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Biodegradable Hydralese™ (PGSU) Microspheres for Controlled Release of Water-soluble Drugs

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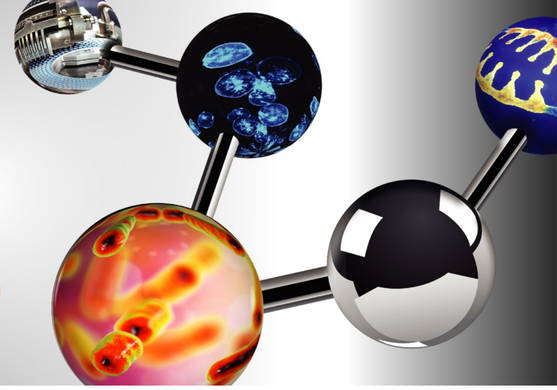


PURPOSE

Secant Group is developing active pharmaceutical ingredient (API)-loaded microspheres manufactured from Hydralese™ (PGSU) (poly(glycerol sebacate) urethane). Hydralese (PGSU) is synthesized by crosslinking poly(glycerol sebacate) (PGS) resin via polyol-isocyanate urethane chemistry. Hydralese (PGSU) is a synthetic biodegradable elastomer known to have regenerative and anti-inflammatory properties. Hydralese (PGSU) can achieve steady release of APIs from a few weeks to months depending on the crosslinking density, degradation rate, API physical form, and API particle size. Additionally, release kinetics of an API depend on the surface area available; hence, microsphere size distribution is crucial.

OBJECTIVES

1) To manufacture and characterize 2'-deoxyadenosine (2'dA)-loaded Hydralese (PGSU) microspheres using large particle and micronized API
2) To compare *in vitro* release of 2'dA from Hydralese (PGSU) microspheres of different loadings, microsphere size distributions, API particle sizes, and degrees of crosslinking

METHODS

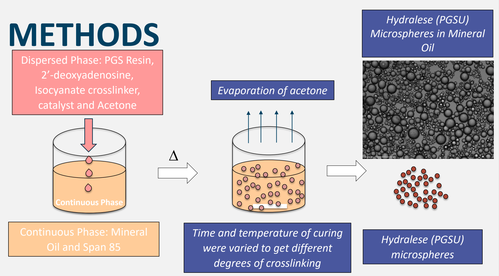


Figure 1. Process of manufacture of Hydralese (PGSU) microspheres.

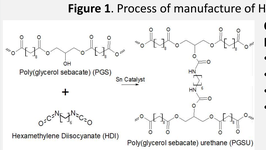


Figure 2. Crosslinking reaction of poly(glycerol sebacate) (PGS) via polyol-isocyanate urethane chemistry.

Characterization of Hydralese (PGSU) Microspheres:

- Optical microscopy
- Scanning Electron Microscopy (SEM)
- Particle size analysis by laser diffraction
- % drug loading was determined by extracting 2'dA with DMSO followed by LC analysis
- *In vitro* release was performed at 37°C in 0.1 M phosphate buffer saline (PBS)

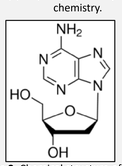


Figure 3. Chemical structure of 2'dA (T_m = 185-187°C).

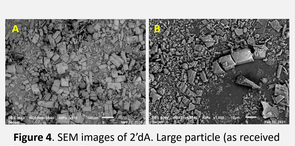


Figure 4. SEM images of 2'dA. Large particle (as received from the manufacturer), 30-100 µm, scale bar 100 µm and **B**. Micronized by freeze drying, 3-10 µm, scale bar 10 µm.

RESULTS

Effect of 2'-deoxyadenosine Particle Size on *In Vitro* Release in PBS

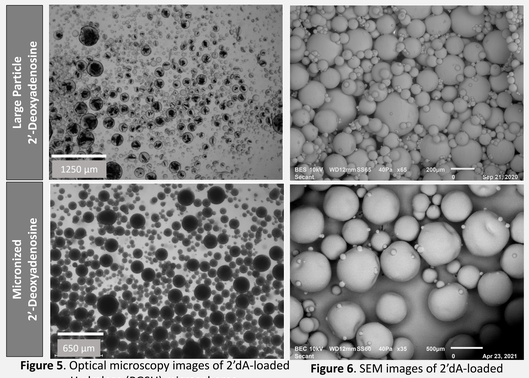


Figure 5. Optical microscopy images of 2'dA-loaded Hydralese (PGSU) microspheres.

Figure 6. SEM images of 2'dA-loaded Hydralese (PGSU) microspheres.

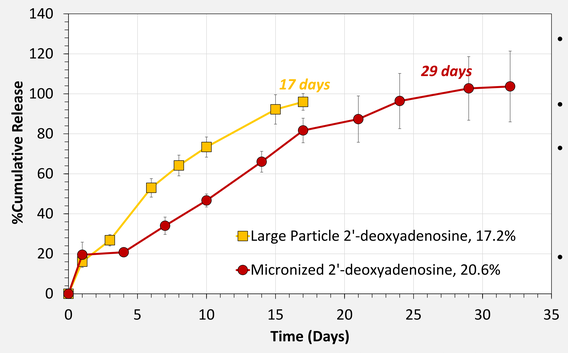


Figure 7. *In vitro* release of large particle and micronized 2'dA from Hydralese (PGSU) microspheres.

- Both the formulations were made similarly by curing at 70°C for 3 hours
- PGS resin:isocyanate crosslinker = 2:1
- Large particle 2'dA loads towards the center of the microsphere depending on the size of the API particle vs microsphere
- Micronized 2'dA is evenly loaded throughout the volume of the microsphere

Effect of Particle Size of Microspheres on *In Vitro* Release in PBS

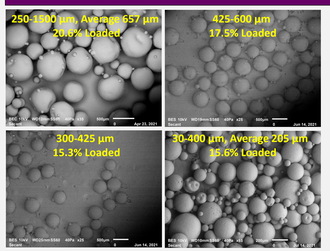


Figure 8. SEM images of micronized 2'dA-loaded Hydralese (PGSU) microspheres. Microspheres in the size ranges 425-600 µm and 300-425 µm were sieved from the same batch as 250-1500 µm.

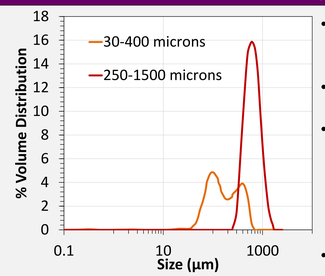


Figure 9. Particle size analysis of micronized 2'dA-loaded Hydralese (PGSU) microspheres measured by laser diffraction.

- All formulations were made similarly by curing at 70°C for 3 hours
- PGS resin:isocyanate crosslinker = 2:1
- 205 µm microspheres were made by changing manufacturing parameters like % PGS content, speed of homogenization, and viscosity of mineral oil
- Sieving down the microspheres of the same batch showed lower % loading

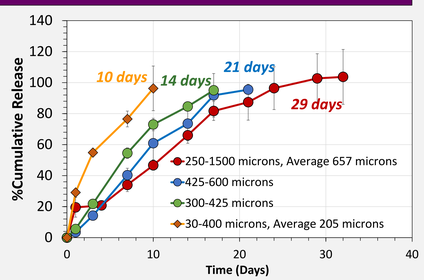


Figure 10. *In vitro* release of micronized 2'-deoxyadenosine from Hydralese (PGSU) microspheres of varying size ranges.

Effect of Degree of Crosslinking of Microspheres on *In Vitro* Release in PBS

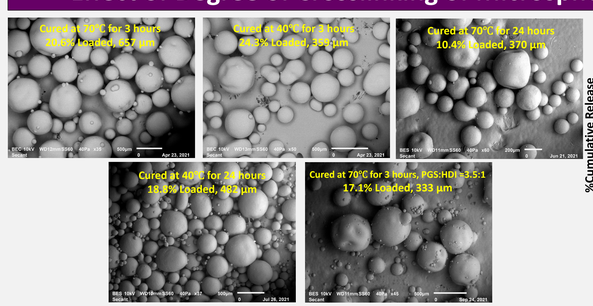


Figure 11. SEM images of micronized 2'dA-loaded Hydralese (PGSU) microspheres of varying degrees of crosslinking made by changing the curing time and temperature or the PGS:isocyanate crosslinker ratio.

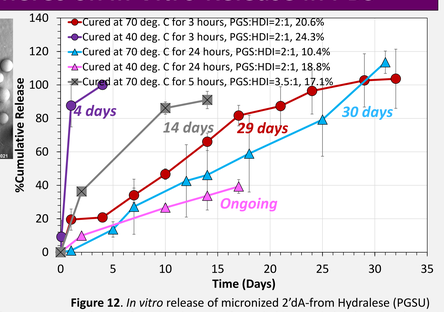


Figure 12. *In vitro* release of micronized 2'dA-from Hydralese (PGSU) microspheres of varying degrees of crosslinking made by changing the curing time and temperature or the PGS:isocyanate crosslinker ratio.

Syringeability

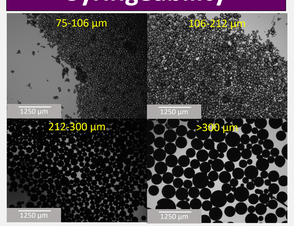
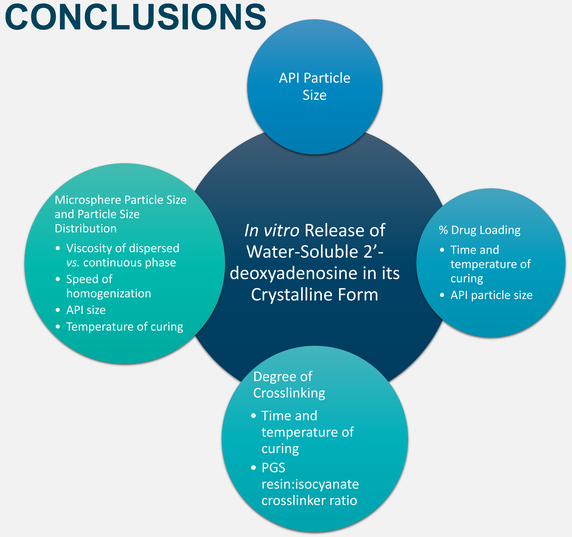


Figure 13. Hydralese (PGSU) microspheres suspended in 0.5% Triton-X.

Table 1. Syringeability of Hydralese (PGSU) microspheres.

Microsphere Size Range	Passed Through
75-100 µm	23G and 22G
106-212 µm	23G and 22G
212-300 µm	22G
>300 µm	None

CONCLUSIONS



- ✓ Hydralese (PGSU) microspheres show linear release of 2'-deoxyadenosine *in vitro*.
- ✓ Various factors affecting the release of 2'-deoxyadenosine from Hydralese (PGSU) microspheres are summarized in the chart above
- ✓ Microsphere particle size and particle size distribution have the biggest effect on release
- ✓ Microsphere size and crosslinking density can be tailored to achieve the desired drug release profile
- ✓ Physical characteristics of the API, like size and crystallinity, can be modified to give the desired release kinetics
- ✓ Microsphere particle size <300 µm is suitable for injection through a 23G or 22G needle used for intramuscular injections
- ✓ Hydralese (PGSU) microspheres are an excellent alternative to more conventional bulk-eroding polyester microspheres; the degradation products are metabolized by the body and cause no adverse immune reactions, ultimately demonstrating that Secant Group's biodegradable Hydralese (PGSU) microspheres are an exceptional choice for sustained drug delivery applications

REFERENCES

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2. Nicholson, C. B., Harris, J. J., Gabriele, P. D. (2016). *U.S. Patent No. 9,359,472*. Washington, DC: U.S. Patent and Trademark Office.
3. Chawathe, M., Reed, S. Biodegradable Hydralese™ (PGSU) (poly(glycerol sebacate) urethane) Microspheres for Controlled Drug Delivery. Poster presented at: American Association of Pharmaceutical Scientists (October 20-November 5, 2020).
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5. https://www.sigmaaldrich.com/US/en/product/sigma/d7400

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