Biodegradable Hydralese™ (PGSU) (poly(glycerol sebacate) urethane) Microspheres for Controlled Drug Delivery

Manasi Chawathe, PhD; Stephanie Reed, PhD

Secant Group, LLC, Telford, PA

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PURPOSE

Secant Group is developing microspheres manufactured from Hydralese™ (PGSU) (poly(glycerol sebacate) urethane), a flexible, synthetic biodegradable elastomer for controlled drug release capable of delivering sustained high drug loadings over a multi-month time period. Hydralese (PGSU) is synthesized by crosslinking poly(glycerol sebacate) (PGS) resin via polyol-isocyanate urethane chemistry and is known to have regenerative and anti-inflammatory properties. Hydralese (PGSU) can achieve steady release of active pharmaceutical ingredients (APIs) from a few weeks to more than a year depending on the crosslinking density and degradation rate. Hydralese (PGSU) degrades by surface erosion, thus maintaining its structure and mechanical strength throughout the duration of its lifespan. Consequently, a drug dispersed in the polymer matrix is released as the polymer matrix erodes, demonstrating that Hydralese (PGSU) can provide long-lasting, zero-order release kinetics for a more controlled drug delivery compared to bulk-eroding polyesters. These unique characteristics make Hydralese (PGSU) an ideal candidate for designing microspheres for steady drug release. The main challenge in developing Hydralese (PGSU) microspheres is timing the reaction between pre-polymer PGS resin and isocyanate as the polymer matrix is shaped into the microsphere.

OBJECTIVES

1. To develop acetaminophen and 2'-deoxyadenosine-loaded Hydralese (PGSU) microspheres by emulsification-solvent evaporation method,
2. To characterize the morphology, chemical structure, and crosslinking density of Hydralese (PGSU) microspheres and evaluate the factors affecting them, and
3. To study the *in vitro* release of the APIs from Hydralese (PGSU) microspheres.

METHODS

Preparation of Hydralese (PGSU) Microspheres by Emulsification-Solvent Evaporation

- The dispersed phase was comprised of the pre-polymer PGS resin (20-50 wt%), crosslinker hexamethylene diisocyanate (HDI) (mass ratio PGS:HDI=2:1), and tin catalyst dissolved in acetone.
- Acetaminophen was dissolved whereas 2'-deoxyadenosine was suspended in the dispersed phase.
- The dispersed phase was emulsified in mineral oil with Span 85 as the stabilizer.
- Two different emulsification techniques were used for the acetaminophen versus 2'-deoxyadenosine-loaded dispersed phases.
- This was followed by evaporating the acetone while simultaneously curing Hydralese (PGSU).

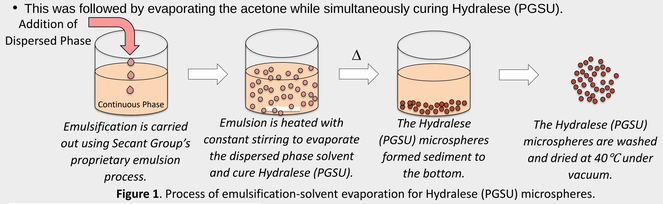

Figure 1. Process of emulsification-solvent evaporation for Hydralese (PGSU) microspheres.

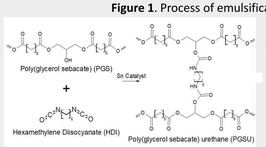

Figure 2. Crosslinking reaction of poly(glycerol sebacate) (PGS) via polyol-isocyanate urethane chemistry.

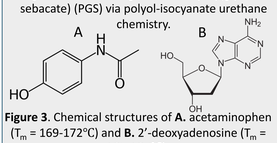

Figure 3. Chemical structures of **A.** acetaminophen (T_m = 169-172°C) and **B.** 2'-deoxyadenosine (T_m = 185-187°C).

Characterization of PGSU Microspheres

- Size and morphology were determined using scanning electron microscopy (SEM).
- Crosslinking density was determined by swell test in tetrahydrofuran (THF).
- Chemical structure was verified using FTIR.
- Extraction and % intact drug loading were measured by extraction of the API from the loaded microspheres using dimethyl sulfoxide (DMSO). They were calculated as:

$$\% \text{ Extraction} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

$$\% \text{ Intact drug loading} = \frac{\text{Weight of Drug}}{\text{Weight of PGS+Weight of Drug}} \times 100$$

- Release of the APIs was studied in 0.1 M phosphate buffer saline (pH 7.4; PBS) at 37°C.
- Drug loading and release of acetaminophen and 2'-deoxyadenosine were quantified using UV-Vis spectrometry and HPLC, respectively.

RESULTS

SEM Analysis of Hydralese (PGSU) Microspheres

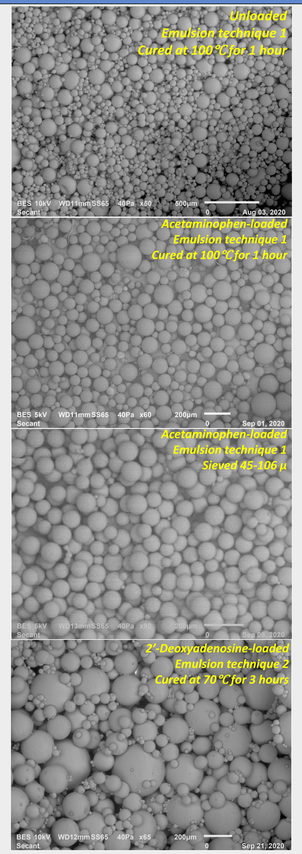

Figure 4. SEM images of unloaded and drug-loaded Hydralese (PGSU) microspheres.

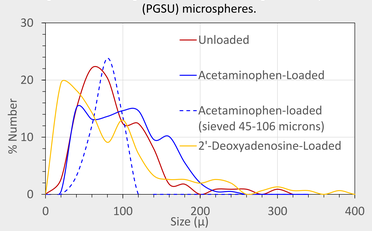

Figure 5. Size distribution of Hydralese (PGSU) microspheres. Diameters of ~200 microspheres were measured with SEM.

Crosslinking Density Measured by Swell Test in THF

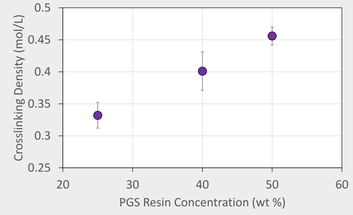

Figure 6. Effect of pre-polymer PGS resin concentration in the dispersed phase on crosslinking density of microspheres made with PGS:HDI=2:1 and cured at 85°C for 1 hour.

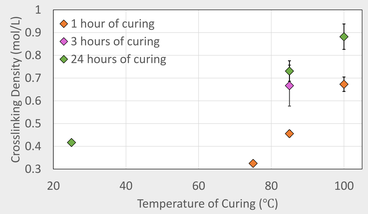

Figure 7. Effect of temperature and time of curing on crosslinking density of microspheres made with 50 wt% PGS resin and PGS:HDI=2:1.

Drug-Loaded Hydralese (PGSU) Microspheres: Process Effects and Drug Release

Table 1. Extraction and % intact drug loading of 25.9% (theoretical) drug-loaded Hydralese (PGSU) microspheres. Acetaminophen was quantified by UV-Vis Spectrometry and 2'-deoxyadenosine by HPLC.

API	% Extraction	% Intact drug loading
Acetaminophen	42.4 ± 1.4	11.0 ± 0.36
2'-Deoxyadenosine	62.3 ± 2.4	17.2 ± 0.28

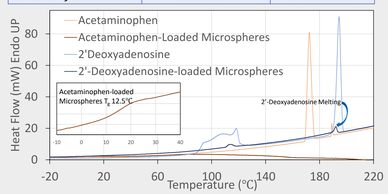

Figure 8. DSC thermograms of neat acetaminophen, 2'-deoxyadenosine, and drug-loaded Hydralese (PGSU) microspheres. Loss of acetaminophen T_m (169°C) and appearance of T_g indicates its amorphous state in the microspheres. Presence of T_m (189°C) in 2'-deoxyadenosine microspheres indicates that it is in its crystalline or semi-crystalline form.

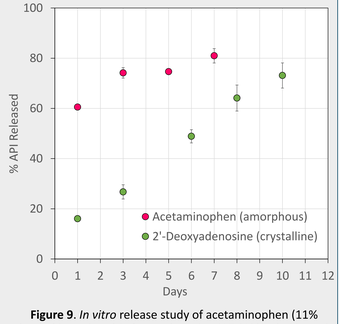

Figure 9. *In vitro* release study of acetaminophen (11% loaded intact) and 2-deoxyadenosine (17.2% loaded intact) Hydralese (PGSU) microspheres in PBS at 37°C quantified by UV-Vis spectrometry and HPLC, respectively. After 1 week in PBS, acetaminophen hydrolyzed and could no longer be detected by UV-Vis.

Acetaminophen-loaded Hydralese (PGSU) Microspheres: Formulation Considerations

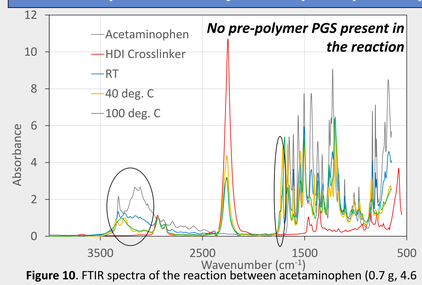

Figure 10. FTIR spectra of the reaction between acetaminophen (0.7 g, 4.6 mmol) and HDI (1 g, 5.9 mmol) at room temperature (RT), 40°C and 100°C for 1 hour. There is a decrease in the intensity of the peaks between 3500-3000 cm^{-1} with increase in temperature, and formation of a new peak at 3270 cm^{-1} (N-H stretch). New C=O ester peaks are formed between 1750-1700 cm^{-1} which are absent in both acetaminophen and HDI. Acetaminophen itself does not decompose up to 100°C.

Table 2. One-cup synthesis standards of acetaminophen-loaded Hydralese (PGSU) to determine extraction efficiency. 2 g pre-polymer PGS and 0.7 g acetaminophen were dissolved in 6.3 g acetone. 1 g HDI crosslinker and 10 mg tin catalyst were mixed in. The mixture was reacted at room temperature (RT), 40°C, and 100°C, and the acetone was allowed to evaporate. After **1 hour**, extraction of acetaminophen was carried out using DMSO.

Temperature (°C)	% Extraction
RT (~21)	97.5 ± 5.5
40	71.1 ± 1.4
100	33.0 ± 0.7

CONCLUSIONS

A. Desired physical characteristics of the Hydralese (PGSU) microspheres can be achieved by controlling the composition of the pre-polymer mixture and process parameters during the emulsification-solvent evaporation process.
   - **a. Microsphere size and size distribution**
     - Size and distribution are established during the emulsification step.
     - The dispersed-to-continuous phase ratio is also a major contributing factor that affects coalescence/aggregation.
     - The size distribution can be narrowed by sieving.
     - Both unloaded and drug-loaded microspheres are spherical with a smooth surface.
   - **b. Crosslinking density** is crucial during the release of the drug and hence needs to be controlled. It is proportionately affected by factors such as:
     - Increase in the pre-polymer PGS resin concentration
     - Increase in the temperature and time of curing

B. Drug-loaded Hydralese (PGSU) microspheres
   - **a. Extraction and % intact drug loading:** The low % extraction of the microspheres indicates some API becomes bound to PGSU during crosslinking due to reaction of the OH of the API with HDI crosslinker. Further studies confirmed no API was lost during process steps. FTIR confirmed both APIs do not decompose at process temperatures.
   - **b. Physical form of the drug encapsulated:** As seen in the DSC thermograms, the acetaminophen encapsulated is in its amorphous form whereas 2'-deoxyadenosine is still crystalline or semi-crystalline. This may be because the acetaminophen was dissolved in the dispersed phase solvent whereas 2'-deoxyadenosine was suspended in its crystalline form.
   - **c. *In vitro* release of drug in PBS at 37°C:** Acetaminophen shows a burst release of 60% whereas only 16% of 2'deoxyadenosine is released on the first day. One of the factors causing this may be acetaminophen being in its amorphous form, thus increasing its solubility. Release thereafter for both the APIs is linear.

C. Formulation considerations for acetaminophen-loaded Hydralese (PGSU) microspheres
   - **a. Reactivity of the API with crosslinker isocyanate:** The most important factor to be considered when encapsulating an API in the Hydralese (PGSU) microspheres is its reactivity with the isocyanate crosslinker (HDI). Typically, APIs with an aliphatic OH are more susceptible to a side reaction with the HDI. In the absence of pre-polymer PGS, increase in temperature drives the cross reaction between acetaminophen and HDI, as seen from Figure 10.
   - **b. Stability of the API to curing temperature:** Both acetaminophen and 2'deoxyadenosine are stable at temperatures they were cured at.
   - **c. Amount of unreacted API in one-cup standards:** One-cup standards were made as a way of eliminating any process parameters as being the cause of API loss. The extraction efficiency will only be affected by the chemical modification/loss of API, acetaminophen in this case, due to reaction with the HDI crosslinker. As seen from Table 2, the % extraction decreases with an increase in temperature. This verifies the results from FTIR spectra indicating that increase in temperature forces the reaction further.

These preliminary results show that there is an intricate balance that brings about the reaction between the pre-polymer PGS and HDI while simultaneously shaping the microsphere and preventing the side-reaction between the API and HDI. This is affected by several factors as demonstrated in this poster. The desired API must be screened for its susceptibility to the HDI crosslinker as well as stability to the curing temperature. While this preliminary work gives an understanding of small molecule encapsulation in PGSU matrix, further studies are needed to ensure that the API loaded in the Hydralese (PGSU) microspheres is chemically unchanged to get the desired therapeutic effect. Further studies correlating the crosslinking density to the *in vitro* release need to be performed.

REFERENCES

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