PDA Training Course Extractables & Leachables

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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 through a polymer
3. Application specific effect
   - Supersaturation
   - Outgassing
   - Blooming

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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**:

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

m_F (t): amount of migrant (mg/kg) in the polymer as a function of time t (s)

A: area of the interface (cm²)

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

$$\alpha = \frac{V_L/V_P}{K_{P,L}}$$

Important factors:

$C_{p,0}$:	initial migrant concentration i/t polymer	MW:	molecular weight of the migrant (Da)
ρ_p:	density of the polymer (g/cm³)	V_L:	volume of the liquid (cm³)
d_p:	thickness of the polymer (cm)	V_P:	volume of the polymer (cm³)
D:	diffusion coefficient (cm²/s)	$K_{P,L}$:	partition coefficient (solubility)
A_p:	"mobility" of the polymer	T:	temperature (K)

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

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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

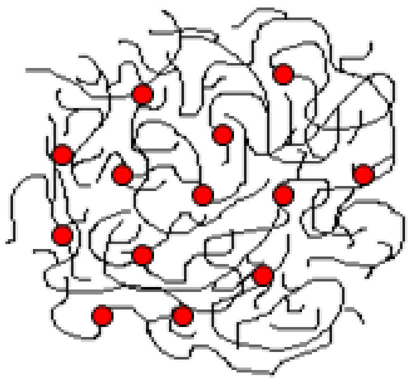
DIFFUSION of a leachable **THROUGH** the polymer

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

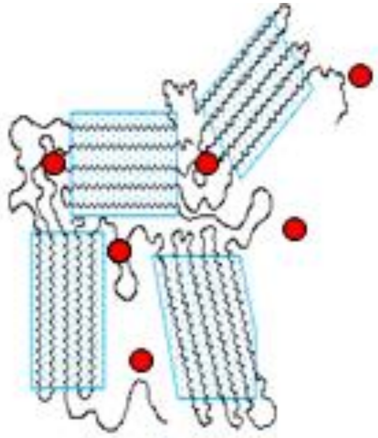
2.1 SOLUBILITY OF A LEACHABLE IN A POLYMER

1. Polymer morphology

AMORPHOUS



SEMI-CRYSTALLINE



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

PC, PVC, PS, PU

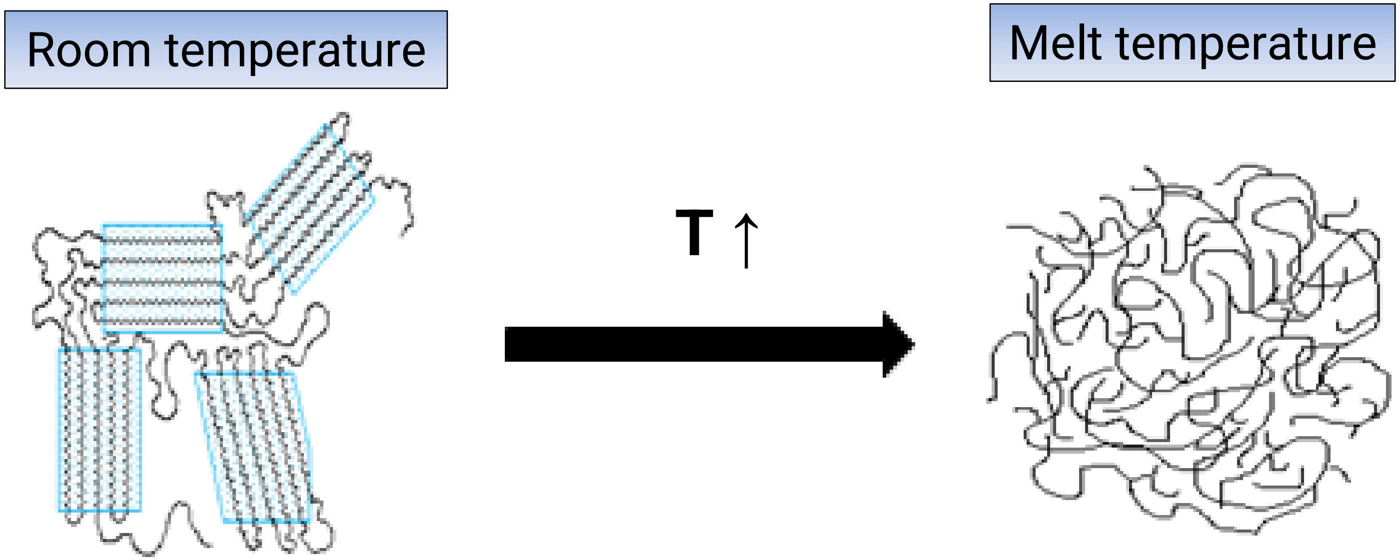
CRYSTALLINE SITES: BARRIER FOR MIGRATION

PE, PP, PET, EVA, PEEK, PA

2.1 SOLUBILITY OF A LEACHABLE IN A POLYMER

2. Temperature

As temperature increases, solubility increases



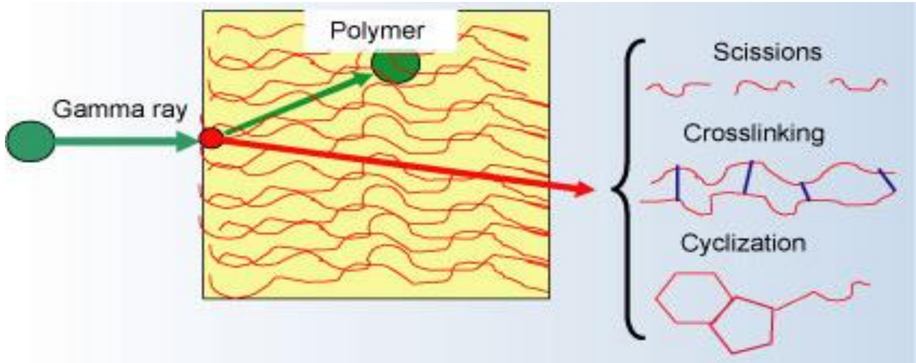
RESULT: **BETTER SOLUBILITY** at higher T

LESS "CRYSTAL BARRIER" for migration

2.1 SOLUBILITY OF A LEACHABLE IN A POLYMER

3. Age / sterilization

- Polymer degradation
- Changes in polymer crystallinity
- Polymer additive degradation



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

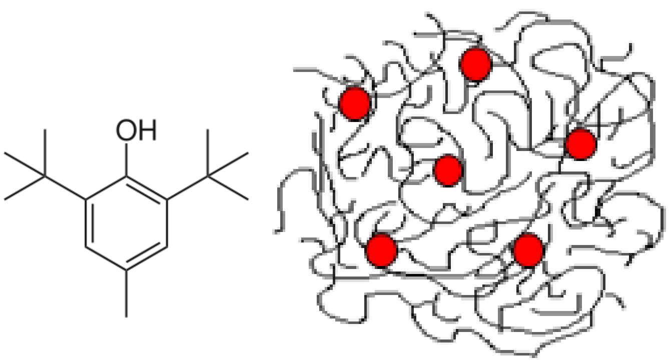
CONCLUSION:

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

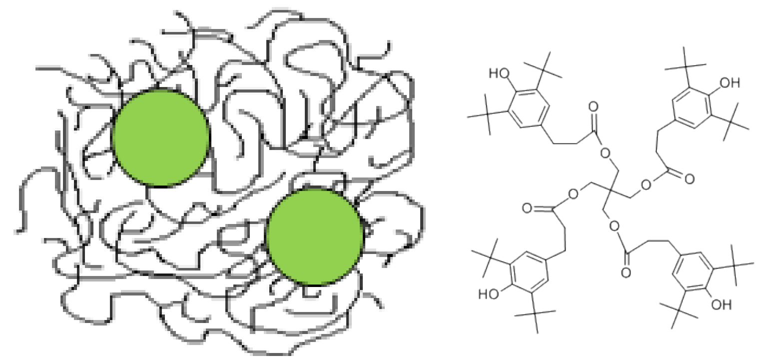
2.1 SOLUBILITY OF A LEACHABLE IN A POLYMER

4. Structure and molecular weight of a leachable

- 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

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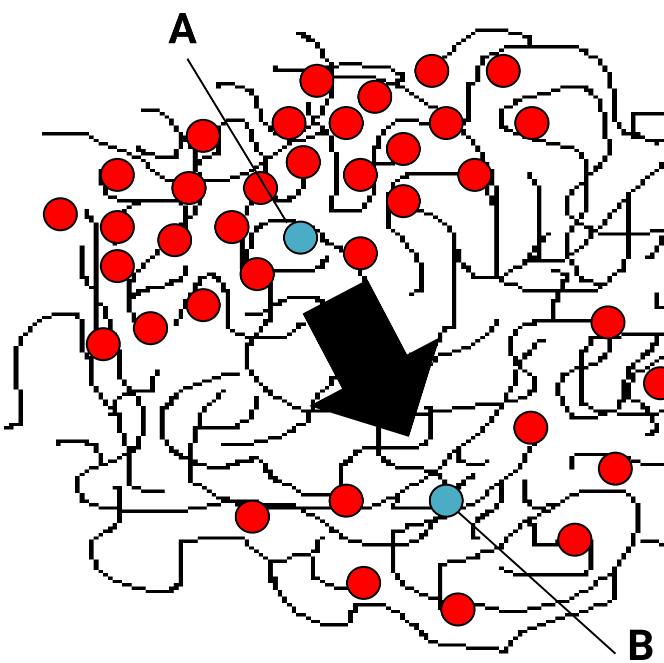
DIFFUSION of a leachable **THROUGH** the polymer

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

2.2 DIFFUSION OF LEACHABLE THROUGH 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 ($x_A \rightarrow x_B$)

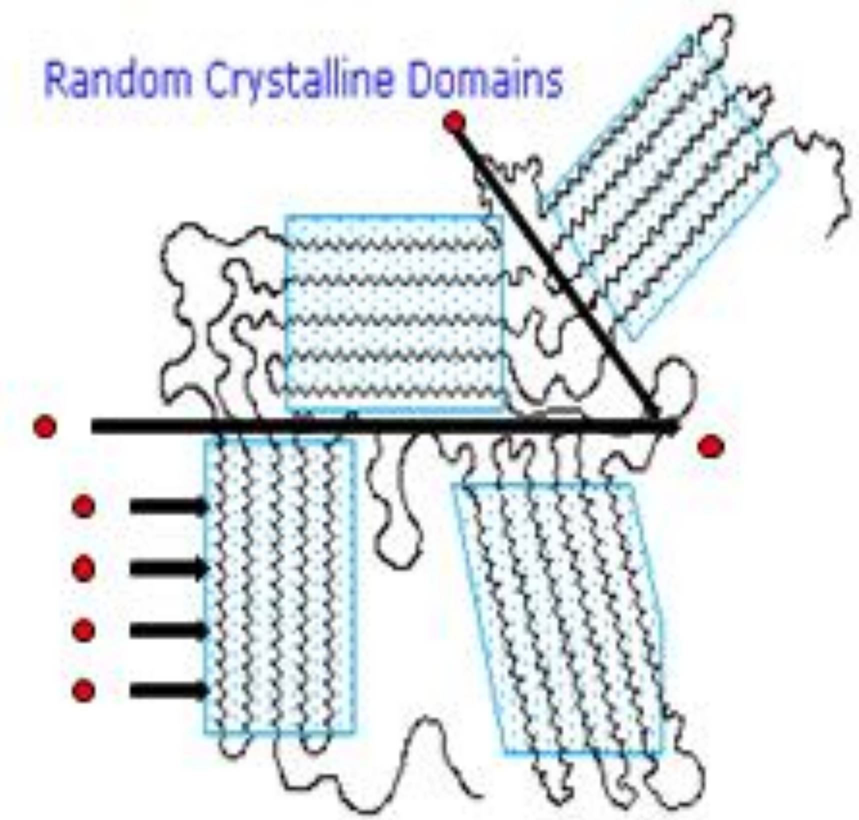
D: Diffusion coefficient

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

2.2 DIFFUSION OF LEACHABLE THROUGH 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 THROUGH 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 THROUGH THE POLYMER

3. Polymer type

Glass Transition Temperature (T_g)

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

EXAMPLES

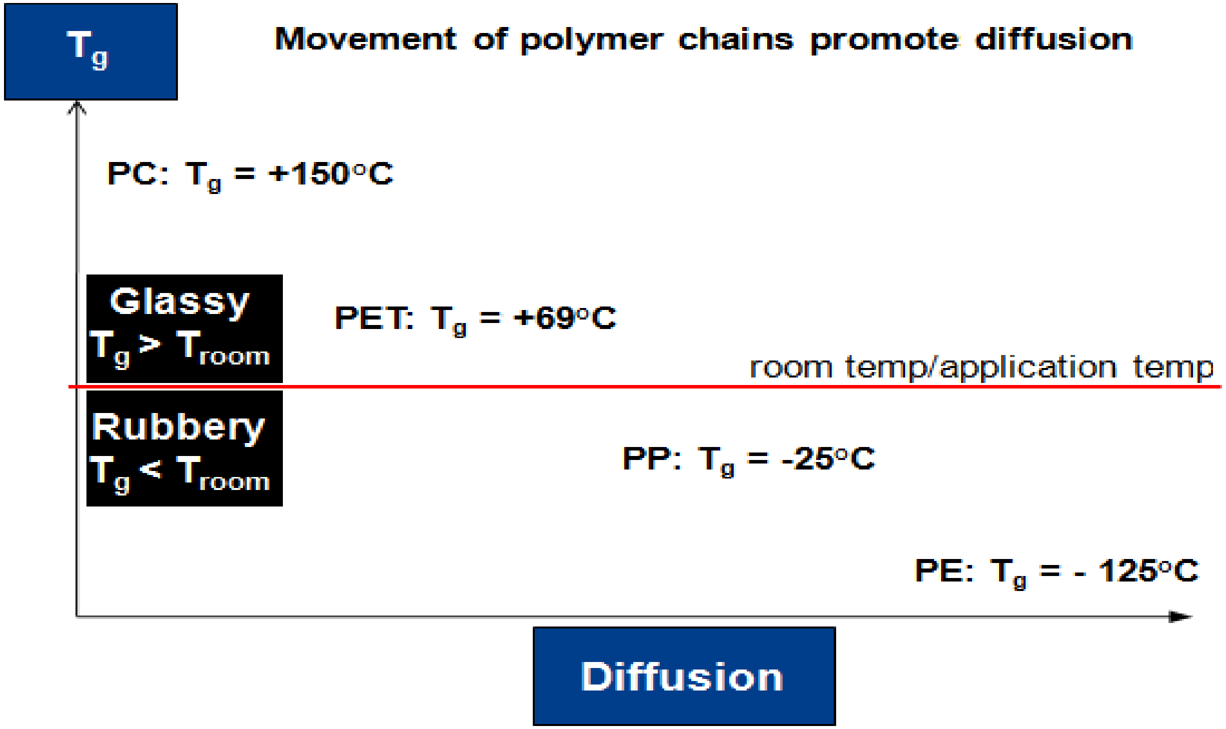
LDPE	T_g = -125 °C	PBT	T_g = 70 °C
POM	T_g = -50 °C	PVC	T_g = 81 °C
PP	T_g = -25 °C	ABS	T_g = 110 °C
		PC	T_g = 150 °C

DIFFUSION IN APOLAR > DIFFUSION POLAR POLYMERS

2.2 DIFFUSION OF LEACHABLE THROUGH THE POLYMER

3. Polymer type

Lower T_g = higher potential for diffusion at room temperature



2.2 DIFFUSION OF LEACHABLE THROUGH THE POLYMER

3. Polymer type

FREE VOLUME

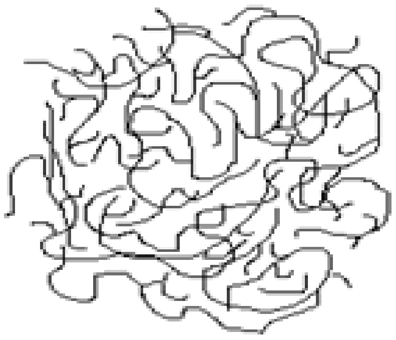
Ratio of:

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

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

Typically have **HIGHER** free volume

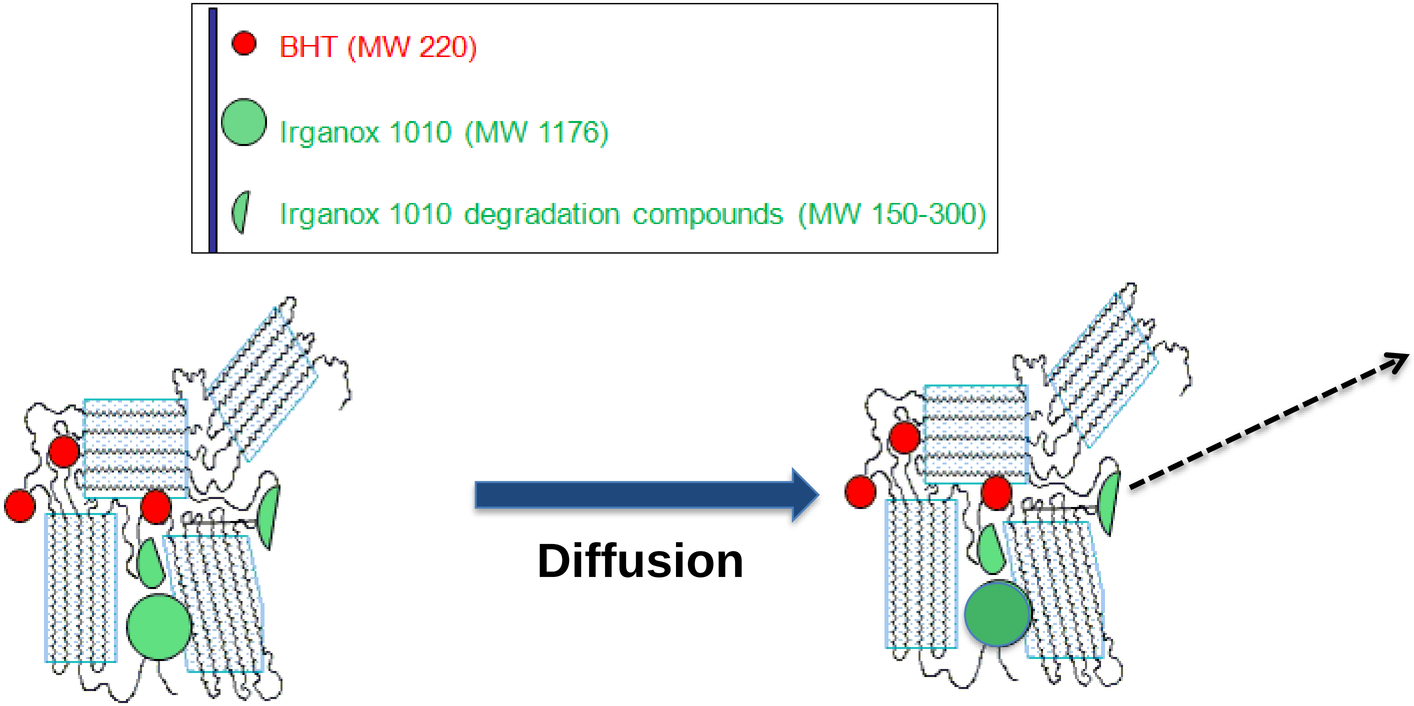
More free volume promotes diffusion



2.2 DIFFUSION OF LEACHABLE THROUGH THE POLYMER

4. Molecular weight of leachable

Diffusion increases with decrease in M.W.



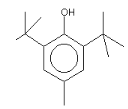
2.2 DIFFUSION OF LEACHABLE THROUGH THE POLYMER

4. Molecular weight of leachable

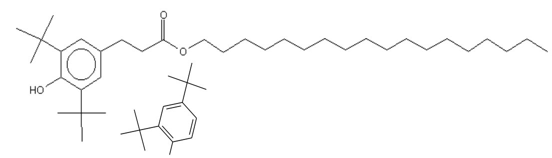
Oligomeric additives → reducing diffusion

High diffusion ↓ Low diffusion

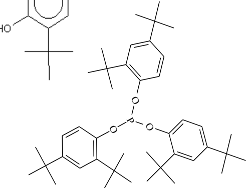
BHT: M.W. 220



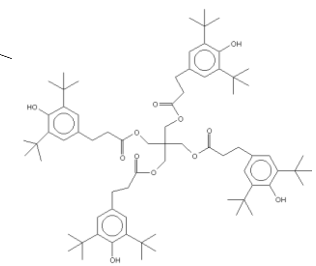
Irganox 1076: M.W. 530



Irgafos 168: M.W. 646

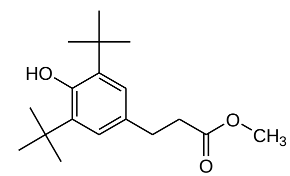


Irganox 1010: M.W. 1176



Polymer additive DEGRADATION into smaller molecules → FASTER DIFFUSION of degradants

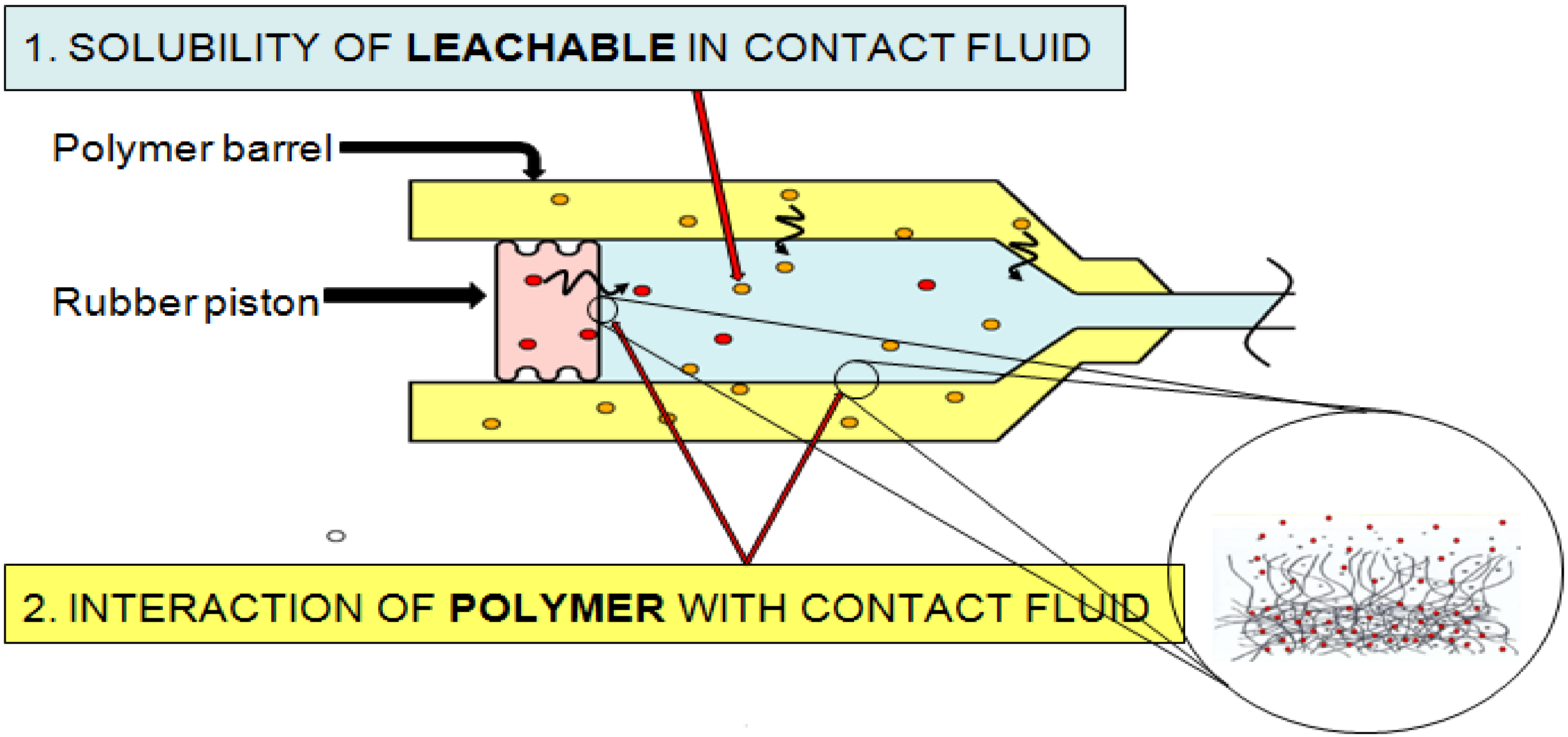
Example: 3,5-Di-*tert*-butyl-4-hydroxyphenyl propionic acid methyl ester
(*Degradation product of Irganox 1010 / Irganox 1076*)



2.2 DIFFUSION OF LEACHABLE THROUGH THE POLYMER

5. Contact fluid / environment

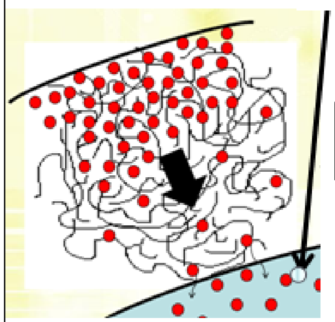
Two Important aspects:



2.2 DIFFUSION OF LEACHABLE THROUGH THE POLYMER

5. Contact fluid / environment

1. Solubility of the leachable in the contact fluid



EFFECTIVE DISSOLUTION OF LEACHABLE AT POLYMER SURFACE

↓

EFFICIENT SURFACE LOSS MECHANISM

↓

LEACHING IS DIFFUSION CONTROLLED

↓

LEACHING IS PROPORTIONAL TO $t^{1/2}$

In general for most organic compounds:

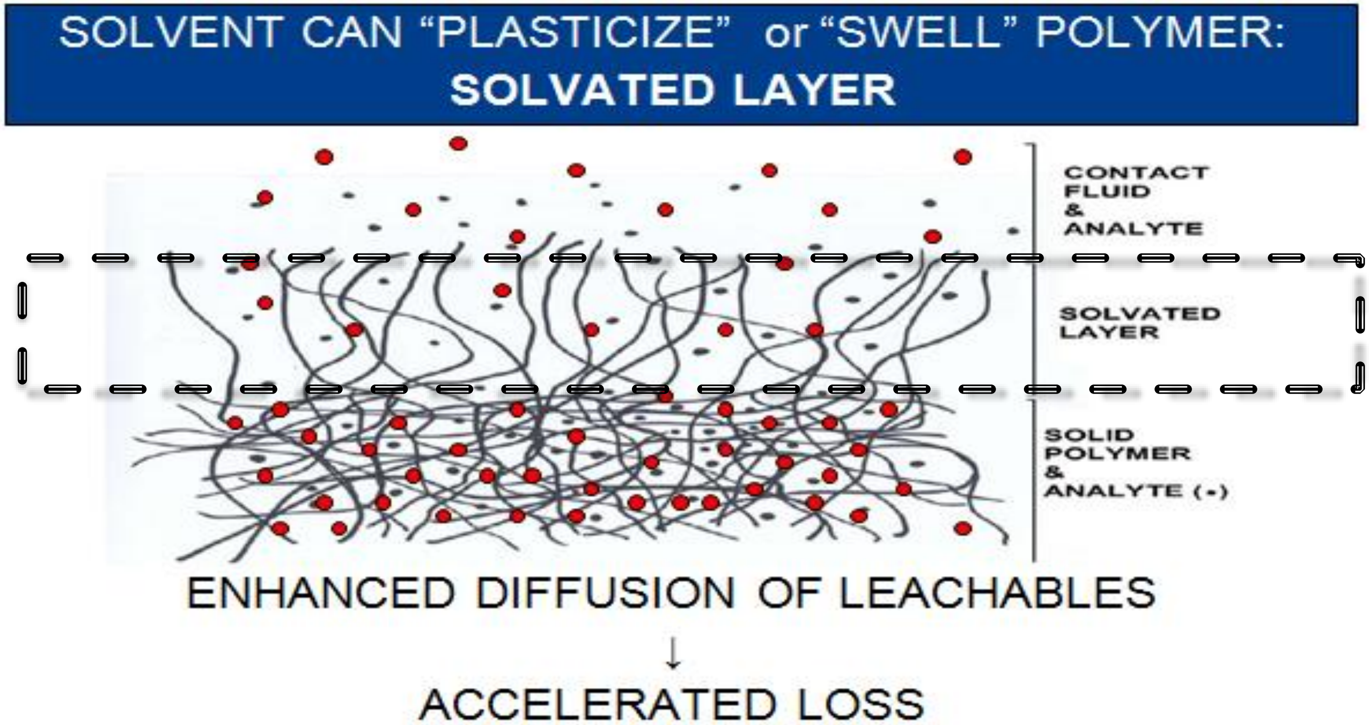
Organic / hydrophobic contact solutions = **HIGH SOLUBILITY** solvents

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

2.2 DIFFUSION OF LEACHABLE THROUGH THE POLYMER

5. Contact fluid / environment

2. Interaction of the contact fluid with the polymer



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3. APPLICATION SPECIFIC EFFECT

1. Supersaturation

LIQUID FILM is formed via
- Evaporation during storage
- Transportation

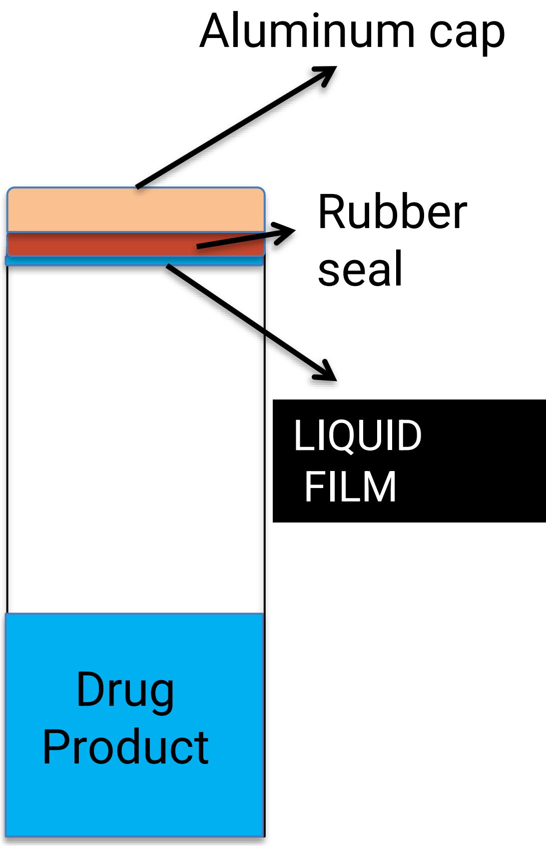
Film may be different in composition than the DP

Diffusion of rubber compounds into small volume
- Metals
- Organic

Can cause **aggregation, particle formation**

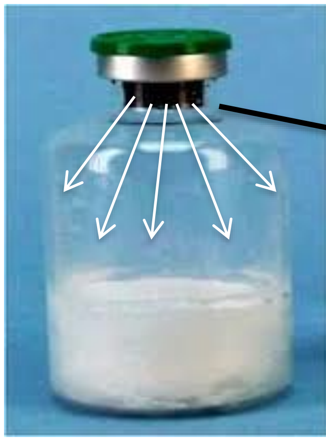
May be **irriversible**
- Particles do not dissolve anymore when in contact with the total DP volume

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



3. APPLICATION SPECIFIC EFFECT

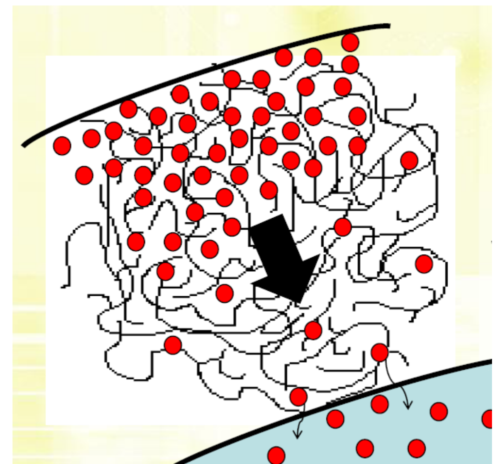
2. Outgassing



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 EFFECT

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?