Formation of nanoparticles for the oral delivery of small molecules by Flash NanoPrecipitation

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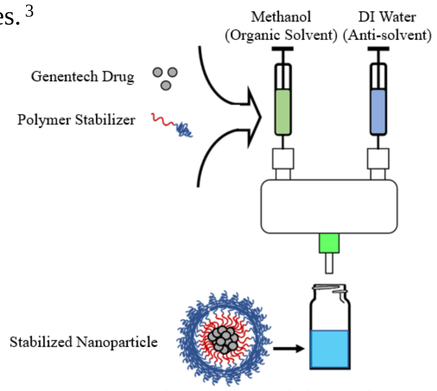
Introduction

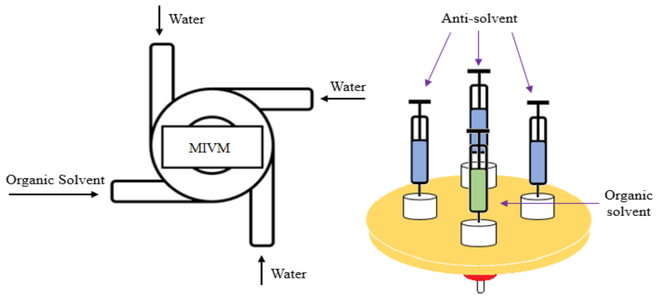
- Oral delivery of poorly water-soluble compounds using a nanoparticle approach can enhance **dissolution rate**, increase **drug solubility**, and improve **bioavailability**. [1]
- **Flash NanoPrecipitation** (FNP) is a **scalable** and **reproducible** approach to generate drug-loaded polymeric nanoparticles. [2]
- In the technique of FNP, drug and stabilizing polymer are dissolved in an organic solvent and rapidly mixed with the aqueous antisolvent in a confined chamber which results in precipitation of nanoparticles. [3]
- The goal of this project is to improve the **oral bioavailability** of a poorly water-soluble drug ("G-1") provided by Genentech through Flash NanoPrecipitation (FNP) to form drug nanoparticles and compare its **dissolution rate** with nanoparticles formed *in vivo* from Genentech's spray-dried dispersion.



Nanoparticles prepared through **Flash NanoPrecipitation** via confined impinging jet mixers.[4]

Experimental Design

- Solubility of "G-1" were investigated in several organic solvents (methanol, THF, and DMSO).
- Formulations were conducted to form nanoparticles with "G-1" through the FNP process via **Multi-Inlet Vortex Mixer** (MIVM)
- Nanosuspensions were lyophilized into dry powder form.
- Cryoprotectants were tested for re-dispersion of dried powders into nanometer-sized particles when placed in water or an alternative water-based environment.



Schematic representation of the **Multi-Inlet Vortex Mixer**. [5]

Results

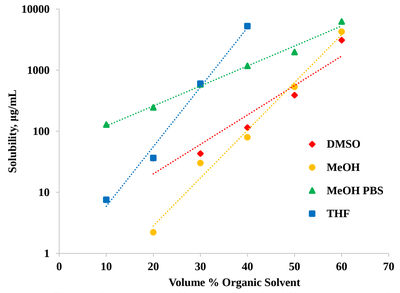


Figure 1. Solubility Curve of "G-1". Mixtures of organic solvents to antisolvent in different percentage. (Methanol:Water, Methanol:PBS, DMSO:Water, and THF:Water.)

- **Supersaturation** is required for nanoparticle formation in the FNP process.
- Mixed solvent consisting of water and drug-containing organic solvents at different ratio were observed for **precipitation**.
- **Solubility** of "G-1" in each final mixed solvent were measured.
- Methanol was selected for the organic stream in the FNP process due to the **low solubility** of "G-1" in the final mixed solvent.

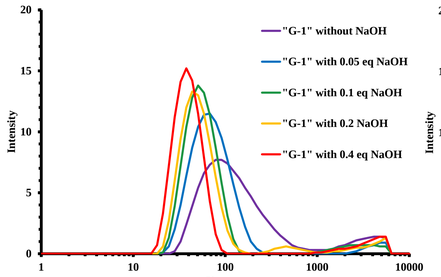


Figure 2. "G-1" particle size distributions measured by DLS. Nanoparticles formed under different equivalence (0 eq, 0.05 eq, 0.1 eq, 0.2 eq and 0.4 eq) of NaOH.

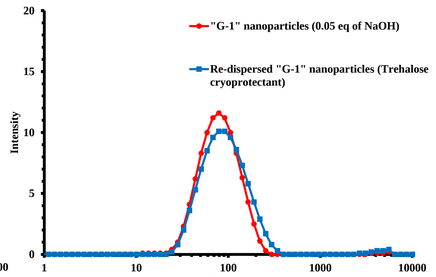
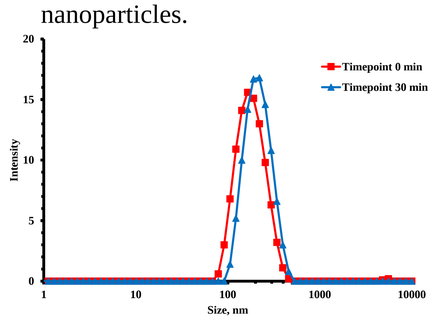


Figure 3. "G-1" particle size distributions measured by DLS before lyophilization and after lyophilization with trehalose. Nanoparticles made with no stabilizer and freeze dried with trehalose.

- NaOH ionized the carboxylic acid functional group of the drug by deprotonation which generated a **charged surface** during nanoparticle formation.
- Trehalose was used as a cryoprotectant to maintain **good redispersibility** of "G-1" nanoparticles.

Formulation	Nanoparticle Concentration (mg/mL)	Trehalose Concentration (mg/mL)	% Drug Loading in Dried Powder	Size (nm)	PDI
Original	8	40	16.7%	88	0.207
Increased Concentration #1	35	40	46.6%	151	0.296
Increased Concentration #2	35	60	36.8%	185	0.416
Increased Concentration #3	35	80	30.5%	126	0.251
Increased Concentration #4	35	120	22.5%	137	0.308

Table 1. Re-dispersion of concentrated "G-1" particles. Concentrated Nanoparticles freeze-dried with different concentration of cryoprotectant (trehalose)



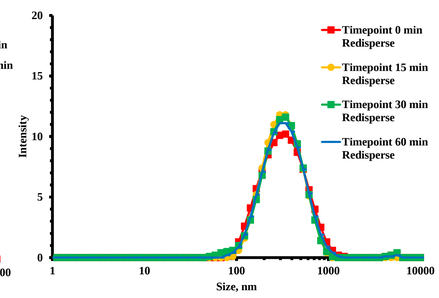


Figure 4. Stability Study of PS-*b*-PEG "G-1" nanoparticles before and after lyophilization. Left: PS-*b*-PEG GDC-0810 nanoparticles formulation: 80% drug + 20% PS-b-PEG in THF (Total mass concentration: 40 mg/mL) and 10 mM HCl in deionized water; Right: Re-dispersed PS-*b*-PEG nanoparticles after lyophilization with 40 mg/mL cyclodextrin.

- Unstable PS-b-PEG nanoparticles were lyophilized with 40 mg/mL of cyclodextrin and redispersed into **stable nanoparticles**.
- Concentrated nanoparticles (35 mg/mL) lyophilized with 80 mg/mL of trehalose was optimal for **good redispersion**.

Discussion

- "G-1" formed ~80 nm particles that are **electrostatically stabilized** without the use of stabilizing polymers.
- "G-1" formed nanoparticles in the FNP process with concentration as high as **160 mg/mL**.
- **Trehalose** acted as an effective cryoprotectant for lyophilization of "G-1" nanoparticles suspension into stable dried powders.
- Release kinetics of "G-1" in its free powder form exhibited **rapid dissolution rate** in the modified biorelevant media (FaSSIF with 1.5% Tween 20).
- PS-*b*-PEG polymers formed **unstable** "G-1" nanoparticles, with sizes ranging from **150 to 300 nm**, and **narrow particle size distributions** (PDI 0.05−0.2).
- **Cyclodextrin** acted as an effective cryoprotectant for lyophilization of PS-*b*-PEG "G-1" nanoparticles suspension and the dry powder redispersed into **stable nanoparticles**.
- Nanoparticles with **higher drug loading** compare to original formulation **(30.5% *versus* 16.7%)** was achieved through tangential flow filtration system.
- Nanosuspensions of these formulations were lyophilized into dried powders using cryoprotectant and sent to Genentech for **dissolution rate studies**.

Conclusion

- The oral bioavailability of "G-1" was improved through the formation of nanoparticles through FNP process.
- The nanoparticles with trehalose show **faster dissolution rate** and **higher flux** than the nanoparticles formed *in vivo* from Genentech's spray dried dispersion.

Works cited

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3. Saad, W. S.; Prud'Homme, R. K. Principles of Nanoparticle Formation by Flash Nanoprecipitation. *Nano Today* **2016**, *11* (2), 212–227.
4. Han, J.; Zhu, Z.; Qian, H.; Wohl, A. R.; Beaman, C. J.; Hoye, T. R.; Macosko, C. W. A Simple Confined Impingement Jets Mixer for Flash Nanoprecipitation. *Journal of Pharmaceutical Sciences* **2012**, *101* (10), 4018–4023.
5. Markwalter, C. E.; Prudhomme, R. K. Design of a Small-Scale Multi-Inlet Vortex Mixer for Scalable Nanoparticle Production and Application to the Encapsulation of Biologics by Inverse Flash NanoPrecipitation. *Journal of Pharmaceutical Sciences* **2018**, *107* (9), 2465–2471.