SUITABILITY OF ELASTOMERIC PUMPS FOR DRUG STORAGE

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Background and objectives

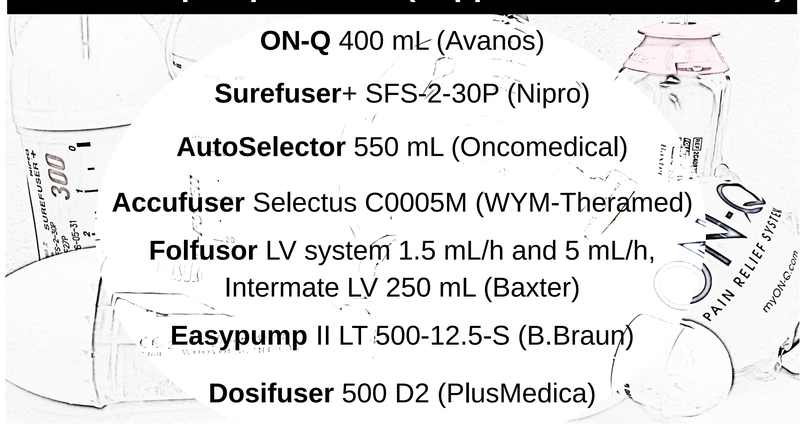
Elastomeric pumps (EPs):

- autonomous application system in outpatient settings (e.g. oncology, infectiology)
- continuous intravenous drug administration
- no electronic pumps needed
- stability data for > 130 active pharmaceutical ingredients for up to 60 days promote storage
- **lack of data about leachables from various polymers and plastic additives**

Examination of storage of hydrophilic solutions in elastomeric pumps over 180 days.

Materials and methods

Examined pump devices (supplier / manufacturer)



Device were filled with ad hoc produced NaCl 0.9% (avoid leaching from plastic materials, simulate hydrophilic solutions).

Measurements (days 1, 7, 28, 90 and 180):

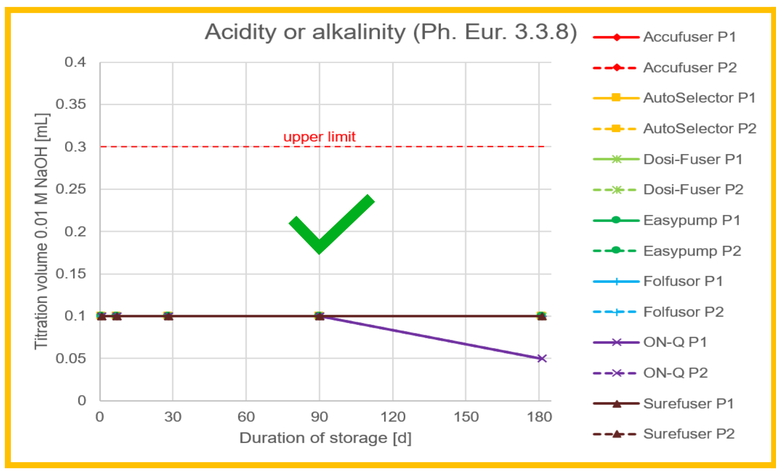
1. **According to European Pharmacopoeia (Ph. Eur.) 3.3.8*** "Sterile single-use plastic syringes" [1,2]
   - **Absorption**
   - **Acidity or alkalinity**
   - **Reducing Substances**

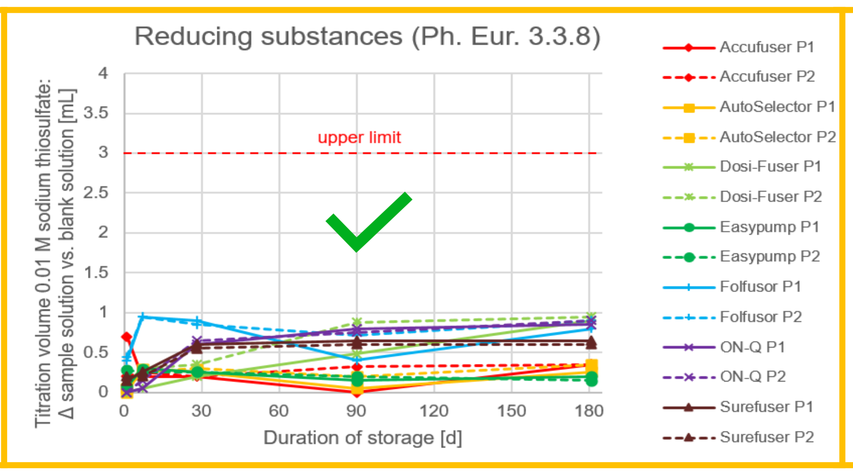
   *Ph. Eur. 3.2.2.1 "Plastic container for aqueous solutions for infusion" requires autoclaving – not possible with EPs [1,2].

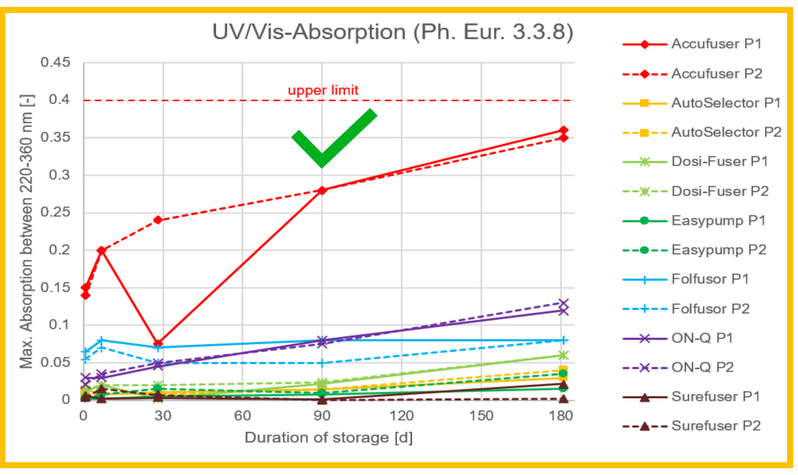
2. **Water vapor permeability -** quantifying weight loss over time

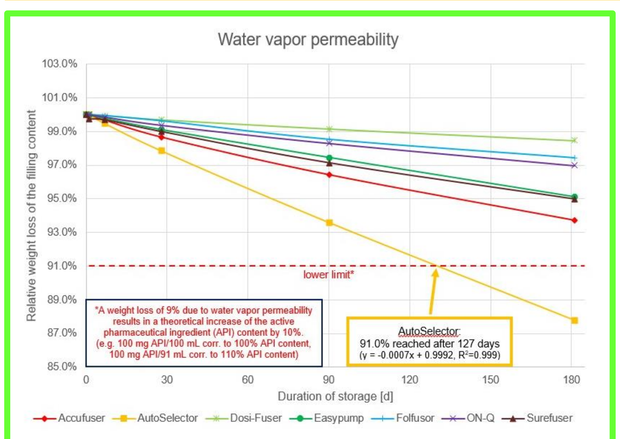
3. **HPLC-MS – identifying leachables** from plastic additives **and recording semi-quantitatively** [3]

Results









Limit value: 9.0%

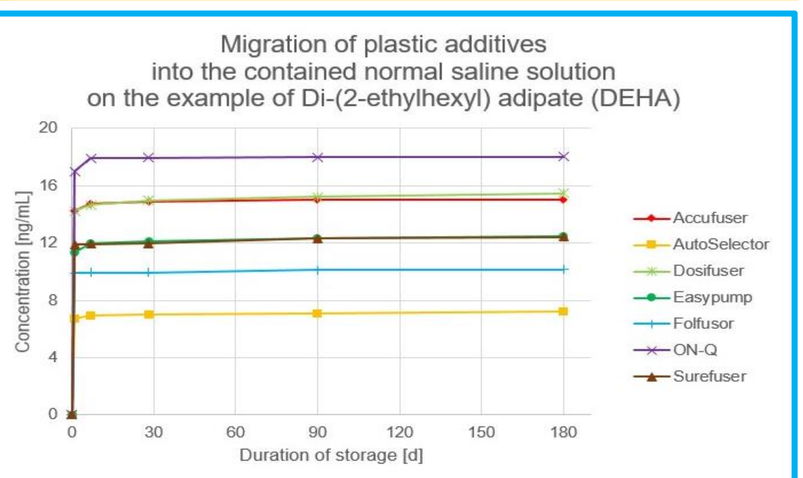
- ✓ **At day 90**
- ✓ **Six of seven EPs at day 180**
- X **AutoSelector out of limit at day 127**

Additive group	Plastic additive (acronym)	Structural formula CAS No	Influence on human health [4]	Detected plastic additives in the contained normal saline solution of the different elastomeric pumps						
				Accufuser	AutoSelector	Dosifuser	Easypump	Folfusor	ON-Q	Surefuser
Antioxidant	2,4-di-tert-butylphenol (2,4-DTBP)	96-76-4	in evaluation	✓	✓	✓	✓	✓	✓	✓
	2,6-di-tert-butyl-p-cresol (BHT = Butylhydroxytoluol)	128-37-0	none	✓	✓	✓	✓	✓	✓	✓
	3,5-di-tert-butyl-4-hydroxybenzoic acid (BHT-COOH)	1421-49-4	not evaluated					✓	✓	✓
	3,5-di-tert-butyl-4-hydroxybenzaldehyde (BHT-CHO)	1620-98-0	not evaluated	✓	✓					
	3-(3,5-di-tert-butyl-4-hydroxyphenyl) propanoic acid (none)	20170-32-5	not evaluated			✓	✓			
Plasticizer	Di-(2-ethylhexyl) adipate (DEHA)	103-23-1	reproductive toxicity 1B or 2 in evaluation	✓	✓	✓	✓	✓	✓	✓
	Triphenyl Phosphate (TPP)	115-86-6	potential endocrine disruptor in evaluation		✓	✓				

Legend: ✓ found; not found

From the database of 200 plastic additives were detected:

- ! **7 different leachables (5 antioxidants, 2 plasticizers)**
- ! **2,4-DTBP, BHT and DEHA from each EP**



- ! Example DEHA: > 90% migration within first 24 hours
- ! **Overall migration in hydrophilic solutions:**
  - **Day 0-1: most migration** (43-97%, **median: 80%**)
  - **Day 1-180: minor migration**

Conclusions

✓ **No transfer of impurities in unacceptable quantities for the period of 180 days** [1,2]

! **Continuous evaporation**

- X **Limits the storage time** (increasing concentration of ingredients)
- X **Promotes precipitation of ingredients** (solubility limit)

! **Migration** of antioxidants and plasticizers **from every EP**

! Not validated HPLC-MS method → **only identification & semi-quantitative detection** (comparison of dimension (ng/mL)) **with**

- **estimated NOAEL** (No Observed Adverse Effect Level) **and**
- **PDE** (Permitted Daily Exposure) limits of the individual plastic additives [3]

! 2,4-DTBP, BHT derivatives, DEHA and TPP: **incomplete data on the toxicology and long-term effects** → **unknown consequences of exposure [4].**

! **Recommendation for use** of the examined EPs:

Patient group	Duration of therapy	
	Days to weeks	Long-term
Adults	✓	✓
Pediatrics	! Prior: risk-benefit assessment*	X

*consideration of duration, application volume and body weight

Hydrophilic solutions can be stored for 127 days (AutoSelector) resp. 180 days (6 other EPs), if the removable volume of parenterals (Ph. Eur. 2.9.17) is observed.

Literature:

[1] European Pharmacopoeia. In: European Pharmacopoeia Commission, editor. European Pharmacopoeia. 11.0. European Directorate for the Quality of Medicines and HealthCare; 2022.

[2] Bracher, F., Heisig, P. & G. Schriba et al.: Kommentar zum Europäischen Arzneibuch - Band 2. In: Wissenschaftliche Verlagsgesellschaft mbH (Hrsg.), Allgemeiner Teil, Methoden 3-5, 72. Aktualisierungslieferung, Stuttgart, Deutschland: Govi-Verlag, 2023

[3] Bello W, Pezzatti J, Berger-Gryllakia M, Rudaz S, Sadeghipour S. J. Pharm. Biomed. Anal. 236 (2023) 115640

[4] https://echa.europa.eu/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table/ [cited: 04.09.2023]

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