PDA Training Course Extractables & Leachables

20 April 2023

THE MECHANISM OF POLYMER MIGRATION - *A DESCRIPTIVE APPROACH*

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OVERVIEW

1. Fabes model – a descriptive approach
2. Factors affecting leaching
   - Solubility of a leachable in a polymer
   - Diffusion of a leachable in a polymer
3. Application specific effect
   - Supersaturation
   - Outgassing
   - Blooming

OVERVIEW

1. **Fabes model – a descriptive approach**
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1. FABES MODEL – A DESCRIPTIVE APPROACH

Migration of leachables from polymers into a liquid can be described by the **FABES MODEL**:

$$\frac{m_{F(t)}}{A} = 0.1\, c_{p,0}\, \rho_p\, d_p \left(\frac{\propto}{\propto +1}\right)\left[1 - \sum_{n=1}^{\infty} \frac{2 \propto (1+\propto)}{1+\propto +\propto^2 q_n{}^2}\, exp\left(-D_p\, t \frac{q_n{}^2}{dp^2}\right)\right]$$

→ **Very complex model: more qualitative discussion of factors in next slides**

OVERVIEW

1. Fabes model – a descriptive approach
2. **Factors affecting leaching**
   - Solubility of a leachable in a polymer
   - Diffusion of a leachable through the polymer
3. Application specific effect
   - Supersaturation
   - Outgassing
   - Blooming

2. FACTORS AFFECTING LEACHING

Leaching will depend upon:

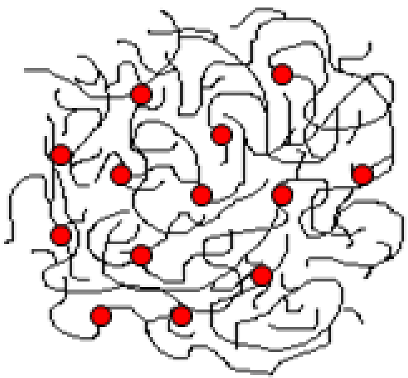
SOLUBILITY of a leachable **IN** the polymer

DIFFUSION of a leachable **THROUGH** the polymer

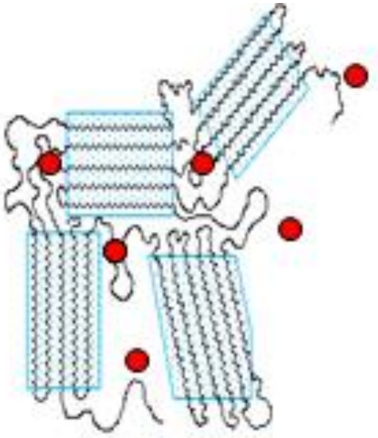
2.1 SOLUBILITY OF A LEACHABLE IN A POLYMER

1. Polymer morphology

AMORPHOUS



SEMI-CRYSTALLINE



Polymer additive/impurity
- Dissolves in amorphous phase
- Insoluble in crystalline phase

PC, PVC, PS, PU

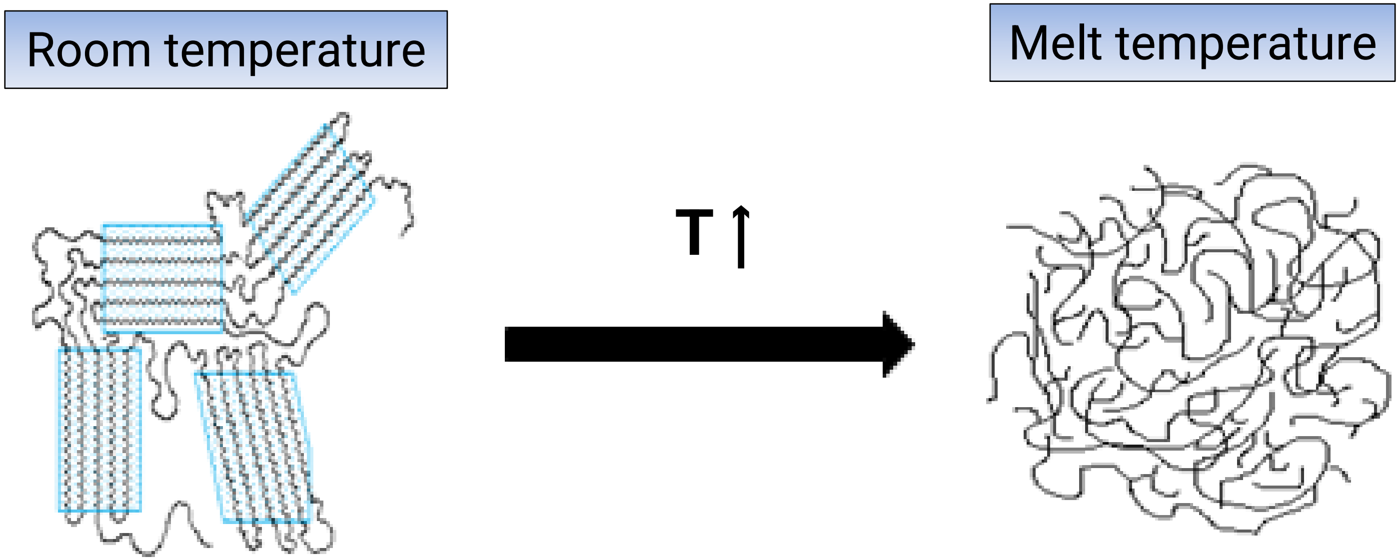
CRYSTALLINE SITES: BARRIER FOR MIGRATION

PE, PP, PET, EVA, PEEK, PA

2.1 SOLUBILITY OF A LEACHABLE IN A POLYMER

2. Temperature

As temperature increases, solubility increases



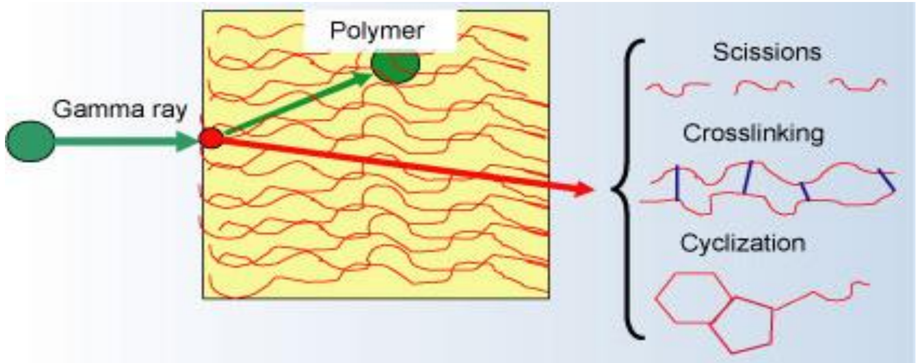
RESULT: **BETTER SOLUBILITY** at higher T

LESS "CRYSTAL BARRIER" for migration

2.1 SOLUBILITY OF A LEACHABLE IN A POLYMER

3. Age / sterilization

- Polymer degradation
- Polymer additive degradation
- Changes in polymer crystalinnity



This will impact the: **LEACHABLES SOLUBILITY**
LEACHABLES MIGRATION

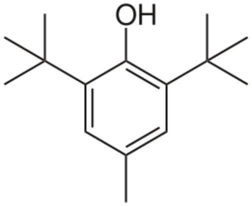
CONCLUSION:

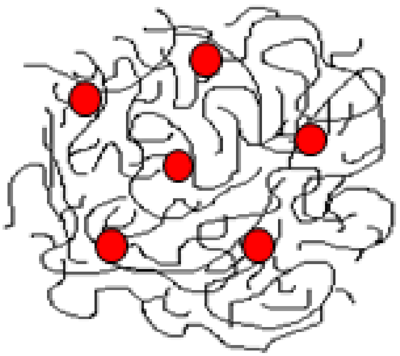
» **Perform E&L testing on final STERILIZED SYSTEMS**

2.1 SOLUBILITY OF A LEACHABLE IN A POLYMER

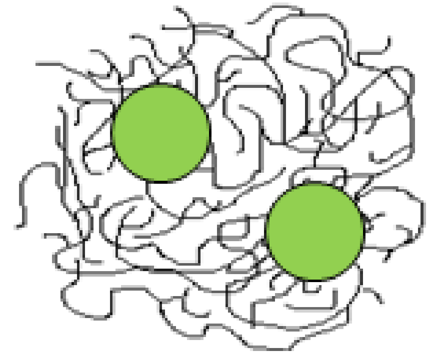
4. Structure and molecular weight of a leachable

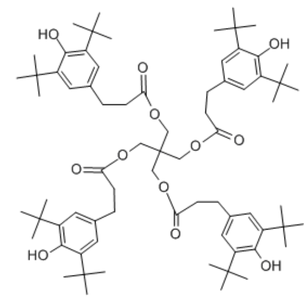
- Molecular weight → larger molecules = lower solubility





vs.





BHT (MW 220)

Irganox 1010 (MW 1176)

- Polarity “match” → structurally ALIKE
- Melting point → higher T_{melt} = lower solubility

  → impacted by molecular symmetry & crystallinity

2. FACTORS AFFECTING LEACHING

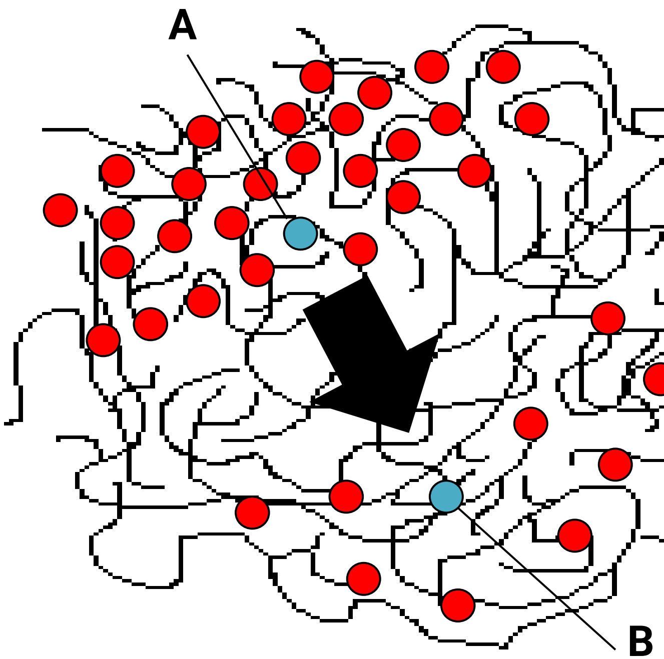
Leaching will depend upon:

SOLUBILITY of a leachable **IN** the polymer

DIFFUSION of a leachable **THROUGH** the polymer

2.2 DIFFUSION OF LEACHABLE TROUGH THE POLYMER

FICK'S 2nd LAW OF DIFFUSION:



$$\frac{dC}{dt} = D\,\frac{d^2C}{dx^2}$$

with C: concentration

t: time ($t_A \rightarrow t_B$)

x: distance ($x_A \rightarrow x_B$)

D: Diffusion coefficient

$D = D_0\,\exp(-E_A/RT)$

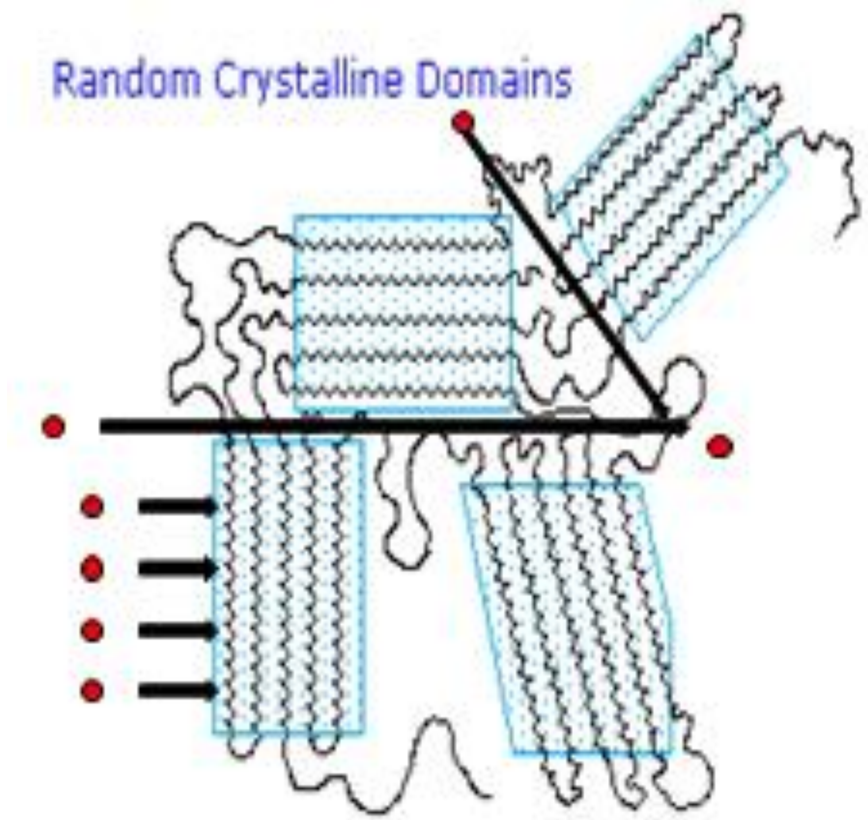
2.2 DIFFUSION OF LEACHABLE TROUGH THE POLYMER

1. Polymer morphology

- **Crystalline sites:**
  Impermeable barrier for polymer additives

- **Filler particles:**
  Diffusion barriers for polymer additives

- **Less diffusion in:**
  Semi-crystalline polymers



2.2 DIFFUSION OF LEACHABLE TROUGH THE POLYMER

2. Temperature

Remember:

$$D = D_0 \exp(-E_A/RT)$$

(E_A: activation energy, R: gas constant, T: temperature)

Therefore:

If T ↑, then D ↑

DIFFUSION of impurities/polymer additives will **increase exponentially** when **temperature increases**

2.2 DIFFUSION OF LEACHABLE TROUGH THE POLYMER

3. Polymer type

Glass TransitionTemperatur (T_g)

Polymer transitions from	**GLASSY**	($T < T_g$)
to	**RUBBERY**	($T > T_g$)

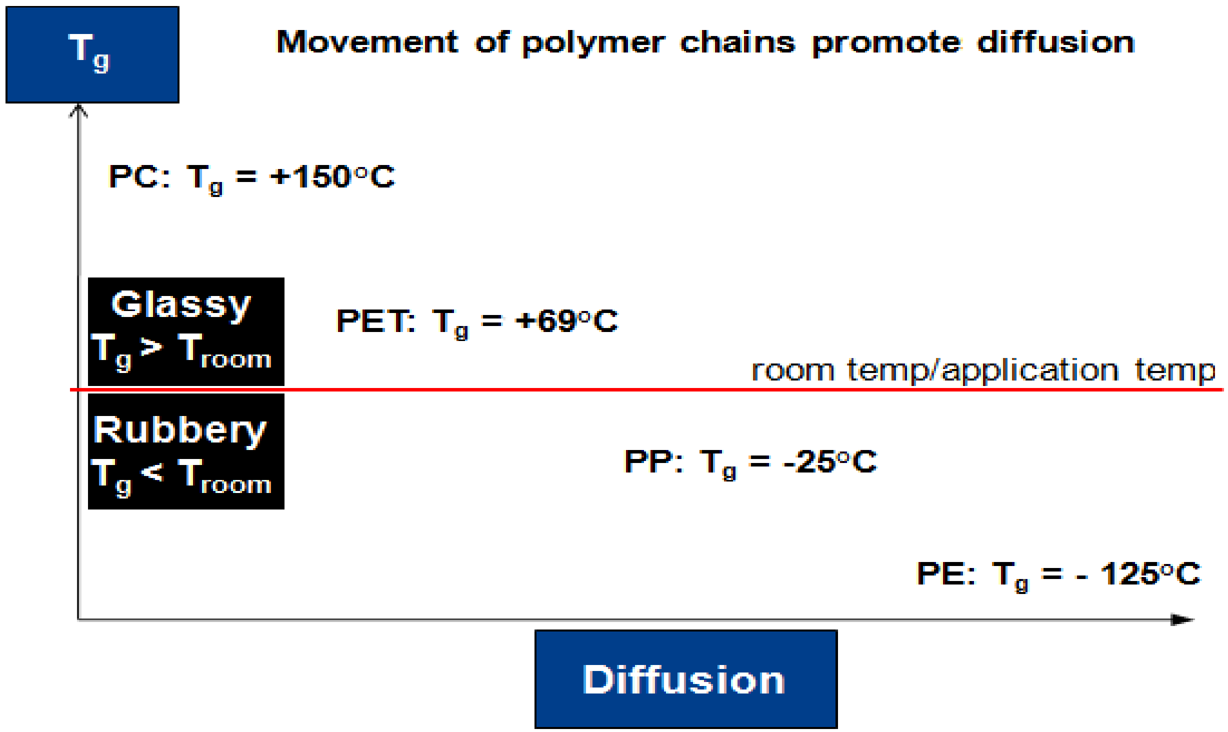
EXAMPLES

LDPE	T_g = -125 °C	PBT	T_g = 70 °C
POM	T_g = -50 °C	PVC	T_g = 81 °C
PP	T_g = -25 °C	ABS	T_g = 110 °C
		PC	T_g = 150 °C

2.2 DIFFUSION OF LEACHABLE TROUGH THE POLYMER

3. Polymer type

Lower T_g = higher potential for diffusion at room temperature



2.2 DIFFUSION OF LEACHABLE TROUGH THE POLYMER

3. Polymer type

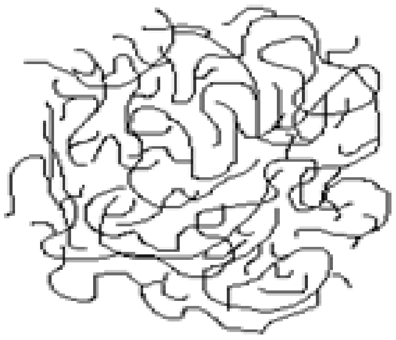
FREE VOLUME

Ratio of:

$$\frac{\text{Interstitial space (between polymer chains)}}{\text{Total volume of the polymer}}$$

Polymers in a **Rubber State** ($T_g < T$)
Typically have **HIGHER** free volume

More free volume promotes diffusion

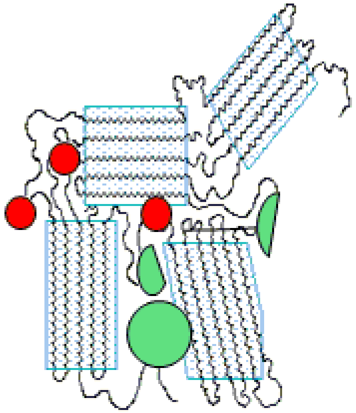


2.2 DIFFUSION OF LEACHABLE TROUGH THE POLYMER

4. Molecular weight of leachable

Diffusion increases with decrease in M.W.

- BHT (MW 220)
- Irganox 1010 (MW 1176)
- Irganox 1010 degradation compounds (MW 150-300)



2.2 DIFFUSION OF LEACHABLE TROUGH THE POLYMER

4. Molecular weight of leachable

Oligomeric additives → reducing diffusion

High diffusion

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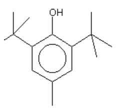
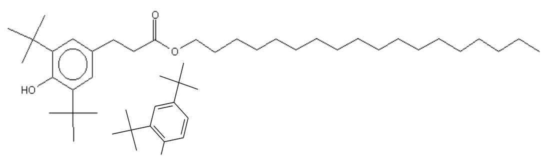
Low diffusion

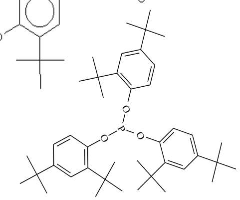
BHT: M.W. 220



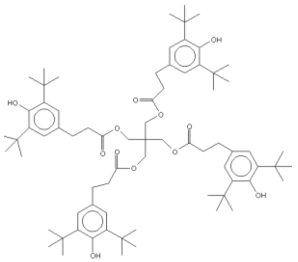
Irganox 1076: M.W. 530



Irgafos168: M.W. 646



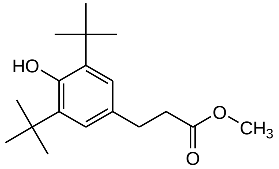
Irganox 1010: M.W. 1176



Polymer additive DEGRADATION into smaller molecules → FASTER DIFFUSION of degradants

Example: 3,5-Di-*tert*-butyl-4-hydroxyphenyl propionic acid methyl ester

(*Degradation product of Irganox 1010 /Irganox 1076*)

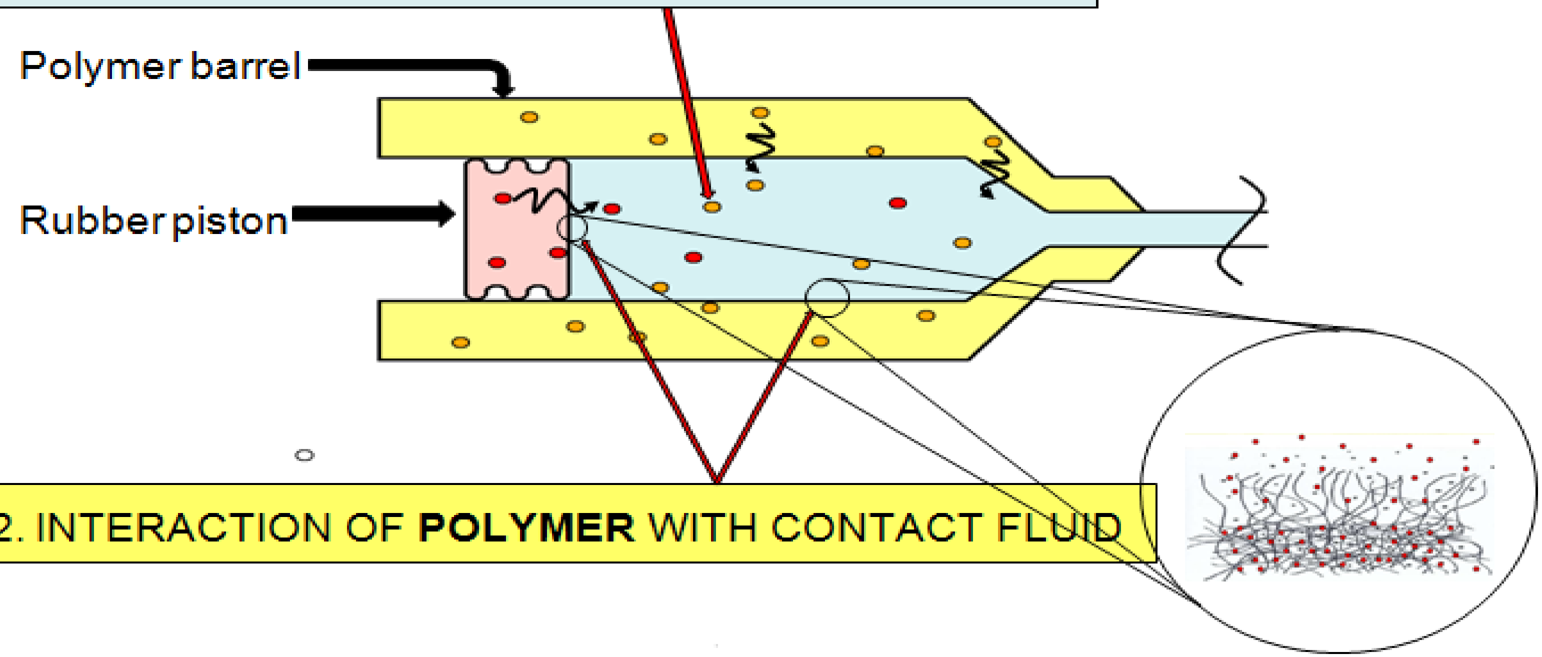


2.2 DIFFUSION OF LEACHABLE TROUGH THE POLYMER

5. Contact fluid / environment

Two Important aspects:

1. SOLUBILITY OF **LEACHABLE** IN CONTACT FLUID

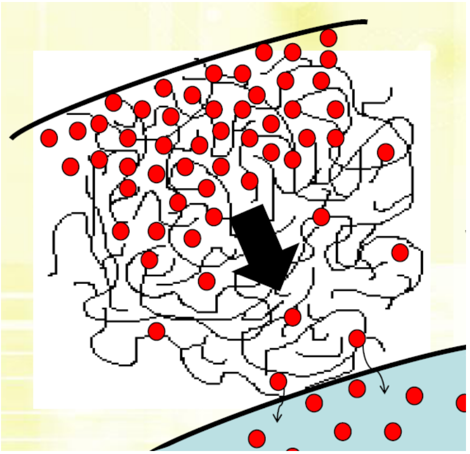


2. INTERACTION OF **POLYMER** WITH CONTACT FLUID

2.2 DIFFUSION OF LEACHABLE TROUGH THE POLYMER

5. Contact fluid / environment

1. Solubility of the leachable in the contact fluid



In general for most organic compounds:

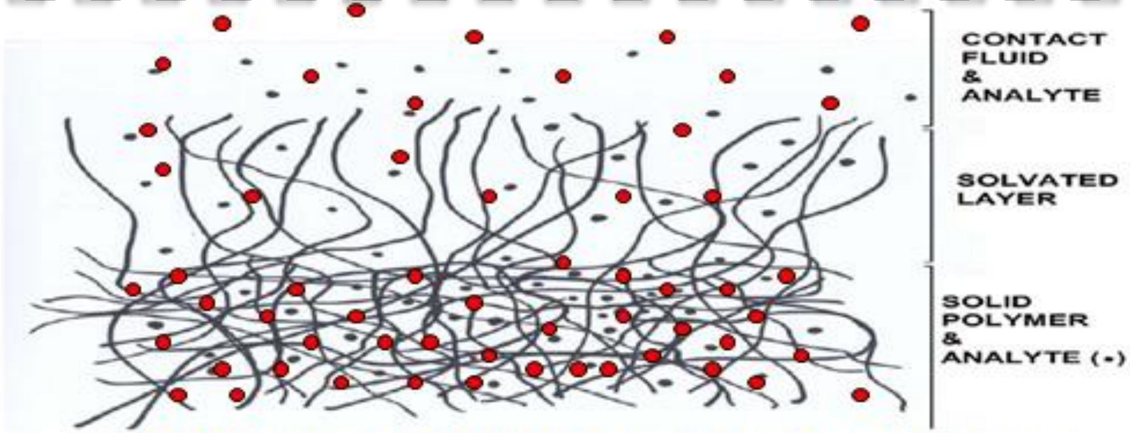
Organic / hydrophobic contact solutions = **HIGH SOLUBILITY** solvents
WFI/hydrophilic contact solutions = **LOW SOLUBILITY** solvents

2.2 DIFFUSION OF LEACHABLE TROUGH THE POLYMER

5. Contact fluid / environment

2. Interaction of the contact fluid with the polymer

SOLVENT CAN “PLASTICIZE” or “SWELL” POLYMER:
SOLVATED LAYER



ENHANCED DIFFUSION OF LEACHABLES

↓

ACCELERATED LOSS

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3. APPLICATION SPECIFIC EFFECTS

1. Super saturation

LIQUID FILM is formed via
- Evaporation during storage
- Transportation

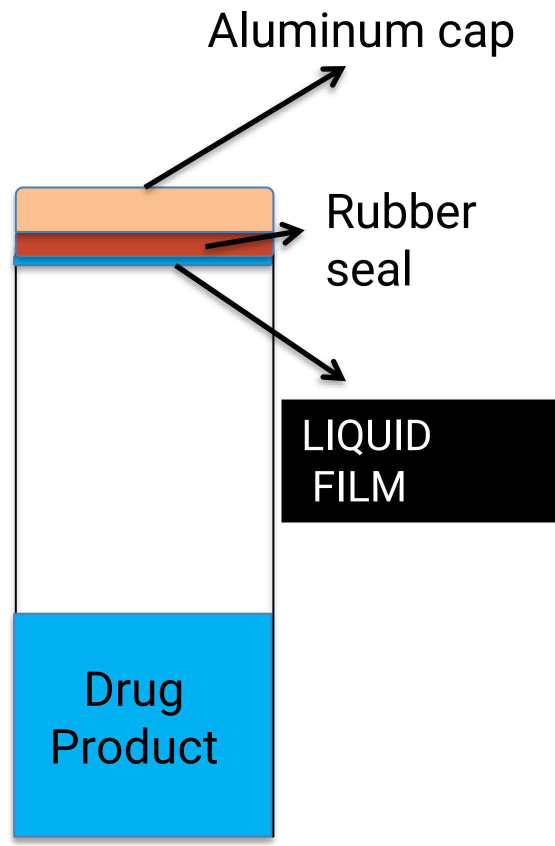
Film may be different in composition than the DP

Diffusion of rubber compounds into small volume
- Metals
- Organic

Can cause **aggregation, particle formation**

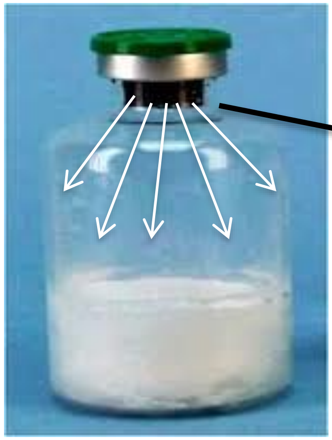
May be **irreversible**
- Particles do not dissolve anymore when in contact with the total DP volume

LIQUID FILM may also act as "**barrier**"
- for migration
- for outgassing (see next slide)



3. APPLICATION SPECIFIC EFFECTS

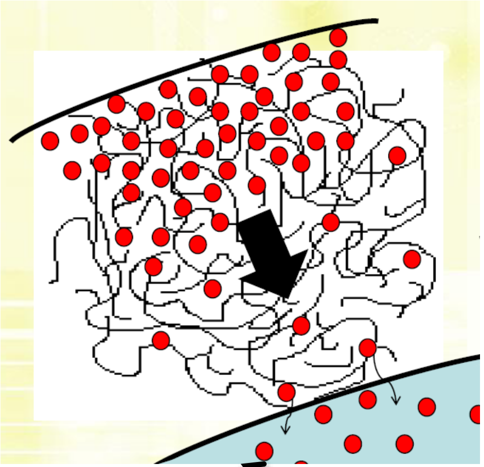
2. Outgassing



OUTGASSING of RUBBER CLOSURE

Lyo Cake
= adsorbent

No "Liquid Film" barrier on rubber
(see previous slide)



Material (e.g.):
Film (Overwrap)

Rubber
(Lyo Vial,
Needle Shield)

Solvent: air, gas phase

Outgassing is mainly an issue for:

- Volatile organic compounds
- Semi-volatile organic compounds

3. APPLICATION SPECIFIC EFFECTS

3. Blooming

What is it?

- Blooming is a physical phenomenon
- Observed in polymers which are (super)saturated with additives
- A process of **diffusion controlled migration** of additives from the **polymer**
- Typical for additives with **low solubility** & **high diffusion rate**

Typical conditions when blooming occurs

- **Low solubility** of the additive in the polymer
- **High diffusion** of the additive through the polymer
- **Dosing** of the additive into the polymer **close to the solubility** of the additive in polymer
- **Low temperature applications** may accelerate blooming process (lower solubility, *but also lower diffusion...*)

QUESTIONS?