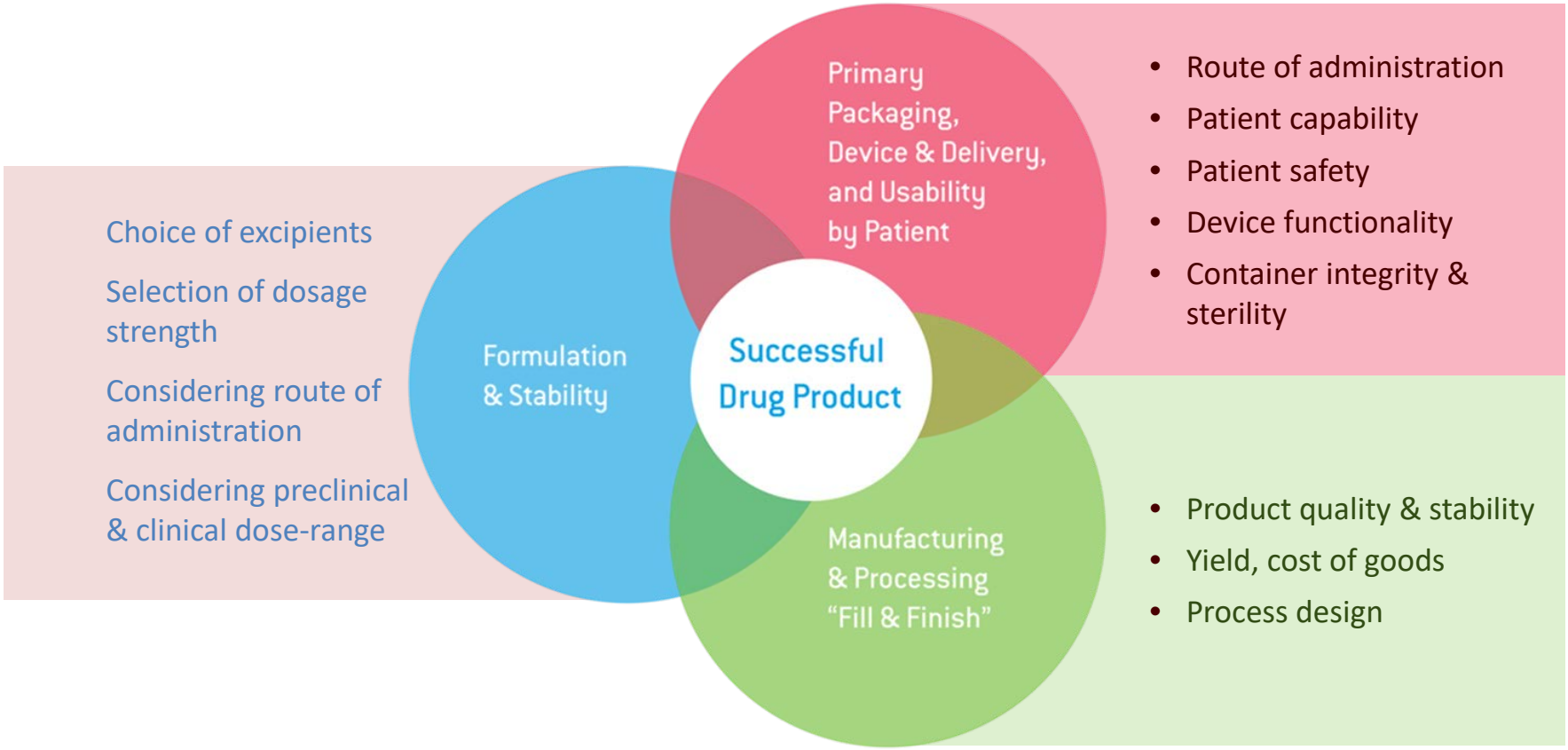
Test Methods for Pre-Filled Syringes

Horst Koller, CEO, HK Packaging Consulting GmbH
Roman Mathaes, PhD, Senior Group Leader, Lonza Drug Product Services

Challenges for Biologics Drug Products at the Interface of Formulation, Primary Packaging



High Concentration Formulations

As enabler of subcutaneous self-administration…

Drug-device combination product to enable successful SC injection

- Ready-to-use injection
- Potential self administration/ home use
- Safety considerations

High concentration formulations (HCFs) to enable successful SC injection of Biologics

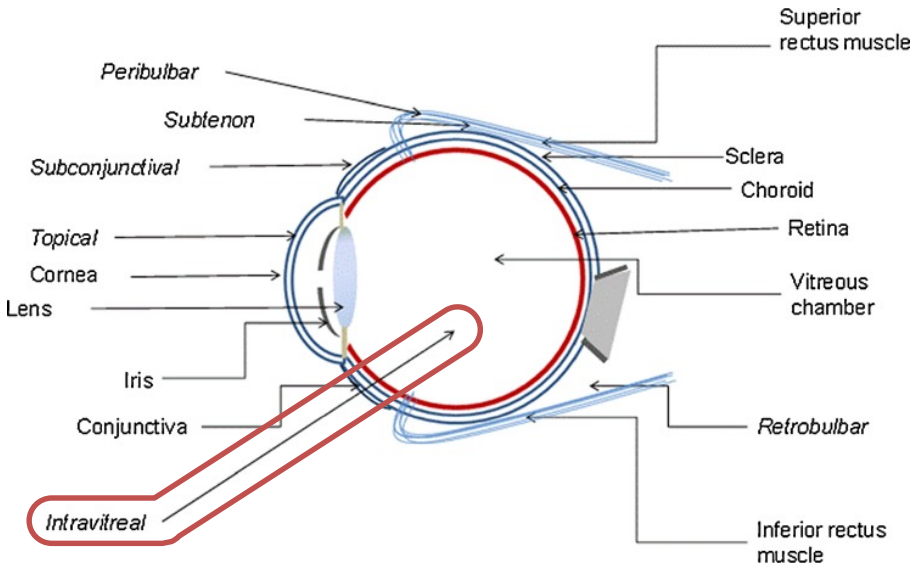
- SC administration as typical route for frequent and long-term treatments
- HCF's to enable high clinical dose requirements, particularly for mAbs
    - Bioavailability typically 60-80%
    - SC injection volume typically max 1-1.5 mL
    - Dosing frequency typically 1-4 injections/ month

Therapeutic protein	Brand name	Disease	Injection volume
Adalimumab	Humira™	Anti-inflammatory	0.8 mL
Canakinumab	Ilaris™	Anti-inflammatory	1 mL
Efalizumab	Raptiva™	Anti-inflammatory	1.25 mL
Insulin	Various	Diabetes	<1mL
Interferon a2a	Roferon-A™	Antiviral	0.5 mL
Golimumab	Simponi™	Anti-inflammatory	0.5 mL
Omalizumab	Xolair™	Anti-inflammatory	1.2 mL
Ustekinumab	Stelara™	Anti-Inflammatory	1 mL
Toclizumab	Actemra™	Anti-Inflammatory	0.9 mL
Certolizumab Pegol	Cimzia™	Anti-Inflammatory	2 × 2ml
Secukinumab	Cosentyx™	Anti-Inflammatory	2 × 1ml

Mathaes, R., Koulov, A., Joerg, S., Mahler, H.C. (2016). J Pharm Sci, 105(8), 2255-9.
DOI: http://dx.doi.org/10.1016/j.xphs.2016.05.029

High Concentration Formulations

As enabler of intravitreal injections…



Gaudana R. et al. (2010). AAPS J, 12(3): 348–360, doi: 10.1208/s12248-010-9183-3.

Intravitreal (IVT) / back of the eye (BOTE) injections

- Direct delivery into vitreous to achieve sustained drug levels and to overcome the limitations of systemic dosing by evading the blood-retinal barrier.
- Biologics are increasingly important for BOTE treatments

Drug-device combination products to enable successful IVT injection

- Ready to use injections
- Sterility of ophthalmic preparation during handling

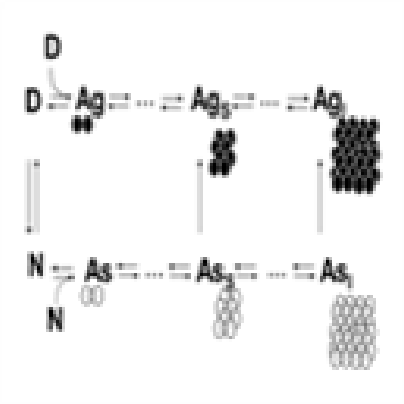
HCFs to enable successful IVT injections

- Low injection volume of max. 50-100 µL
- Prolonging therapeutic levels and reducing the frequency of injection

Integrated Drug Product Development

High Concentration Drug-Device Combination Product

Formulation & Stability

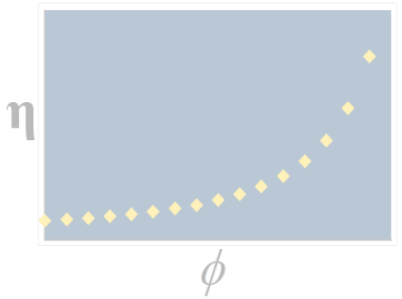


- Aggregation, subvisible and visible particles
- Special considerations

Container Closure System & Device

- Primary packaging compatibility
- Container closure integrity
- Functionality of devices

Application



- Viscosity and injection time
- Administration challenges
- High volume injections

Formulation & Stability Challenges

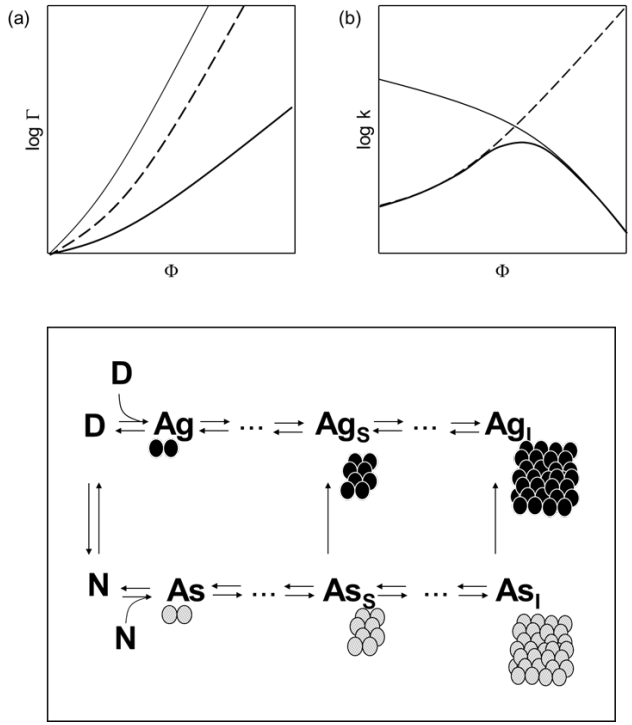
Formulation development at high concentration

High concentration formulations (HCF) come along with (known) stability challenges

- With increasing concentration, propensity to self associate and aggregate increases
- Thermodynamic non-ideality ("macromolecular crowding") leading to potentially increased level of
  - native, reversible self-association
  - aggregates, sub-visible and visible particles
- Potential impact on solution color (intrinsic or extrinsic) and opalescence (increased Tyndall effect, aggregates, liquid phase separations)

Special Considerations for IVT formulations

- Limited availability of excipients and more stringent endotoxin levels for IVT use
- Reduce off-label use for IVT formulations



Matheus S., Ph.D. thesis, 2006
Mahler H.C., Muller R., Friess W., Delille A. and Matheus S. (2005). Eur J Pharm Biopharm. 59:407-17

Sub-visible and Visible Particles

Occurrence and clinical relevance

Particulates can be different things and can be of different relevance

- Particles can occur spontaneously on DP stability
  Poor formulation, poor manufacturing process or poor primary packaging?
- Particles can also be something else than protein:
  e.g. environmental contaminants, silicone, air bubbles

Little is known about clinical relevance of particles

- There is no clear 'threshold' of particles with an established link to safety
- Safety concerns are however prevalent. FDA expects product specific limits for BLAs [1])
- Typically, benchmark what is in the market and aim to minimize as much as possible

Special concerns of particulates after IVT injection

- Uveitis, blockade of the Schlemm's canal; Increased intra-ocular pressure
- Impaired vision depending on the particle nature and its behavior in the vitreous humor

A. Rosenberg (2012): Workshop on Protein Aggregation andImmunogenicity, Breckenridge

Sub-visible and Visible Particulates

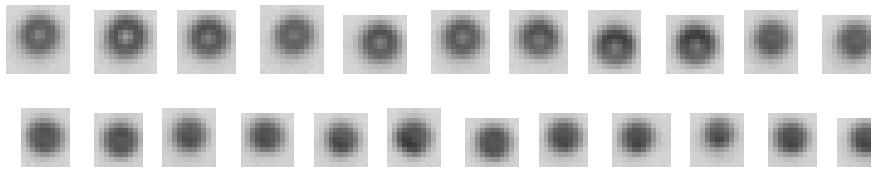
Occurrence and clinical relevance

Visible Particles

- **Visible particle requirements:**
  - USP <1>:
    "essentially free from particles"
  - Ph.Eur. Parenterals
    "practically free from particles"
- **Visible particles tests:**
  - USP <790>, Ph.Eur. 2.9.20
  - operator based and probabilistic test method

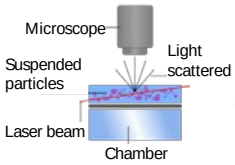
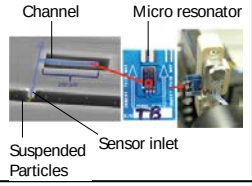
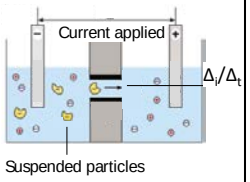
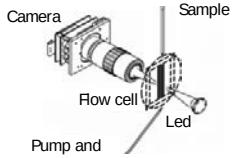
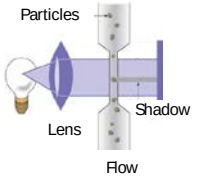
Sub-visible particles

- **Light obscuration test**
  - USP <789>
    NMT 50 particles/ mL ≥ 10 µm
    NMT 5 particles/ mL ≥ 25 µm
    USP <771> (ophthalmic preparations, draft/in revision)
  - Ph Eur 2.9.19
    NMT 6000 particles/ container ≥ 10 µm
    NMT 600 particles/ container ≥ 25 µm
- **Filing of product-specific limits according to clinical exposure**



Analytical Toolbox for Particles

No single analytical method can assess the whole size range

	Nano track analysis	Resonant mass	Coulter counter	Flow imaging microscopy	Light obscuration
					
	NTA	**Archimedes**	**CC**	**MFI** **FC**	**HIAC**
Principle	Tracking of Brownian motion of individual particles 	Changes in frequency due to added mass 	Changes in resistance due to volume displacement 	Weighing of single particles passing through a flow cell 	Drop in current due to the amount of light blocked 
Raw data	Video**, #/mL/size	#/mL/size, particle buoyancy	#/mL/size	#/mL/size, images**, particle morphology	#/mL/size
Optimal size rage [um]*	0.03 – 0.05 – 0.20 – 0.30 – 0.60 – 0.50 – 0.80 – 1.00 – 2.00 – 5.00 – 18.0 – 25.0				
Optimal sample concentration *[particles/mL]**	$3x10^8$ - $1x10^9$, ~20-70 centers per frame	< $8x10^6$	~ $2x10^5$, coincidence < 5%	MFI: < $9x10^4$ FC: < $1.5x10^6$	< $1x10^4$

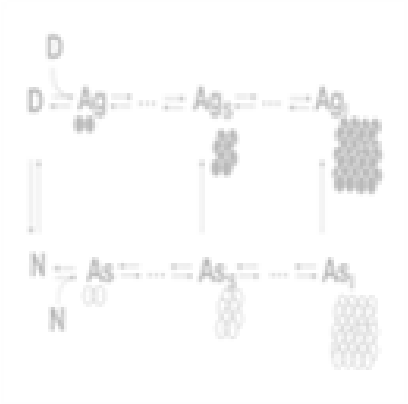
* As for the supplier. In all the cases, the optimal sample concentration is much more higher than the typically found in non stressed high concentrated protein samples or in stressed samples at relevant conditions ** Further analysis needed to get #/mL/size ▨ Informative data

Ríos Quiroz A et al. Pharm Res. 2015;33(2):450-461.

Integrated Drug Product Development

High Concentration Drug-Device Combination Product

Formulation & Stability

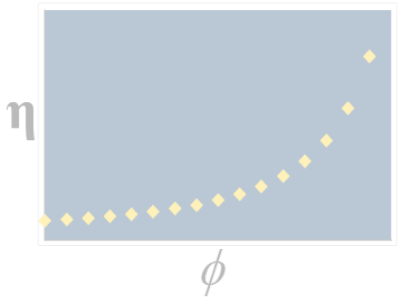


- Aggregation, subvisible and visible particles
- Special considerations

Container Closure System & Device

- Primary packaging compatibility
- Container closure integrity
- Functionality of devices

Application



- Viscosity and injection time
- Administration challenges
- High volume injections

Primary Packaging Challenges

Container Closure System (CCS) compatibility

- **"A container closure system refers to the sum of packaging components that together contain and protect the dosage form."**

- **Suitability for intended use**
  - Protection of dosage form and drug
  - Compatibility (CCS with drug)
  - Safety (E&L related patient impact)
  - Performance (Functionality of drug delivery system)

- **Info on suitability of storage (shipping) of biologics should be included**

  …greater potential for adverse impact on quality of biologics during storage and shipping

Table 1
Examples of Packaging Concerns for Common Classes of Drug Products

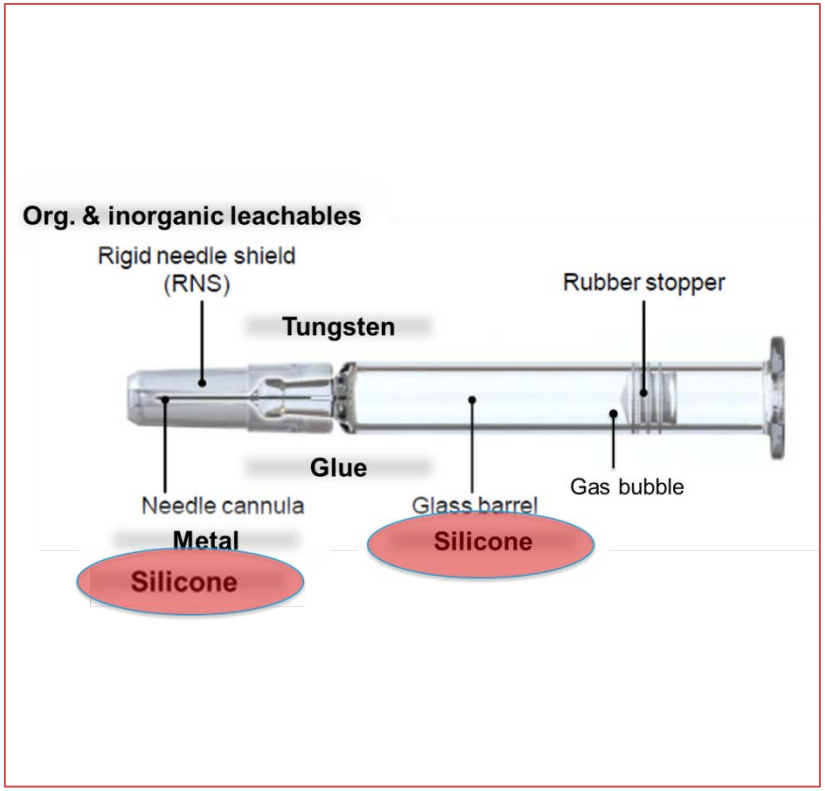
Degree of Concern Associated with the Route of Administration	Likelihood of Packaging Component-Dosage Form Interaction		
	High	Medium	Low
Highest	Inhalation Aerosols and Solutions; Injections and Injectable Suspensions*	Sterile Powders and Powders for Injection; Inhalation Powders	
High	Ophthalmic Solutions and Suspensions; Transdermal Ointments and Patches; Nasal Aerosols and Sprays		
Low	Topical Solutions and Suspensions; Topical and Lingual Aerosols; Oral Solutions and Suspensions	Topical Powders; Oral powders	Oral Tablets and Oral (Hard and Soft Gelatin) Capsules

* For the purposes of this table, the term *suspension* is used to mean a mixture of two immiscible phases (e.g., solid in liquid or liquid in liquid). As such, it encompasses a wide variety of dosage forms such as creams, ointments, gels, and emulsions, as well as suspensions in the pharmaceutical sense.

FDA Guidance for Industry – Container Closure Systems for Packaging Human Drugs and Biologics (1999)

Prefilled Syringes

Development concerns to address



Factor	Concerns for CCS suitability	Mitigation
Tungsten residues	• Oxidation • Aggregation • Syringe-to-syringe variability of residuals	• Spiking studies (pin extracts, salts of W) • Stability studies
Silicone oil	• Aggregation • Subvisible and visible particles	• Spiking studies (silicone oil emulsion) • Stability studies (including worst case siliconised syringe)
Multiple contact materials	• Organic and inorganic leachables (Rubbers of stopper / RNS, needle glue) • Latex allergy • Compatibility	• E&L studies • Assess components for dry natural rubber (DNR) components / Latex allergens [1)] • Stability studies

1) see new FDA Guidance on Labeling, March2013

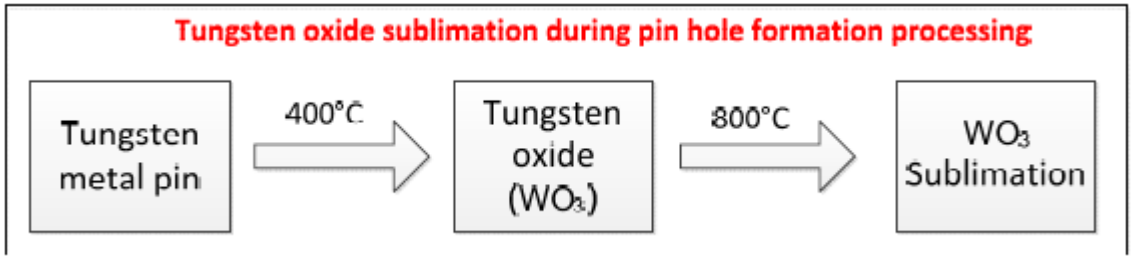
Adler M. (2012), AmPharmRevw, 15(1), 96
Badkar, A. et al. (2011). AAPS PharmSciTech, 12(2), 564–572. http://doi.org/10.1208/s12249-011-9617-y

Prefilled Syringes

Tungsten

- **Tungsten pins are used to form the fluid path (needle channel)**
  - High temperature process with possibility for metal particles deposits (tungsten oxide, tungstate)
  - Interaction with glass leads to formation of tungsten residuals
- **Tungsten may cause protein oxidation and aggregation** [1)]
  - Effect of tungsten (within process variability) on stability of protein should be assessed.
  - However, for most protein formulations, tungsten is of no issue.
- **Risk assessment**
  - Formulation – pH, concentration, ionic strength consideration (Solubilisation of Tungsten increases below pH 6)

Manufacturers' process



1) Jiang, Y. et al. (2009), J. Pharm. Sci., 98: 4695–4710. doi:10.1002/jps.21778

Prefilled Syringes

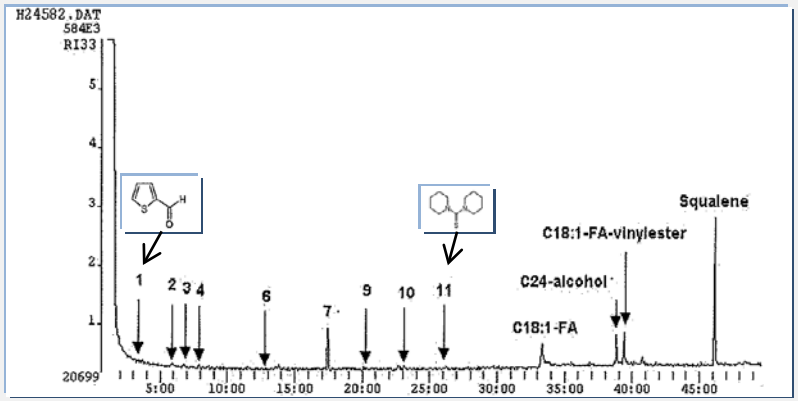
Extractables & Leachables

- **EXTRACTABLES: Chemical components that are removed from a material by exertion of an artificial exaggerated force.**
  For a rubber stopper, e.g.
  - Ingredients of the rubber formulations
  - Impurities of these ingredients
  - Reaction/degradation products during rubber manufacturing

  NB. Extraction conditions not universal.

- **LEACHABLES: Chemical compounds that migrate from a contact material into drug products during storage at "normal" simulated use conditions**
  - Typically a «subset» of extractable
  - Quantification & identity relevant

- **IMPORTANCE OF E/L-TESTING**
  - TOXICITY (incl. acute, chronic, genotox)
  - May REACT with API, DRUG COMPONENTS
  - Other (e.g. Matrix Interference with Analytical Method/QC)

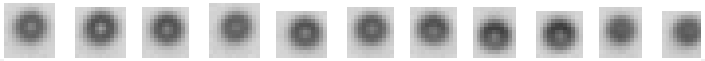


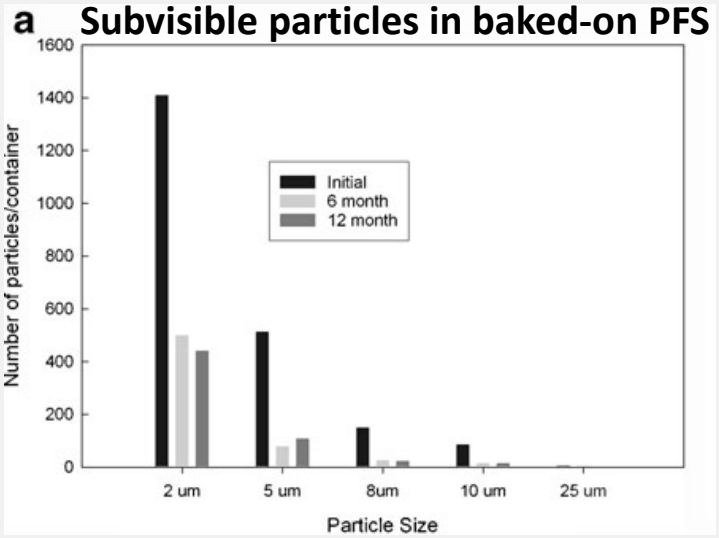
Prefilled Syringes

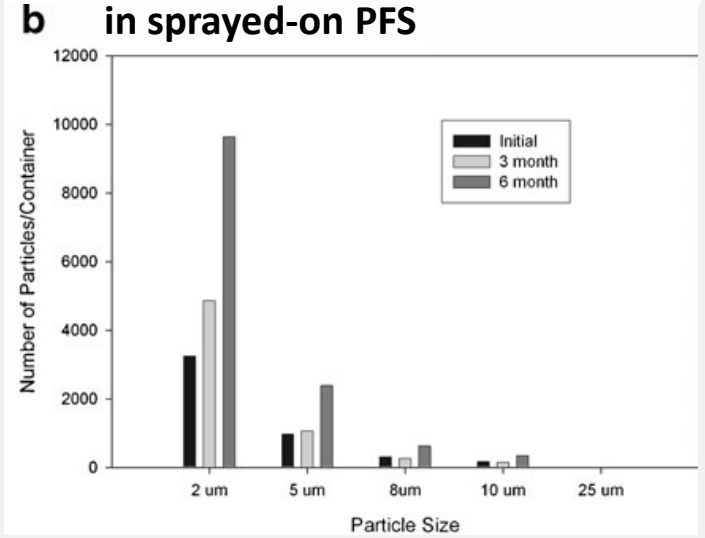
Silicone oil

- **Silicone oil is used for lubrication of the syringe glass barrel.**
  - Baked-on silicone oil: ~ 0.1 mg/barrel
  - Sprayed-on (free) silicone oil ~ < 1 mg/barrel, ideally ~ 0.5 mg/barrel
- **Impact on drug product stability to be evaluated** [1) 2)]

- **(Free) Silicone shows up in Drug Product as "Particulates"**
  - Sampling and measurement technique most relevant, e.g. use of flow imaging) [3)]
  - Appropriate characterization required, likely considerable a non-CQA







1) Jones, LaToya S. et al. (2011). J Pharm Sci, 94(4), 918-27
2) Goldbach, 6th Annual Protein Formulation Development and Drug Delivery Forum, (2015)
3) Badkar, A. et al. (2011). AAPS PharmSciTech, 12(2), 564–572. http://doi.org/10.1208/s12249-011-9617-y

Is Silicone a safety concern for ocular products

Intravitreal Silicone Oil Droplets After Intravitreal Drug Injections

Bakri, Sophie J. MD; Ekdawi, Noha S. MD

Retina
July/August 2008
Vol. 28 - Issue 7: pp 996-1001

Collapse ☆ Favorite PDF

Abstract

Purpose: To present the finding of tiny silicone oil droplets in 15 eyes of 15 patients after intravitreal injections of an anti–vascular endothelial growth factor agent or triamcinolone acetonide and to discuss the likely source of silicone oil.

Methods: In an observational case series, charts of patients who had undergone intravitreal injections by one surgeon were reviewed retrospectively. The finding of intravitreal silicone oil droplets was noted. The following information was also documented: number and type of injections before the appearance of silicone oil droplets, symptoms and evidence of ocular inflammation, visual acuity before and after silicone oil droplets, length of follow-up, and visual acuity at the last examination.

Results: Fifteen eyes of 15 patients were found to have silicone oil droplets documented after a various number of injections (range, 1–16). Patients were asymptomatic, and there were no adverse side effects associated with the presence of silicone oil droplets at examination.

Conclusions: Silicone oil droplets may occur in the vitreous cavity after intravitreal drug injections. There were no adverse effects found associated with silicone oil in the vitreous after injections of anti–vascular endothelial growth factor agents or triamcinolone acetonide. The likely source of silicone oil is the needles and syringes used for the injections.

Is Silicone a safety concern for ocular products

Intravitreal Silicone Oil Droplets After Intravitreal Drug Injections

Bakri, Sophie J. MD; Ekdawi, Noha S. MD

Retina
July/Au
Vol. 28

Ab

Purp
dropl
inject
agen
likely source of silicone oil.

Methods: In an observational case series, charts of patients who had undergone intravitreal injections by one surgeon were reviewed retrospectively. The finding of intravitreal silicone oil droplets was noted. The following information was also documented:

injections of an anti–vascular endothelial growth factor agent or triamcinolone acetonide and to discuss the likely source of silicone oil.

Methods: In an observational case series, charts of patients who had undergone intravitreal injections by one surgeon were reviewed retrospectively. The

Conclusions: Silicone oil droplets may occur in the vitreous cavity after intravitreal drug injections. There were no adverse effects found associated with silicone oil in the vitreous after injections of anti–vascular endothelial growth factor agents or triamcinolone acetonide. The likely source of silicone oil is the needles and syringes used for the injections.

Conclusions: Silicone oil droplets may occur in the vitreous cavity after intravitreal drug injections. There were no adverse effects found associated with silicone oil in the vitreous after injections of anti–vascular endothelial growth factor agents or triamcinolone acetonide. The likely source of silicone oil is the needles and syringes used for the injections.

Functionality Challenges

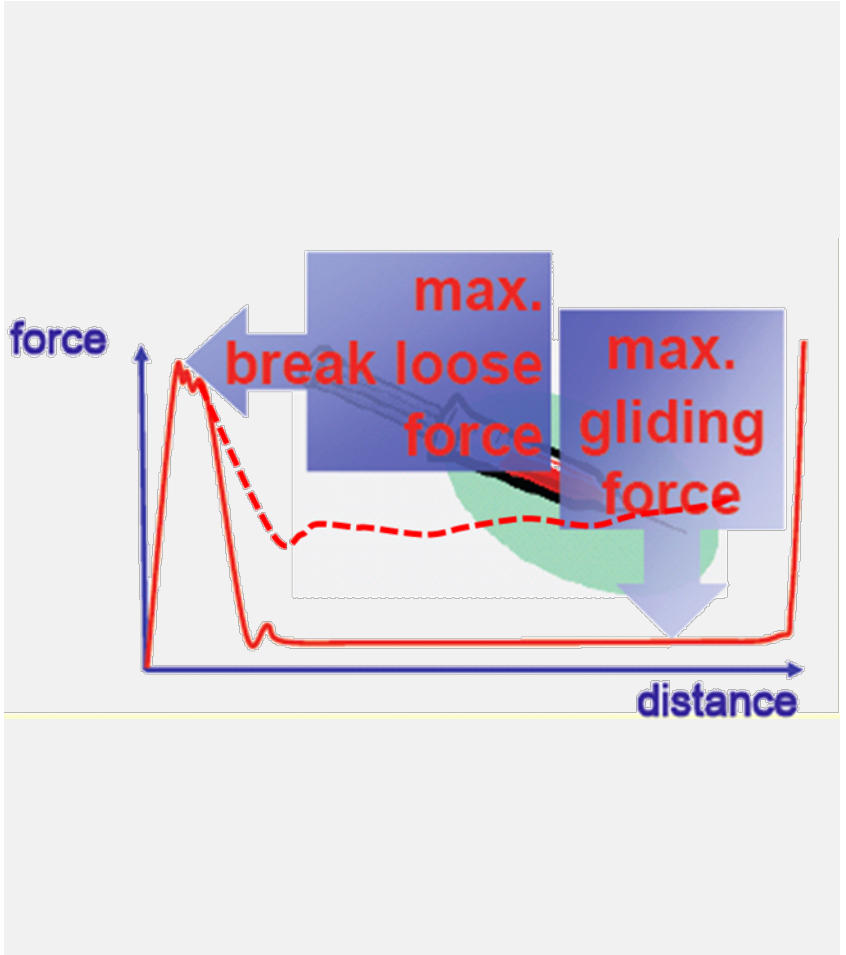
Functionality testing

Distribution of silicone oil is critical

- impacted by e.g. spray pattern, storage/aging, formulation interaction
- Characterize and understand lot-to-lot variability
- Set acceptance criteria
  - minimum siliconization for performance
  - maximum siliconization for particle control
- Correlate to critical functional parameters

Functionality testing on Stability

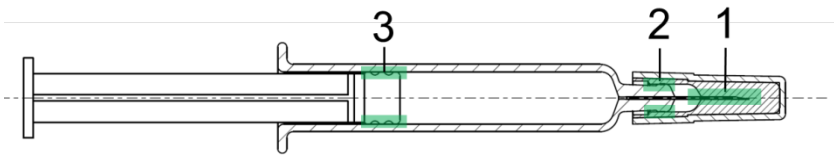
- Ensure syringe functionality over shelflife (PFS may «get stuck»)
  - Piston release force (Break Loose force)
  - Piston travel force (Glide or Extrusion force)
- Power injection function force (autoinjectors)
- Tip cap removal force

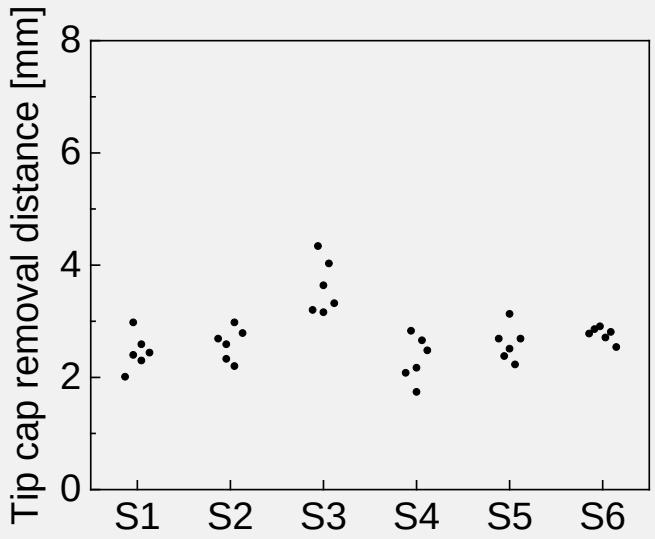


Prefilled Syringes

Ensuring sterility - CCIT

- All products labeled as sterile are required to be free of microbial contamination throughout their shelf life (obligatory CQA)
- Container closure integrity (CCI) addresses the maintenance of integrity to prevent microbiological ingress in sterile product packaging until the time of use
- Complex combination products feature several sealing areas and moveable parts
- Assessment of individual sealing areas with helium leak CCIT is necessary, e.g. sealing area 2 to ensure a sterile needle



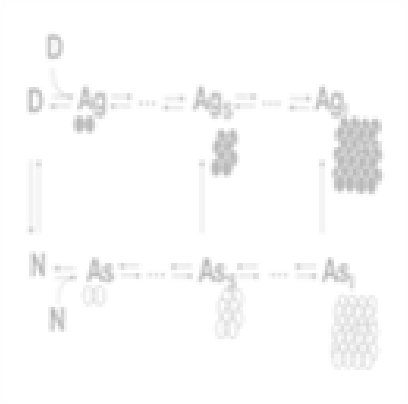


Data from R. Mathaes, S. Pelaez, Lonza Drug Product Services

Integrated Drug Product Development

High Concentration Drug-Device Combination Product

Formulation & Stability

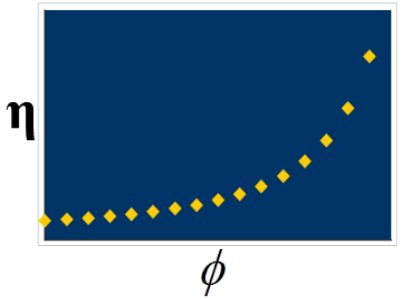


- Aggregation, subvisible and visible particles
- Special considerations

Container Closure System & Device

- Primary packaging compatibility
- Container closure integrity
- Functionality of devices

Application



- Viscosity and injection time
- Administration challenges
- High volume injections

Administration Challenges

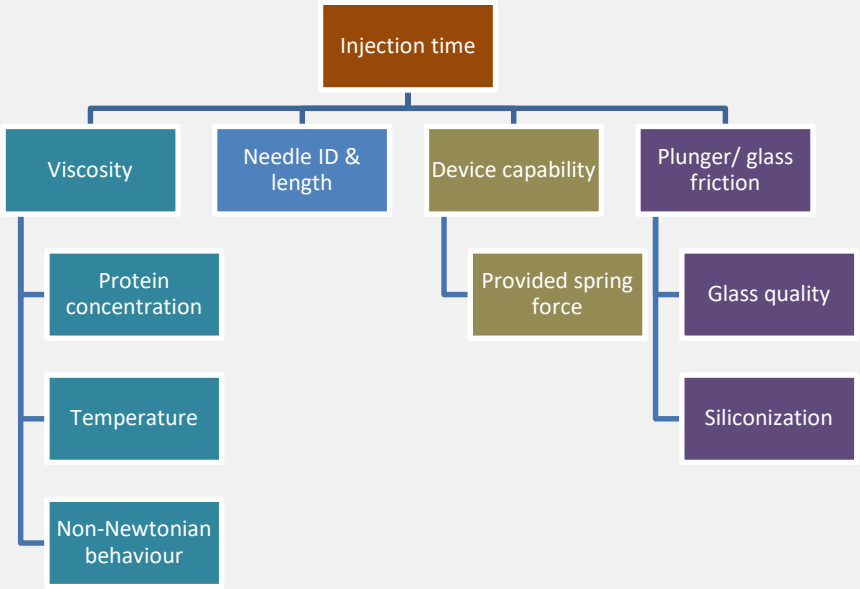
Syringability and injection time

Injection time depending on Hagen Poiseuilles's law for laminar flow in tubes:
What matters for syringability/injection time?

- Administration device configuration (needle inner diameter & length, autoinjector performance, plunger/glass friction).
- Viscosity = f(temp, conc, shear rate)
  - Protein concentration is critical (upper concentration spec!)
  - Temperature can be significant (product temperature prior use)
  - Protein can make a difference (Newtonian vs. Non-Newtonian behaviour).
- When estimating injection forces representative for in vivo situation, back-pressure of the tissue has to be considered.

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

Q = flow rate
μ = viscosity
r = radius of the needle
ΔP = pressure drop
L = length of the needle



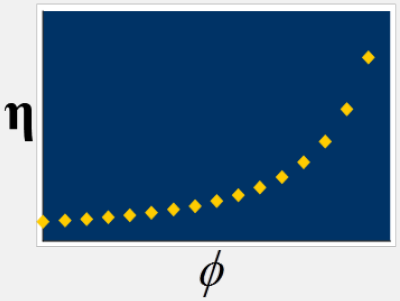
Rathore N. et al. (2012), J Pharm Sci, 101(12): 4472-4480. DOI 10.1002/jps.23297
Allmendinger, A. et al. (2015), Pharm Res 32: 2229-2240. DOI 10.1007/s11095-014-1611-0

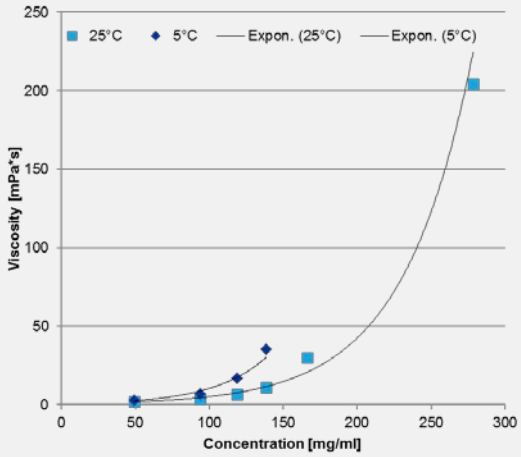
Viscosity Challenges

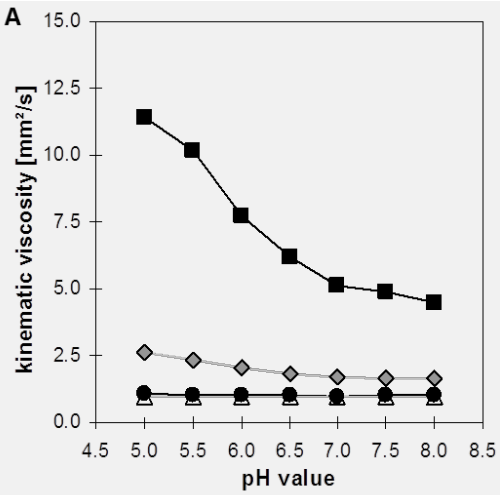
Syringability and injection time

- **Exponential increase of viscosity of mAb formulations with concentration**
  - "Macromolecular crowding": Mooney equation
  - Formulation dependent: electrostatic interactions, surface net charges
  - Temperature dependent
- **A rheological characterization prior to product development is key to meet the QTTP.**

$$\eta = \eta_0 \exp\left[\frac{2.5\phi}{1-k\phi}\right]$$







Mooney M. J colloid Sci 6, 162, 1951

Matheus S., Ph.D. thesis, 2006

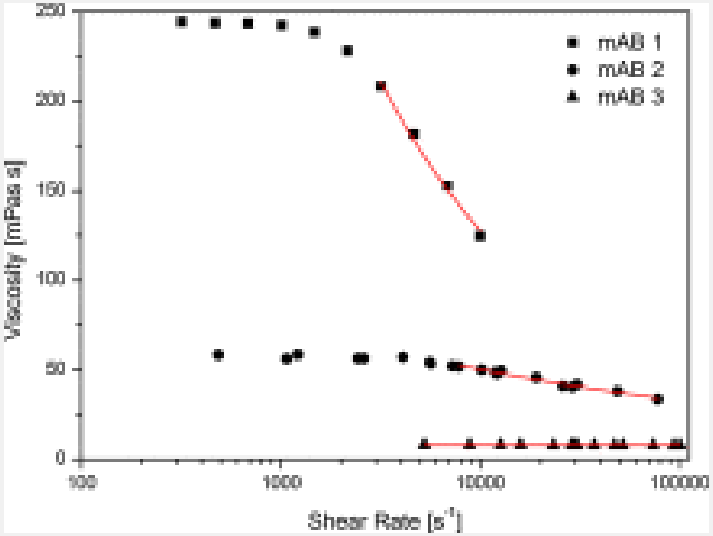
Viscosity Challenges

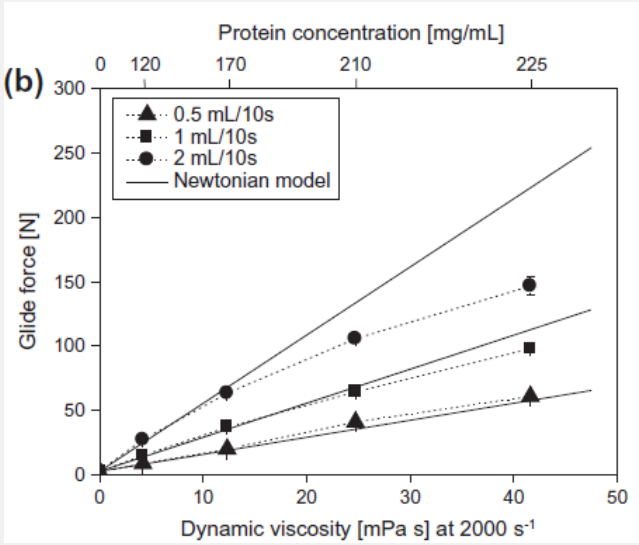
Shear dependent viscosity matters

- Many proteins show shear-thinning behaviour, with decreasing viscosity at higher shear rates according to the “power law” model.

$$\mu = Kx\,\dot{\gamma}^{n-1}$$

- High shear rates up to 10^{-6} s^{-1} occurring at the needle wall (Weissenberg–Rabinowitsch–Mooney equation)





Fischer I. et al. (2015), Int J Pharm, 493 (1-2)
Allmendinger A. et al. (2014), EJPB, 87: 318-28

Viscosity Challenges

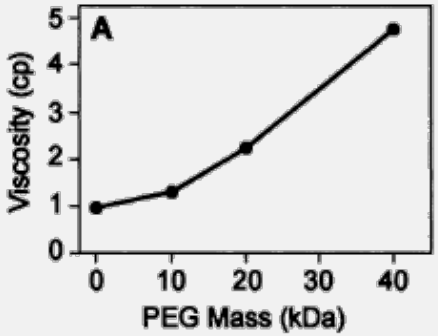
Specific molecules or protein/protein mixtures

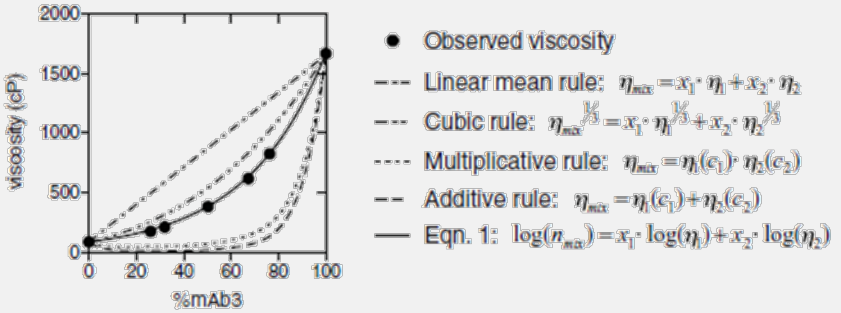
Molecule specific viscosity challenges

- Viscosity in formulations of PEGylated molecules
- Impact of polymer size, variability, branching
- Few ways of reducing viscosity by excipients

Protein/Protein Mixtures

- Viscosity and rheological properties of mixtures of different proteins (e.g. mAbs) need to be experimentally evaluated
- Viscosity is expected to be different to simple additive/multiplicative rules





Manjula et al Bioconjugate Chem., 14(2), 2003
Galush et al., J Pharm Sci, 101(3), 2011

Administration Challenges

Specific molecules or protein/protein mixtures

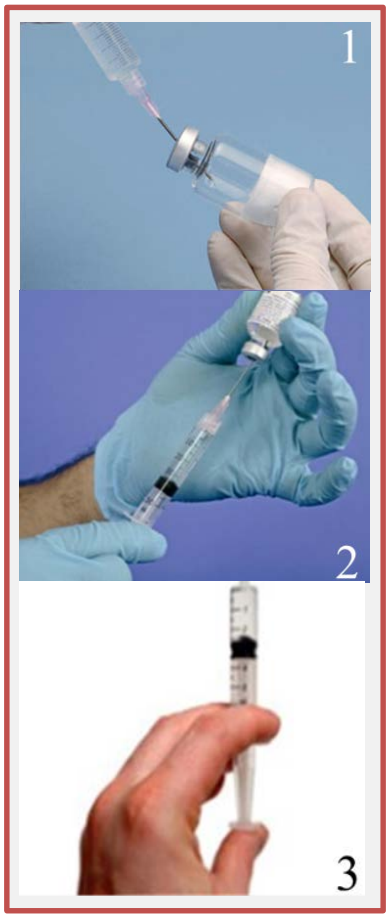
During clinical studies: preparation of IVT dosing solution from a vial

- Potential lyophilsate reconstitution and withdrawal of solution from vials
- Potential dilution steps
- Downdosing: “Eject” liquid to the desired injection volume

Commercial products: often pre-filled syringe

Dosing accuracy as main challenge

- Precise delivery devices needed for low volumes. Variability in syringes used by HCP.
- High user dependent variability (e.g. air bubble etc.)
- Precision hard to achieve with HCFs:
  - Small inaccuracies in injected volume can have big impact on absolute dose delivered
  - High viscosity may impact user dependent variability.



1 https://www.lumizyme.com/healthcare/treating_patients/handling_and_preparation.aspx
2 http://slideplayer.com/slide/5778115/
3 http://slideplayer.com/slide/4311396/

Alternatives to High Concentrations

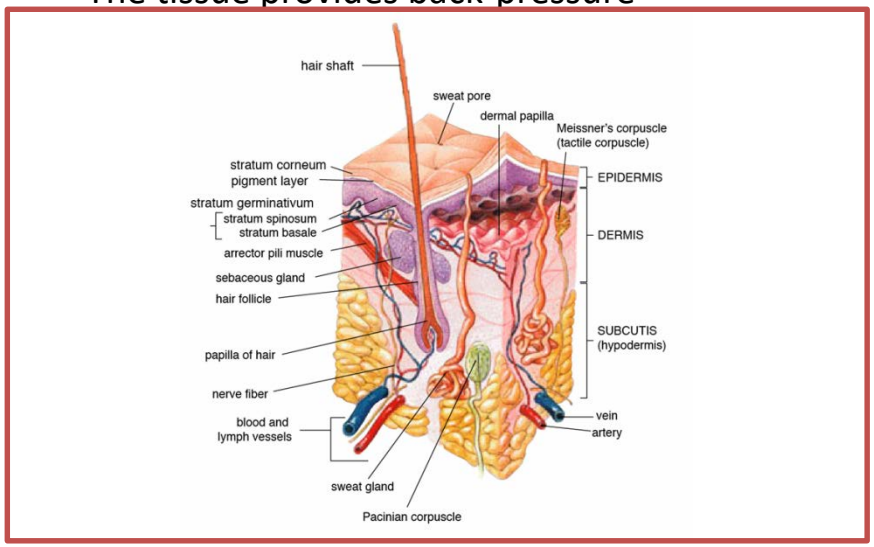
Pushing the Boundaries of SC Administration

Historic View on SC administration volumes

- **Limited s.c. injectable volume** (human) of approximately **1 to 1.5 ml** (Gatlin et al., 1999)
- **"…Maximum medication volume** to be injected (SC) into the site at one time should be less than or equal to **2.5 mL…**." (Caritas Health Group, Community Care Services, Regional Palliative Care Program)
- Humans and other furless animals have fibrous bands in the panniculus adiposus that reach into the deep fascia [McMinn, Rose] . These anchors reduce the compliance of the tissue space to injected fluids, such that **subcutaneous injections are generally limited to less than 2ml** (Frost, 2007)

What speaks against higher SC volumes

- Interstitial matrix limits SC injection
- Hyaluronic Acid and collagens provide a matrix and barrier in the interstitial tissue
- The tissue provides back-pressure



http://web.archive.org/web/20080612093735/http://training.seer.cancer.gov/ss_module14_melanoma/images/illu_skin01.jpg

Increasing the SC Dosing Volume

Knows and unknowns about SC administration related to injection pain

Injection pain influencing factor	Explanation
Injection speed	Slow injection speed is considered to cause less injection pain
Injection site	The hypodermis is a highly variable tissue, which significantly differs across body sites
Temperature of the drug product	Drug Products at body temperature are considered to cause less injection pain
Formulation parameters	Limited relevant clinical data available Viscosity: Influencing spreading, Osmolality, pH: Directly influence injection pain
Patient-to-patient differences in pain tolerance	Subjective experience of pain
Injection depth within the SC tissue	No relevant clinical data available
Injection needle	No relevant clinical data available A smaller needle gauge (larger needle diameter) is considered to cause greater injection pain
Pretreatment	Application of topical anesthetics before actual injection is considered to reduce injection pain

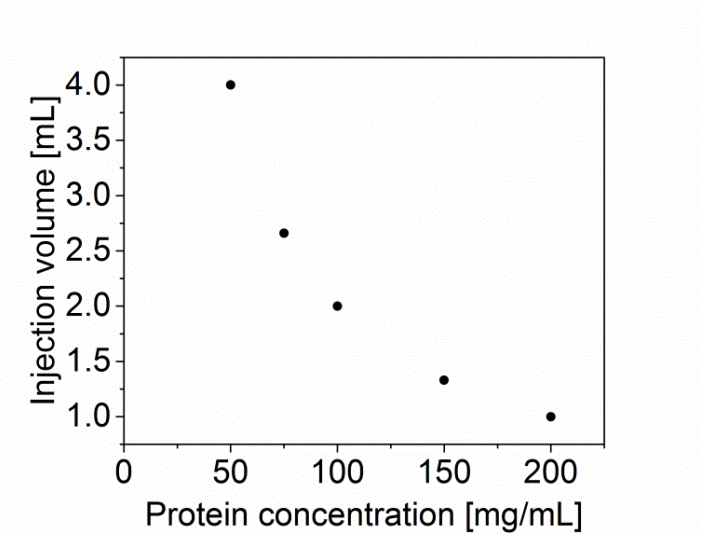
Mathaes, R., Koulov, A., Joerg, S., Mahler, H.C. (2016). J Pharm Sci, 105(8), 2255-9.DOI: http://dx.doi.org/10.1016/j.xphs.2016.05.029

Alternatives to High Concentrations

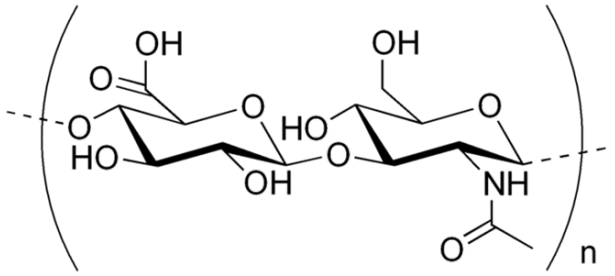
Pushing the Boundaries of SC Administration

- **Increasing the SC dosing volume**
  - Recent study on injection volumes of one 1.2-mL bolus injection over 5 s and three **3.5-mL injections over 1, 4, and 10 min** confirmed that all injections **were well tolerated** (Dias et al., AAPS PharmSciTech 2015)

Pushing max injection volume boundaries beyond the 1ml is considered a viable option



- **Other options to overcome**
  - Permeation enhancers (e.g. halozyme)
  - Increase bioavailability
  - Decrease dosing frequency
  - Increase activity: Molecular assessment

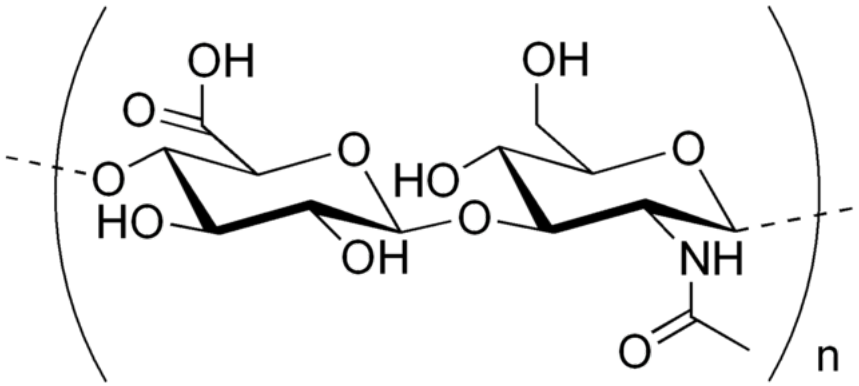


Mathaes, R., Koulov, A., Joerg, S., Mahler, H.C. (2016). J Pharm Sci, 105(8), 2255-9.DOI: http://dx.doi.org/10.1016/j.xphs.2016.05.029
Hyaluronic acid. (2016, May 7). In Wikipedia, The Free Encyclopedia. Retrieved 22:10, May 17, 2016, from https://en.wikipedia.org/w/index.php?title=Hyaluronic_acid&oldid=719117852

Increasing the SC Dosing Volume

Permeation enhancer Hyaluronidase (Enhancer)

Therapeutic protein	Trade name	Disease	Injection volume
Trastuzumab	HerceptinSC®	Oncology	5 mL
Rituximab	MabtheraSC®	Oncology	11.7 mL
Immune Globulin 10%	Hyqvia®	Primary immuno-deficiency	100 mL



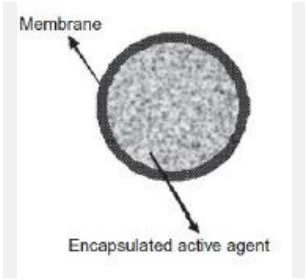
- **Functionality of hyaluronan (hyaluronic acid)**
  - Controls the hydrolytic conductivity
  - Impacts spreading of a SC injected fluid in the ECM
  - Enzymatic hyaluronan cleavage is reversible within 1-2 days
- **Cleavage of hyaluronan by hyaluronidase leads to**
  - Reduction of tissue back-pressure
  - Enables fast administration

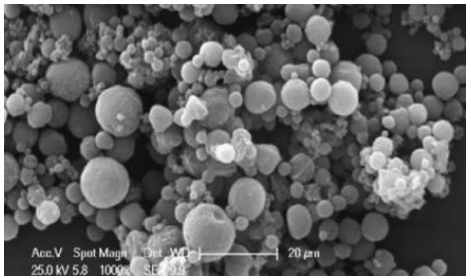
Hyaluronic acid. (2016, May 7). In Wikipedia, The Free Encyclopedia. Retrieved 22:10, May 17, 2016, from https://en.wikipedia.org/w/index.php?title=Hyaluronic_acid&oldid=719117852

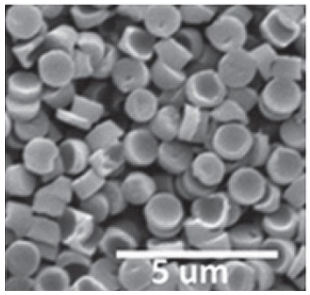
What's next for IVT Administration

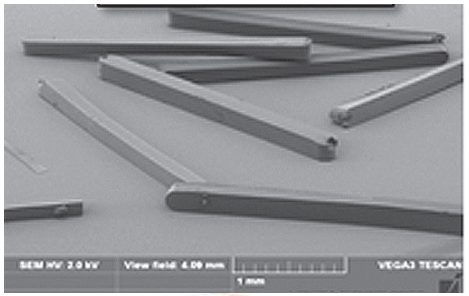
Ocular long-acting drug delivery

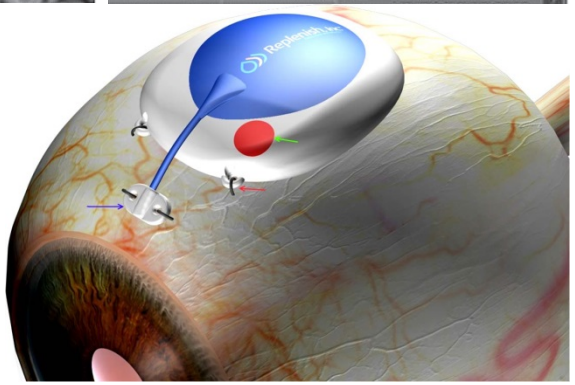
- **Drug Delivery approaches**
  - Hydrogels / in-situ gelling systems
  - Liposomes, nanoparticulates, microparticulates [1)]
  - Biodegradable implants (injectable) [2)]
  - Implanted reservoirs or pumps (surgery) [3)]
- **Factors to consider:**
  - High drug loading/ low burst release/ long release
  - Injectability with small Gauge needle
  - Particle movement / vitreous clouding
  - Ocular immune system tolerance
- **The alternative: molecular approaches**
  - Combination therapies
  - Conjugation to polymer/ fusion to carrier proteins











1) Jamekhorshid et al. (2014), Renewable & Sustainable Energy Reviews, 31: 531-42
2) Navratil et al., On Drug Delivery: Ophthalmic Drug Delivery, 48, 2014; and DSM biopolymer
3) Gutiérrez-Hernández, J.-C. et al.. (2014). Translational Vision Science & Technology, 3(4), 8. http://doi.org/10.1167/tvst.3.3.8

Summary

- **Increased need for high concentration formulations remains for SC and IVT administration**
- **Viscous high concentration protein formulations pose (expected) challenges involving**
  - DP stability
  - DP-CCS compatibility and functionality
  - DP administration.
- **An integrated Drug-device combination product development approach is recommended.**
- **High concentration formulations may not be the only solution.**
  - Increasing the max. SC injection volume
  - Ocular long acting drug delivery approaches

Acknowledgements