Primary Packaging & Delivery Systems Interaction

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Provided September 26, 2017 as part of an oral presentation and is qualified by such, contains forward-looking statements, actual results may vary materially; Amgen disclaims any duty to update.

Outline

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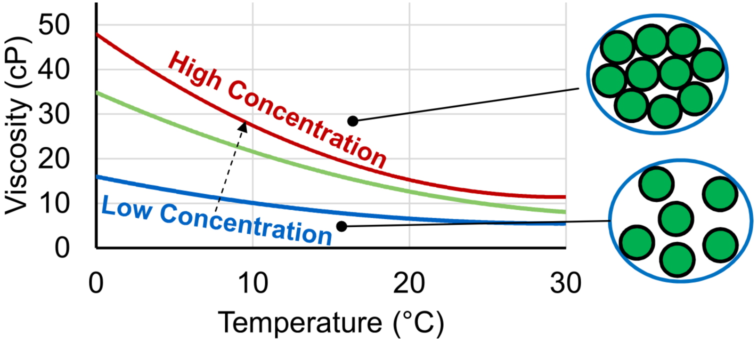
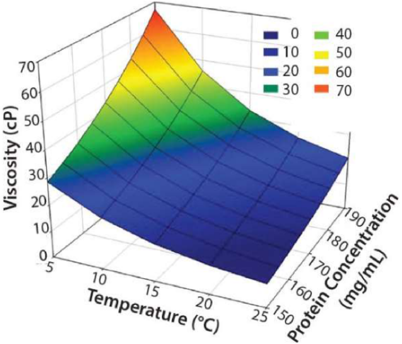
Concentrations of monoclonal antibodies

The concentration of monoclonal antibodies and by extension the drug product viscosities have been increasing in order to competitively meet patient needs.





With high concentrations of monoclonal antibodies we can expect large variations in fluid viscosity with environmental conditions.

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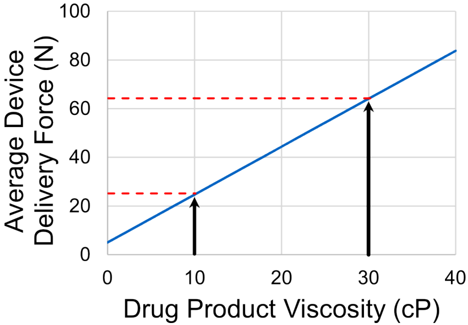
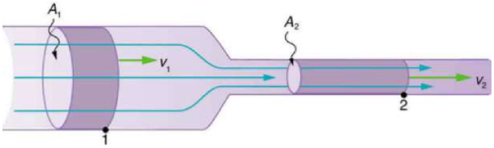
Performances of delivery systems

High concentrations of monoclonal antibodies can have a direct impact on the fluid properties of drug products that are relevant to primary packaging and device performances.





$$F = 8\pi\mu L V_2 \left(\frac{A_1}{A_2}\right)$$

$$F = 8\pi\mu L \left(\frac{A_1}{A_2^2}\right)\left(\frac{V}{t}\right)$$

Drug Viscosity

↓

Intended Delivery Time

↓

Device Delivery Force

As drug products become more concentrated and viscous, challenges arise with meeting regulatory commitments on dose timing.

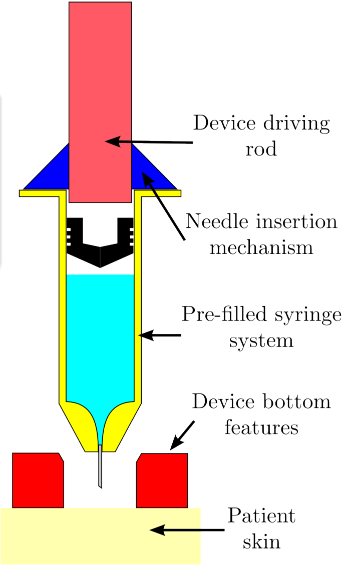
How drug delivery devices work

Drug delivery devices are essentially responsible for two main actions:

1. insertion of the combination product into the patient
2. delivery of the medicament to the patient

Step 1: Activation

- System is at the initial state;
- The device is primed and ready for activation;
- Needle shield or cap has been removed.

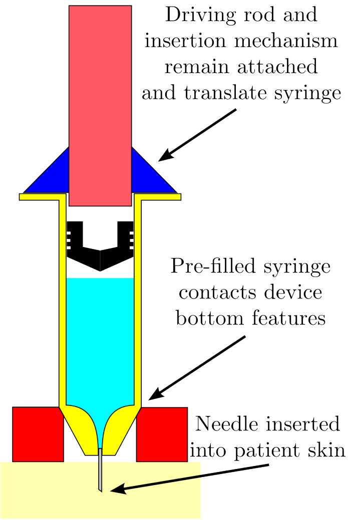


How drug delivery devices work

Step 2: Needle insertion

- The syringe is first accelerated forward to insert the needle into the patient skin;

- The syringe is decelerated once the desired injection depth is achieved;

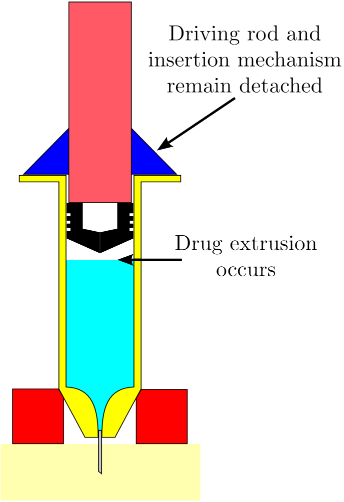


How drug delivery devices work

Step 3: Extrusion/delivery

- The syringe has reached injection depth and initiated extrusion;
- The syringe barrel is pressurized as the drug is delivered to the patient.

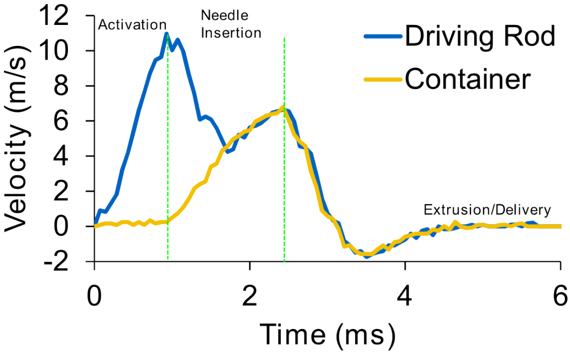
Many drug delivery devices operate under different conditions. For the purpose of this presentation this simple configuration will be considered.

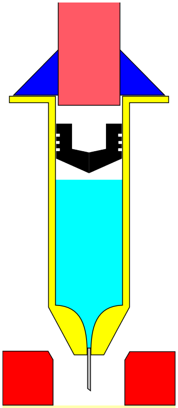


How drug delivery devices work

To minimize device design complexity, often times the drive mechanisms responsible for drug delivery are also responsible for the events at device activation making the activation process an extremely transient series of events.

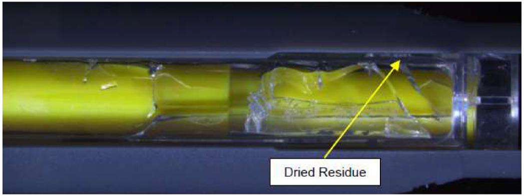
These highly transient events can lead to impulsive forces that may compromise container integrity.

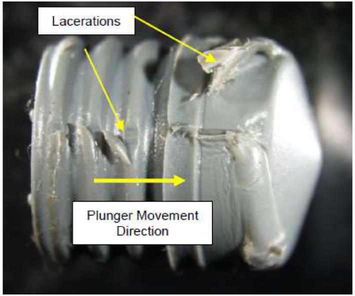




Details of glass breakage

Field Observations



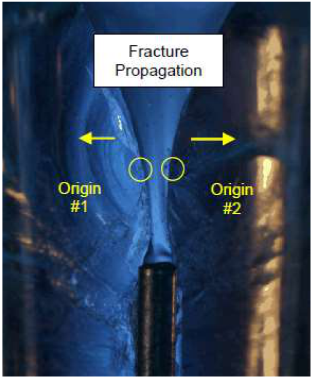


Forensic key findings:

- Low occurrence rate;
- Fracture initiates between device activation and extrusion.

Details of glass breakage

Field Observations



Forensic key findings:

- Unique fracture patterns (no detectable glass flaw or defect);
- Fracture origin occurs from inside syringe cone and propagates out.

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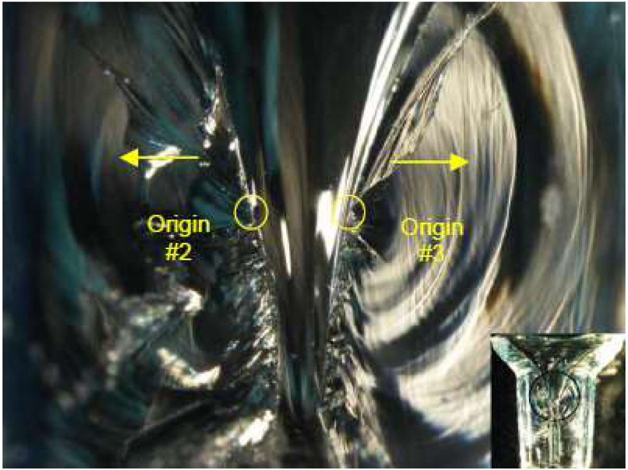
Details of glass breakage

Field Observations



Forensic key findings:

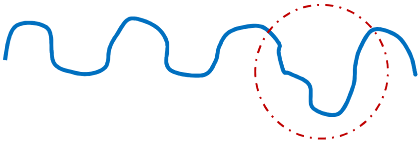
- Fracture origin due to excessive hoop stress within the container;
- Breakage originates from strongest region of syringe:
  - Thickest glass;
  - Free formed area (no tooling contact).

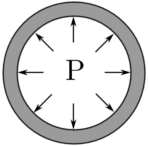
Details of glass breakage

Fractographic analysis

Glass will break or a crack will occur when a tensile stress field is combined with an imperfection or flaw in the glass.

- Two things must be present at the glass surface in order for breakage to occur:
  1. Stress field (typically in tension);
  2. Defect or flaw at the surface.





$$\sigma_\theta \approx \frac{RP}{t}$$

$$\epsilon_\theta \approx \frac{\sigma_\theta}{E}$$

$$\epsilon_\theta \approx \frac{\Delta R}{R}$$

Outline

Examples of pressure transients

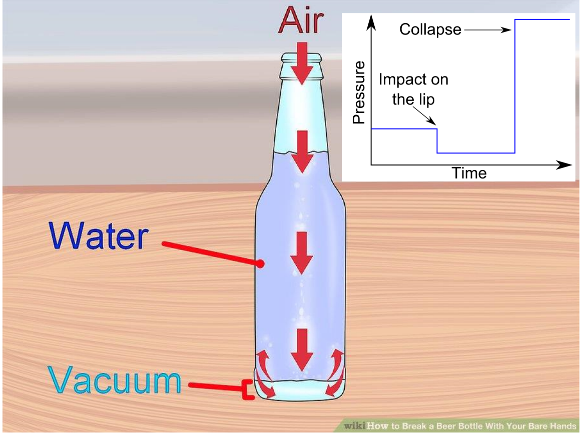
Beer bottle experiment

- Fill a glass beer bottle with water;
- Hold the beer bottle firmly with one hand;
- Impact on the lip of the beer bottle with your other hand;
- The bottom of the beer bottle breaks!

Examples of pressure transients

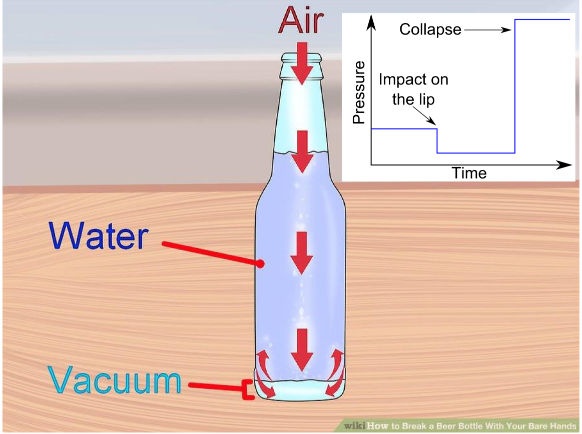
Beer bottle experiment

- Impact on the lip → bottle moves, but not the liquid inside;
- This produces a tension wave, creating a cavity (vacuum) at the bottom of the bottle;
- The cavity then collapses → water impacts on the bottom;
- This results in a large pressure which breaks the bottom;



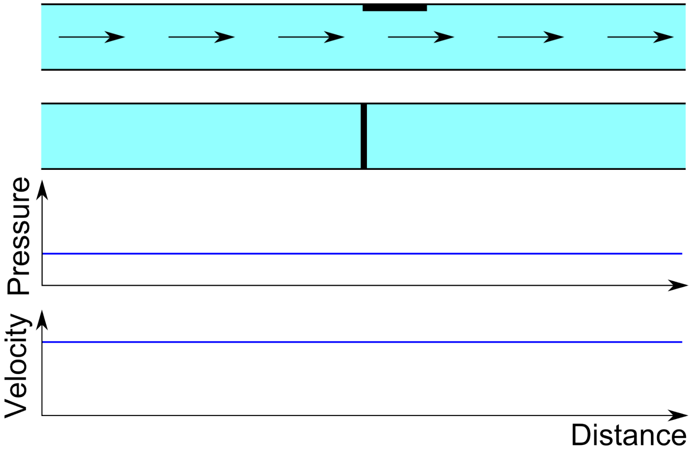
Examples of pressure transients

Beer bottle experiment



Examples of pressure transients

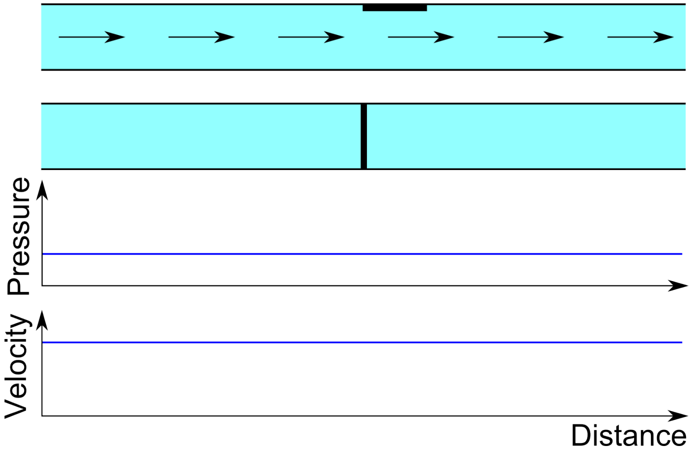
Water hammer



- Liquid flowing in a pipe at constant velocity;
- Rapid closure of a valve;
- Compression wave traveling to the left;
- Tension wave traveling to the right;
- Compression & tension waves $\rightarrow$ bring the liquid to rest.

Examples of pressure transients

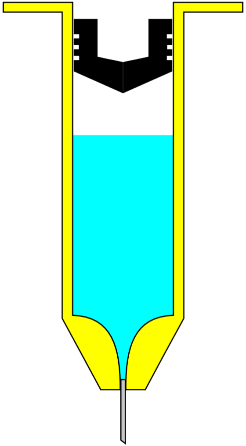
Water hammer



- The pressure transient can cause failure of pipes and hydraulic machinery;

Pressure transients inside a syringe

Impulsive acceleration of the syringe

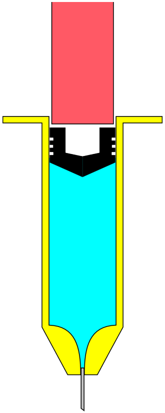


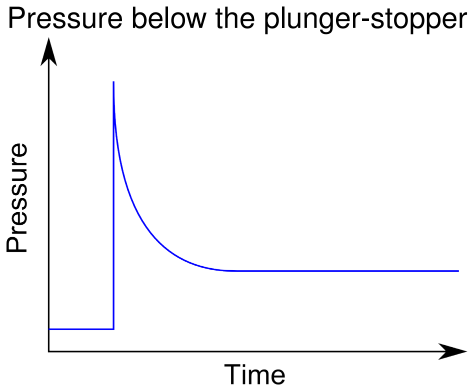
- Abrupt acceleration of the syringe;
- The syringe moves, but not the liquid inside $\rightarrow$ formation of a cavity
- Tension waves are produced in the cone area $\rightarrow$ this produces a downward acceleration of the liquid;
- The cavity collapses.

The collapse of the cavity causes a large pressure increase in the cone area.

Pressure transients inside a syringe

Impact on the plunger-stopper

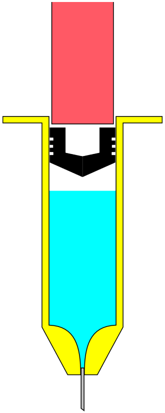


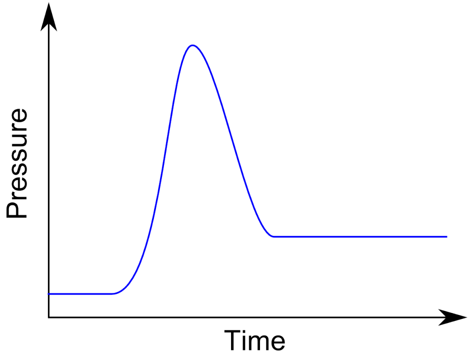


- The plunger-stopper is forced to start moving;
- The fluid immediately below the plunger-stopper starts moving;
- This sends a compression wave in the liquid;
- $P_{max} \approx \rho c U_0$

Pressure transients inside a syringe

Impact on the plunger-stopper

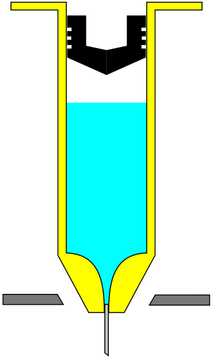




- The plunger-stopper is forced to start moving;
- The air gap is compressed ($\approx$ isentropically) $\rightarrow$ pressure in the gap increases;
- This sends compression waves in the liquid;

Pressure transients inside a syringe

Impulsive deceleration of the syringe

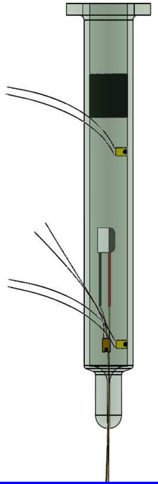


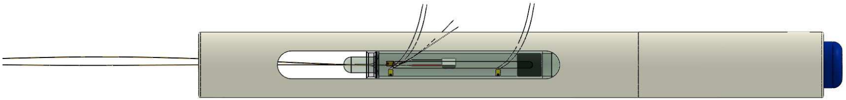
- Syringe reaches its travel limit and comes to a sudden stop;
- The fluid and solid elements near the point of contact come to a stop immediately;
- Compression wave in the liquid and the solid above the point of contact;
- Tension wave in the solid below the point of contact.

Outline

In-situ measurements

Methodology

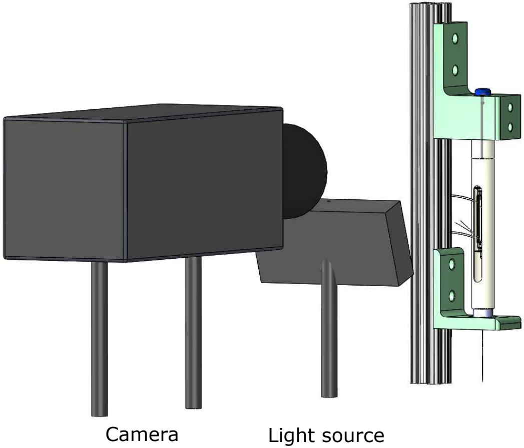




- Remove the needle from the syringe;
- Make a slit in the syringe carrier;
- Miniature pressure transducer floating inside the syringe;
- Miniature strain gauges mounted on the outside wall of the syringe.

In-situ measurements

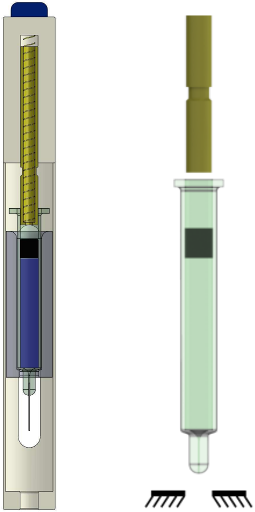
Methodology

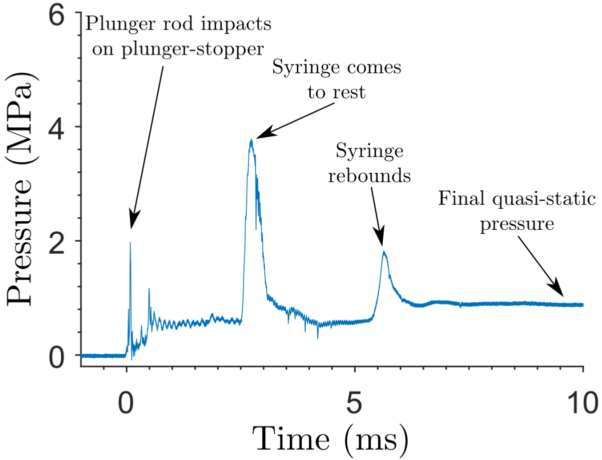


- Instrumented autoinjector is mounted on a special fixture;
- Light source(s) is used to illuminate the autoinjector;
- Digital high-speed video camera(s) to visualize the syringe.

In-situ measurements

Without an air gap

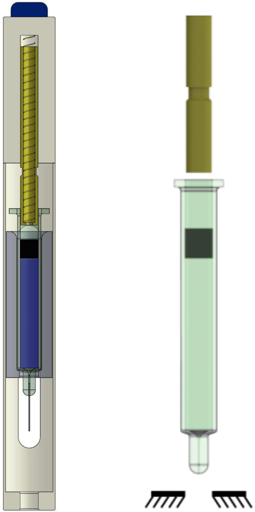




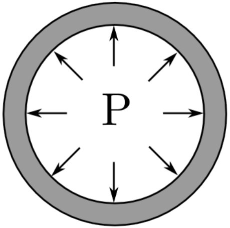
- Peak pressure is ≈ 4 times larger than quasi-static pressure;
- Need to consider the dynamics to predict the peak pressure.

In-situ measurements

Without an air gap



- The liquid pressure deforms the syringe;
- It creates stresses and strains in the glass syringe (especially hoop strains ϵ_θ).



$$\sigma_\theta \approx \frac{RP}{t}$$

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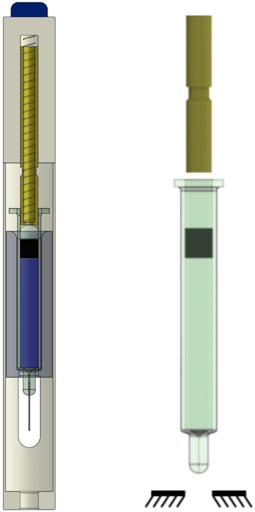
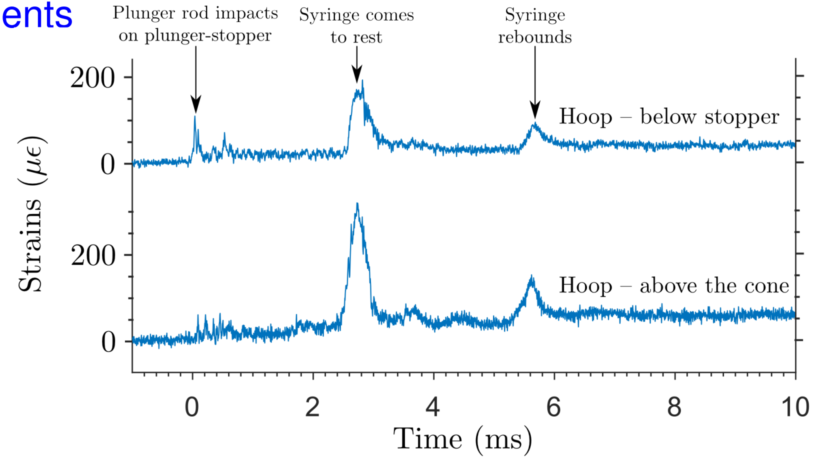
In-situ measurements

Without an air gap

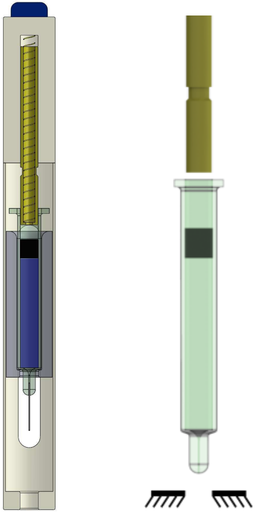


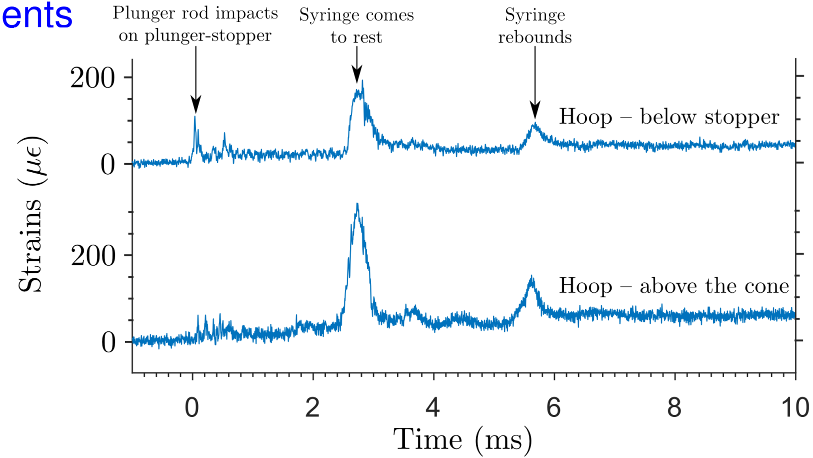


- Peak ϵ_θ are $\approx$ 4 times larger than quasi-static ϵ_θ;
- Need to consider the dynamics to predict the peak ϵ_θ.

In-situ measurements

Without an air gap



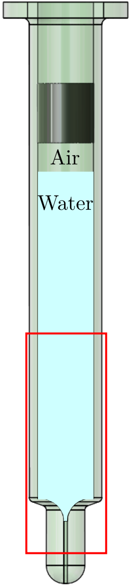


- Peak ϵ_θ corresponds to peak $\sigma_\theta \approx 20$ MPa;
- In practice, should keep maximum stress at or below 7 MPa for high reliability structures.

In-situ measurements

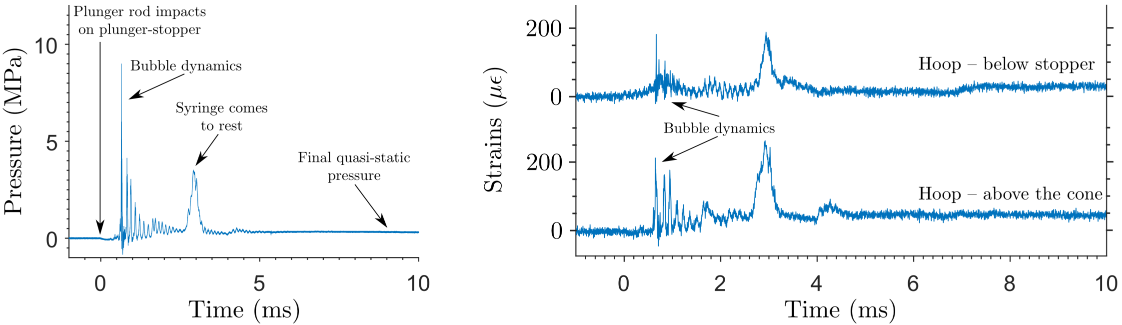
With an air gap

- With an air gap, the pressurization of the syringe happens slowly;
- Large acceleration of the syringe prior to the pressurization;
- Very similar to the beer bottle example: large bubbles form and collapses violently;
- Collapsing bubbles can generate very large pressures (shock waves).



In-situ measurements

With an air gap

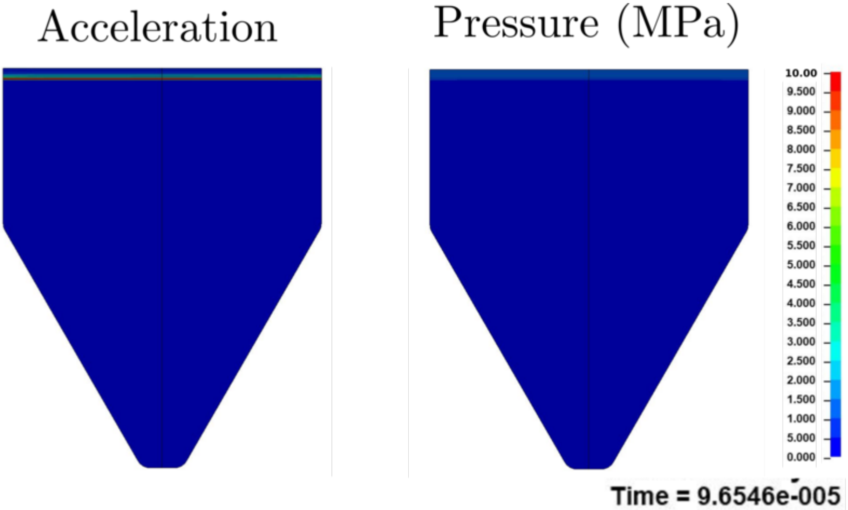


- Evidence of bubble dynamics on pressure and strains;

Outline

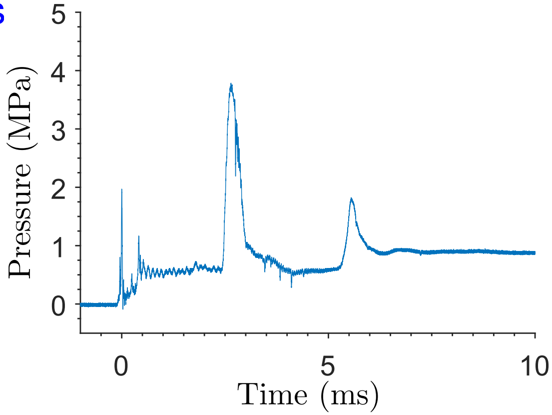
Pressure in the cone area

γ= 30 deg



Mitigation of the pressure transients

- Reduce the magnitude of the acceleration/deceleration;
- Reduce the impact velocities;
- Acceleration and pressurization of the syringe in sync.



Simply using damping material (viscoelastic foam) is a good start!

Mitigation of the pressure transients

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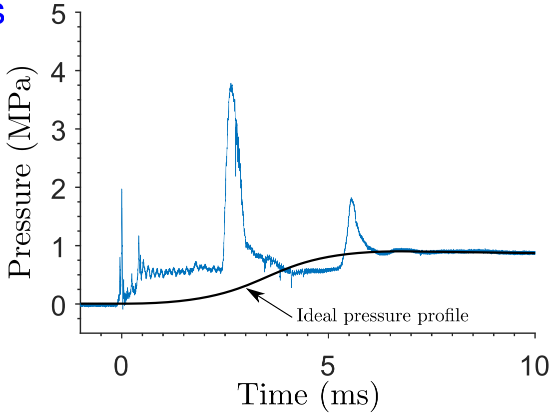

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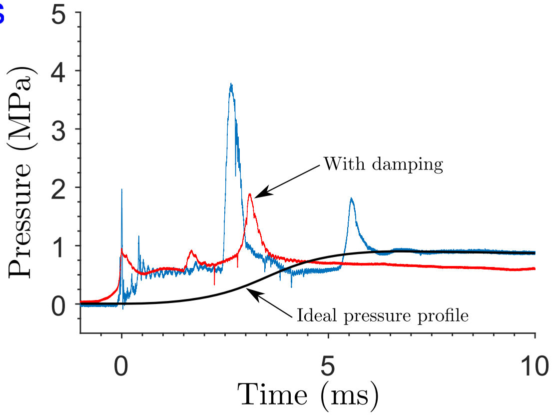

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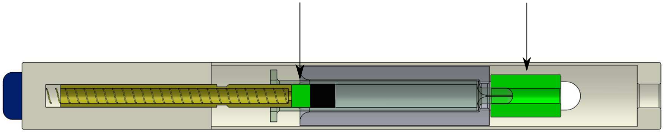


Outline

Conclusion

1. Drug solutions are becoming more viscous $\rightarrow$ injection force increases;
2. There can be impacts between the components of the autoinjector and the acceleration of the syringe can be substantial;
3. Pressure and stress transients can exceed the values expected from static analysis;
4. The transients can be large enough to cause failure of autoinjector devices.

A paradigm shift is needed!

To improve the robustness of autoinjectors $\Rightarrow$ need to consider the dynamics of the device.

Future work

Develop a better understanding of:

- the effect of the air gap size;
- the effect of the syringe geometry in the cone area;
- the effect of the syringe material (e.g., plastic vs glass);
- the effect of the device drive mechanism.

Questions?

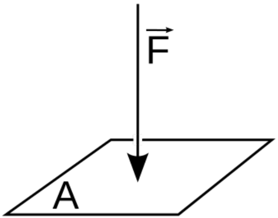
Details of glass breakage

Industry implications

- Minimal impact to patient safety;
- Low occurrence rate;
- Partial or no dose delivered;
- Patient perception of product quality;
- Patient prescription adherence.

Pressure

- **Pressure:** force applied perpendicular to the surface of an object per unit area over which the force is distributed;
- The SI unit of pressure, the pascal (Pa), corresponds to one meter per square meter (N/m^2);



- It is possible to think about the pressure as an energy density:
- $\frac{N}{m^2} = \frac{N \cdot m}{m^3} = \frac{J}{m^3}$

- 1 MPa = 1×10^6 Pa;
- 1 MPa = 10 atm (atmosphere);
- 1 MPa = 145 psi (pound per square inch).

Pressure waves

- **Weak pressure waves**, or acoustic waves, travel at the sound speed (c);
- Mathematically, the sound speed is: $\sqrt{\left(\frac{\partial p}{\partial \rho}\right)_s}$;
- The sound speed is not a constant for a given material and depends on the thermodynamic state.

Typical sound speeds at ambient conditions:

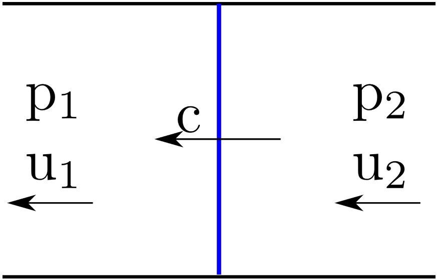
- Air: 343 m/s
- Water: 1481 m/s;
- Plastic (polycarbonate): 2270 m/s
- Glass (Pyrex): 5640 m/s;

A pressure wave with magnitude Δp is a weak pressure wave when $\Delta p \ll \rho c^2$.

Pressure waves

When a weak pressure wave passes by:

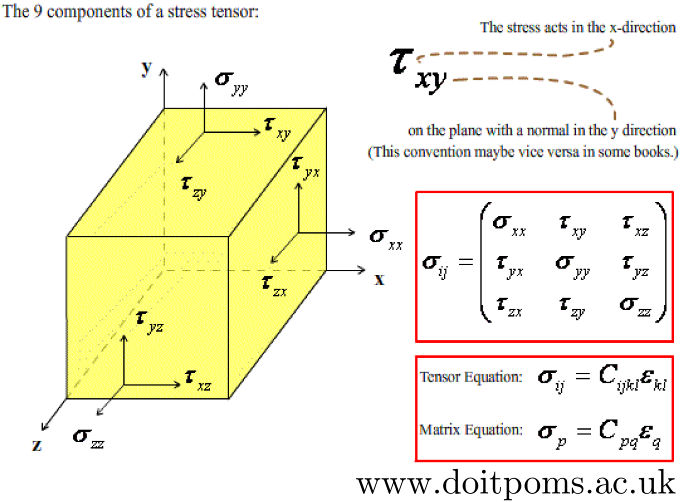
- The pressure changes;
- The velocity of the fluid elements changes.



- The magnitude of the wave is $\Delta p = p_2 - p_1$;
- The velocity change is related to the pressure change, the sound speed and the density: $\Delta p = \rho c(u_2 - u_1)$.

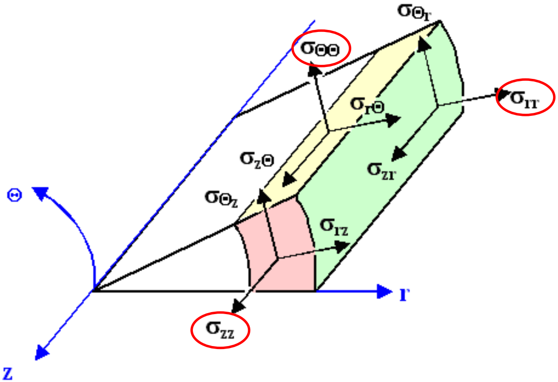
For a weak (acoustic) pressure wave, the change of density and sound speed are negligible such that $\rho_1 = \rho_2 = \rho$ and $c_1 = c_2 = c$

Stresses



- Stresses are forces per unit area (just like pressure)
- In fact, $p = \frac{1}{3} tr(\sigma_{ij}) = \frac{\sigma_{ii}}{3}$

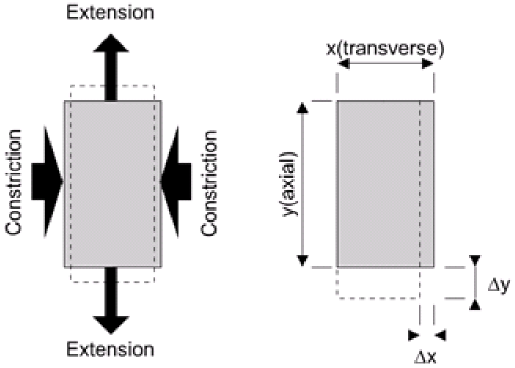
Stresses in cylindrical coordinates



- σ_{zz}: axial stress, acting along the z-axis on a plane perpendicular to the z-axis;
- σ_{rr}: radial stress, acting along the r-axis on a plane perpendicular to the r-axis;
- $\sigma_{\theta\theta}$: hoop stress, acting along the θ-axis on a plane perpendicular to the θ-axis.

Engineering strains

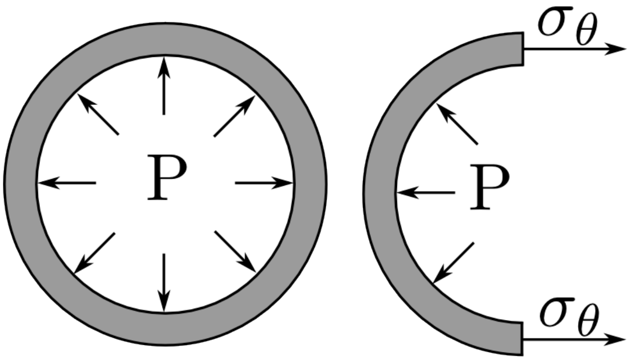
- Stresses produce strains;
- Consider the 2D example below:
  - A stress is applied in the y-direction;
  - This stress produces a deformation along the y-axis;
  - This stress also produces a deformation along the x-axis.



- $\epsilon = \Delta L / L_0$
- $\epsilon_x = \frac{1}{E}(\sigma_x - \nu\sigma_y)$
- $\epsilon_y = \frac{1}{E}(\sigma_y - \nu\sigma_x)$

Hoop strains

Cylinder under internal pressure



$$\sigma_\theta \approx \frac{RP}{t}$$

$$\epsilon_\theta \approx \frac{\sigma_\theta}{E}$$

$$\epsilon_\theta \approx \frac{\Delta R}{R}$$

Pressure in the cone area

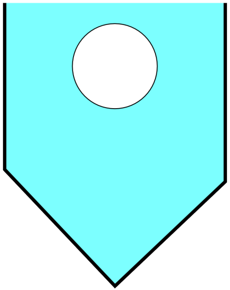
Sharp pressure waves

- Pressure/strains shown before $\rightarrow$ along the barrel;
- What happens in the cone area?

- Cone can amplify sharp pressure waves;
- Stress concentration.

Sharp pressure waves arise from:

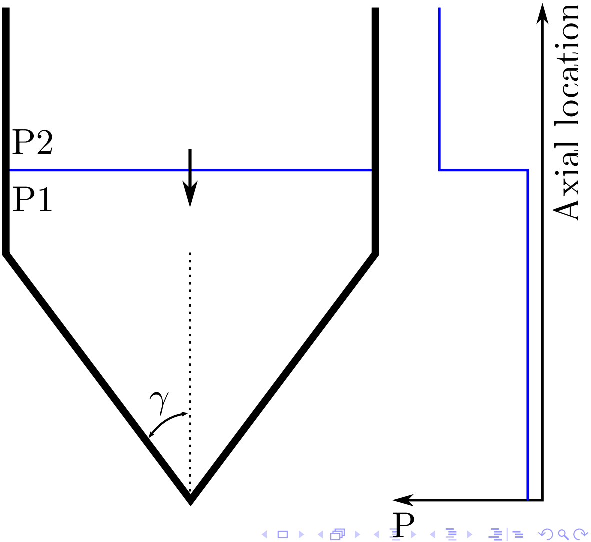
- impact of plunger rod on the plunger-stopper;
- the violent collapse of bubbles (cavitation);



Pressure in the cone area

Amplification mechanism

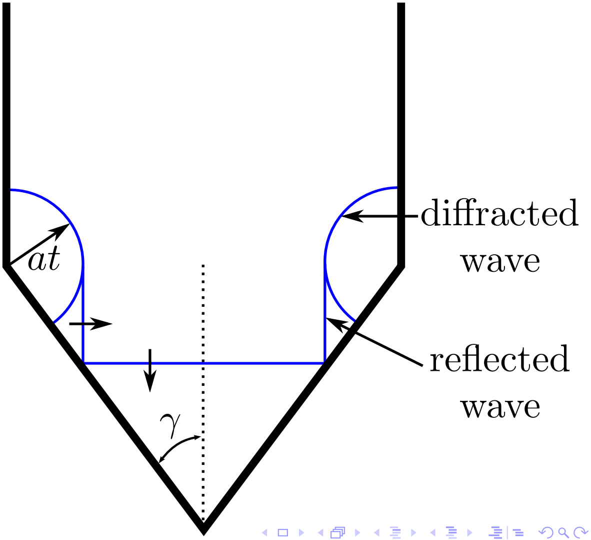
- Sharp pressure wave is entering the cone;



Pressure in the cone area

Amplification mechanism

- Sharp pressure wave is entering the cone;
- Reflected and diffracted waves form;
- Reflected and diffracted waves converge on the axis of symmetry;
- Energy is *focused* on the axis $\rightarrow$ pressure rises.



Effect of the cone – syringe geometry