PDA Training Course Extractables & Leachables

23-24 October 2025

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

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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:

$$\frac{m_{L,t}}{A} = 0.1 c_{P,0} \rho_P d_P \left(\frac{\alpha}{\alpha+1}\right)\left[1 - \sum_{n=1}^{\infty} \frac{2\alpha(1+\alpha)}{1+\alpha+\alpha^2 q_n^2} \exp\left(-D_P t \frac{q_n^2}{d_P^2}\right)\right]$$

$$D_P = 10^4 \, exp\left[A_P - 0.1351(MW)^{2/3} + 0.003MW - 10450/T\right]$$

Important factors:

- $C_{p,0}$: initial migrant concentration i/t polymer
- ρ_p: density of the polymer (g/cm³)
- d_p: thickness of the polymer (cm)
- D: diffusion coefficient (cm²/s)
- A_p: ''mobility'' of the polymer
- MW: molecular weight of the migrant (Da)
- V_L: volume of the liquid (cm³)
- V_P: volume of the polymer (cm³)
- T: temperature (K)
- $K_{P,L}$: partition coefficient $\left(= \frac{c_{L,t=\infty}}{c_{P,t=\infty}}\right)$

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

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Plastic Packaging *Interactions with Food and Pharmaceuticals,* Otto G. Piringer and Albert L. Baner, Wiley 2008

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

1. Polymer morphology
2. Temperature
3. Age/sterilization
4. Structure and molecular weight of a leachable

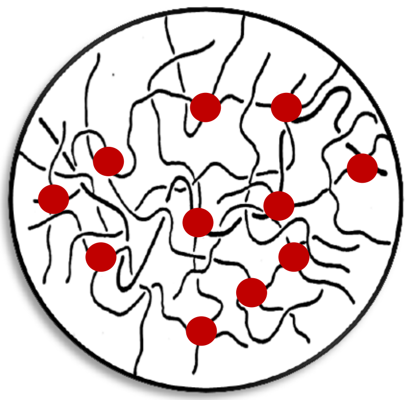
DIFFUSION of a leachable ***THROUGH*** the polymer

1. Polymer morphology
2. Temperature
3. Polymer type (T_g)
4. Molecular weight of a leachable
5. Contact fluid/environment

2.1 SOLUBILITY OF A LEACHABLE IN A POLYMER

1. Polymer morphology

Amorphous



PC, PVC, PS, PU

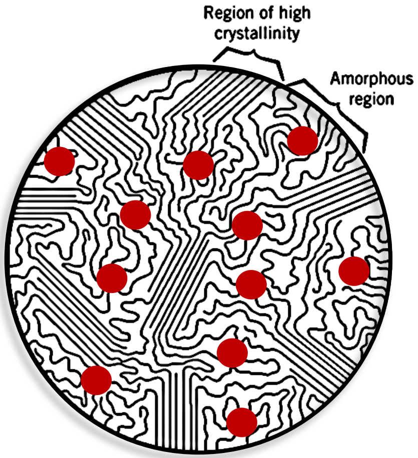
Polymer additive/impurity

» Dissolves in amorphous phase

» Insoluble in crystalline phase

CRYSTALLINE SITES: BARRIER FOR MIGRATION

Semi-crystalline

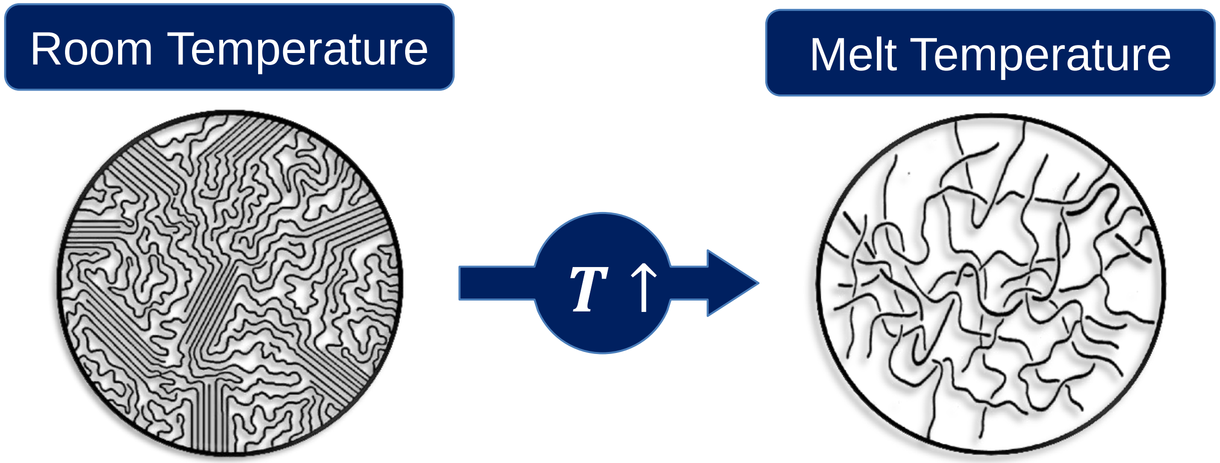


PE, PP, PET, EVA, PEEK, PA

2.1 SOLUBILITY OF A LEACHABLE IN A POLYMER

2. Temperature

As temperature increases, solubility increases



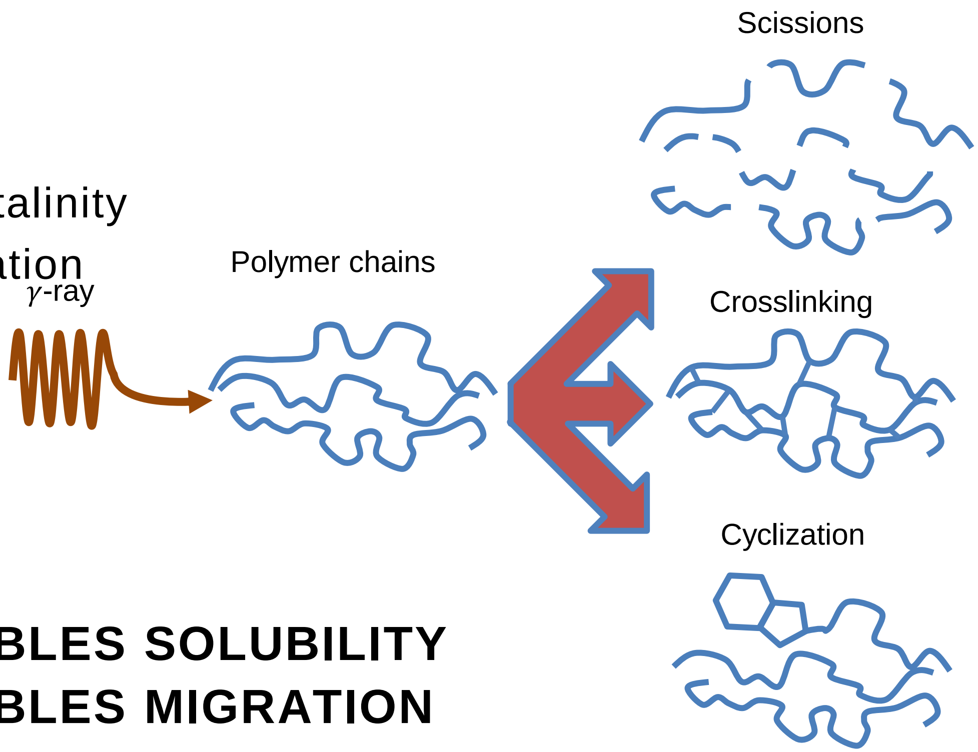
RESULT: **BETTER SOLUBILITY** at higher *T*

LESS "CRYSTAL BARRIER" for migration

2.1 SOLUBILITY OF A LEACHABLE IN A POLYMER

3. Ageing / sterilization

- Polymer degradation
- Changes in polymer crystalinity
- Polymer additive degradation



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

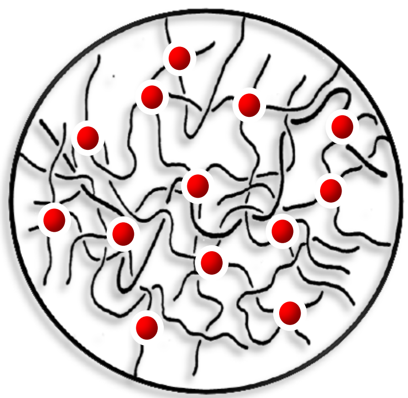
CONCLUSION:

» **PERFORM E&L TESTING ON FINAL (STERILIZED) SYSTEMS**

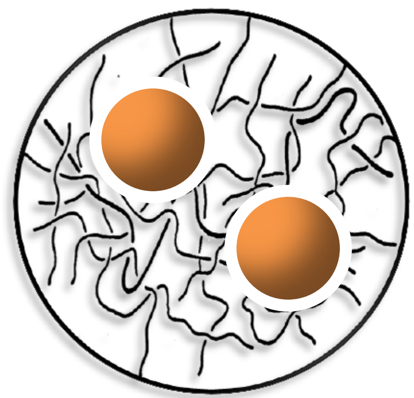
2.1 SOLUBILITY OF A LEACHABLE IN A POLYMER

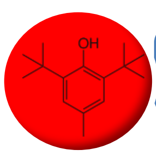
4. Structure and molecular weight of a leachable

I. Molecular weight → larger molecules = lower solubility



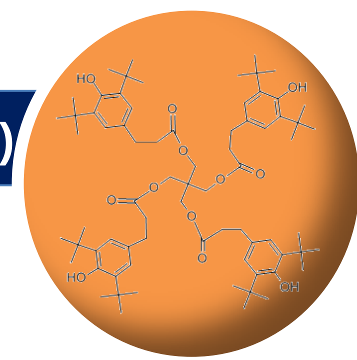
vs.





BHT (MW 220)

Irganox 1010 (MW 1178)



II. Polarity “match” → structurally ALIKE

III. Melting point → higher T_{melt} = lower solubility
→ impacted by molecular symmetry & crystallinity

2. FACTORS AFFECTING LEACHING

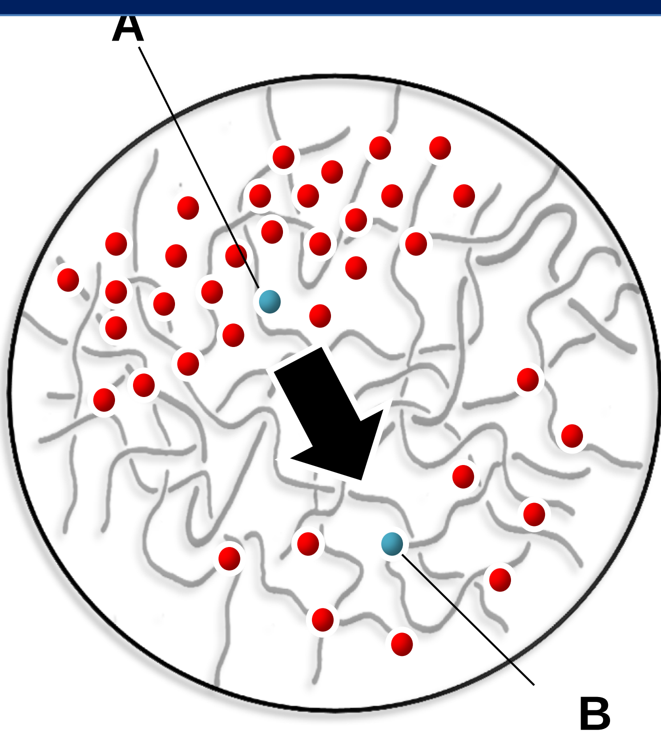
Leaching will depend upon:

SOLUBILITY of a leachable **IN** the polymer

DIFFUSION of a leachable **THROUGH** the polymer

2.2 DIFFUSION OF A LEACHABLE TROUGH THE POLYMER

FICK'S 2nd LAW OF DIFFUSION:



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

Concentration gradient

with

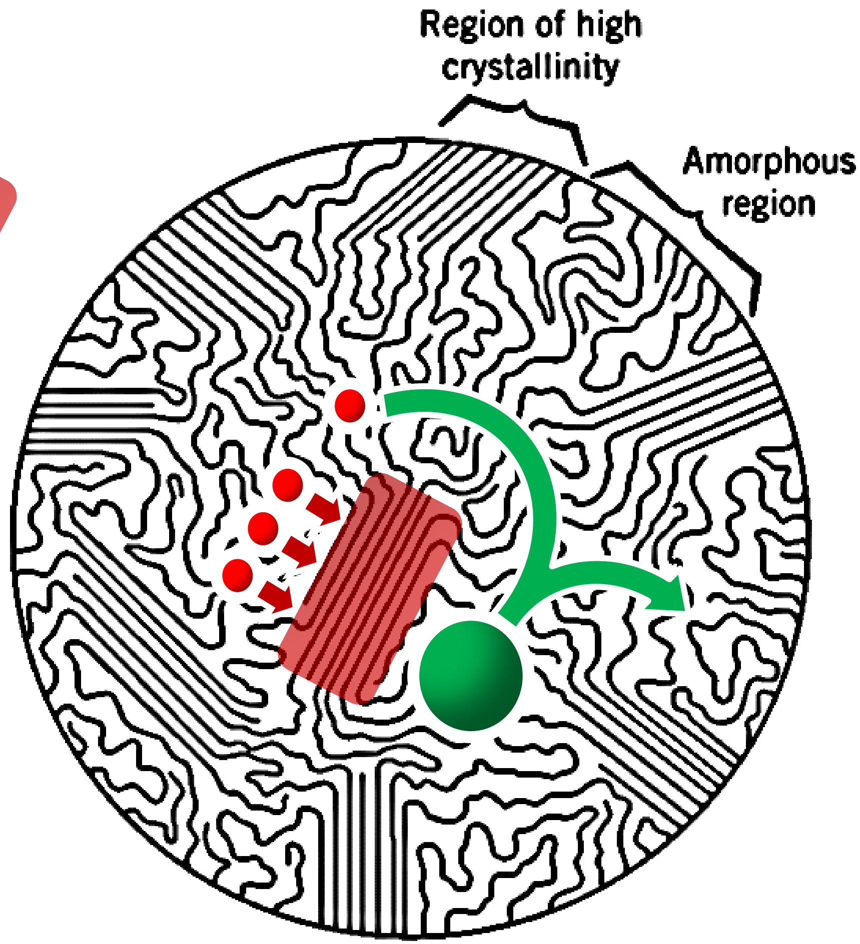
- C: concentration
- t: time ($t_A \rightarrow t_B$)
- x: distance ($x_A \rightarrow x_B$)
- D: Diffusion coefficient → measure for "mobility "

$$\rightarrow D = D_0 e^{-\frac{E_A}{RT}}$$

2.2 DIFFUSION OF A LEACHABLE TROUGH THE POLYMER

1. Polymer morphology

- **Crystalline sites:**
  Impermeable barrier for polymer additives
- **Filler particles:**
  Diffusion barriers for polymer additives
- **More barrier for diffusion in:**
  Semi-crystalline polymers



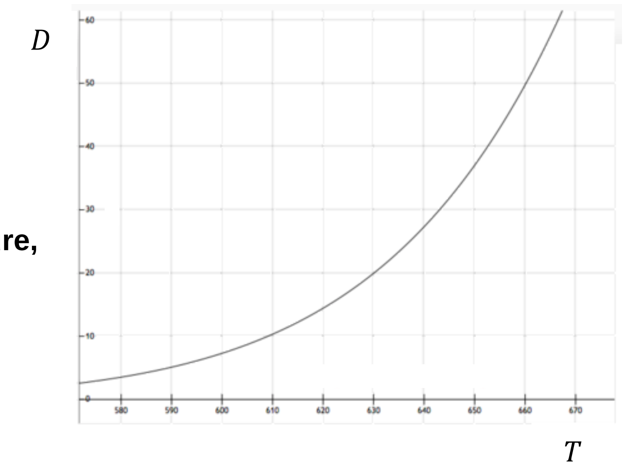
2.2 DIFFUSION OF A LEACHABLE TROUGH THE POLYMER

2. Temperature

Remember:

$$D = D_0 e^{-\frac{E_A}{RT}}$$

(E_A: activation energy, R: gas constant, T: temperature, D_0 the maximal diffusion coefficient (at infinite T))



Therefore:

If T ↑, then D ↑

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

2.2 DIFFUSION OF A LEACHABLE TROUGH THE POLYMER

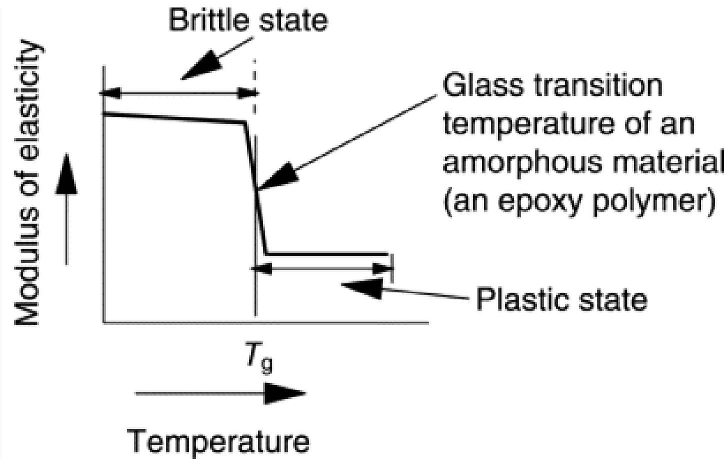
3. Polymer type

I. Glass Transition Temperature (T_g)

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

EXAMPLES

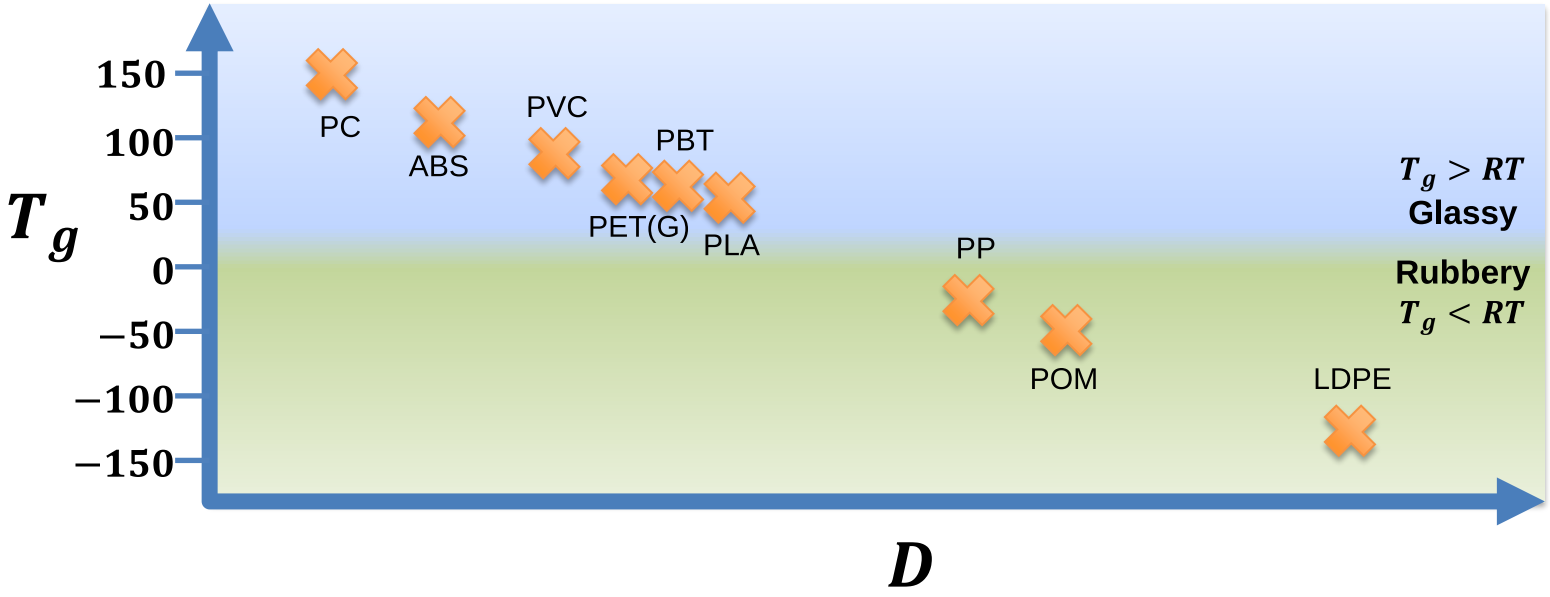
LDPE	$T_g = -125\ °C$
POM	$T_g = -50\ °C$
PP	$T_g = -25\ °C$
PBT	$T_g = 70\ °C$
PVC	$T_g = 81\ °C$
ABS	$T_g = 110\ °C$
PC	$T_g = 150\ °C$



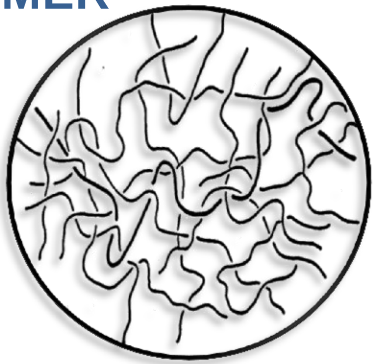
2.2 DIFFUSION OF A LEACHABLE TROUGH THE POLYMER

3. Polymer type

Lower T_g = higher potential for diffusion at room temperatures



2.2 DIFFUSION OF A LEACHABLE TROUGH THE POLYMER



3. Polymer type

(FRACTIONAL) FREE VOLUME

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

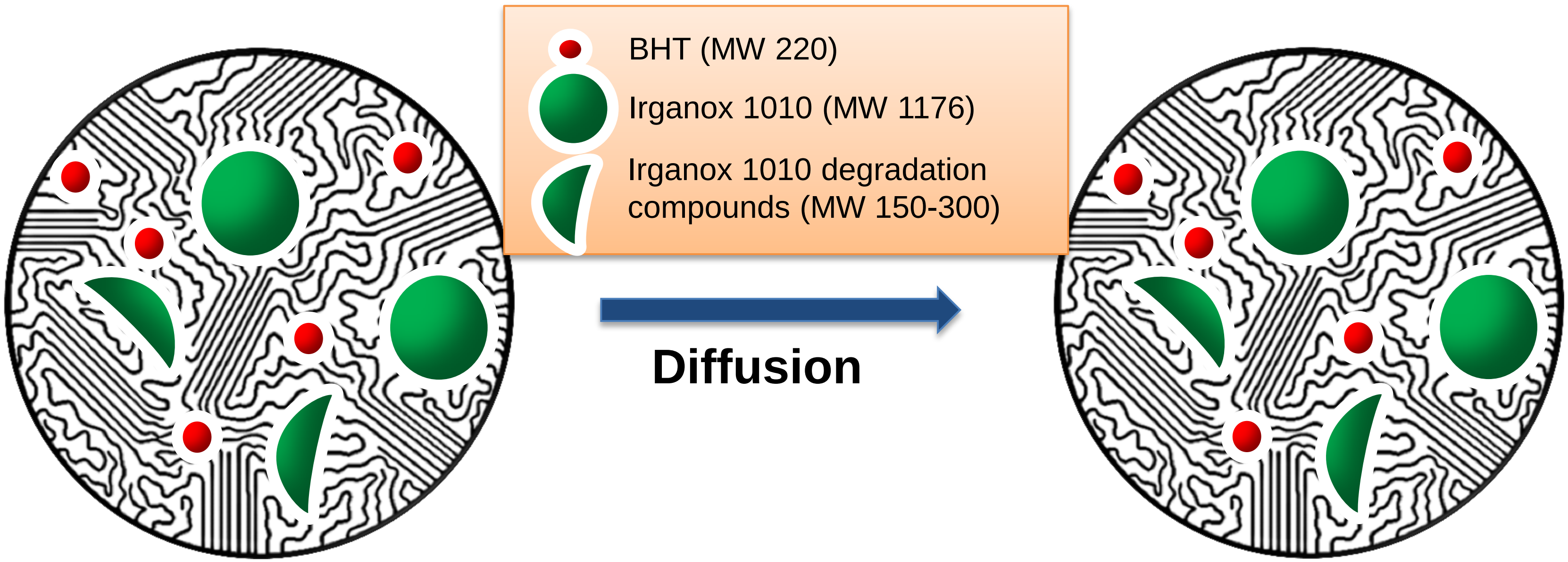
Polymers in a **Rubber State** ($T_g < T$) typically have **HIGHER** free volume

More free volume promotes diffusion

2.2 DIFFUSION OF A 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

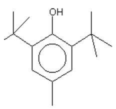
Oligomeric additives → reducing diffusion

High diffusion

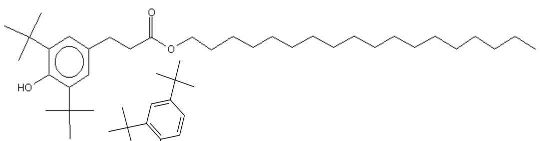
↓

Low diffusion

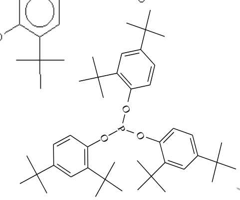
BHT: M.W. 220



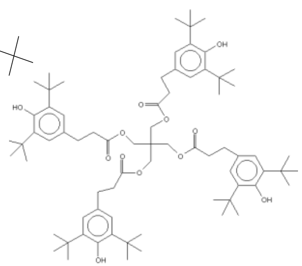
Irganox 1076: M.W. 530



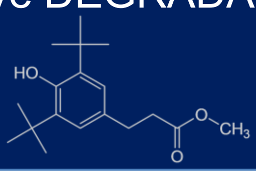
Irgafos168: M.W. 646



Irganox 1010: M.W. 1176



Additive DEGRADATION into smaller molecules → FASTER DIFFUSION of degradants



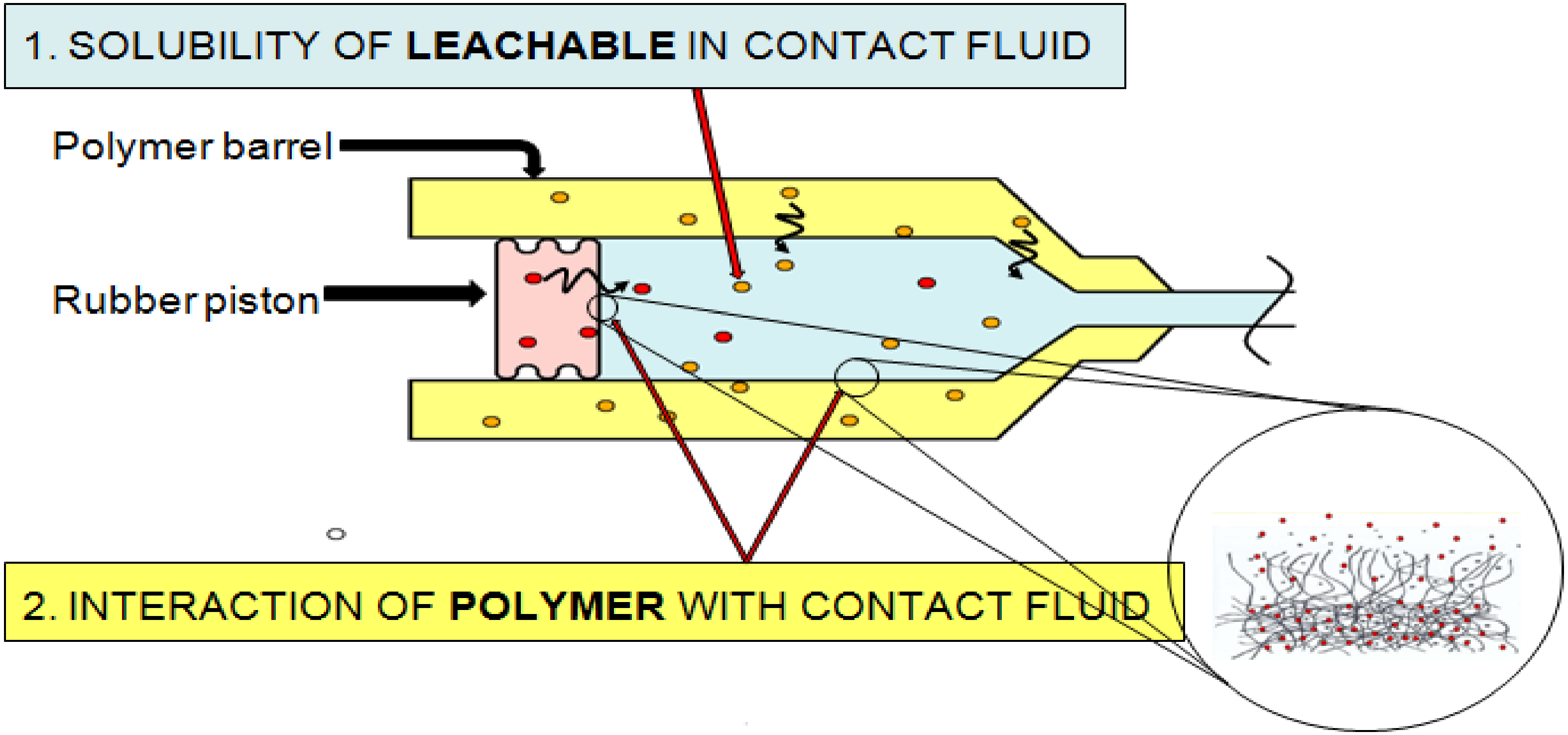
Example: 3,5-Di-*tert*-butyl-4-hydroxyphenyl propionic acid methyl ester

Degradation product of Irganox 1010 /Irganox 1076

2.2 DIFFUSION OF LEACHABLE TROUGH THE POLYMER

5. Contact fluid / environment

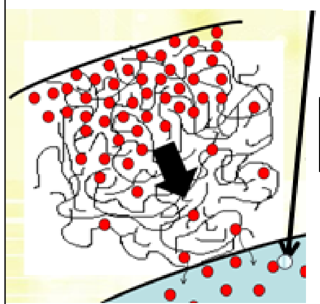
Two Important aspects:



2.2 DIFFUSION OF A LEACHABLE TROUGH THE POLYMER

<u>5. Contact fluid/environment</u>

1. Solubility of the leachable in the contact fluid



EFFECTIVE DISSOLUTION OF LEACHABLE AT POLYMER SURFACE

↓

EFFICIENT SURFACE LOSS MECHANISM

↓

LEACHING IS DIFFUSION CONTROLLED

In general for most organic compounds:

Organic / hydrophobic contact solutions = **HIGH SOLUBILITY** solvents

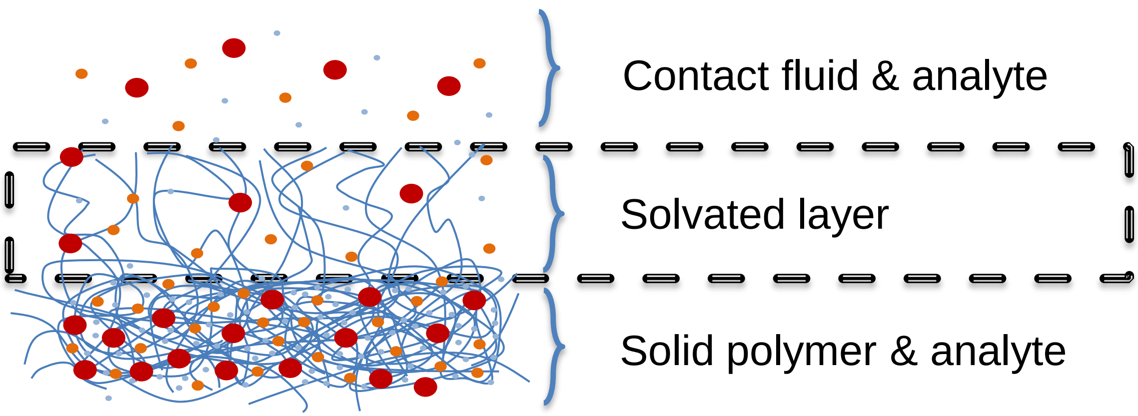
WFI/hydrophilic contact solutions = **LOW SOLUBILITY** solvents

2.2 DIFFUSION OF A LEACHABLE TROUGH THE POLYMER

5. Contact fluid/environment

Interaction of the contact fluid with the polymer

Solvent can "plasticize" or "swell" a polymer
SOLVATED LAYER



ENHANCED DIFFUSION OF LEACHABLES

ACCELERATED LOSS

OVERVIEW

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   - Solubility of a leachable in a polymer
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   - Supersaturation
   - Outgassing
   - Blooming

3. APPLICATION SPECIFIC EFFECTS

1. Super saturation

LIQUID FILM is formed via
- Evaporation during storage
- Transportation

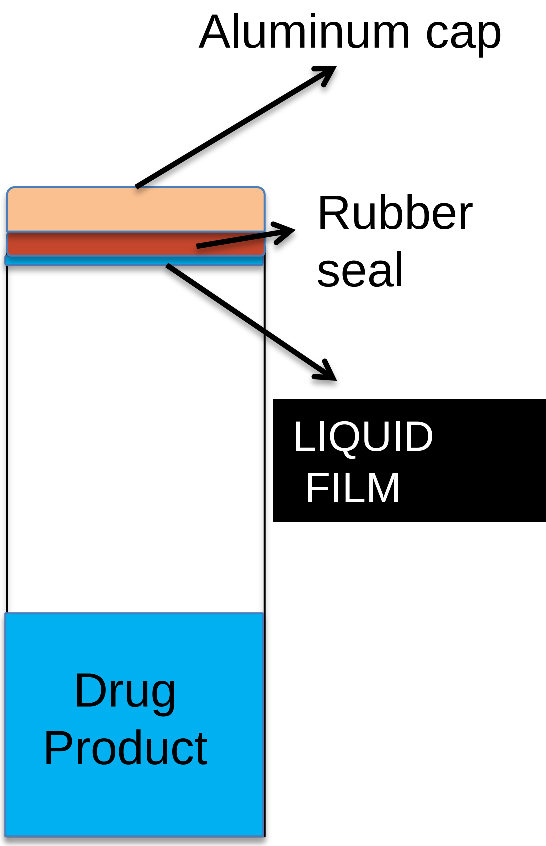
Film may be different in composition than the DP

Diffusion of rubber compounds into small volume
- Metals
- Organic

Can cause **aggregation, particle formation**

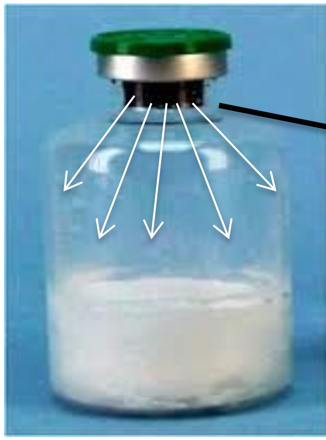
May be **irreversible**
- Particles do not dissolve anymore when in contact with the total DP volume

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



3. APPLICATION SPECIFIC EFFECTS

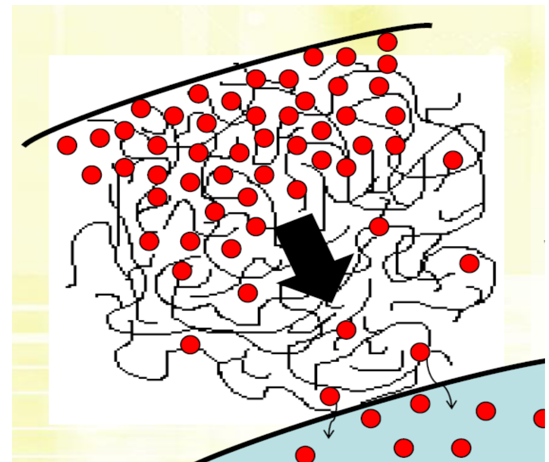
2. Outgassing



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?

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