Applications of First Principles to Semi-finished Syringe and Auto Injector System Design

Seung-yil Yoon, Ph.D.

Contents

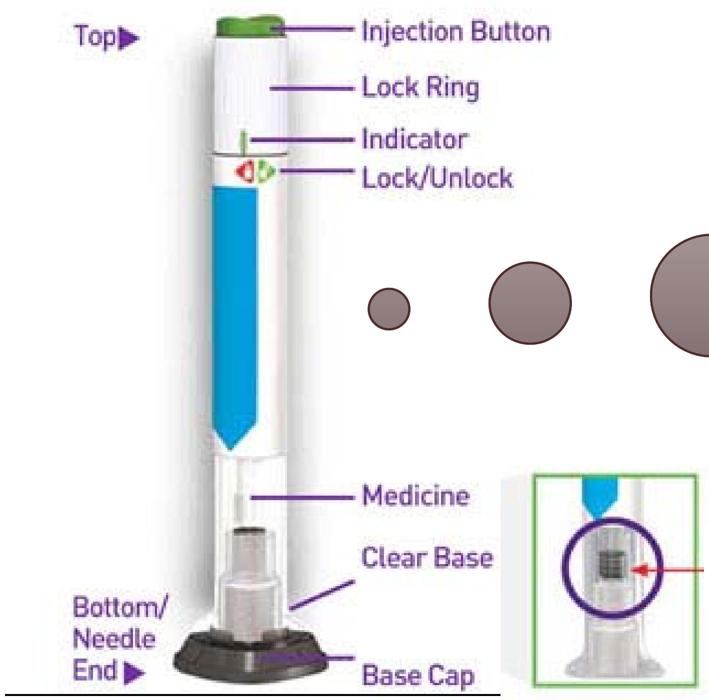
Introduction – benefits from 1st principles and modeling

1. 1st principles and modeling (e.g., finite element analysis) are a useful tool to design container closure and device systems.
2. A good example of QbD (Quality by Design) paradigm.
3. Robust and reliable system design verification covering the entire design space.
4. New parts, materials and designs can be quickly assessed.
5. Good root cause analysis tool for unexpected situations.

Note: Modeling verification is rigorously performed with experimental results.

Operation of a Syringe Based Auto Injector

- Key steps: press the injection button → plunger moved by the spring force → plunger stopped at the bottom of the syringe
- Force balance between the spring force, plunger frictional force and hydraulic force



plunger

Dynamic operation: spring force, plunger speed, coefficient of friction, air bubble volume, hydraulic pressure, etc.

A Syringe Based Auto Injector System Design Verification

Individual system design verification

Semi-finished syringe

- Glide force
- Plunger sealing pressure
- Others

Auto injector

- Tolerance stack-up
- Stress from drop
- Others

Product

- Viscosity
- Fill volume

Total system design verification

Syringe based auto injector system

- Injection time
- Dose accuracy, etc.

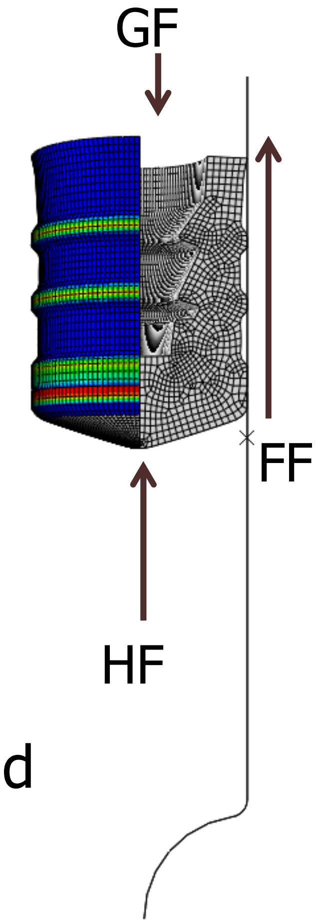
Ultimate goal: Inject drug and retract needle as designed

Case study 1. Semi-finished syringe design verification focusing on plunger and barrel

- Critical design factors: glide force, plunger sealing pressure, etc.

- Plunger compressed against the barrel
  - Hyperelastic and incompressible rubber mechanical properties
  - Non-linear material models for stress-strain
- Glide Force = Frictional Force + Hydraulic Force
  - Frictional Force = COF x plunger contact force
  - Hydraulic Force determined from Hagen-Poiseuille equation

$$\Delta P = \frac{8\mu L Q}{\pi r^4}$$



- Finite element analysis (FEA) modeling can estimate forces and deformation on the plunger.

Modeling DOE and FEA Results

- Sample: 1 mL long syringe (ISO standard)
  - Plunger OD: 6.8 to 7.0 ± 0.1 mm
  - Barrel ID: 6.35 ± 0.1 mm
- Parameters to determine the glide force and sealing pressure: plunger OD, barrel ID, needle ID & length, product viscosity, injection speed, rubber formulation, plunger design, etc.

e.g., Plunger OD (3) x Barrel ID (3) x Product Viscosity (3) = 27 combinations

Plunger OD (mm)	Barrel ID (mm)	Interference fit (mm)	Product viscosity (cP)	Estimated Glide force (N)	Estimated Sealing pressure (MPa)
6.7	6.25	0.225	0	1.5	1.6
6.9	6.25	0.325	0	2.5	2.2
6.9	6.35	0.275	1	2.6	1.9
6.7	6.45	0.125	6	4.0	1.0
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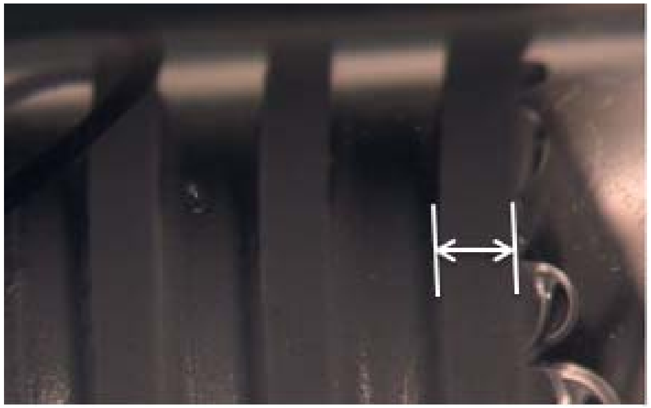
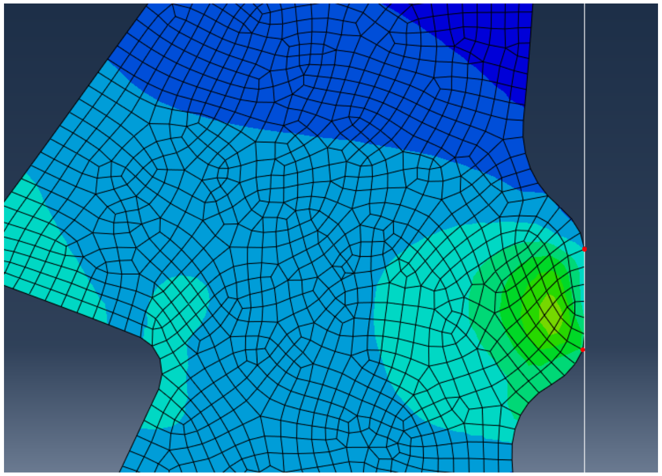
Robust and reliable system design verification covering the entire design space!!

Modeling verification

- Compare to experimentally determined glide force
  - Verify the model for the target dimensions
  - Use the verified model to the entire design space
- Compare to experimentally measured plunger deformation
  - Stress or pressure is difficult to be measured
  - Stress and strain are correlated. Therefore, if the model is verified for the strain (deformation), it is verified for the stress as well.

An example of deformation measurement - contact length of a plunger rib





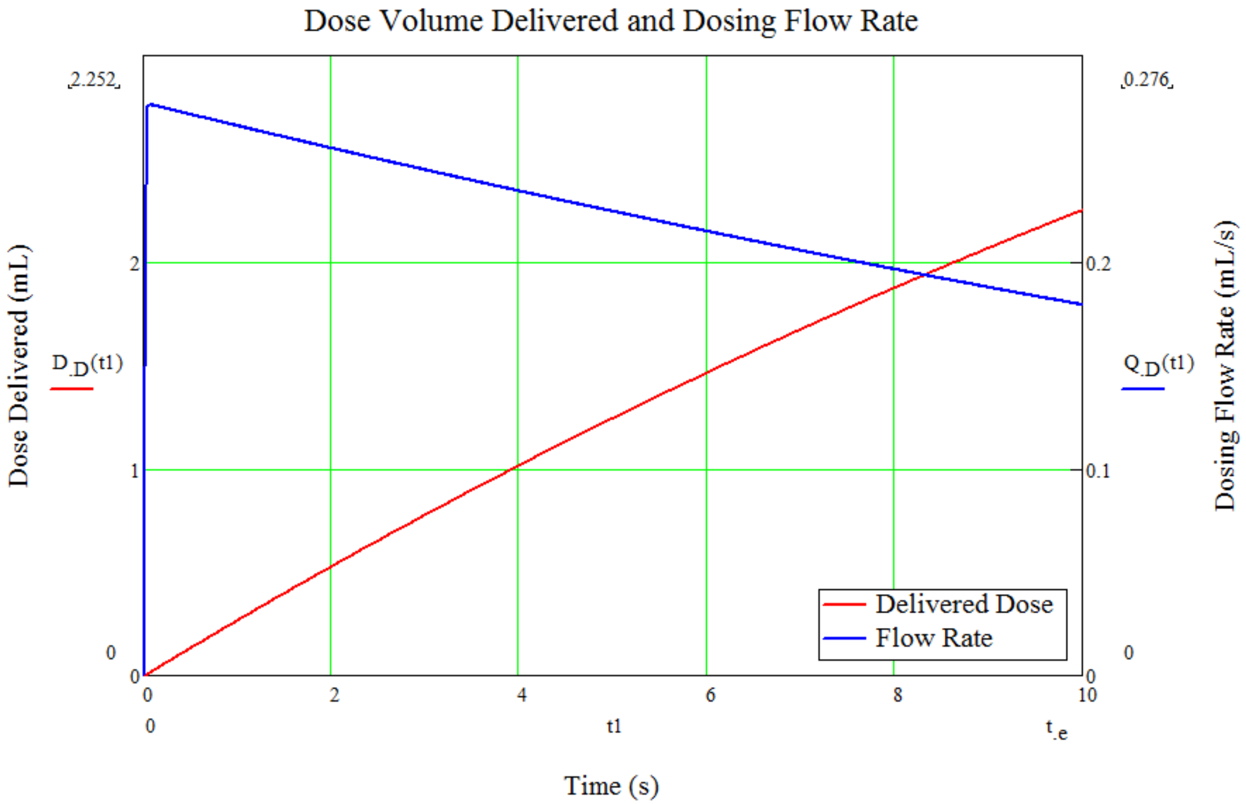
Case study 2. Total syringe based auto injector system design verification

- Critical design factors: injection time, etc.

- Dynamic operation: spring force, speed of plunger movement, air bubble volume, COF, hydraulic pressure, etc.
- Plunger frictional study – develop a mathematical relationship between glide force, speed of plunger movement and hydraulic pressures e.g., glide force = A + B $\times$ Ln (speed) + C $\times$ hydraulic pressure.
- Develop differential equations and solve variables using a numerical solution tool (e.g., MathCad).
- Models can be verified with experimentally determined injection time.

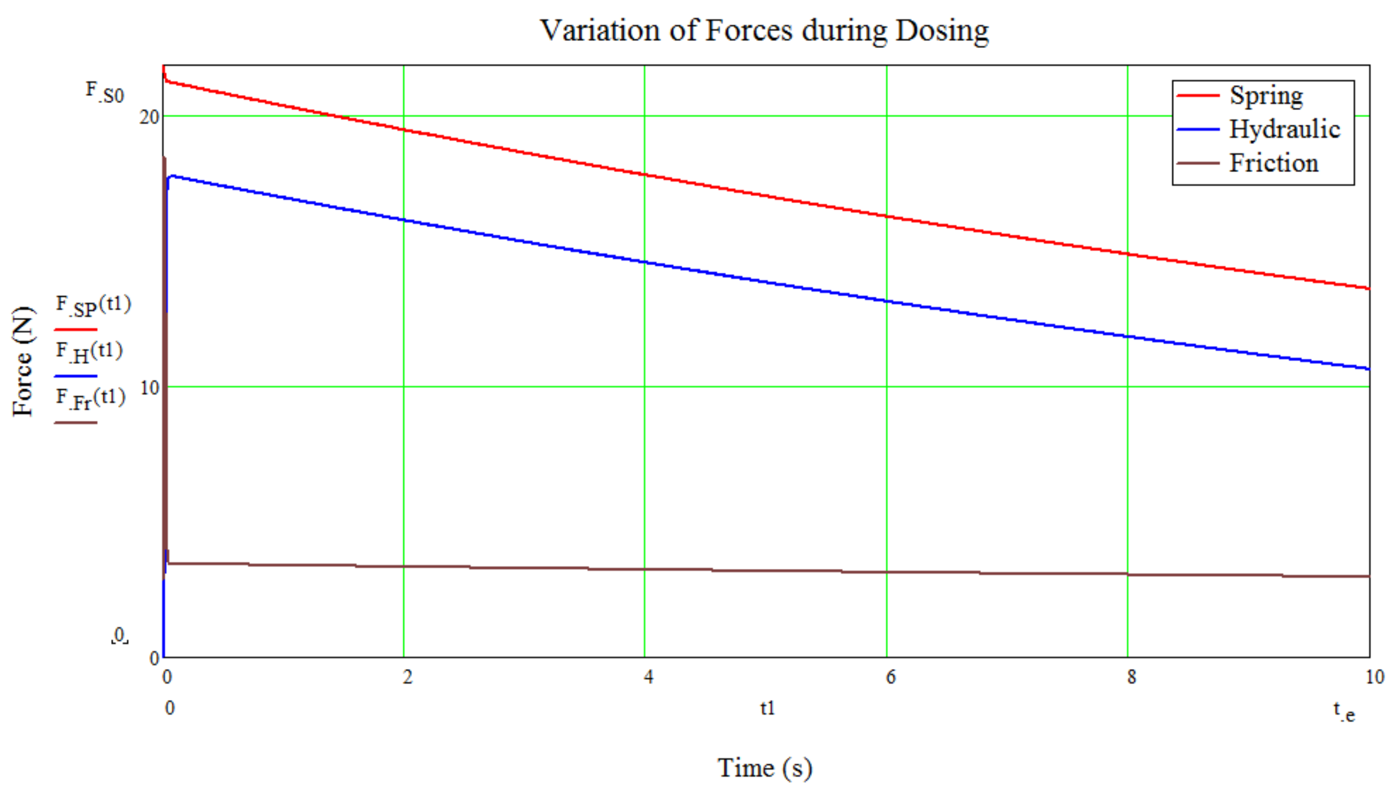
Modeling results – injection time

- Dynamically changed flow rate and the amount of drug delivered can be estimated.
- The dosing time can be estimated from different springs, product viscosity, etc.



Modeling results – force balance

- Glide force = frictional force + hydraulic force
- Most of the spring force is used to dispense the liquid via a tiny diameter needle
- For a high viscosity drug, better to work on needle to reduce the injection time instead of working on the plunger design



Conclusions

1. Modeling is a powerful QbD tool to cover the entire design space.
2. First principles and modeling can minimize non-essential work but maximize necessary work.
3. Overall, the cycle time for a robust syringe and auto injector system design can be reduced.
4. Necessary process to design complex syringe and auto injector system from a proliferation of new drug formulations and injection mechanisms.
5. High confidence in selecting or designing new syringe and auto injector systems.