



Packing materials

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Disclosure for Vagn Handlos

Nothing to disclose!

but:

- Assigned professor, Faculty of Pharmaceutical Sciences, Copenhagen University
- Member of the Danish Pharmacopoeia Commission
- Chairman of the European Pharmacopoeia expert group on plastic material
- Member of the EDQM working party of quality of pharmacy preparations
- DESR at the EAHP



EAHP Academy summit 2010



General comments on containers from the European Pharmacopoeia (Ph.Eur.) :

“ ..is an article that contains or is intended to contain a product and is, or may be, in direct contact with it.”

Protect the product and/or the environment keep the quality of the product.

The container does not interact physically or chemically with the content in a way that alter the quality beyond the limits tolerated...

Type sample: The container agreed between the producer and the user.



Materials to be dealt with in this presentation:

Glass

Plastic

(Rubber)

(Metals,

Ceramics,

Paper and

Lacquers is outside the scope)





Glass.

Glass is a physical state as liquid, gaseous

Glass is amorphous solid material

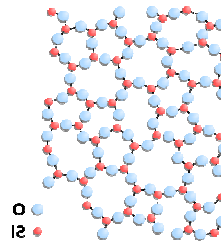
European Pharmacopoeia (Ph.Eur.) classification:

Neutral glass

Bo, Al and alkali oxides

Soda Lime silica glass

SiO₂ and Ca, Na oxides



Glass classification

Classified according to the hydrolytic resistance (HS)

Type I, Neutral glass with high HS, due to the composition of the material.

For general use

Type III, Soda lime silica glass with moderate HS

For solids and aqueous solution for non parenteral use

Type II, type III glass given a surface treatment to increase the hydrolytic resistance

For general use except for parenteral alkaline solutions

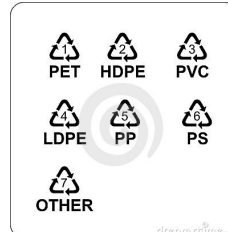
Test: Water autoclaved at 121°C for 60 min. Titration with 0.01 M HCl



Materials for plastic containers (Ph. Eur 3.1.)

Monographs of commonly used materials:

- Polyethylene
- Polypropylene
- Polyvinyl chloride
- Polyethylene terephthalate and Poly ethylene vinyl acetate
- All as homopolymers and copolymers or alloys
- Silicone oil and elastomers



General chapters in a plastic material monograph:

Definition

What's the material based on
pure polymer, mixed and additives

Production

Additives and residual monomer

Characters

Powder, beads, granules

Identification (IR)

Test

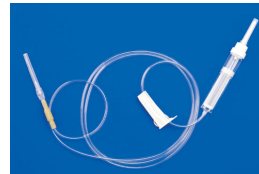
On water extract or organic solvent





Plastic "containers" in the Ph. Eur.

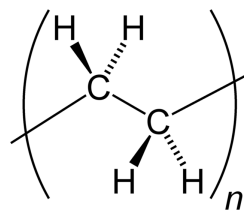
- Plastic containers for Aqueous sol. for infusion
- Sterile containers for Human blood and components
- Sterile containers of plasticised PVC for human blood
- Sets for transfusion
- Sterile single use plastic syringes
- Rubber closures



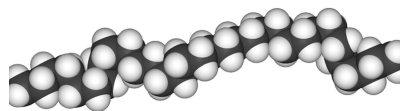
Polyethylene.

Homopolymer of ethylene
and copolymer of alkenes up
to C₁₀.

Thermoplastic material
Thermoset



Chain structure: linear and
branched





Polyethylene

1. Old ICI process.

Polymerization free radical chain process

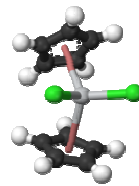
High pressure and oxygen as catalyst

2. New process

Low pressure,

metallocene, Ziegler-Natan catalyst

(look for Al, Cr, Va, Zr and Ti)



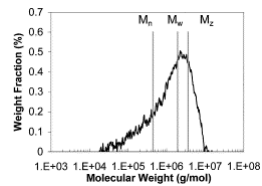
Polyethylene.

Molecular weight:

From wax to hip joints

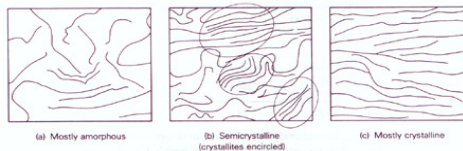
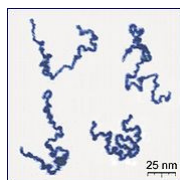
and skies.

Hexane test in Ph.Eur.



Crystallinity:

Densities from: 0,9 – 1.0 g/cm³





Polyethylene

Interactions

No solvents at room temperature (low interaction) also low interaction with drugs.

Additives:

Antioxidants, fatty acids <1%
Ca stearate, ZnO



Temperature resistance:

From < 90°C to 122°C
Increase with density

Sterilization

(Steam), Gas (EO) and Radiation

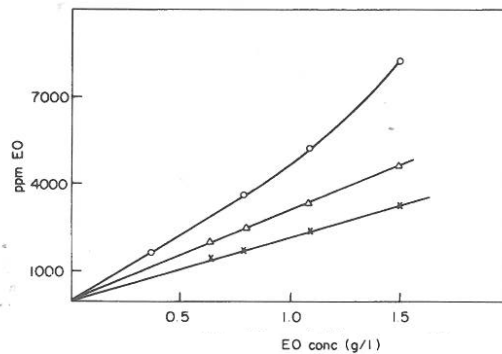


Figure 7 Solubility of EO in LD-PE, ○; MD-PE, △; HD-PE, ×; at 40°C

Data from Handlos 1980

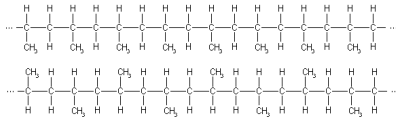


Polypropylene

Monomer



Polymer stereospecific
Isotactic, syndiotactic



Thermal properties
Crystal melting point 165°C, glass
transition temperature 4°C



European association
of hospital pharmacists



Polypropylene

Additives, crystallinity and other information, as
polyethylene

Polymer blends

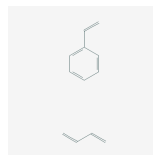
Kraton (SBS copolymer)

Thermoplastic elastomer

S – Styrene B- Butadiene

-S-S-S-S-S-B-B-B-B-S-S-S-

Increase flexibility and transparency of PP



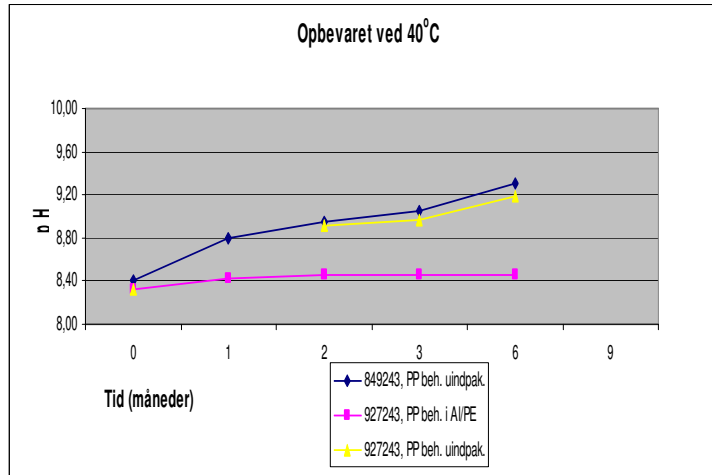
European association
of hospital pharmacists

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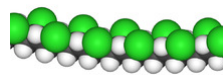
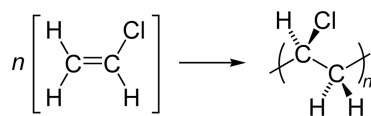


Polypropylene Permeability of CO₂

Bicarbonate Infusion Liq. 84g/l stability data Handlöf



Polyvinyl chloride



Polymerisation process: Suspension in water

Monomer content < 1ppm

Additives

Plasticizers < 40% DEHP

Stabilizer Zn and Ca salts of fatty acids

Epoxydised oils

Ultramarine blue (color)



Polyvinyl chloride

Strong interactions with many chemical: Solvents

Acetone, cyclohexanone, DMF, DMSO ..(cyclophosphamide)

Non solvents,

Aliphatic and aromatic hydrocarbons (VC) alcohols

Interactions with solubilised hydrophobic drugs and biological drug

Resist

Steam sterilisation at 121°C

Etylene oxide and (radiation sterilisation)



DEHP migration from PVC to blood,

Gerlai et al, Chromatographia vol 24, 403-6

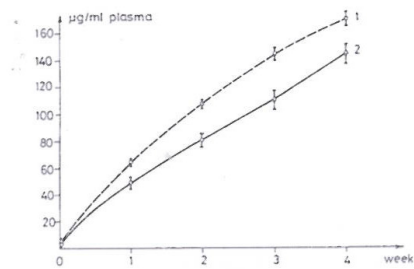


Fig. 4

Correlation between DEHP level (\pm SD) in whole blood plasma and time. Blood was stored at 4°C for 4 weeks in Maco-Pharma PSV 3202 (1) and Draka PSV 3250 (2) bags.



Permeation of Cyclophosphamide through infusion bags.

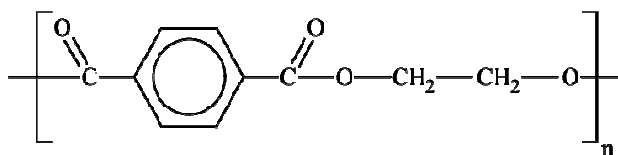
Exposure, hours	Amount of CP on surface of PVC	Amount of CP on surface of Laminate			
1	<0,05 ng/cm ²	1,2 ng/cm ²			
44	<0,02 ng/cm ²	<0,15 ng/cm ²			
217	6,4 ng/cm ²	0,33 ng/cm ²			

250 ml bags Isotonic NaCl solution added 1 g Cyclophosphamide, each result average of 3 samples

Data from Handlos not published



Polyethylene terephthalate



n from 100-200

Polycondensate (polyester) of terephthalic acid and ethylene glycol

Not for parenteral use

Additive Silica <0.5%

Residual acetaldehyde <10 ppm

Migration to water, alcohol and 0,01 M HCl and NaOH

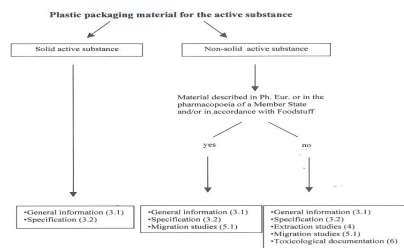
Test for heavy metals



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GUIDELINE ON PLASTIC IMMEDIATE PACKAGING MATERIALS

8 APPENDIX E: DECISION TREE ON THE PRESENTATION OF THE DOCUMENTATION



Summaries:

- Define your container “Type sample”
- Use a material covered by Ph.Eur.
- Be sure to use a “Type sample” for your stability testing
- If no monograph on the container is available in the Ph. Eur, instigate a test protocol relevant to your product.
- Have a contract with your supplier of container to ensure the uniform quality of delivered product from batch-to-SHS2/2102843 batch.
- Carry out conformity test by every new bath received. Have to conform with the test of the type sample