Stability Evaluation of Injection Device Functionality Including Polymer-based Prefilled Syringe with Biologics

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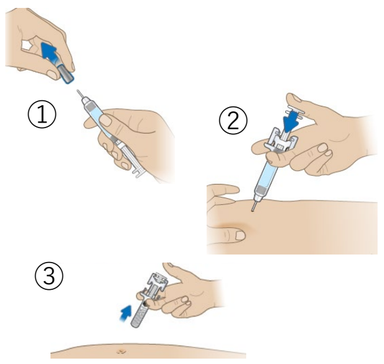
Abstract

Prefilled syringe and autoinjector contribute to patient convenience for self-administer biologics via subcutaneous administration. These injection devices are constructed with various materials. The properties of constituent materials impacted on the functional properties of injection devices. The functional performance is changed by the degradation rate of the constituent materials performance over time. This study primarily focuses on the chemical degradation process, which potentially exhibits environmentally dependent effects. Within the realm of injection device development, a procedure termed the '10-degree rule' has been traditionally applied to the Arrhenius model, grounded in collision theory, to predict the shelf life of these devices. However, the universality of this approach raises concerns, as it may not be applicable to all materials, particularly those in direct contact with drug solutions. The barrel interior of prefilled syringes is typically coated with silicone oil for lubrication to aid plunger movement at the time of administration. Actually, data indicated that the physical state of the siliconized surface and lubrication function with cyclic olefin polymer (COP) prefilled syringe (PFS) can change over time in contact with biologics drug product. We evaluate statistical model such as the 10-degree rule for the functional degradation based on the obtained data.

Introduction

☐ **Typical functionality test items for PFS with Needle safety device (NSD) to control drug delivery function**

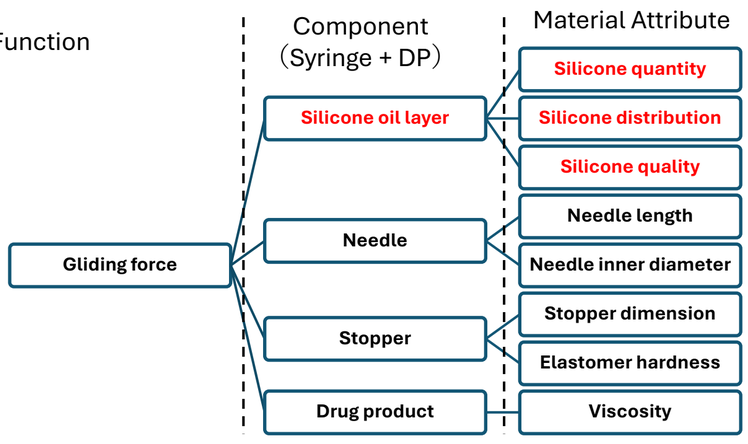


① Cap removal force
Measuring rigid needle shield (RNS) removal force

② Injection force
Measuring break loose force and gliding force during injection

③ Needle pull out force
Measuring needle pull out force from syringe tip

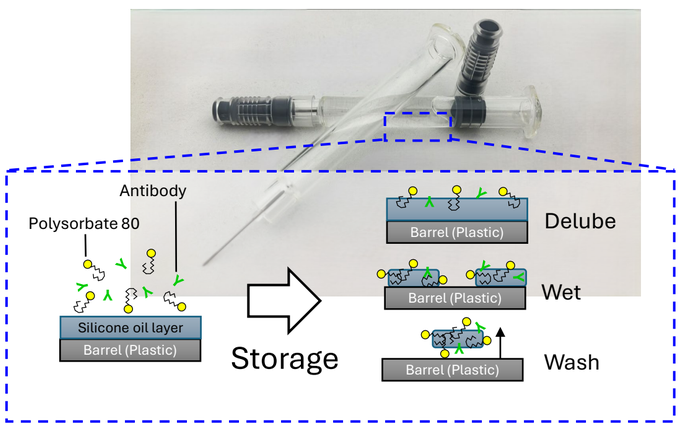
☐ **The properties of constituent materials impacted on the functional (e.g. gliding force)**



- The functional performance is changed by the degradation rate of the constituent materials performance over time.
- The functional performance change is dependent on a faster deteriorating components.

Red color: components expected to deteriorate faster than other components

☐ **Potential mechanism for COP syringe silicon oil layer by Biologic drug product**



- It is proposed that silicone oil change on glass syringe is caused by formulation excipients and a complex set of phenomena summarized as “wet, wash, and delube” processes (1).
- Glass syringe siliconization: baked-on siliconization or sprayed-on siliconization
- COP syringe siliconization: sprayed-on siliconization

☐ **Feasibility of procedure termed the '10-degree rule’ based on the Arrhenius model for the shelf-life prediction**

$$Time_{T1} = Time_{RT} / Q_{10}^{(T_1 - T_{RT})/10}$$

$Time_{T1}$ = time under accelerated aging temperature
$Time_{RT}$ = time under room temperature (ambient/ use/storage)
T_1 = accelerated aging temperature
T_{RT} = room temperature (ambient/ use/storage)
Q_{10} = reaction-rate coefficient

Table Equivalent storage period for refrigerated (5°C ± 3°C) products at various temperature conditions (Q10 = 2.0)

Simulated real-time under intended storage condition	Storage time accerelated aging condition (months)		
	25° C	40° C	55° C
6 months	1.5	0.5	0.2
12 months	3.0	1.1	0.4
18 months	4.6	1.6	0.6
24 months	6.1	2.2	0.8
36 months	9.1	3.2	1.1

- An accelerated ageing approach according to ASTM-F1980-16 was proposed to support leveraging the data from injection device (2).
- However, the universality of this approach raises concerns, as it may not be applicable to all materials, particularly those in direct contact with drug solutions.

Stability samples and conditions

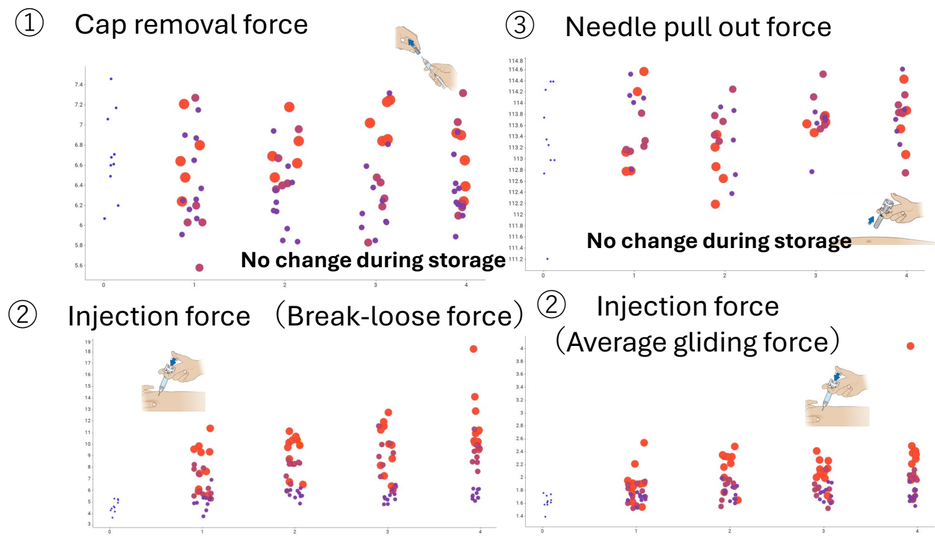
Table Stability samples

Sample ID	Syringe	Sample	Filled Volume
1	COP syringe (1 mL)	Formulation buffer	1.0 mL
2		Biologic drug product (DP) A (Protein concentration: 80 mg/mL)	1.0 mL
3		Biologic drug product (DP) B (Protein concentration: 5 mg/mL)	1.0 mL
4		Ultrapure water	1.0 mL

Table Stability conditions and testing time points

Storage temperature (°C)	Storage time				
	initial	1 weeks	2 weeks	3 weeks	4 weeks
25	Samples stored under 5°C	T	T	T	T
40		T	T	T	T
55		T	T	T	T

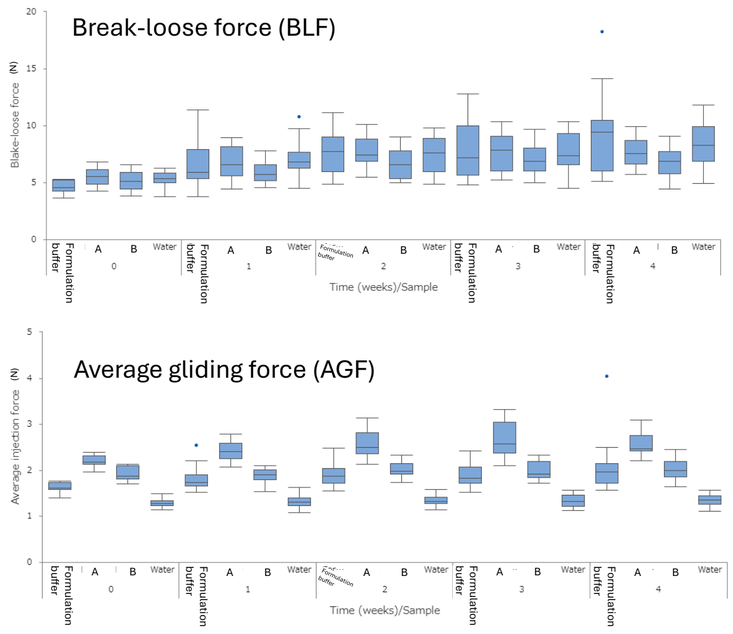
Functionality data: PFS with formulation buffer



Cap removal force and Needle pull out force show no changes over time, but the injection force increased over time.

Stability indicating: Injection force (Break-loose force and Average gliding force)

PFS injection force results

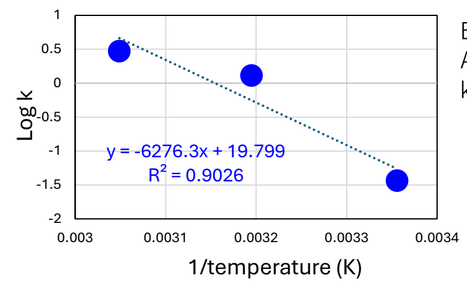


- Increasing over time was indicated in all samples
- Increasing over time was dependent on the filled drug solution
- Proteins and other formulation components impacted these time-dependent changes

Increasing rank:
DP A (80mg/mL)⇒DP B (5mg/mL)⇒ Formulation Buffer⇒Water

Arrhenius plots of injection force

Break-loose force (BLF)



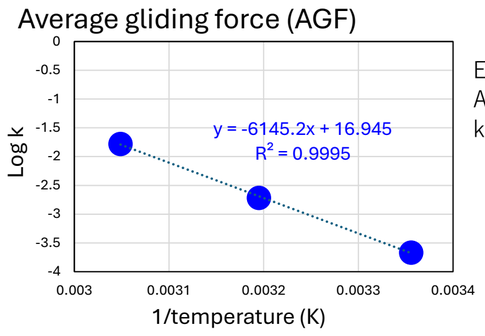
Ea: 52184.3 J/mol
A: 3.97.E+08 l/(mol x s)
k'/k: 2.2

Arrhenius equation

$$k = Ae^{\frac{-E_a}{RT}}$$

k = rate constant
A = pre-exponential factor
E_a = activation energy (in the same units as R*T)
R = universal gas constant
T = absolute temperature (in Kelvin)

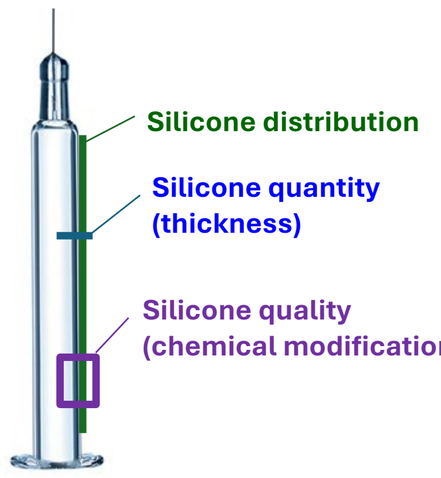
Average gliding force (AGF)



Ea: 51094.3 J/mol
A: 2.29.E+07 l/(mol x s)
k'/k: 2.2

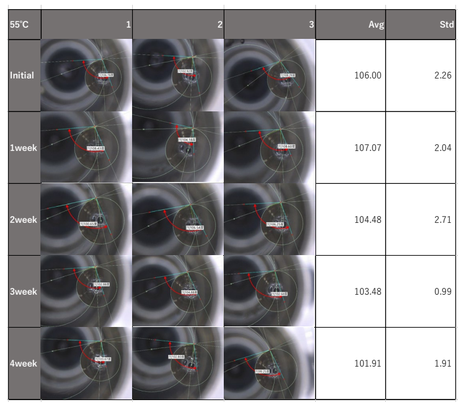
Both BLF and AGF Arrhenius plots demonstrate linearity. It was suggested that 2.2 fold of actual storage shelf-life can be predicted at a 10℃ rise.

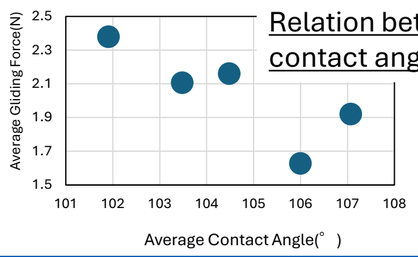
Siliconization direct monitoring



Siliconization monitoring method candidates:
- 3D-laser scanning microscopy (3D-LSM)
- Time of flight secondary ion mass spectrometry
- Raman microscopy
- SEM (scanning electron microscope)
- Contact angle measurement

Contact angle results from formulation buffer sample





Relation between contact angle and AVG

Conclusion

The obtained results of injection force and contact angle indicated that the silicone oil layer degrades relatively quickly. However, the Arrhenius plot results for functional test items related to the silicone oil layer showed a reaction rate coefficient of 2.2, exceeding the generally conservative reaction rate coefficient (Q10 = 2.0). This suggests that the guideline-specified 2.0 (10-degree rule) can continue to be applied for a COP PFS.

Reference

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2. Hemmerich, Karl J. General aging theory and simplified protocol for accelerated aging of medical devices. *Medical Plastic and Biomaterials* 1998, **5,** 16-23.