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Variability in Syringe Components and its Impact on Functionality of Delivery Systems

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ABSTRACT: Prefilled syringes and autoinjectors are becoming increasingly common for parenteral drug administration primarily due to the convenience they offer to the patients. Successful commercialization of such delivery systems requires thorough characterization of individual components. Complete understanding of various sources of variability and their ranking is essential for robust device design. In this work, we studied the impact of variability in various primary container and device components on the delivery forces associated with syringe injection. More specifically, the effects of barrel size, needle size, autoinjector spring force, and frictional forces have been evaluated. An analytical model based on underlying physics is developed that can be used to fully characterize the design space for a product delivery system.

KEYWORDS: Break-loose forces, Extrusion force, Device, Autoinjector, Prefilled syringe, Delivery forces

LAY ABSTRACT: Use of prefilled syringes (syringes prefilled with active drug) is becoming increasingly common for injectable drugs. Compared to vials, prefilled syringes offer higher dose accuracy and ease of use due to fewer steps required for dosage. Convenience to end users can be further enhanced through the use of prefilled syringes in combination with delivery devices such as autoinjectors. These devices allow patients to self-administer the drug by following simple steps such as pressing a button. These autoinjectors are often spring-loaded and are designed to keep the needle tip shielded prior to injection. Because the needle is not visible to the user, such autoinjectors are perceived to be less invasive than syringes and help the patient overcome the hesitation associated with self-administration.
In order to successfully develop and market such delivery devices, we need to perform an in-depth analysis of the components that come into play during the activation of the device and dose delivery. Typically, an autoinjector is activated by the press of a button that releases a compressed spring; the spring relaxes and provides the driving force to push the drug out of the syringe and into the site of administration. Complete understanding of the spring force, syringe barrel dimensions, needle size, and drug product properties is essential for robust device design.
It is equally important to estimate the extent of variability that exists in these components and the resulting impact it could have on the performance of the device. In this work, we studied the impact of variability in syringe and device components on the delivery forces associated with syringe injection. More specifically, the effect of barrel size, needle size, autoinjector spring force, and frictional forces has been evaluated. An analytical model based on underlying physics is developed that can be used to predict the functionality of the autoinjector.

Introduction

The last decade has witnessed an increase in the popularity and sales of prefilled syringes with an annual growth rate of 20% in the U.S. market (1). The primary factors driving the growth include ease of administration and added convenience for health care workers and patients (1, 2). Compared to vial configuration, a higher accuracy can be achieved with prefilled syringes and fewer steps are required for dosage. An added benefit is the reduced overfill amount due to significantly lower hold-up volumes associated with syringes. Errors in dosage, and risk of misidentification and contamination, are also minimized. Plastic prefillable syringes made of cyclic olefins are now available as an alternative to glass syringes (3). Convenience to end users and market advantage can further be boosted through the use of delivery devices. Delivery systems that are preferred by the patients and

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perceived to be less invasive than syringes (4) will provide commercial advantage to the drug manufacturer. Novel delivery systems for commercial products also offer a mechanism to maintain the competitive edge in the marketplace (5).

Successful commercialization of prefilled syringe configurations and autoinjectors requires complete understanding of the mechanism of delivery and the parameters contributing to the delivery forces and injection time. The delivery force is attributed to the break-loose force (initial force required to set the plunger in motion) and the extrusion force needed to sustain the plunger movement by overcoming the hydrodynamic pressure and the frictional forces. Several factors contribute to these forces, including but not limited to:

- Barrel siliconization, which primarily affects the frictional forces
- Syringe geometry, including barrel size and needle gauge, which primarily affects the force due to hydrodynamic pressure drop
- Syringe type, such as siliconized glass or plastic
- Stopper type and geometry
- Product attributes, including its interaction with the barrel surface and its rheological properties
- Driving forces, such as the spring for mechanical autoinjectors
- Injection volume and time
- Subcutaneous resistance

In order to design a robust product presentation, it is important to understand the role of each of these components, estimate their inherent variability, and calculate the resulting impact on injection force or time. The objective of this study is to characterize and measure the effect of variability in components associated with a syringe delivery system, such as syringe barrel size, needle size, friction forces, and spring characteristics of the autoinjector. The role of product properties and its interaction with the syringe surface is equally critical and has been evaluated under a separate study. Results from that study will be published in a separate article. Subcutaneous resistance is also expected to increase the delivery forces; however, the impact of interstitial pressure is outside the scope of this work. The measurements of extrusion forces are performed using Instron, a material testing system. A predictive model based on the Hagen-Poiseuille equation has been developed to understand the flow behavior of drug through the delivery systems and to help identify malfunctions and failure points associated with the delivery system. The mechanistic model helps to identify the key process parameters, assess their importance, and predict the impact they would have on the extrusion force or injection time variability.

TABLE I
List of Syringe Types and Lots Used in This Study

Syringe Vendor	Number of Lots Studied	Syringe Type
Vendor 1	3 lots	Siliconized glass
Vendor 2	3 lots	Siliconized glass
Vendor 3	2 lots	Siliconized glass
Vendor 4	1 lot	Plastic

Materials and Methods

Siliconized glass syringes and plastic syringes procured from different vendors (see Table I) were used in this study. Plunger stoppers from two different vendors were also evaluated for siliconized glass syringes.

Force measurements for syringes were performed using Instron, a material testing system. A load cell of 500 N was used to drive the syringe plunger at a constant crosshead speed while measuring the resulting force on the plunger (repeatability of ±0.25% of reading over a range of 0.4% to 100% of capacity). A schematic of the instrument is shown in Figure 1. Variation in needle size is measured by a syringe flow rate fixture which measures the pressure drop for a liquid (water) flowing across the syringe barrel and needle at a constant flow rate. The set up consists of a pump connected to a water reservoir and a pressure sensor. The pump discharges water at constant flow rate in the capillary, and the sensor measures the corresponding pressure drop that is representative of the effective internal radius of the needle. Variation in barrel size of the syringes is measured by the barrel bore internal diameter (ID) gauge. It is first calibrated using a barrel of known ID. The instrument is then

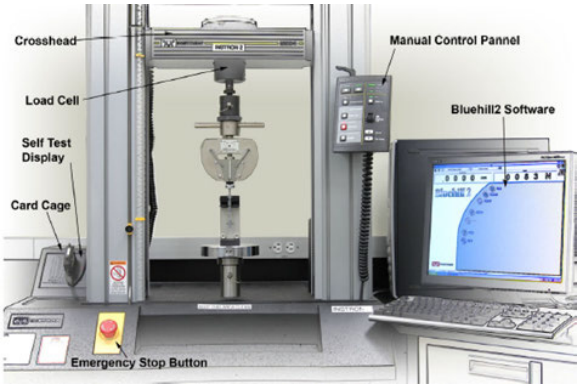

Figure 1

Picture of the Instron system used for measuring extrusion forces.

used to measure the barrel size of different syringes at different depths along the syringe axis.

Theory

The system under consideration is fluid flow through a prefilled syringe. The syringe consists of a needle of length L_n and mean effective internal radius r_n attached to the barrel of mean effective internal radius r_b. The syringes are filled to a specified volume and stoppered using an automated stopper placement unit. The stopper holds the end of the plunger rod through which a force F_{total} is applied in order to drive the fluid with a plunger speed $\bar{v}$ (linear speed in length over time dimensions).

Break-loose force refers to the maximum force required to set the plunger into motion. *Extrusion force* is the total force required to sustain the plunger rod in motion while maintaining the desired flow rate of the liquid through the needle. This study characterizes the total extrusion force associated with delivery of a product through syringe injection.

Figure 2 shows the schematic of a syringe system. The inner surface of the glass barrel is lubricated with silicone oil as shown in the figure. The force balance on the stopper at any time during injection gives

$$F_{total} = F_{friction} + F_{hydrodynamic} \quad (1)$$

where F_{total} is the total force needed for driving the plunger (also referred to as extrusion force), $F_{friction}$ is the friction force between the stopper and the syringe wall, and $F_{hydrodynamic}$ is the hydrodynamic force required to drive the fluid out of the needle. The details of these forces are discussed in the following sections.

A. Friction Force

The friction force arises from the interaction between the walls of the stopper and the barrel. The inner surface of the glass syringe is lubricated (siliconized) with a thin layer of silicone oil as shown in Figure 2. The friction force thus results from the glass-silicone oil-stopper interaction. Using the lubrication approximation, and assuming a uniform silicone oil layer on the inner wall of the barrel, the relation between the friction force and the injection speed is

$$F_{friction} = \left(\frac{2\pi\mu_{oil} r_b l_{stopper}}{d_{oil}}\right)\bar{v} = K_f \bar{v} \quad (2)$$

where μ_{oil} is the viscosity of lubricating oil, d_{oil} is the thickness of lubrication layer, $l_{stopper}$ is the length of the stopper in contact with glass, and $\bar{v}$ is the injection speed (linear piston speed with dimensions of length over time). Equation 2 shows that there is a linear dependence of the friction force on the injection speed and K_f is the constant of proportionality for a given

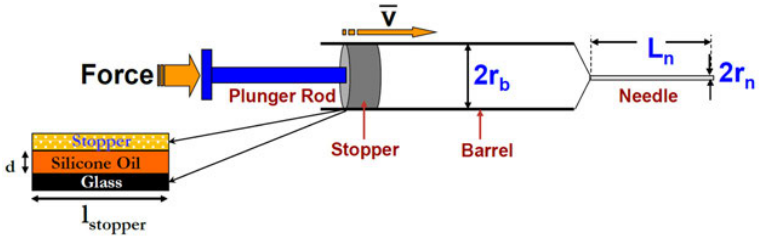

Figure 2

A schematic of the various components and forces associated with the syringe delivery system. The figure also shows a schematic of the lubrication of the syringe wall with silicone oil.

thickness of silicone oil. The friction force would increase with injection speed due to the increase in velocity gradient within the lubrication layer. Variability in friction force could arise due to non-uniformity in the thickness of the silicone oil layer on the inside surface of the barrel, as well as variations in the geometry of the barrel and stopper. Protein-barrel interactions could further affect the friction force.

B. Hydrodynamic Force for Newtonian Fluids

The hydrodynamic force results from the pressure drop required to drive the fluid out of the syringe. For Newtonian fluids, the relationship between the pressure drop ΔP and the volumetric flow rate Q (units: volume/time) can be obtained using the Hagen-Poiseuille law as

$$\Delta P = \frac{8\mu LQ}{\pi r^4} \tag{3}$$

where μ is the viscosity of fluid, r is the radius, and L is the length of the cylindrical channel. The equation assumes laminar flow ($Re < 2300$) for an incompressible liquid though a channel of constant cross section diameter of 2r. For a 27 G syringe needle and 1 mL syringe barrel used in this study, a plunger speed of 304.8 mm/min corresponds to a Reynolds number of less than 100. Assuming no interference from the glue used in producing a staked needle syringe, the total hydrodynamic force associated with flow in a syringe will depend on the pressure drop across the barrel and needle. Equation 3 shows that for constant flow rate Q, $\Delta P \sim r^{-4}$. In the syringe system, the radius of the barrel is much larger than the radius of the needle ($r_b/r_n \cong 30$). As a result, the pressure drop across the barrel is negligible when compared to the pressure drop across the needle ($\sim O(10^{-6})$). There is also an entry loss when the fluid enters into a constriction, but its magnitude is much smaller than the pressure drop across the needle ($\Delta P_{loss} \sim \rho v^2/2 \sim O(10^{-7})$). Neglecting the pressure drop across the syringe barrel and the entry loss, the hydrodynamic force at a given temperature can be estimated from eq 3 as

$$F_{hydrodynamic} = \left(\frac{8\pi\mu L_n r_b^4}{r_n^4}\right)\bar{v} = K_h\bar{v} \tag{4}$$

where K_h is a constant that depends on syringe size and fluid properties. Variation in operating temperature would affect the solution viscosity and the hydrodynamic force. Equation 4 shows the linear dependence of the hydrodynamic force on the injection speed. Equations 2 and 4 can be combined to give the total extrusion force associated with syringe delivery:

$$F_{total} = \left(\frac{2\pi\mu_{oil} r_b l_{stopper}}{d_{oil}}\right)\bar{v} + \left(\frac{8\pi\mu L_n r_b^4}{r_n^4}\right)\bar{v}. \tag{5}$$

C. Hydrodynamic Force for Non-Newtonian Fluids

The flow of non-Newtonian fluids is more complex due to the fact that their viscosity is not constant with the shear rate. A power law model is most commonly applied to represent the viscosity for such fluids:

$$\tau_w = K(\gamma)^n \quad \text{and} \quad \mu = K(\gamma)^{n-1} \tag{6}$$

where τ_w is the shear stress at the wall or barrel surface, γ is the shear rate and n is the power law index (where $n = 1$ represents a Newtonian fluid), K is the defined as the flow consistency index, and μ is the apparent viscosity.

For non-Newtonian fluids, the relation between the pressure drop ΔP required to drive the fluid at flow rate Q in a cylindrical channel of radius r and length L can be derived by solving the Navier-Stokes equation for a flow in a cylinder (6). Neglecting the pressure across the barrel, the hydrodynamic force required to drive a non-Newtonian fluid with an injection speed $\bar{v}$ can be derived as

$$F_{hydrodynamic} = \left(\frac{3n+1}{n}\right)^n \frac{2\pi K L_n r_b^{2n+2}}{r_n^{3n+1}}\bar{v}^n = K_h\bar{v}^n. \tag{7}$$

It should be noted that while the hydrodynamic force was linear with injection speed for the case of Newtonian fluids, it has a non-linear dependence on injection speed for non-Newtonian fluids. The total extrusion force can then be estimated by adding the friction force to the hydrodynamic component:

$$F_{total} = \left(\frac{2\pi\mu_{oil} r_b l_{stopper}}{d_{oil}}\right)\bar{v} + \left(\frac{3n+1}{n}\right)^n \frac{2\pi K L_n r_b^{2n+2}}{r_n^{3n+1}}\bar{v}^n. \tag{8}$$

D. Injection Time Calculation for Autoinjector

Modeling of an autoinjection device involves a physical understanding of the effects of all the components

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