THE MECHANISM OF POLYMER MIGRATION
A DESCRIPTIVE APPROACH

PDA WORKSHOP
EXTRACTABLES – LEACHABLES
Sevilla
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Perhaps **FABES MODEL** could make our lives easier…

General Formula for Modeling the Migration of Leachables

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

OOPS… **not that easy after all!**

Leaching Will Depend Upon:

1. **Solubility** of LEACHABLE <u>IN</u> Polymer

2. **Diffusion** of LEACHABLE <u>THROUGH</u> Polymer

Is Impacted By

A. **Polymer Morphology**

B. **Temperature**

C. **Age/Sterilization**

D. **Structure & Molecular Weight of LEACHABLE**

Is Impacted By

A. **POLYMER MORPHOLOGY**

B. Temperature

C. Age/Sterilization

D. Structure & Molecular Weight of LEACHABLE
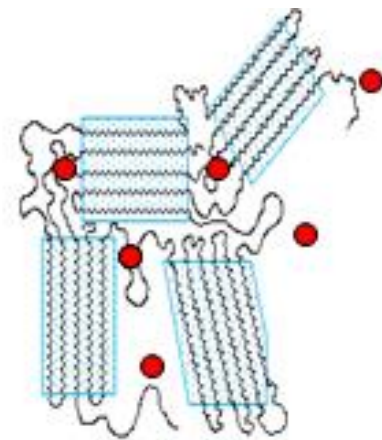
A. POLYMER MORPHOLOGY

AMORPHOUS   ## SEMI-CRYSTALLINE

Polymer Additive/Impurity

» Dissolves in
Amorphous Phase

» Insoluble in
Crystalline Phase

PC, PVC,
PS, PU

PE, PP, PET,
EVA, PEEK, PA

CRYSTALLINE SITES:
BARRIER FOR MIGRATION

Is impacted by

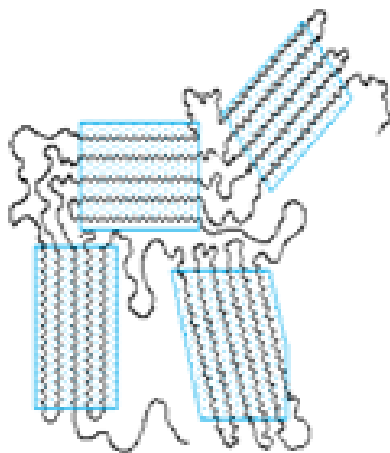A. Polymer Morphology

B. TEMPERATURE

C. Age/Sterilization

D. Structure & Molecular Weight of LEACHABLE

B. TEMPERATURE

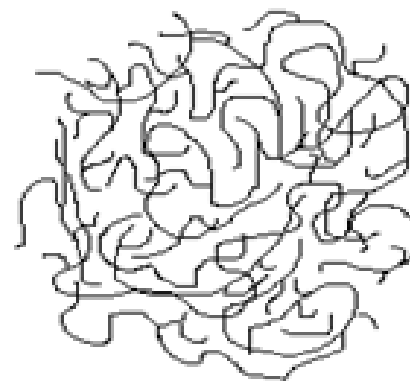## As Temperature Increase, Solubility Increases

Room Temperature		Melt Temperature

T ↑

RESULT: **BETTER SOLUBILITY** at higher T

LESS "CRYSTAL **BARRIER**" FOR MIGRATION
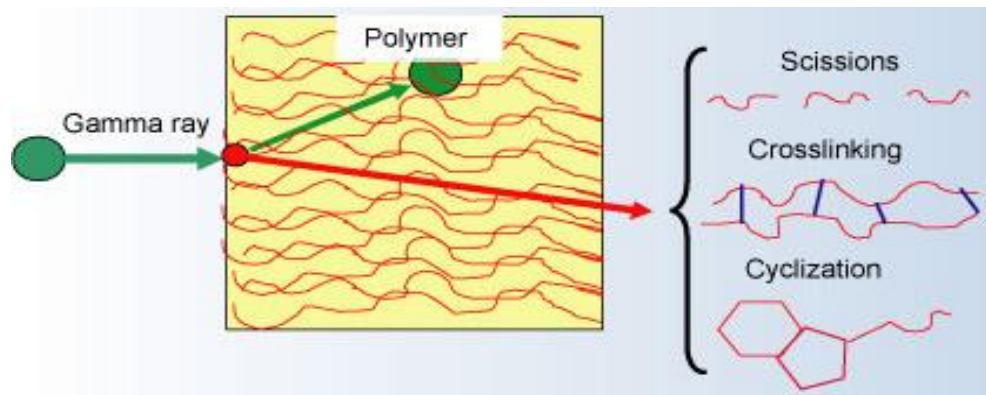
Is impacted by

A. Polymer Morphology

B. Temperature

C. **AGE/STERILIZATION**

D. Structure & Molecular Weight of LEACHABLE

C. AGE/STERILIZATION

Polymer Degradation
Polymer Additive Degradation
Changes in Polymer Crystallinity

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

CONCLUSION:

» **Perform E&L Testing on Final STERILIZED SYSTEMS**

Is Impacted By

A. Polymer Morphology

B. Temperature

C. Age/Sterilization

D. STRUCTURE & MOLECUALR WEIGHT of Leachable

D. Structure & Molecular Weight of LEACHABLE

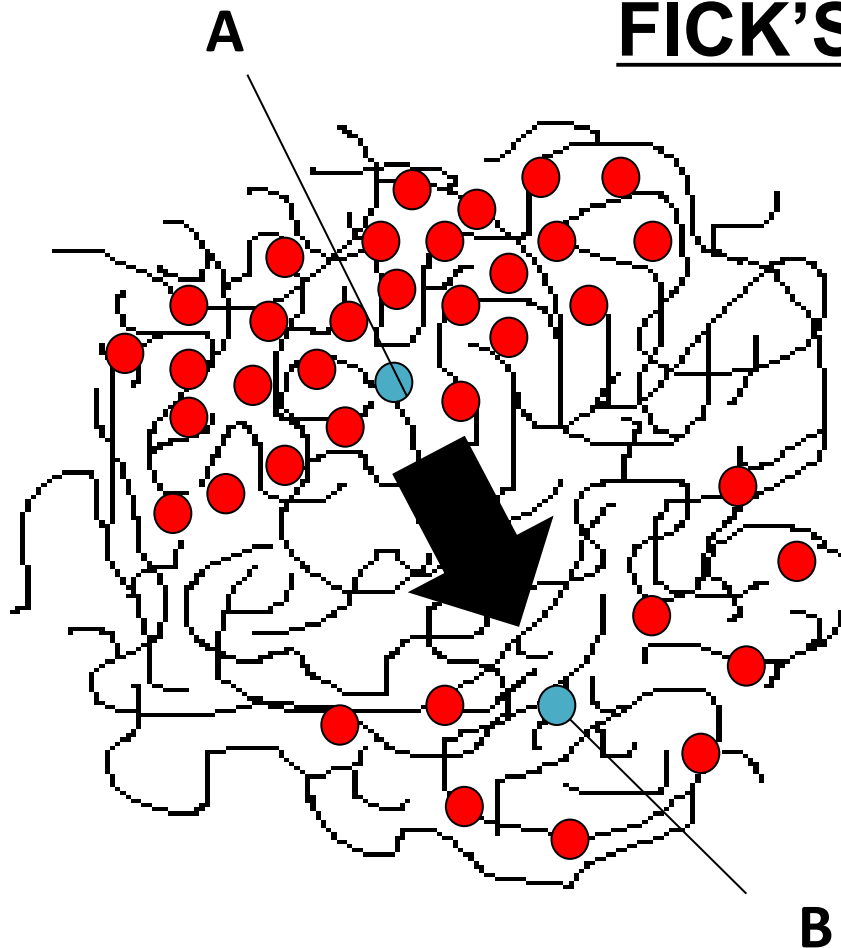» **Molecular Weight**: Larger Molecules = Lower Solubility

BHT (MW 220)

vs.

Irganox 1010 (MW 1176)

» **Polarity "Match":** Structurally ALIKE

» **MELTING POINT**:   higher T_{melt} - lower solubility

impacted by: - molecular symmetry
- crystallinity

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1. **Solubility** of LEACHABLE <u>IN</u> Polymer

2. **Diffusion** of LEACHABLE <u>THROUGH</u> Polymer

FICK'S LAW

A

B

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

With D = Diffusion coefficient
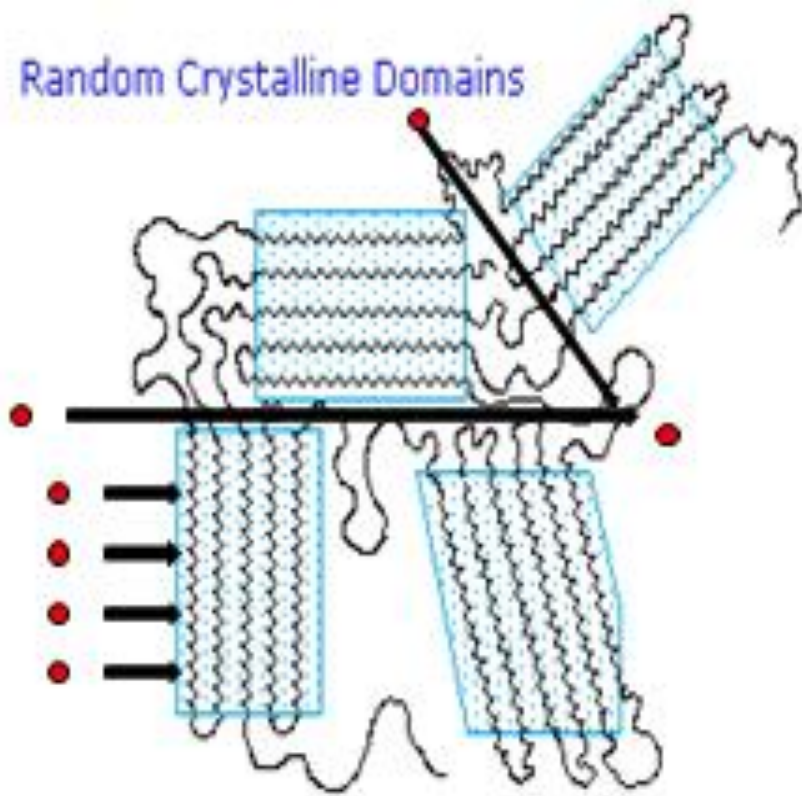
D = D$_0$ exp(-E/RT)

Is Impacted By

A. Polymer Morphology

B. Temperature

C. Polymer Type (T_g)

D. Molecular Weight of LEACHABLE

E. Contact Fluid/Environment

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Is Impacted By

A. POLYMER MORPHOLOGY

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A. Polymer Morphology

Random Crystalline Domains

» **Crystalline Sites:**
   Impermeable Barrier
   for Polymer Additives

» **Filler Particles:**
   Diffusion Barriers for
   Polymer Additives

» **<u>Less Diffusion in:</u>**
   SEMI-CRYSTALLINE POLYMERS

Is Impacted By

A. Polymer Morphology

B. TEMPERATURE

C. Polymer Type (T$_g$)

D. Molecular Weight of LEACHABLE

E. Contact Fluid/Environment

B. Temperature

Remember:

$$D = D_0 \, e^{(-E/RT)}$$

Therefore:

If T ↑, then D ↑

DIFFUSION of impurities/polymer additives will <u>**Increase Exponentially**</u> when <u>**Temperature Increases**</u>
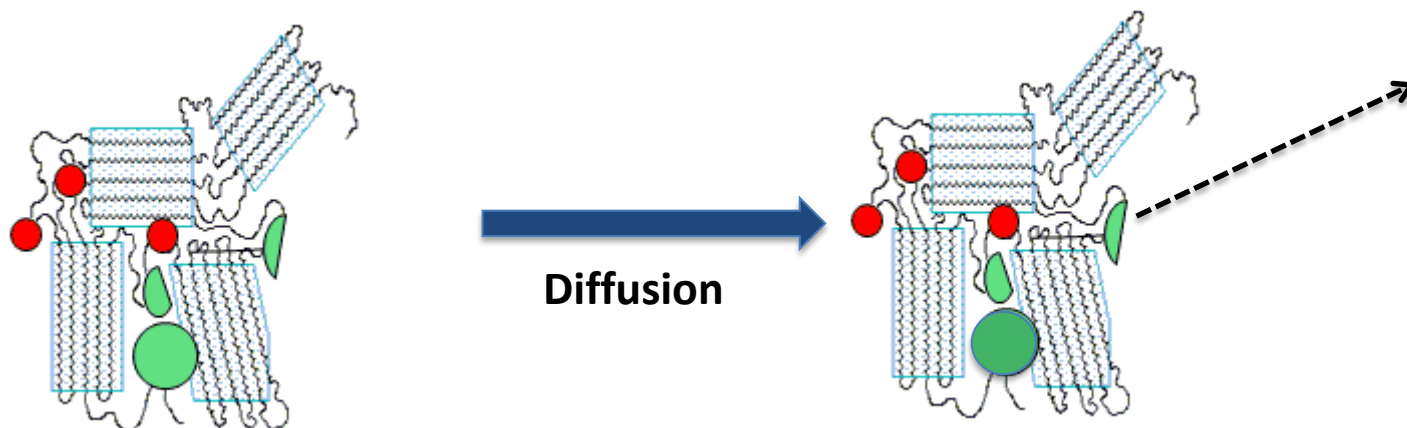
Is Impacted By

A. Polymer Morphology

B. Temperature

C. **POLYMER TYPE (T_g)**

D. Molecular Weight of LEACHABLE

E. Contact Fluid/Environment

C. Polymer Type

Glass Transition Temperature (T_g)

Polymer transitions from   **GLASSY** $(t < T_g)$

to   **RUBBERY** $(t > T_g)$

EXAMPLES

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

DIFFUSION IN APOLAR > DIFFUSION POLAR POLYMERS

C. Polymer Type

FREE VOLUME

Ratio of:
<u>Interstitial space (between polymer chains)</u>
Total Volume of the Polymer

Polymers in a **Rubber State** ($T_g < t$)
Typically have **HIGHER** Free Volume

More <u>Free Volume</u> PROMOTES Diffusion

Is impacted by

A. Polymer Morphology

B. Temperature

C. Polymer Type (T_g)

D. **MOLECULAR WEIGHT OF LEACHABLE**

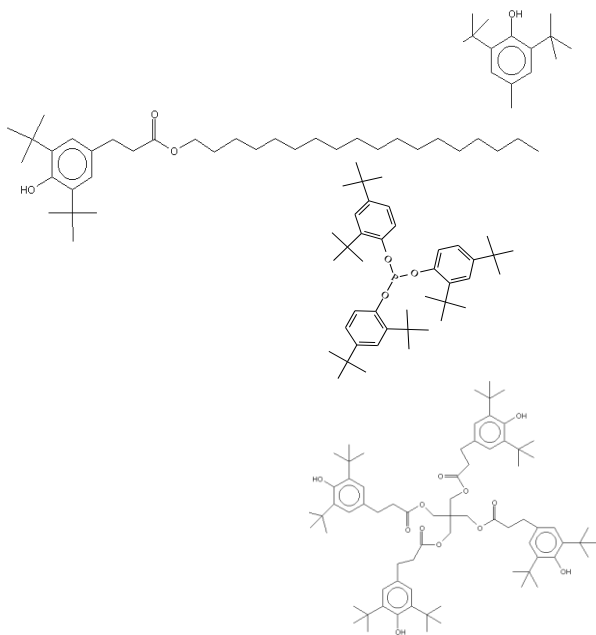E. Contact Fluid/Environment

D. Molecular Weight of LEACHABLE

Diffusion Increases with Decrease in M.W.

Diffusion

OLIGOMERIC ADDITIVES → REDUCING DIFFUSION

BHT: M.W.   220: **HIGH DIFFUSION**
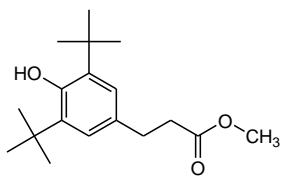
Irganox 1076: M.W.   530

Irgafos 168:   M.W.   646

Irganox 1010: M.W. 1176: **LOW DIFFUSION**

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

Is Impacted By

A. Polymer Morphology

B. Temperature

C. Polymer Type (T_g)

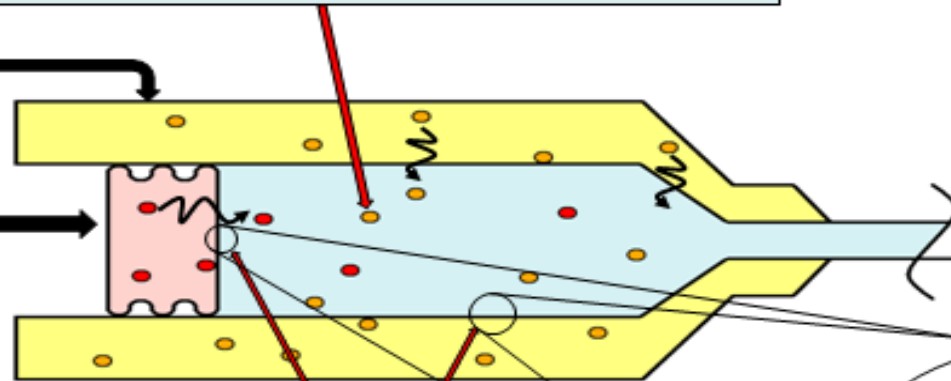D. Molecular Weight of LEACHABLE

E. **CONTACT FLUID/ENVIRONMENT**
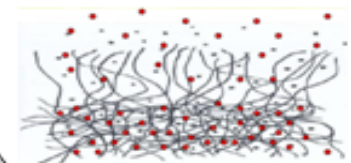
E. Contact Fluid/Environment

Two Important Aspects

Connecting People, Science and Regulation®

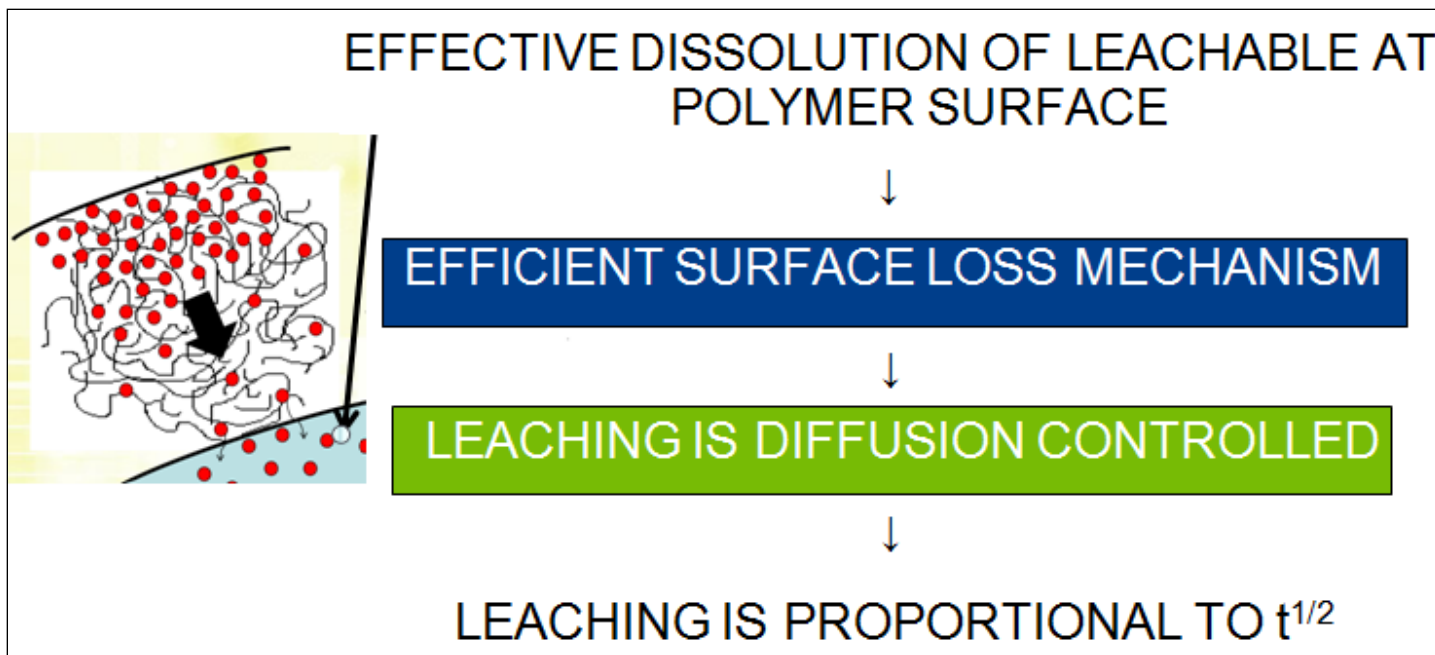## 1. INTERACTION CONTACT FLUID - LEACHABLE
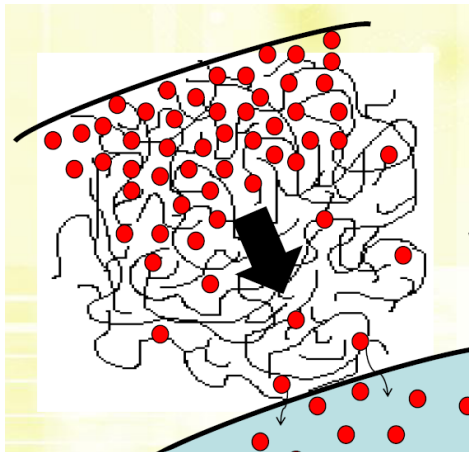
IN GENERAL:

For most Organic Compounds:

ORGANIC/HYDROPHOBIC CONTACT FLUIDS = **HIGH SOLUBILITY** SOLVENTS

WFI/**HYDROPHILIC** CONTACT FLUIDS = **LOW SOLUBILITY** SOLVENTS
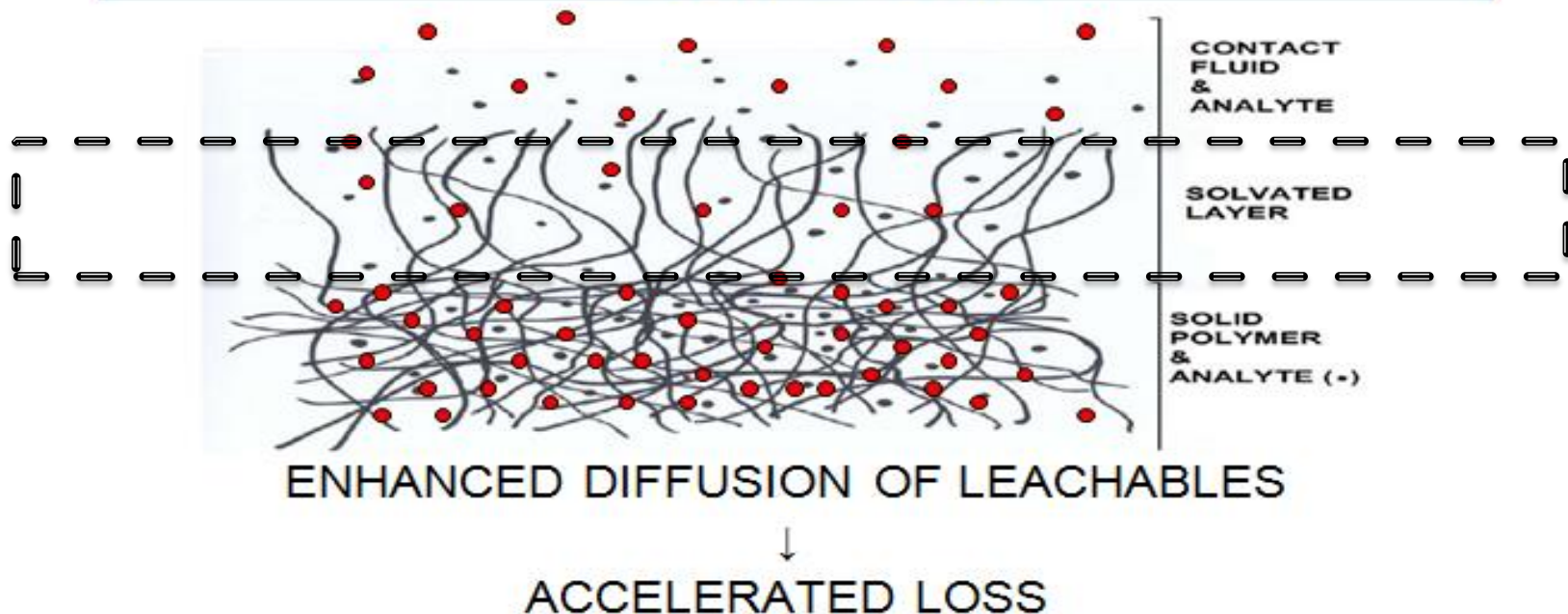
E. Contact Fluid/Environment

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 $t^{1/2}$

E. Contact Fluid/Environment

2. Interaction of the Contact Fluid with the Polymer

1. **Super Saturation**

2. **Outgassing**

3. **Blooming**

SUPERSATURATION

Aluminum cap

Rubber seal

LIQUID FILM

Drug Product
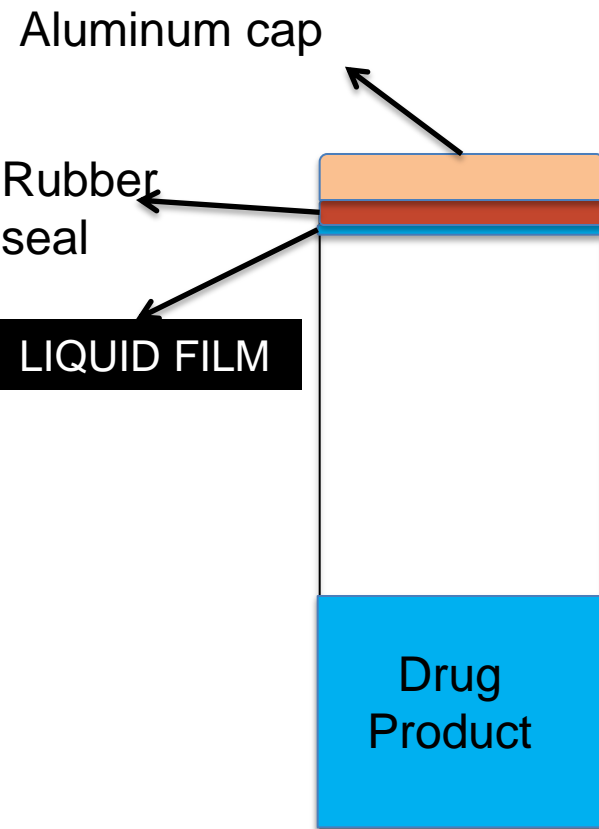
LIQUID FILM is formed via
- Evaporation during storage
- Transportation

Film may be different in composition than the DP

Diffusion of Rubber Compounds into small volume
- Metals
- Organic

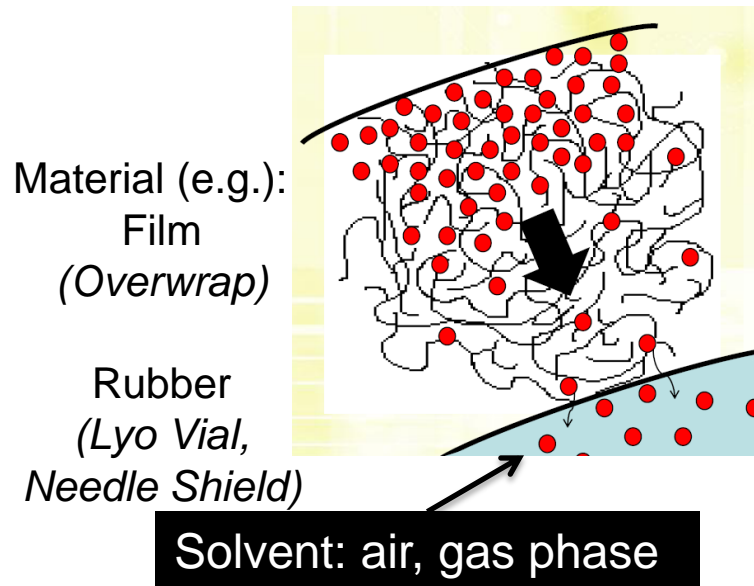Can cause **Aggregation, Particle Formation**

May be **irriversible**
- Particles do not dissolve anymore when in contact with the total DP volume
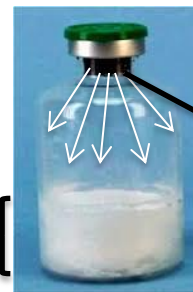
LIQUID FILM may also act as **"barrier"**
- for migration
- for outgassing (see next slide)

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

Rubber
*(Lyo Vial,
Needle Shield)*

Solvent: air, gas phase

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

Lyo Cake
= adsorbent

OUTGASSING of
RUBBER CLOSURE

Outgassing is mainly an issue for:
- Volatile Organic Compounds
- Semi-Volatile Organic Compounds

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...*)

LUNCH TIME ;-)

… buon appetito!