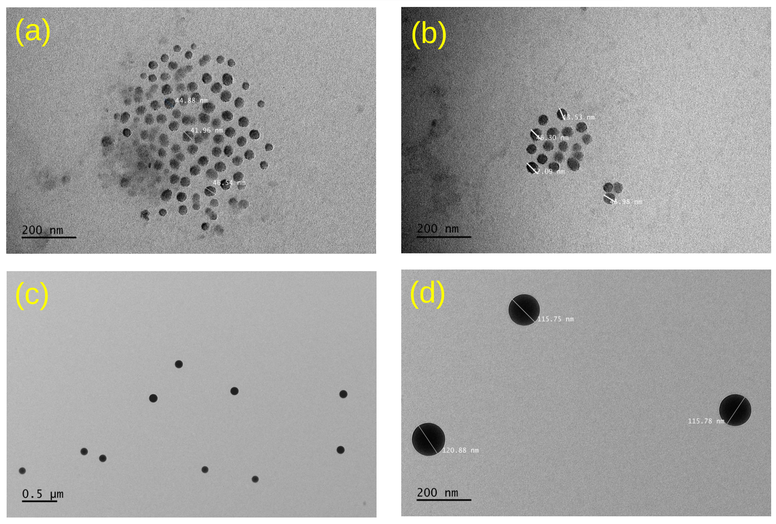


Figure 5: **TEM** analysis of surfactant-stabilised PGA-NAT 80% substituted polymer nanoparticles (1 mg/ml) prepared using 0.04 %w/v of surfactants (a) **Tween 80**, showing nearly spherical particles with size about 40 – 50 nm, (b) **Kolliphor HS 15**, showing nearly spherical particles with size about 40 – 50 nm, and (c, d) **Lecithin powder**, showing spherical particles with size about 100 – 120 nm. Images were captured at 18500X magnification (4800X for image (c)) and scale bars presented at 200 nm (0.5 µm for image (c)).

Conclusions

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

Acknowledgments

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References

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CONTACTS