PDA Training Course Extractables & Leachables

19-20 October 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:

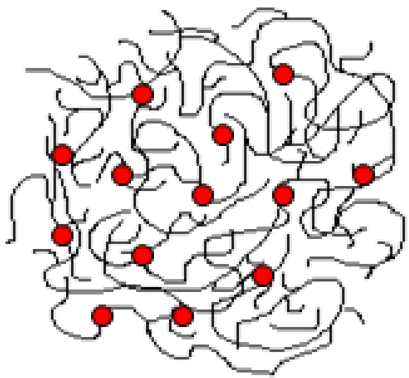
SOLUBILITY of a leachable **IN** the polymer

DIFFUSION of a leachable **THROUGH** the polymer

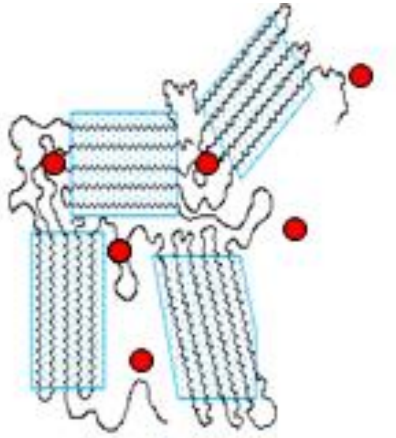
2.1 SOLUBILITY OF A LEACHABLE IN A POLYMER

1. Polymer morphology

AMORPHOUS



SEMI-CRYSTALLINE



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

PC, PVC, PS, PU

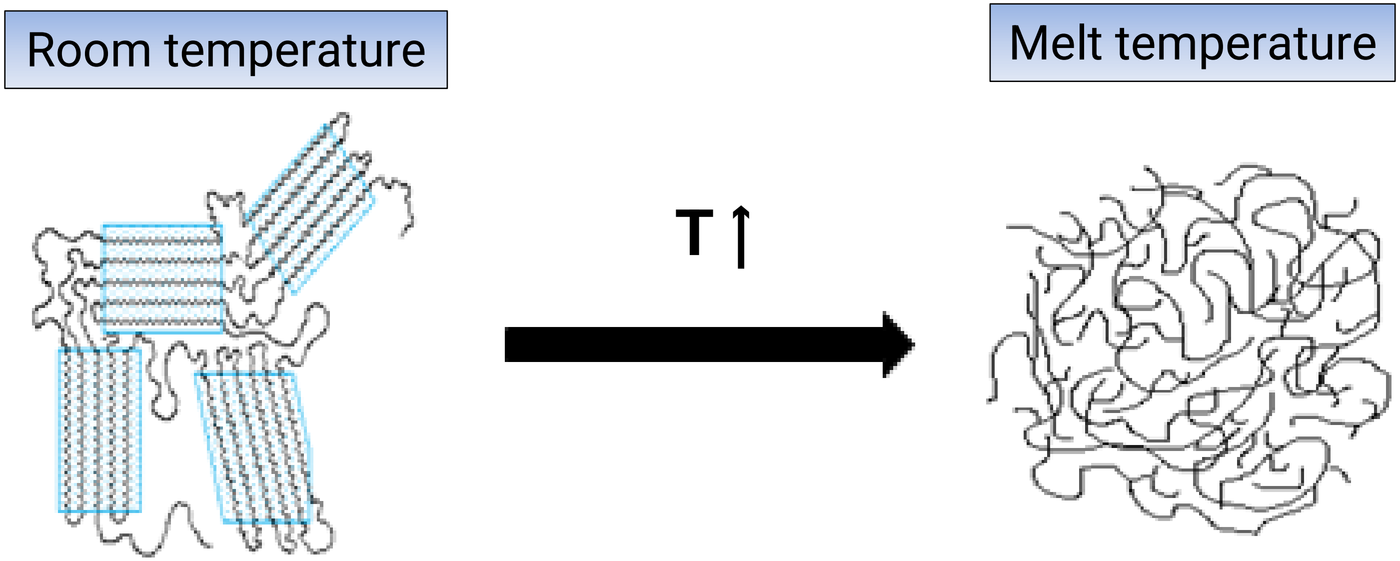
CRYSTALLINE SITES: BARRIER FOR MIGRATION

PE, PP, PET, EVA, PEEK, PA

2.1 SOLUBILITY OF A LEACHABLE IN A POLYMER

2. Temperature

As temperature increases, solubility increases



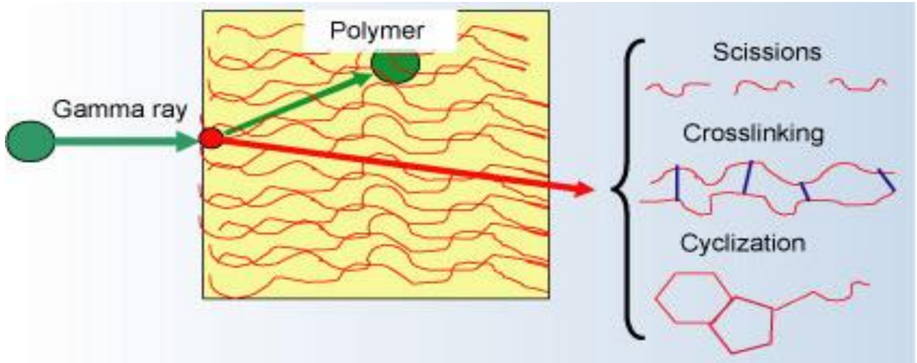
RESULT: **BETTER SOLUBILITY** at higher T

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

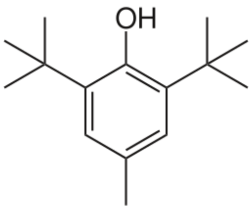
CONCLUSION:

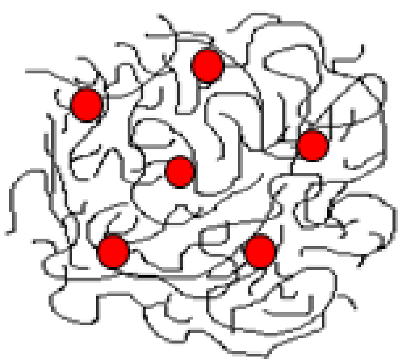
» **Perform E&L testing on final STERILIZED SYSTEMS**

2.1 SOLUBILITY OF A LEACHABLE IN A POLYMER

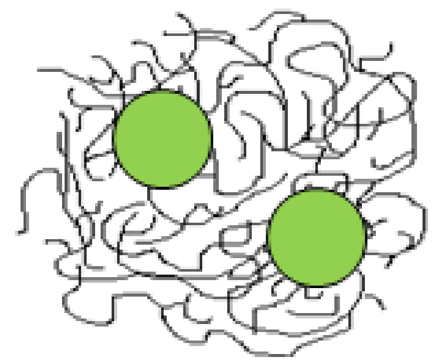
4. Structure and molecular weight of a leachable

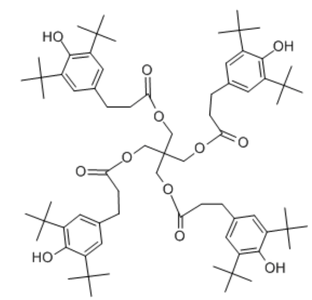
- Molecular weight → larger molecules = lower solubility





vs.





BHT (MW 220)

Irganox 1010 (MW 1176)

- Polarity "match" → structurally ALIKE
- Melting point → higher T_{melt} = lower solubility
  → impacted by molecular symmetry & crystallinity

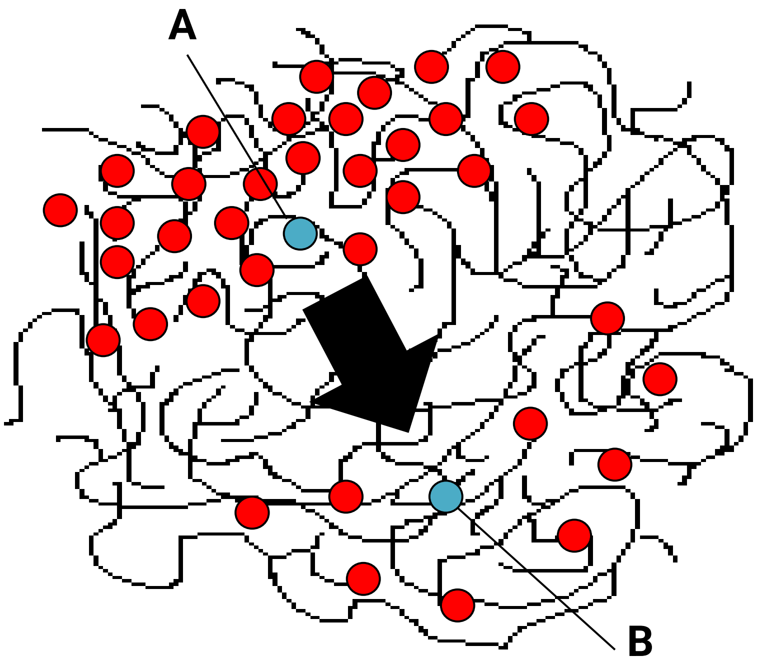
2. FACTORS AFFECTING LEACHING

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

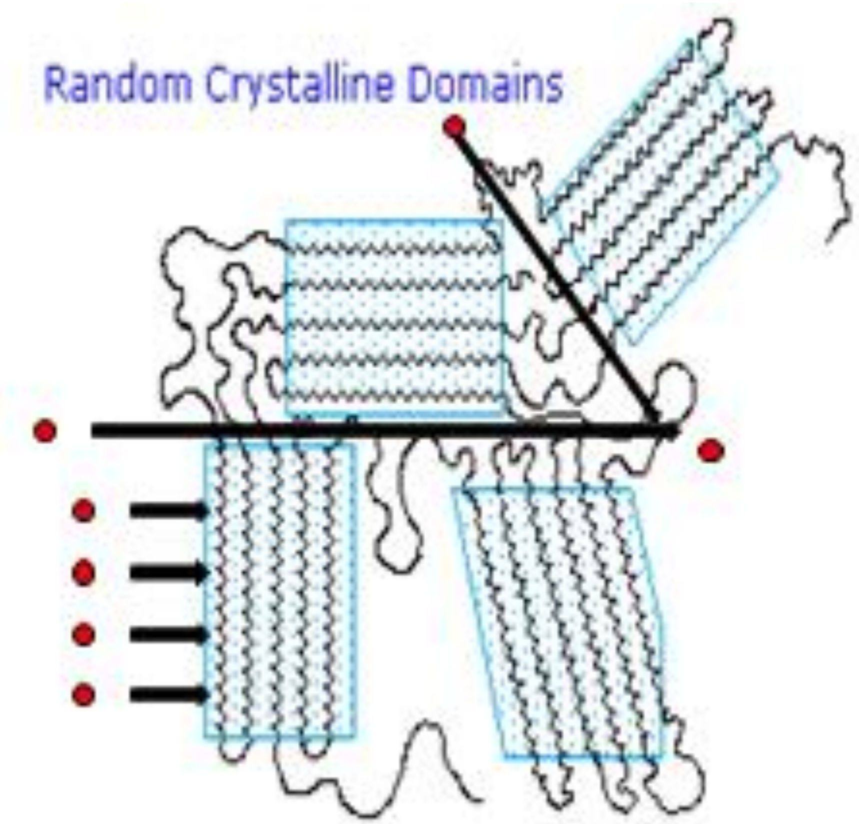
2.2 DIFFUSION OF LEACHABLE TROUGH THE POLYMER

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**	($T > T_g$)

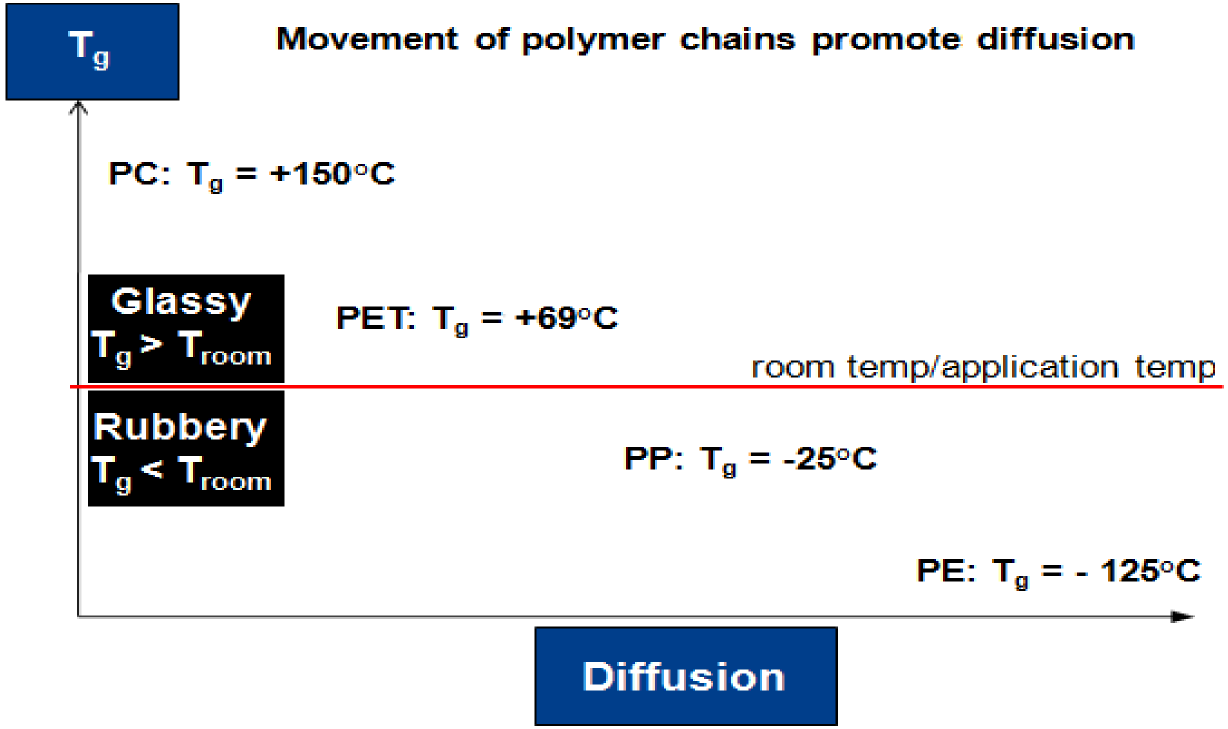
EXAMPLES

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

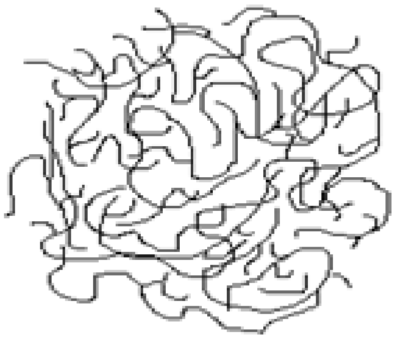
Ratio of:

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

Polymers in a **Rubber State** ($T_g < T$)

Typically have **HIGHER** free volume

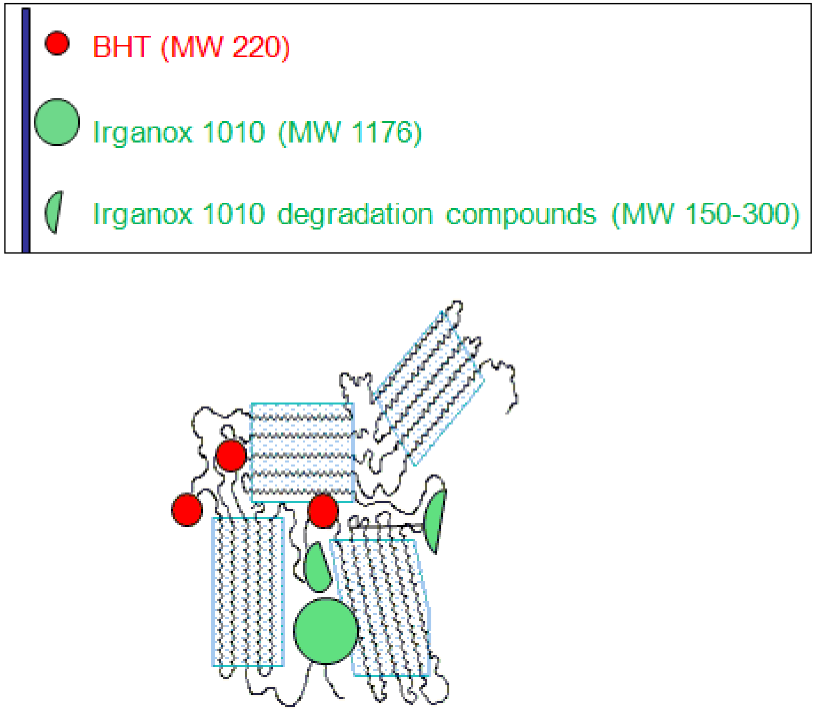
More free volume promotes diffusion



2.2 DIFFUSION OF LEACHABLE TROUGH THE POLYMER

4. Molecular weight of leachable

Diffusion increases with decrease in M.W.



2.2 DIFFUSION OF LEACHABLE TROUGH THE POLYMER

4. Molecular weight of leachable

Oligomeric additives → reducing diffusion

High diffusion

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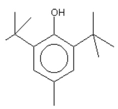
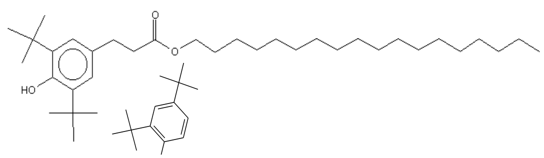
Low diffusion

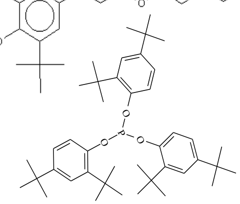
BHT: M.W. 220



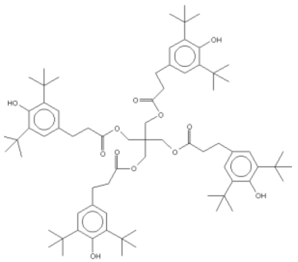
Irganox 1076: M.W. 530



Irgafos168: M.W. 646



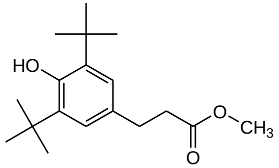
Irganox 1010: M.W. 1176



Polymer additive DEGRADATION into smaller molecules → FASTER DIFFUSION of degradants

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

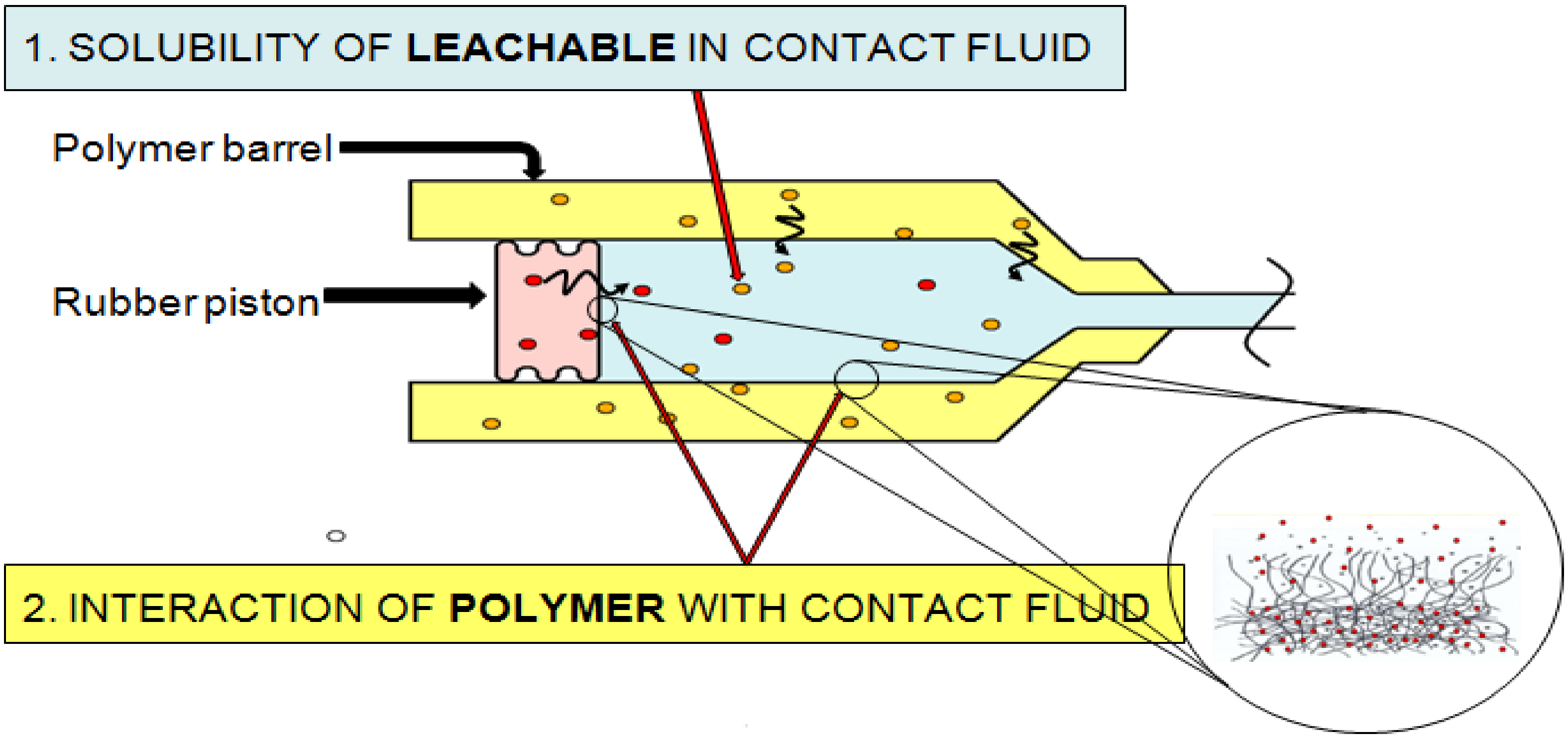
(*Degradation product of Irganox 1010 /Irganox 1076*)



2.2 DIFFUSION OF LEACHABLE TROUGH THE POLYMER

5. Contact fluid / environment

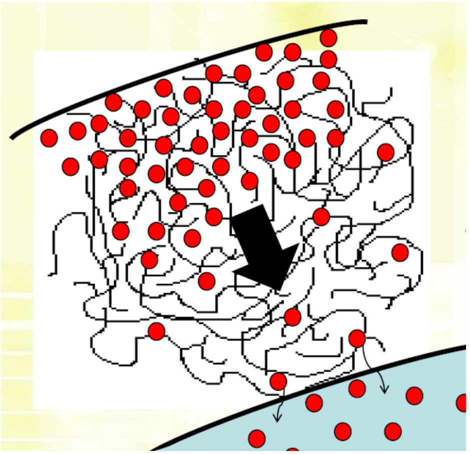
Two Important aspects:



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

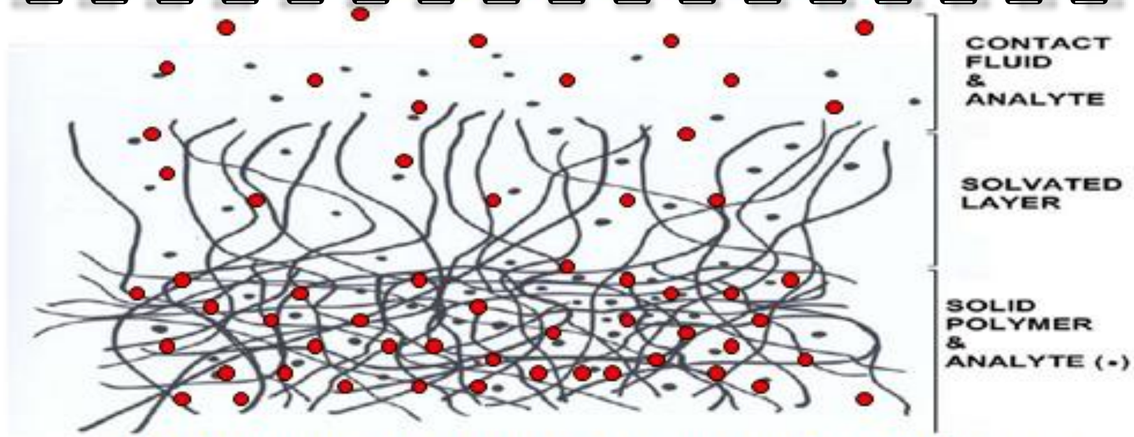
WFI/hydrophilic contact solutions = **LOW SOLUBILITY** solvents

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

OVERVIEW

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3. APPLICATION SPECIFIC EFFECTS

1. Super saturation

LIQUID FILM is formed via
- Evaporation during storage
- Transportation

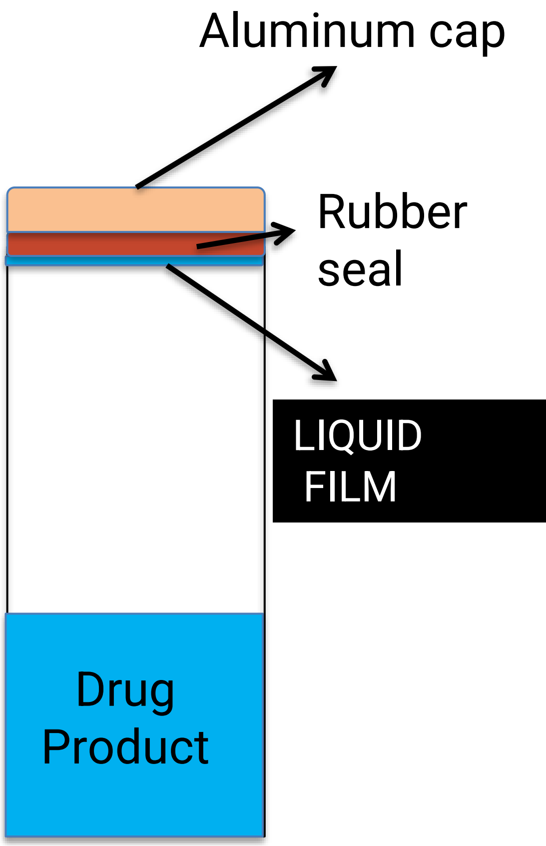
Film may be different in composition than the DP

Diffusion of rubber compounds into small volume
- Metals
- Organic

Can cause **aggregation, particle formation**

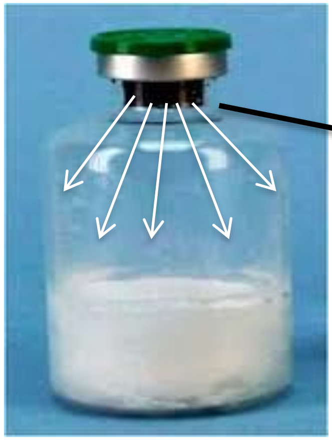
May be **irreversible**
- Particles do not dissolve anymore when in contact with the total DP volume

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



3. APPLICATION SPECIFIC EFFECTS

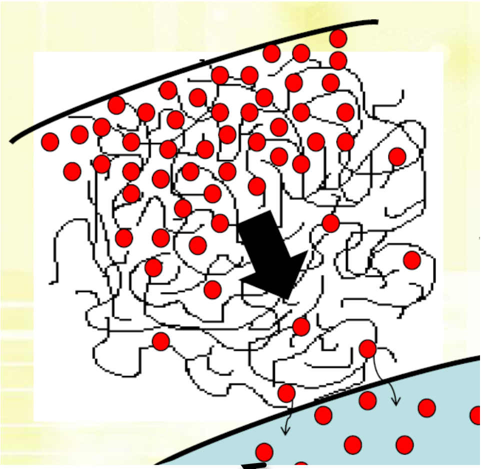
2. Outgassing



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?