Polymer Syringes

Material, Properties, Processing and Quality

Bernd Zeiß, Gerresheimer, Manager Technical Support Medical Systems

Presentation Overview

1. Gerresheimer
2. Glass/COP/COC/Polypropylene
3. Manufacturers
4. Broad data base on COP
5. COP made glass syringes better
6. Some new data on properties
7. Processing/Quality
8. Questions

Glass - borosilicate glass (type I glass acc. to Pharmacopeia)

Manufactueres of tubes (slightly different glass compositions)

- Schott
- Nipro
- Corning
- Nippon Electric Glass

Glass container manufactueres converting tubes (for syringes, vials, cartridges, ampoules)

- Gerresheimer
- Nouva Ompi
- Schott
- Nipro
- Becton Dickinson
- Some more companies
- producing vials, ampoules, cartridges

Polymers: COP, COC, PP

Manufacturers of approriate polymer resins

- COP: Zeonex (Zeon), Arton (JSR)
- COC: Topas (TAP), APEL (Mitsui)
- PP – suited only for certain diluents like WFI, emergency medication - many manufacturers active – not core PFS market

Molding polymer into syringes or other containers

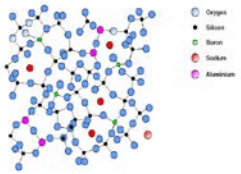
- Gerresheimer, Taisei Kako (COP)
- Schott (COC)
- West, Daikyo (COP: CZ)
- BD (COP: CCP)
- Terumo (COP)
- SiO2
- and some more companies working on customized containers/specialties

Comparison of Barrel Materials

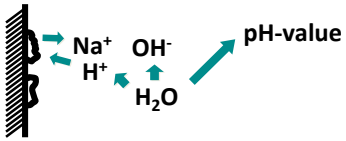
Glass Type 1 – borosilicate glass:

- Composition example*

- SiO_2 73,0%
- $B2O_3$ 11,2%
- $Al2O_3$ 6,8%
- Na_2O 6,8%
- K_2O 1,2%
- CaO 1,0%



- pH shift*:

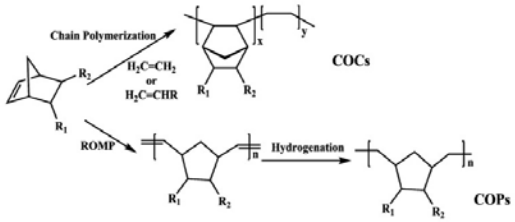


- Delamination esp. in vials
- Breakage risk
- Gas tight
- Very well analysed and well suited for long-term storage

Source: Gerresheimer

COP and COC

- Chemical structure**:



- Glass like transparency
- No pH shift
- No delamination
- Not fully gas tight
- Suited for long term storage of drugs

**Source: Jin Cui et al.

Polypropylene

(not *core* PFS market)

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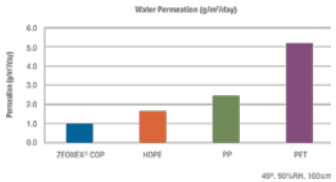
- Mainly for flush PFS and emergency applications
- Not fully transparent (visual inspection impossible)
- Gas and water vapour transmission comparatively high



Source: Zeon

Glass-COP-COC Properties

Properties	Glass	COP	COC	PP	PE	PP	PA	PET
Break resistance	-	+	+	+	+	+	++	++
O2-barrier	++	O	O	-	-	-	+	-
CO2-barrier	++	O	O	-	-	-	+	-
Water vapour barrier	++	+	+	++	O	++	O	+
Chemical resistance	+	+	+	+	+	+	O	+
pH-resistance	-	++	++	+	+	+	O	++
Extractables	+	++	++	+	+	+	+	O
Transparency	++	++	++	O	-	O	++	++
Steam sterilizable	++	+	+	+	-	+	+	-
Sterilisable by X-ray	-	+	+	+	+	+	+	O
Sterilisable by heat	++	-	-	-	-	-	-	-

Souce: Taisei Kako

Comparison of Test Results Plastic

Properties	Measurement methods	Unit	COP	COC	PP	PC	Test
Specific gravity	ASTM D792	-	**1.01**	**1.02**	0.90	1.2	**Weight**
Water absorption	ASTM D570	%	**<0.01**	**<0.01**	<0.01	0.15	**Moisture-proof**
Water vapor transmission	JIS K7129	$g/m^2 \cdot 24hr$	**0.31**	**0.35**	0.56	14.5	**Moisture-proof**
Light transmittance	ASTM D1003	%	**92**	**92**	-	89	**Transparency**
Glass transition temperature	DSC	℃	**136**	**140**	-10	145	**Heat-resistance**
Tensile strength	ASTM D790	MPa	**62**	**66**	31-41	63	**Damage, cracking**
Tensile breaking strain	ASTM D638	%	**100**	**4**	100-600	90	**Damage, cracking**
Flexural strength	ASTM D638	MPa	**91**	**74**	39	92	**Damage, cracking**
Dupont impact strength	ASTM D256	J	**23**	**0.2**	1.6	33	**Damage, cracking**

Souce: Taisei Kako

COP and COC are well-studied

broad data base from manufacturers gives security

Comprehensive investigations

- Materials
- Sterilization (γ, E-beam, steam, EtO)
- Colour change (γ, E-beam)
- Leachables & Extractables
- Protein adsorption
- Break loose and gliding forces
- Gas permeation
- Particles (SVP)
- Auto-injector use
- CCI testing
- Labeling
- Adhesives migration
- Long-term experience

Under investigation

- Barrier coatings
- Lubricant coatings
- Barrier layers / scavengers

Advantages COP/COC

- Break resistant
- Glue free
- Silicone free possible
- Tungsten free
- No delamination risk
- No pH-shift, no ion-release
- Tight tolerances
- High moisture barrier
- Protein adsorption low
- Freedom of design/customization

Challenges

- Dedicated stoppers needed (silicone free)
- Scratch sensitive
- Oxygen barrier worse than glass
- Line adaptions necessary
- Not cheaper than glass

Regulations

- DMF Type III
- Major chapters of ISO 10993 “Biocompatibility” fulfilled
- USP 661.1 Approvals
- EP , USP, JP Pharmacopoeia approvals
- Chapter 3.1.16 in EP (draft under evaluation at EDQM)
- ISO 11040-6 Prefilled syringes - Part 6: Plastic barrels for injectables

Material Competition - COP Syringes Made Glass Syringes Better

Breakage risk

Addressed by Glass industry

Break resistance improved:

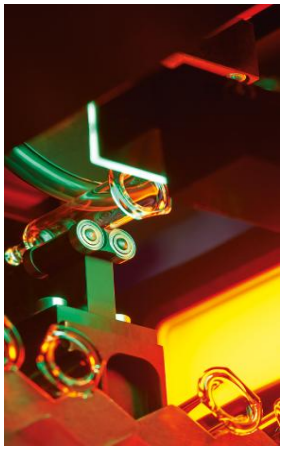
- New production lines
  - No glass to glass contact
  - High end camera inspection (crack prevention)
- Adjusted designs
  - small round finger flange for auto-injector use
  - cone breakage improvement
- New glass types

Wide tolerances

Addressed by Glass industry

Tighter tolerances achieved:

- Improved production technology
- High end camera inspection

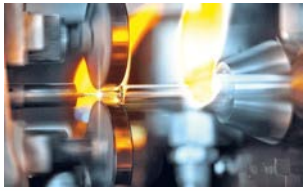


Tungsten issue

Addressed by Glass industry

Many approaches to solve tungsten problem:

- Lower, specified tungsten levels possible (<<500 ng/sy)
  - Improvements in production
  - Washing
- Tungsten free production with alloy pins
- Metal free syringes available using ceramic pins



Lubricant free system

Under investigation

- Silicone reduced syringes are available, e.g. baked-on siliconized RTF syringes (90% particle reduction)
- Silicone free glass syringes are possible:

Dedicated rubber stoppers needed: Gore, Sumitomo, Injecto *Lubrigone*, Taisei Kako *ClearX*

- Alternative lubricants (e.g. PFPE, Octamethylcyclotetrasiloxane) in test phase - new material added

Barrier Properties and Migration of Molecules through COP

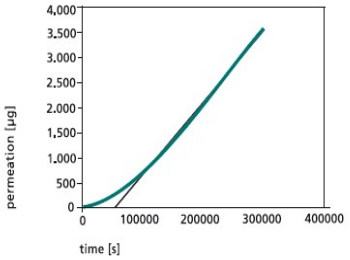
Migration depends on

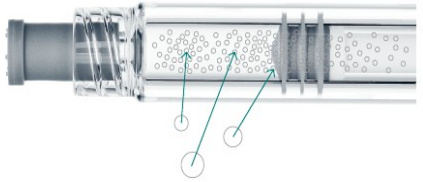
- Barrel material (COP)
- Barrel thickness
- Temperature
- Molecule weight (g/mol) or size (Å^3) of migrant

Lag time = delay effect of material on permeation

- Lag time for COP syringes can be calculated for *any* known molecule
- Migration into and out of container
- No migration of large molecules
- Can be calculated to save laboratory cost and -time

Exact lag time calculations can be carried out with a calculation tool – the lag time calculator

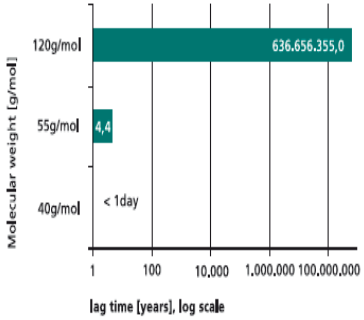




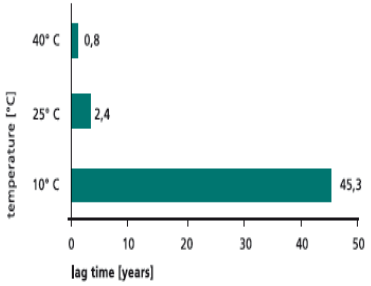
Lag time concept: 2 steps of permeation (migration):

1. Dynamic process: time lag is the difference between the time at which the migrant enters the barrier and time at which a steady state is reached
2. Steady state of permeation (migration)

Lag time dependant on molecular weight at 25°C, barrel thickness 1,8 mm



Lag time dependant on temperature, exemplary molecule 53.5 g/mol, barrel thickness 1.8 mm



Protein Adsorption and Aggregation in COP and Glass Syringes

Adsorption and particle generation (SVP) dependant on many parameters such as

- Protein structure
- Ionic strength
- Buffer, excipients, salts
- pH, surfactants
- Measuring method
- Siliconization of barrel and plunger stopper
- Sterilization of syringe
- Storage time
- Temperature

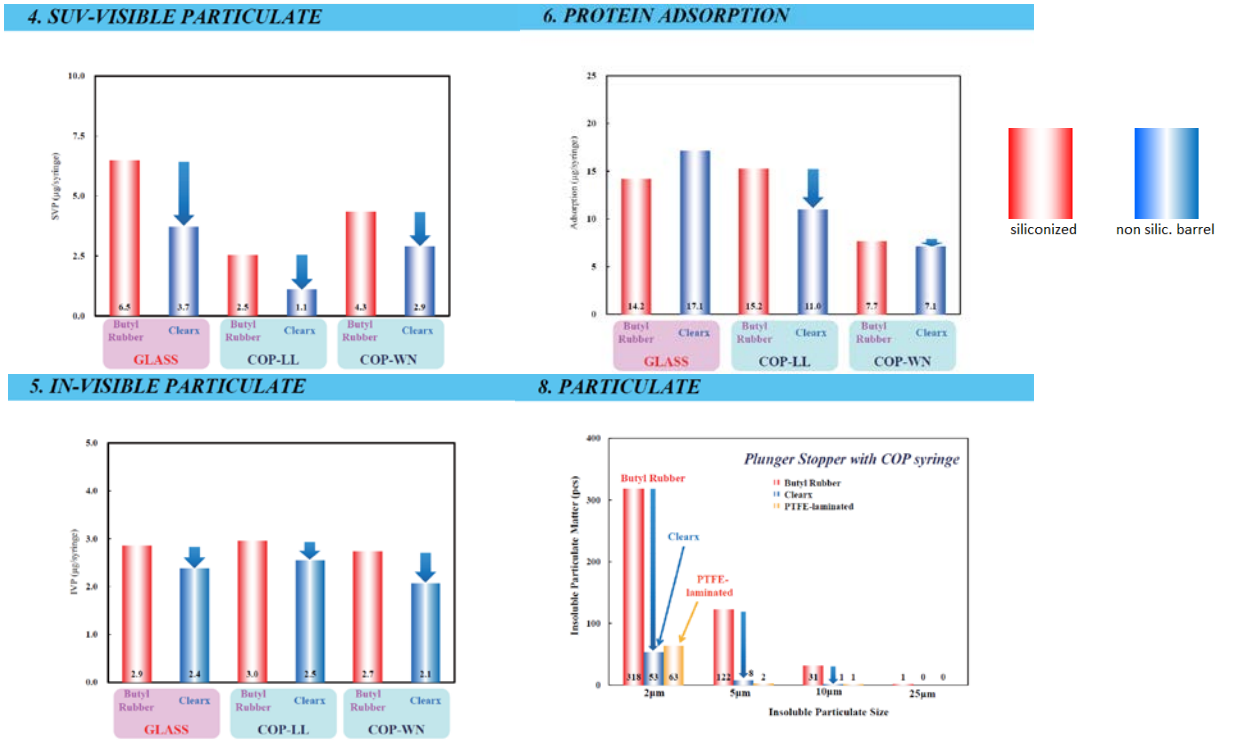
✓ Best syringe needs to be found by testing each individual formulation in stability studies

✓ COP is a good barrel material often better than glass

✓ Less SVP in silicone free syringes

✓ Siliconized syringes with higher protein adsorption, except:

Non-siliconized glass with higher adsorption



Aggregation (SVP, IVP) and **adsorption** of IgG (1mg/mL in PBS pH7) on COP and Glass in differently treated syringes.
Non siliconized, siliconized, with butyl-stopper vs. ClearX (lubricant free system)
Particulates in COP syringes
Taisei Kako, own data, PDA PFS 2017 (Poster)

Further investigations

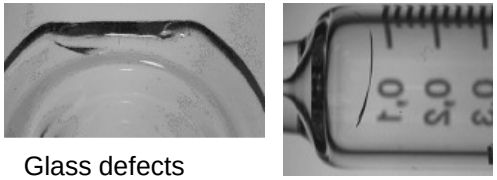
- Taisei Kako PDA PFS Poster 2017
- Zeon
- Terumo
- Prof. Winter, B. Werner (LMU Munich)
- Prof. Uchiyama (Osaka University)

Processing and Quality

Generally all existing filling lines can be used to process COP syringes

Some special requirements are

- Single transport for scratch prevention
- Soft transport chucks
- Touch syringe outside the main barrel body - gripping the luer lock or finger flange
- “Pick and place” preferred to passive transport
- Slower transport speed compared to glass syringe filling
- Antistatic prevention to avoid attraction of charged dirt particles
- Avoid contact of metal parts (filling needles, pipes, grippers)
- Feeders for silicone free plunger stoppers need to be adapted
- Adapt visual inspection (“a scratch is not a crack”)
- Terminal sterilization possible
    - Adapt benign autoclaving to avoid tip cap pop off and side effects on barrel (whitening of barrel)
    - Adapt lowest as possible gamma sterilization to avoid colour change



Glass defects

Acknowledgements

COP/COC studies - References

Presentations and Posters sourced from for this presentation

- Sterilization (γ, E-beam, steam, EtO): Zeon PDA Poster Oct. 15, Terumo SMI Jan 17; Taisei Kako PDA Oct 15
- Leachables & Extractables: Terumo Poster PDA Oct. 15; Zeon Poster PDA Oct 15
- Protein adsorption- Taisei Kako PDA Nov.17; Zeon SMI Jan 17, Topas, Zeon
- Break loose and gliding forces -Taisei Kako PDA Oct 15
- Gas permeation - Taisei Kako, Zeon
- Permeability – Terumo/Toxicon: PDA Mar. 15
- Particles – Terumo: Journal of Pharmaceutical Sciences 106 (2017)
- Auto-injector use: Terumo, Ypsomed PDA May 14
- Labeling: Gerresheimer, UBM Raflatac PDA Mar 15
- Adhesives migration - Gerresheimer, Schreiner Medical Poster PDA Oct 2015

Resin manufacturers

https://www.zeonex.com/pharmaceuticals.aspx.html#techdata

http://www.topas.com/markets/healthcare/perfect-parenteral-packaging

COP/COC syringe manufactureres

https://www.gerresheimer.com/en/products/pharmaceutical-primary-packaging/syringes-made-of-plastics.html

http://www.taisei-g.co.jp/english/equipment/index.html

http://www.schott.com/pharmaceutical_packaging/german/products/syringes/polymer_syringes.html

http://www.terumo-europe.com/en-emea/pharmaceutical-solutions/syringes/pre-fillable-syringe-systems-cop

https://www.westpharma.com/products/prefillable-systems/daikyo-syringe-systems

http://drugdeliverysystems.bd.com/pharmaceutical-products/pre-fillable-syringe-systems/acute-care-and-specialty-syringes/sterifill-advance-polymer-pre-fillable-syringe

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