PDA Training Course Extractables & Leachables

23-24 October 2025

The AET Challenge for Large Volume Parenterials (LVPs): Extractables Simulation Studies and How to Design Them

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Training Outline

- What is an Large Volume Parenteral (LVP)?
- The LVP Challenge – How Low Can You Go?
- The Simulation Study as a Means of Addressing the LVP Challenge
- Design Parameters for Effective Simulation Studies
  - Extraction Solvent Composition
  - Temperature and Duration
  - Stoichiometry

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Pharmaceutical Dosage Forms

Different Dosage Forms

Types of Dosage Forms

Classifications Based on Route/ Method of Administration

- Topical Dosage Forms
- Parenteral Dosage Forms
- Vaginal Dosage Forms
- Nasal Dosage Forms
- Oral Dosage Forms
- Rectal Dosage Forms
- Respiratory/Inhaled Dosage Forms
- Ophthalmic Dosage Forms
- Otic Dosage Forms

Classifications Based On the Physical Form of the Dosage Form

- Solid Dosage Forms
- Semi-solid Dosage Forms
- Liquid Dosage Forms
- Gaseous Dosage Forms

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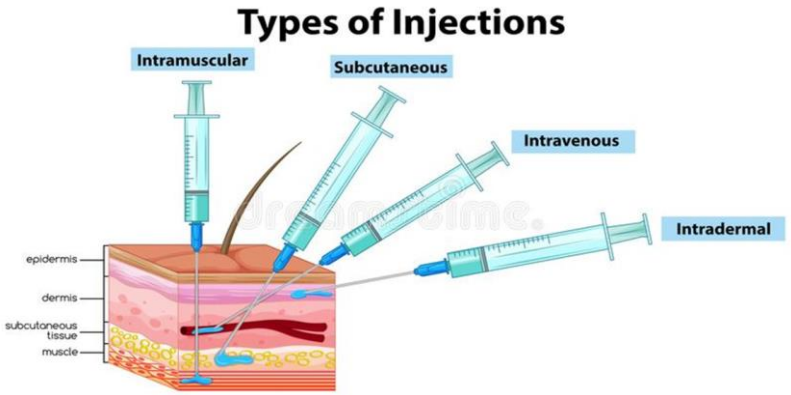
Parenteral Dosage Forms

Parenteral drug products are injected through the skin or other external boundary tissue, or implanted within the body, **to allow the direct administration of the active drug substance**(s) into blood vessels, organs, tissues, or lesions. Parenteral dosage forms include solutions, suspensions, emulsions, sterile powders for solutions and suspensions (including liposomes), implants (including microparticles), and products that consist of both a drug and a device such as drug-eluting stents.

Routes of Parenteral Administration

- Intravenous injections and infusions
- Subcutaneous injections
- Intramuscular injections
- Intradermal injections
- Intra-arterial injections
- Intra-cardic injections
- Intraspinal injections
- Intra-articular injections



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What is an LVP?

A **single-dose injection** that is intended **for intravenous use** and is packaged in containers labeled as containing **more than 100 mL**.

Characteristics of LVPs

- Packaged in glass bottles or in large volume flexible containers.
- May contain greater than 100 mL to greater than 1 or 2 L
- Sterile (e.g., many LVP are **sterilized in their container via heat**, although some are sterile-filled)
- Pyrogen-Free
- Essentially free of particulate matter
- No anti-microbial agents
- Isotonicity
- Longer term use

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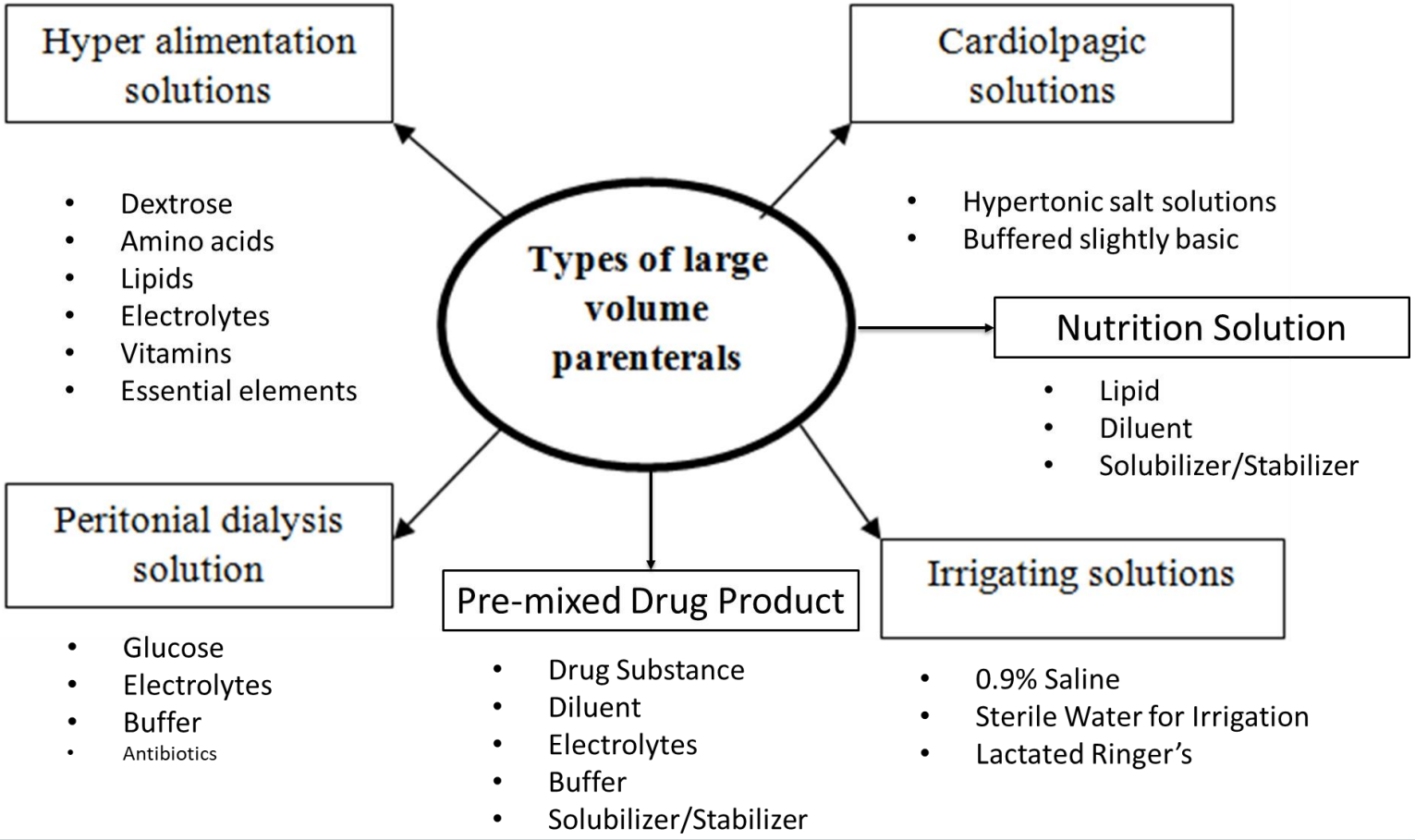
Types and Compositions of LVPs



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Generic Composition of an LVP

- **Vehicle**
  - Water
  - Water miscible vehicle
  - Non-aqueous vehicle
  - Solid Vehicle
- **Active ingredient**
- **Added substances**
  - Tonicity Adjusters
    - Electrolyte, NaCl, 0.5 – 0.9%
    - Non-electrolyte, Dextrose, 4 – 5%
  - Buffers
    - Acetate/Citrate, pH 3 - 6
    - Phosphate, pH 6 - 8
    - Glutamate, pH 8 - 10
  - Antioxidant, 0.1 – 0.5 %
  - Preservatives, 1 – 2%
  - Complexing agents, 0.01 – 0.05%
  - Surfactants, 0.05 – 0.5%
  - Competitive Binders, variable
  - Antimicrobial agents, 0.01%
  - Cryoprotectors/Lyoprotectors (Bulking agents), e.g., 1 – 10%
  - Etc.

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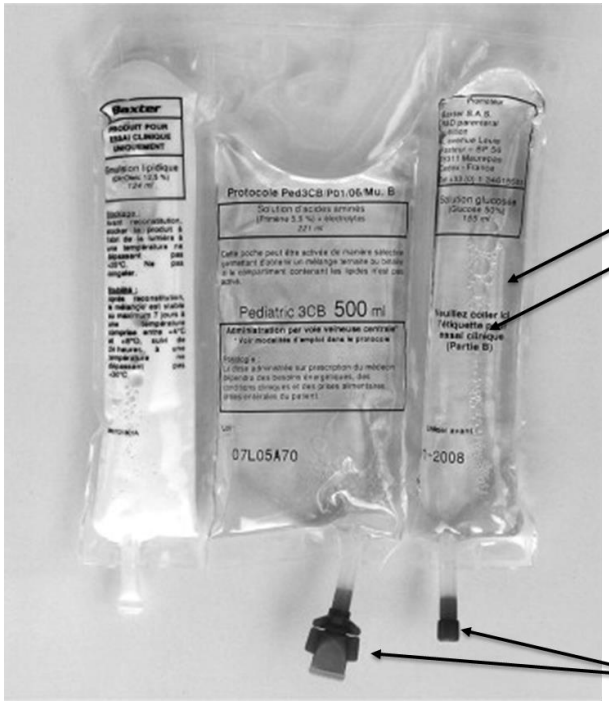
Packaging for LVPs



Container

Printing (label)

Access Port
(elastomeric septum not shown)

Printing (label) on overwrap

Overwrap

Auxiliary Items
(e.g. oxygen absorber)

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The LVP Challenge for Leachables

Among the numerous characteristics that differentiate Large Volume Parenterals (LVPs) from other dosage forms, their **composition** and **large daily dose volume** are particularly noteworthy because of the practical implications of composition and dose volume to the safety assessment of packaging system leachables.

versus

versus

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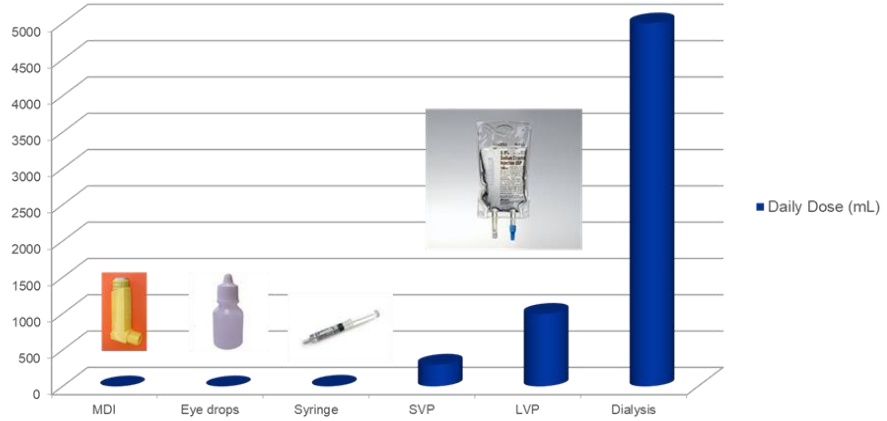
The LVP Challenge for Leachables

Composition

Leachables Profiling Scale:

Easier to do — 0 1 2 3 4 5 6 7 8 9 10 — Harder to do

Daily Dose Volume



Leachables Profiling Scale:

Easier to do — 0 1 2 3 4 5 6 7 8 9 10 — Harder to do

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Why is Daily Dose Volume Important?

One of the most basic concepts in toxicological assessment is that:

“The dose makes the poison.”

A substance can adversely affect health only if the amount of the substance to which an individual is exposed (dose) exceeds a tolerable threshold.

Paracelsus, the “Father” of modern toxicology

Dose = concentration in medication x volume of medication used

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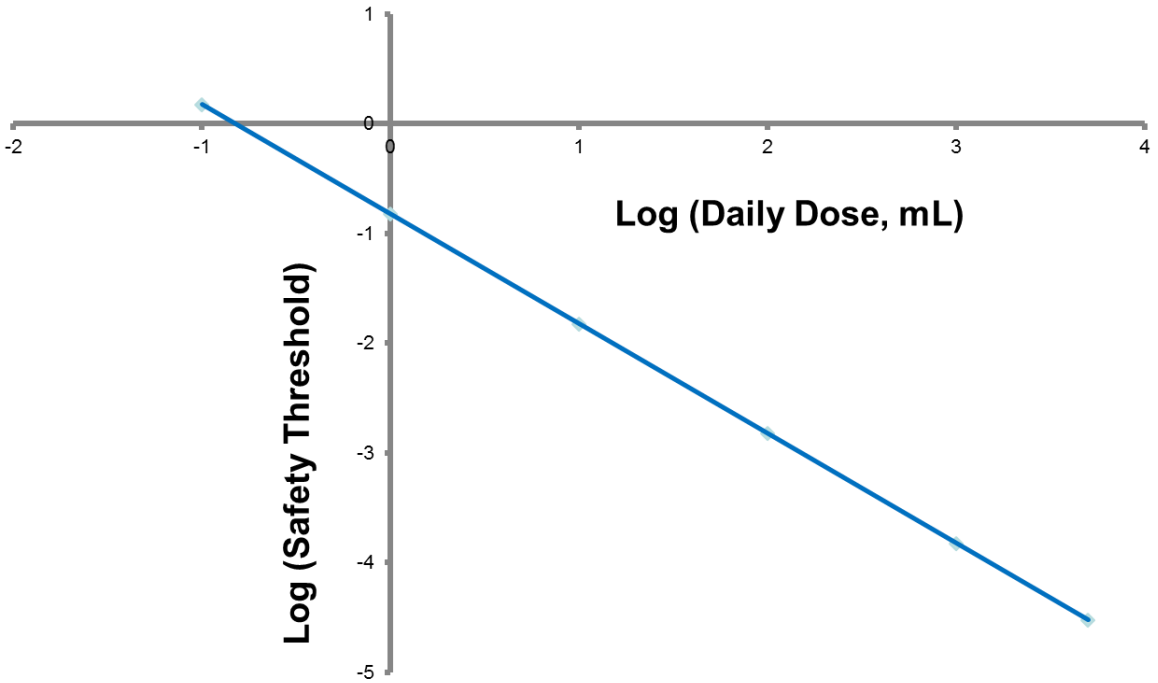
Why is Daily Dose Volume Important?

The value of the Safety Threshold decreases in direct proportion to the increase in Daily Dose Volume.



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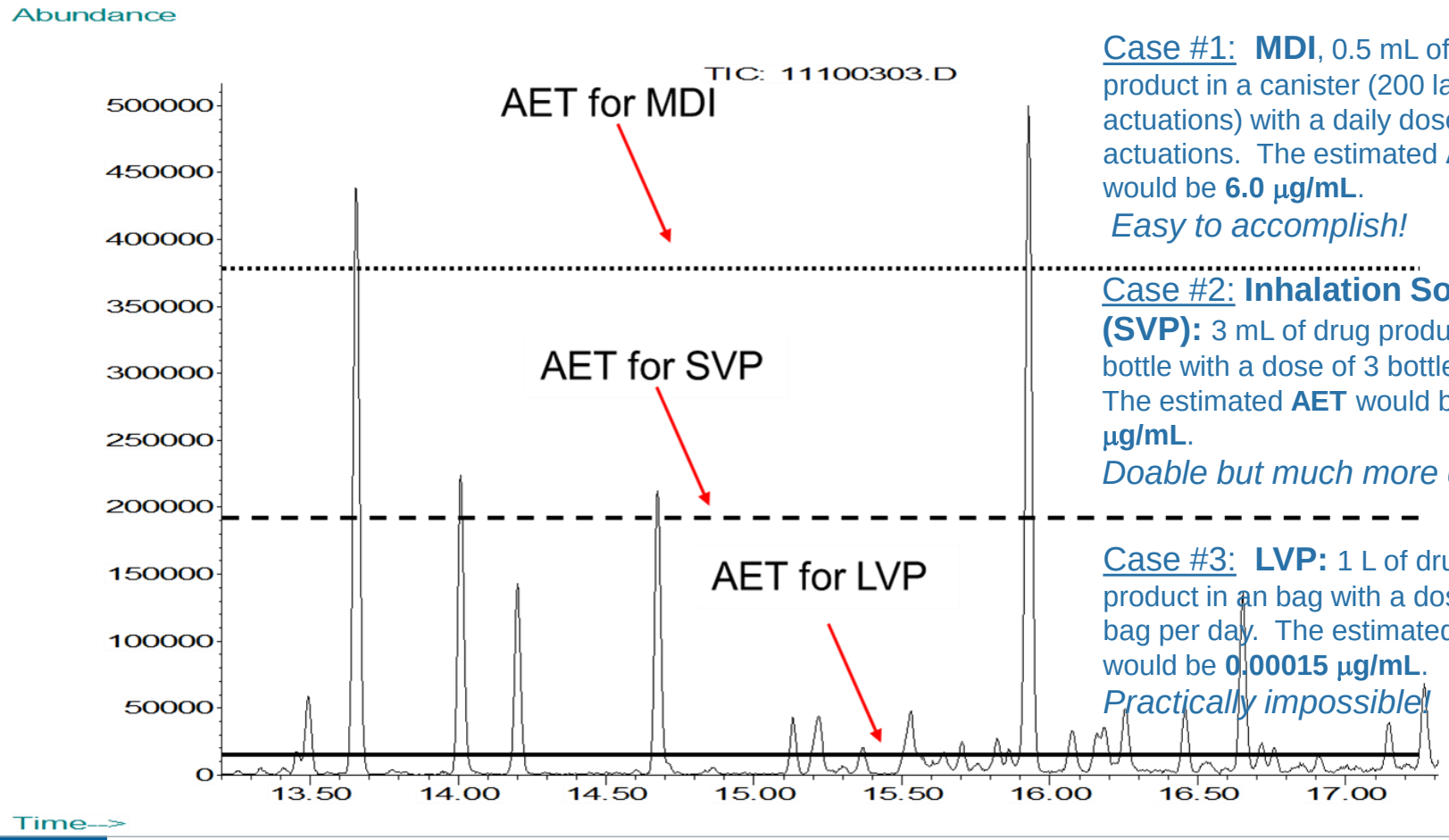
Daily Dose Volume and the AET



Case #1: **MDI**, 0.5 mL of drug product in a canister (200 labeled actuations) with a daily dose of 10 actuations. The estimated **AET** would be **6.0 µg/mL**.

Easy to accomplish!

Case #2: **Inhalation Solution (SVP):** 3 mL of drug product in a LDPE bottle with a dose of 3 bottles per day. The estimated **AET** would be **0.017 µg/mL**.

Doable but much more difficult!

Case #3: **LVP:** 1 L of drug product in an bag with a dose of one bag per day. The estimated **AET** would be **0.00015 µg/mL**.

Practically impossible!

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The LVP Challenge: How Low Can You Go?

AETs for LVPs may be so low that even state of the art, best demonstrated practice analytical methods may not be able to accomplish the functions of discovery and identification for all necessary leachables.

If leachables cannot be detected and identified then obviously they cannot be toxicologically assessed by numerical means and thus their potential safety impact cannot be established by such numerical means.

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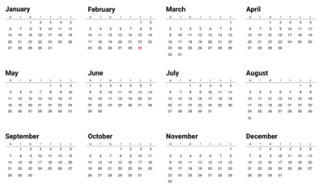
The Simulation Study Goes Low!

1. The drug product formulation has been replaced with one or more simulating solvents that are easier to test.

2. The actual use conditions of contact have been accelerated.



3. The test article may have been altered (somewhat) to provide an exaggerated and presumably worst case.

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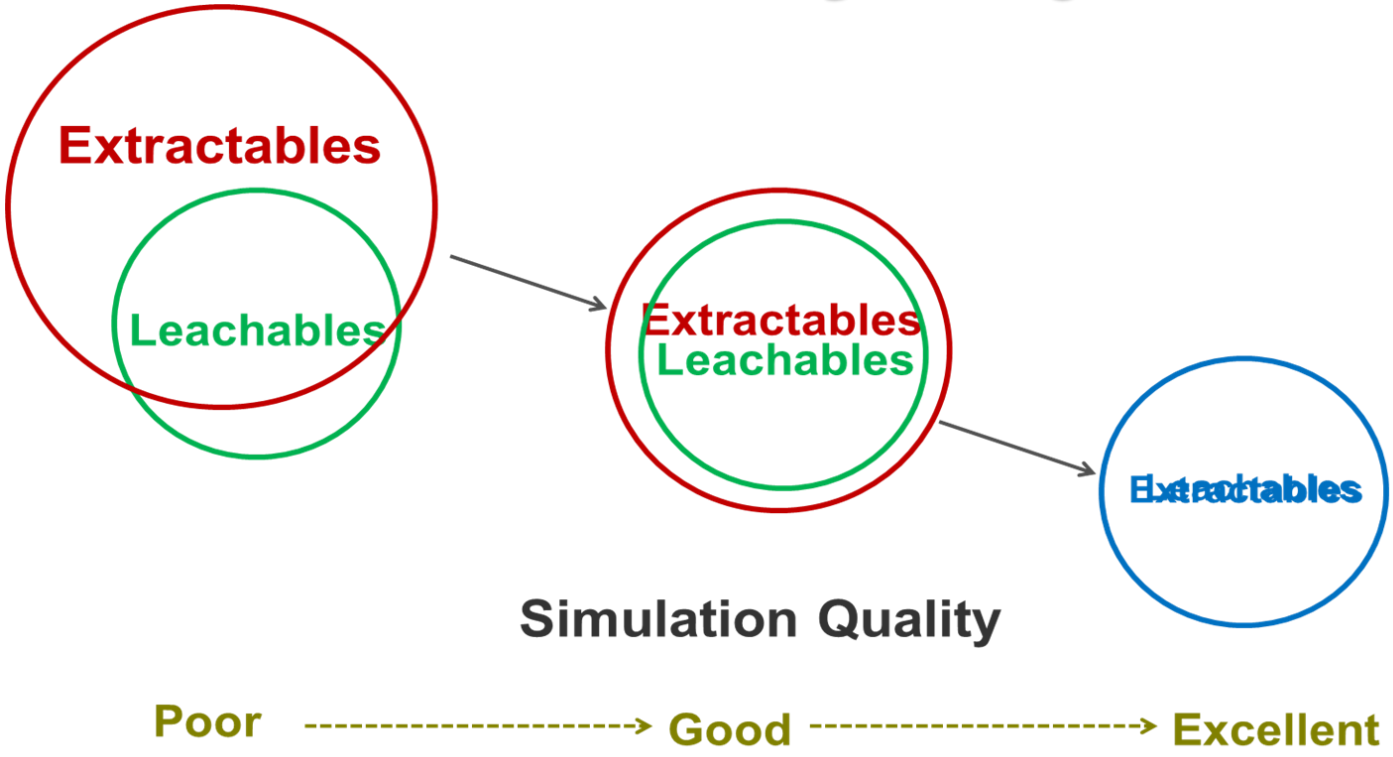
Simulation Study Objectives



An extractables profile that is the same as a drug product's leachables profile (meaning that the extractables profile includes all the members of the leachables profile with extractables levels being greater than or equal to the leachables levels).

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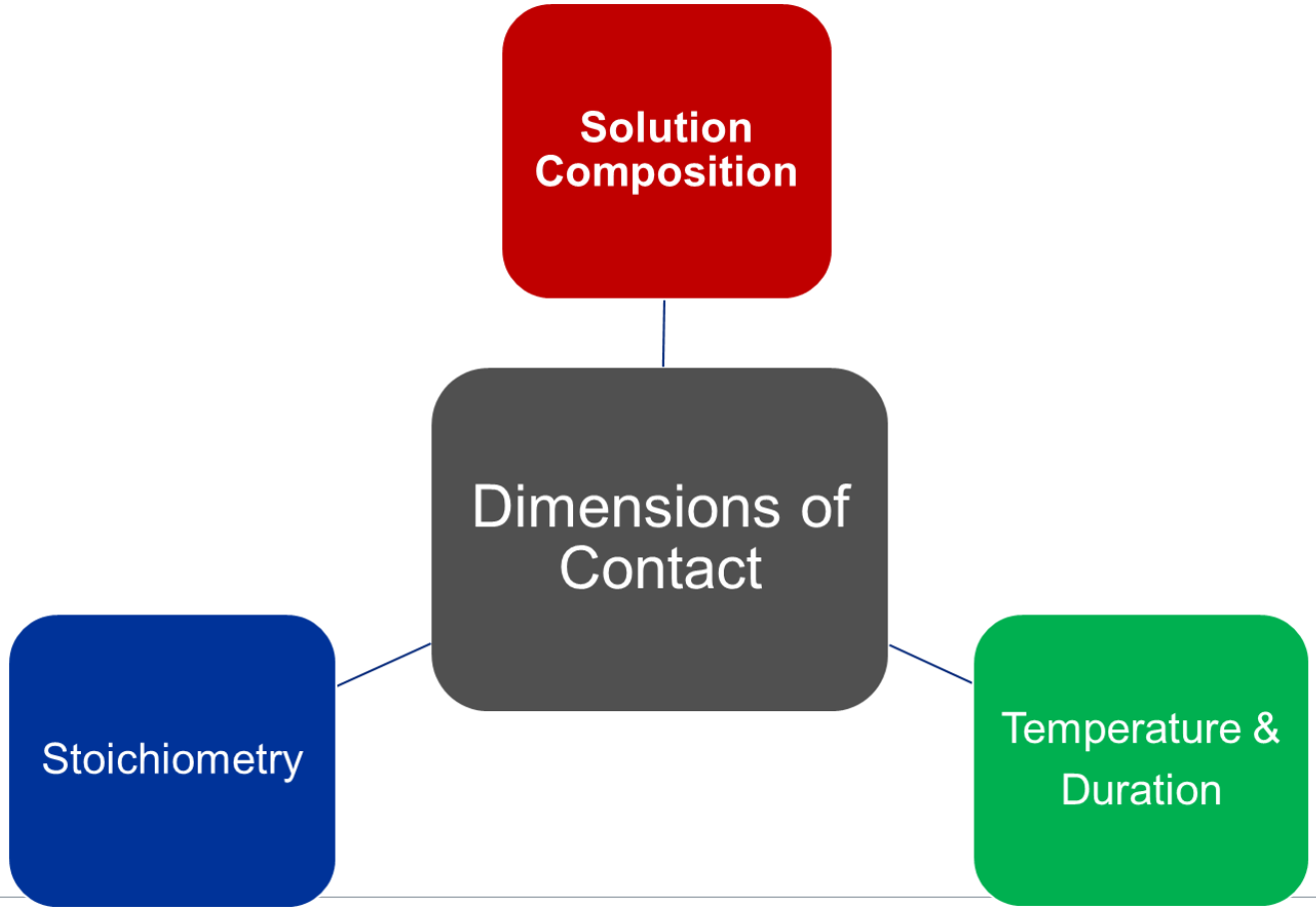
Key Design Parameters to Simulate



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Simulating Solution Composition

Solution Composition

1. Polarity
2. pH
3. "Reactivity"

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Simulating Polarity

- **A leachable will accumulate in a drug product to a level dictated by its solubility in the drug product.**
- **A leachable's solubility in a drug product will depend on the "polarity" of the leachable and the drug product ("Like dissolves like").**

Means of Establishing a Solution's Polarity:

1. Polarity Tables for Solvents
2. Correlation with Measurable Fundamental Properties – Dielectric Constant
3. Use of Polarity Markers (e.g., solvatochromic Reichardt's dye)
4. Experimental Determination via "Extraction Power" Scales

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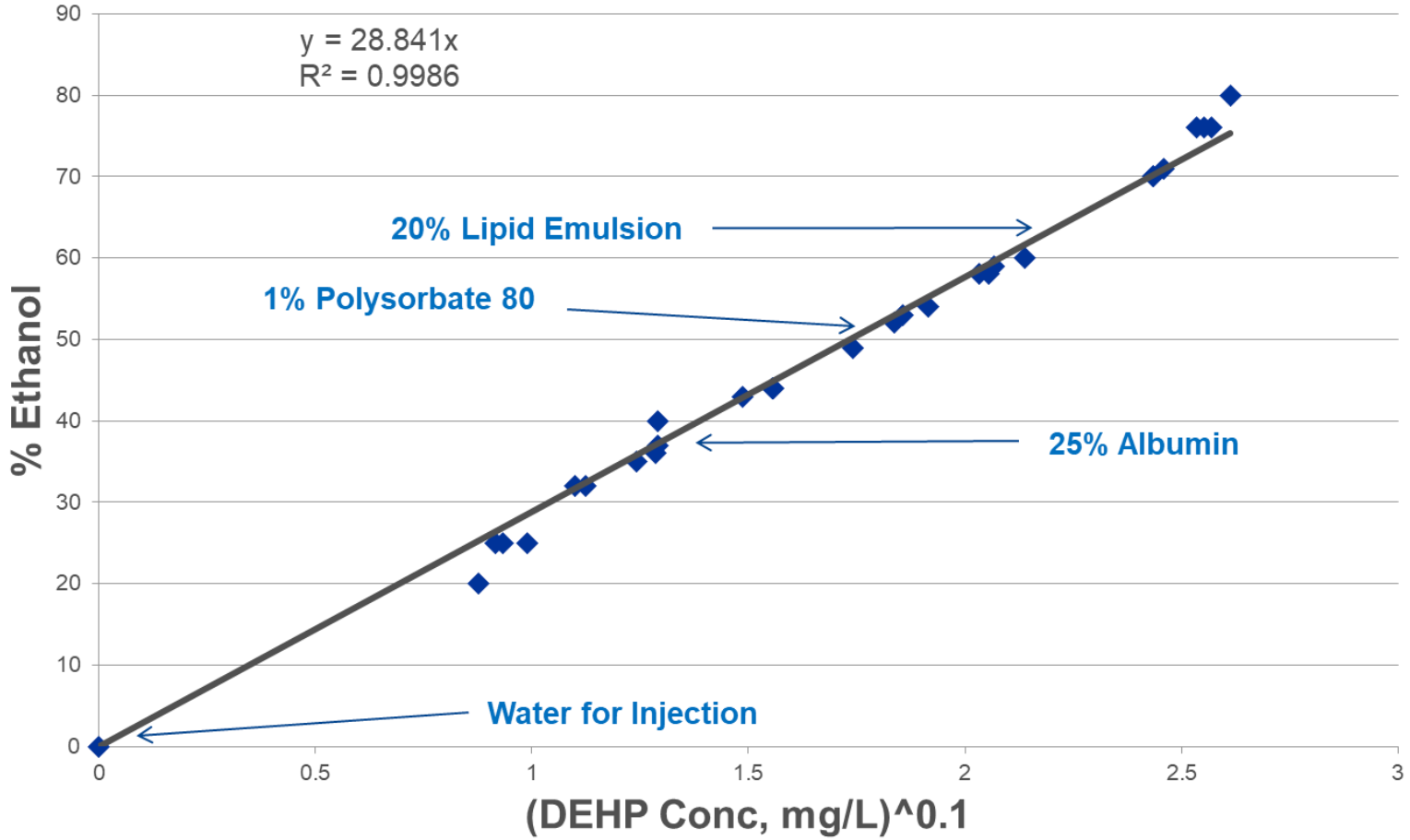
An “Extraction Power” Scale



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Source: Jenke, D.; Liu, N.; Hua, Y.; Swanson, S.; Bogseth, R. A means of establishing and justifying binary ethanol/water mixtures as simulating solvents in extractables studies. *PDA J Pharm Sci Technol.* **69(3):** 366-38 2(2015).

Realistic Expectations About Simulating Polarity

Realistically,

- Many LVP's are aqueous solutions containing inorganic and organic salts, acids, bases and organic compounds of high aqueous solubility (e.g., dextrose) and no solubility enhancers (e.g., Tween 80). In these cases, use of polar simulating extraction solvents is appropriate.
- A few LVPs, for example nutritional products, may contain lipids and proteins in relatively high concentrations (e.g., up to 20 - 25% by weight). As the presence of these lipids and proteins makes the products more non-polar, use of semi-polar extraction solvents (such as alcohol/water mixtures) may be appropriate.
- LVP's are NEVER non-polar solvents and thus non-polar extraction solvents are NEVER appropriate.

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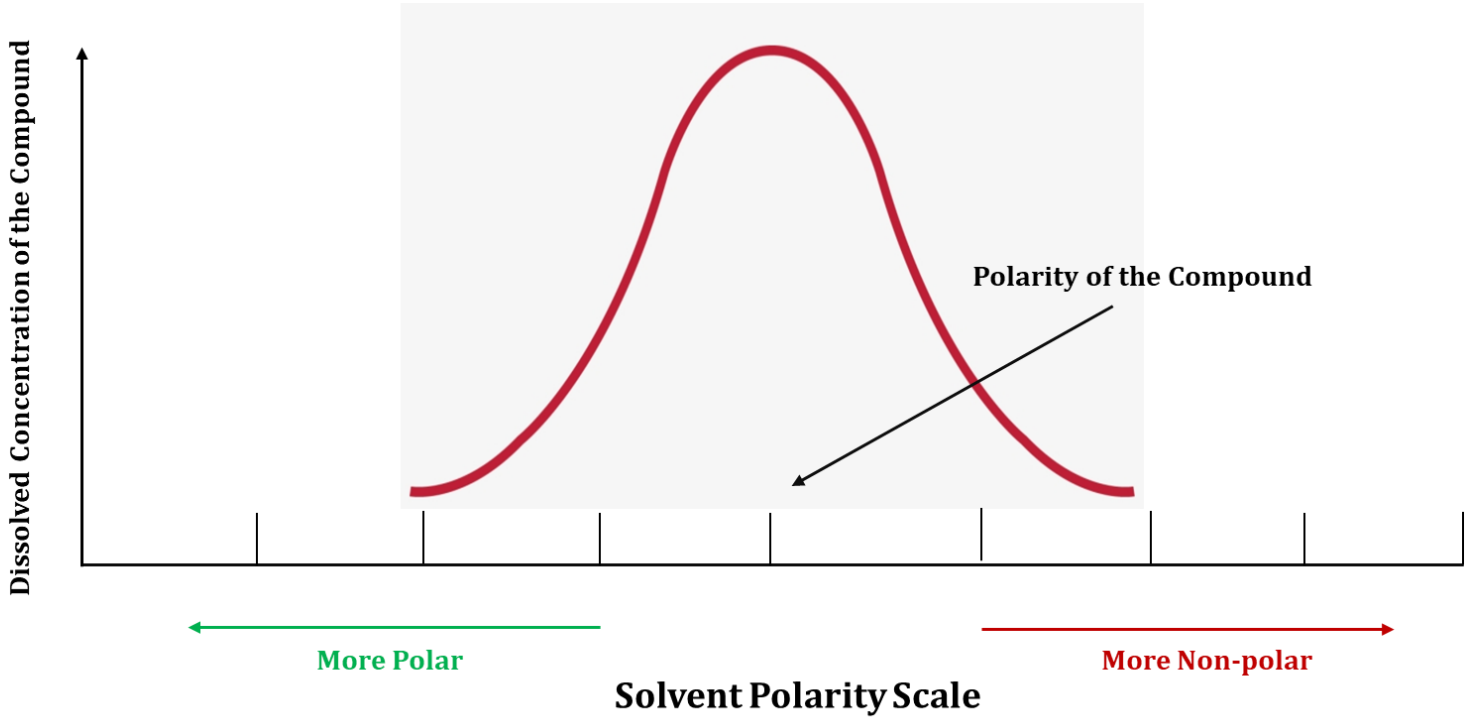
A Brief Lesson on Polarity

In chemistry, "like dissolves like" means that solutes and solvents with similar intermolecular forces tend to dissolve in each other. Specifically, polar and ionic solutes dissolve in polar solvents, while nonpolar solutes dissolve in nonpolar solvents.



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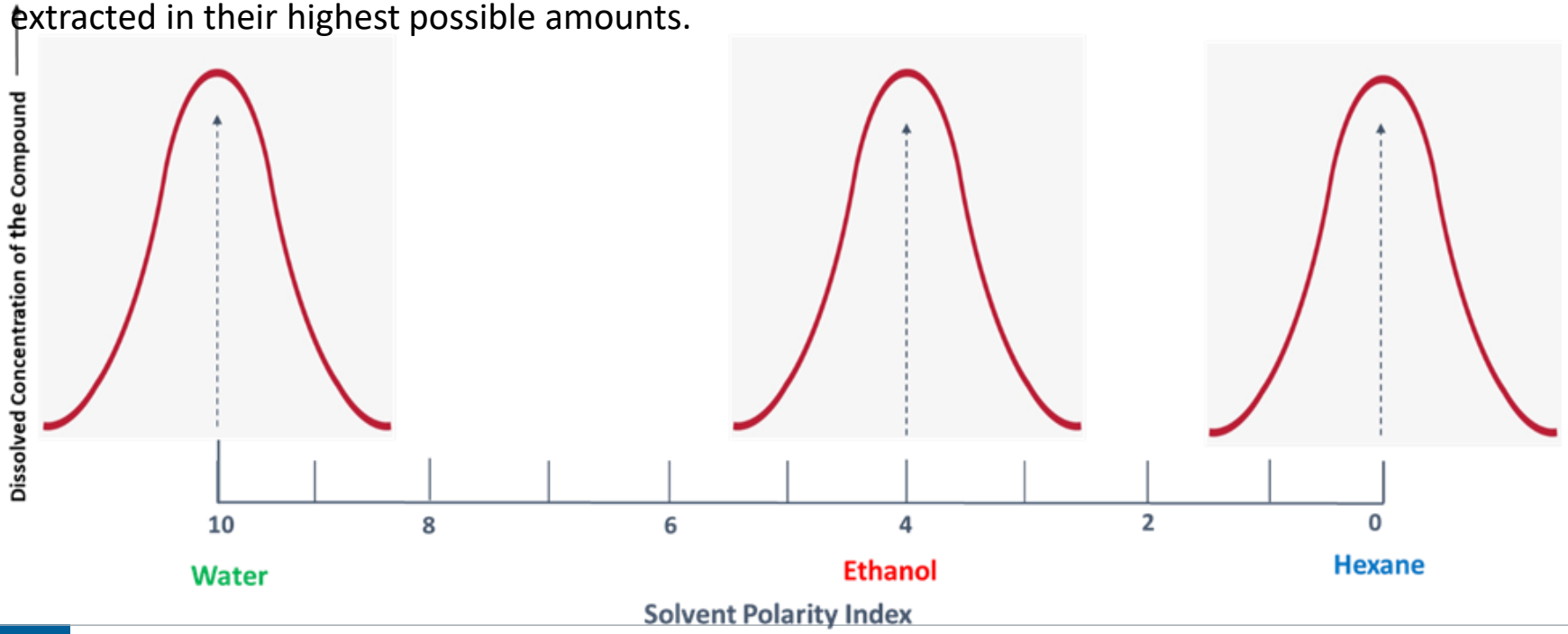
Example Extractables Profiles

Illustration of the Ability of Multiple Solvents to Produce a Worst-Case Extractables Profile; Perfect Case. In this Case, the extractable constituents of a test article include three compounds, one of each having the same polarity as water (polar), ethanol (semipolar), and hexane (non-polar). The arrows denote the extractables profile obtained with the specified extraction solvents. If this test article is extracted with water, ethanol, and hexane, then the extractable profile (all extractables detected in all extraction solvents) will include all three constituents, extracted in their highest possible amounts.



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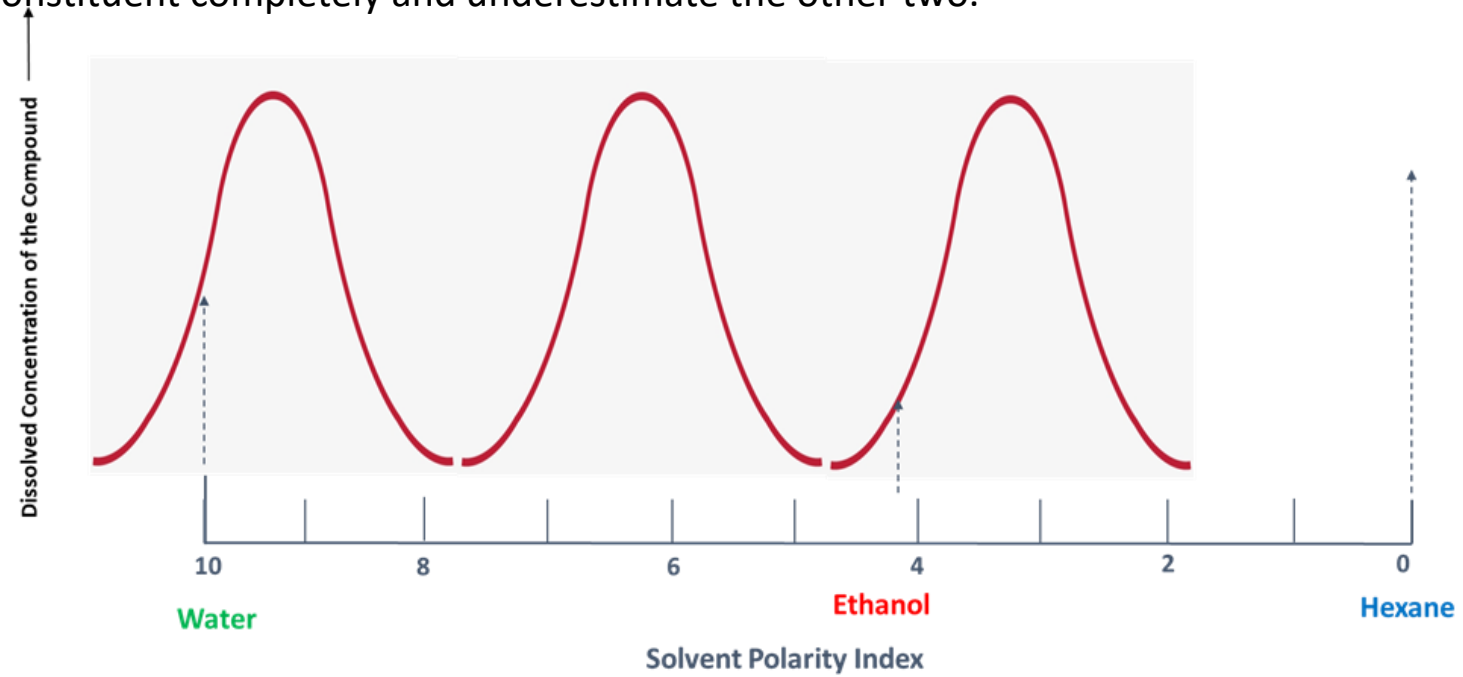
Example Extractables Profiles

Illustration of the Ability of Multiple Solvents to Produce a Worst-Case Extractables Profile; Unfortunate case. In this Case, the extractable constituents of a test article include three compounds, none of which have are non-polar. The arrows denote the extractables profile obtained with the specified extraction solvents. If this test article is extracted with water, ethanol. and hexane, then the extractable profile (all extractables detected in all extraction solvents) will miss one constituent completely and underestimate the other two.



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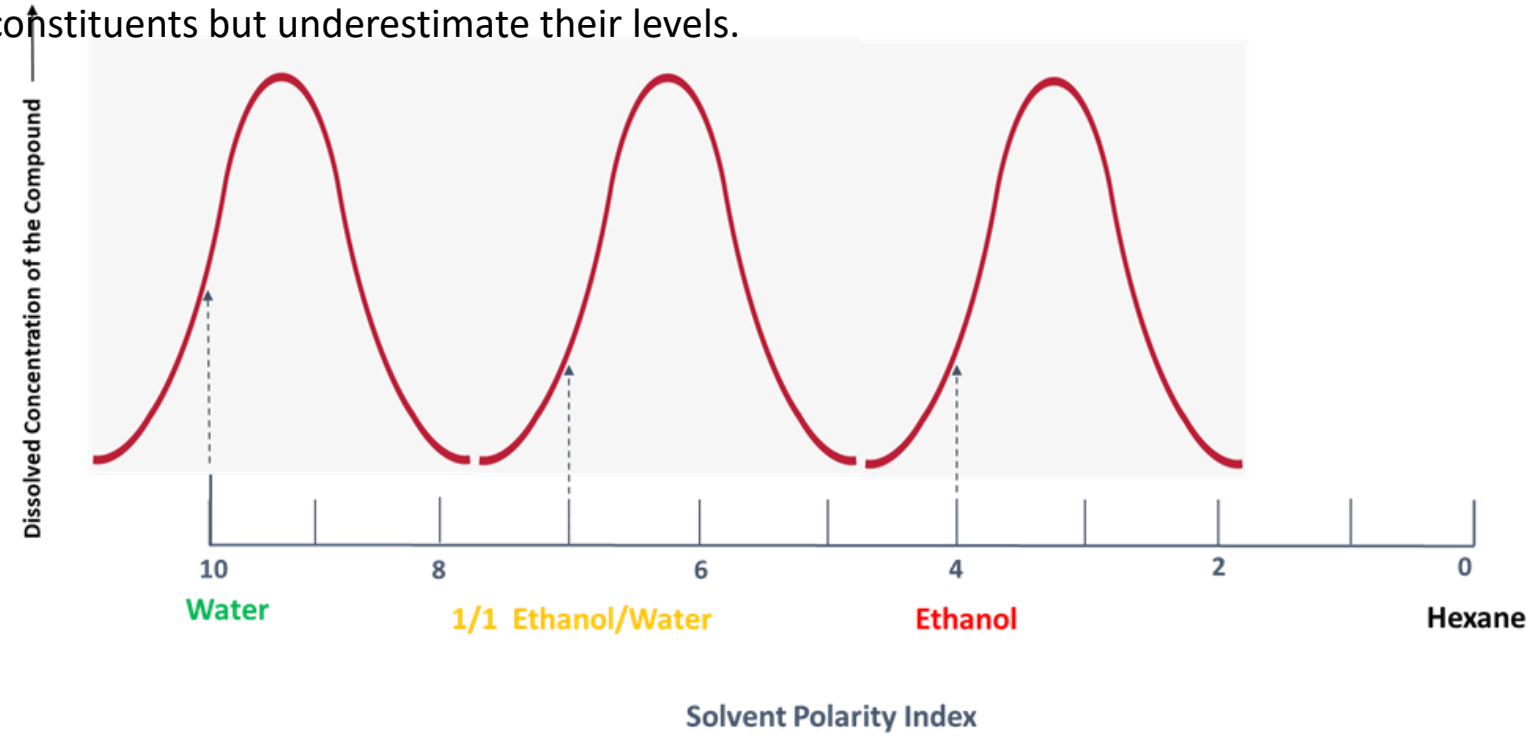
Example Extractables Profile

Illustration of the Ability of Multiple Solvents to Produce a Worst-Case Extractables Profile; Shortening the Playing Field. In this Case, the extractable constituents of a test article include three substances of varying polarity (same substances). The arrows denote the extractables profile obtained with the specified extraction solvents. If this test article is extracted with water, 1/1 ethanol/water and water, then the extractable profile (all extractables detected in all extraction solvents) will include all three constituents but underestimate their levels.



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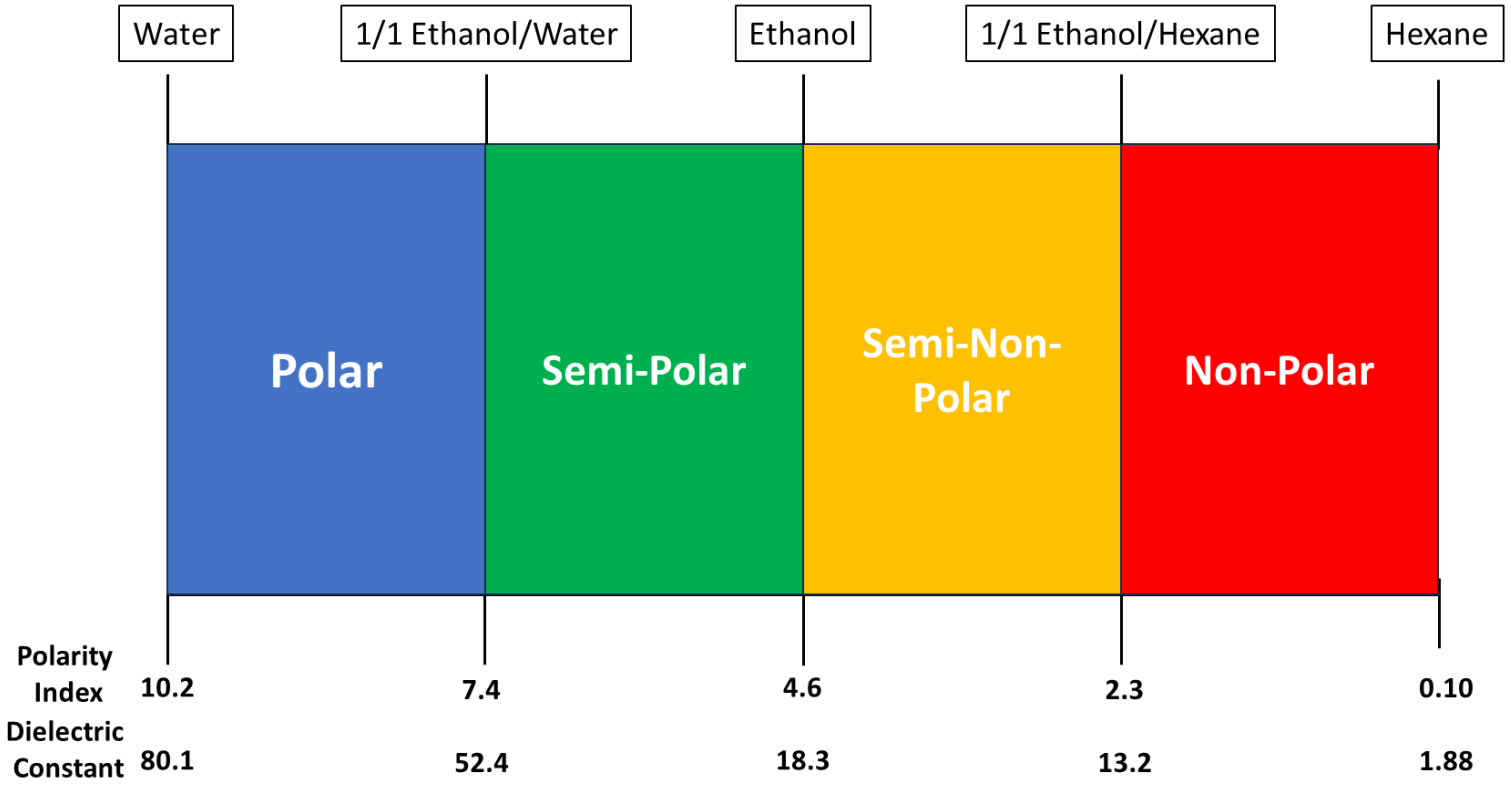
Shorting the Playing Field

By introducing a fourth polarity region (semi-non-polar) and applying the premise that non-polar extraction solvents are irrelevant to implanted medical devices, extraction solvents in the non-polar region are note used, increasing the likelihood that extractables profiles obtained using multiple extraction solvents are relevant to implanted medical devices.



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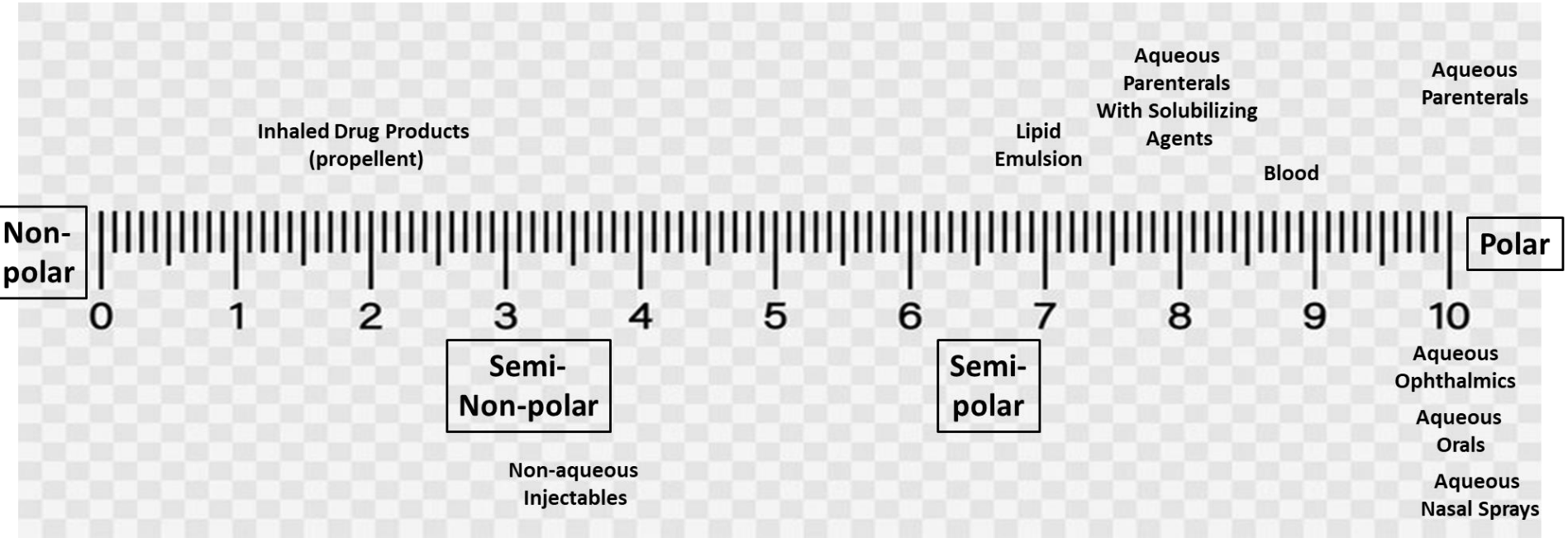
Shorting the Playing Field

Estimated Polarity Indices of Drug Products. None of the considered items are estimated to be non-polar.



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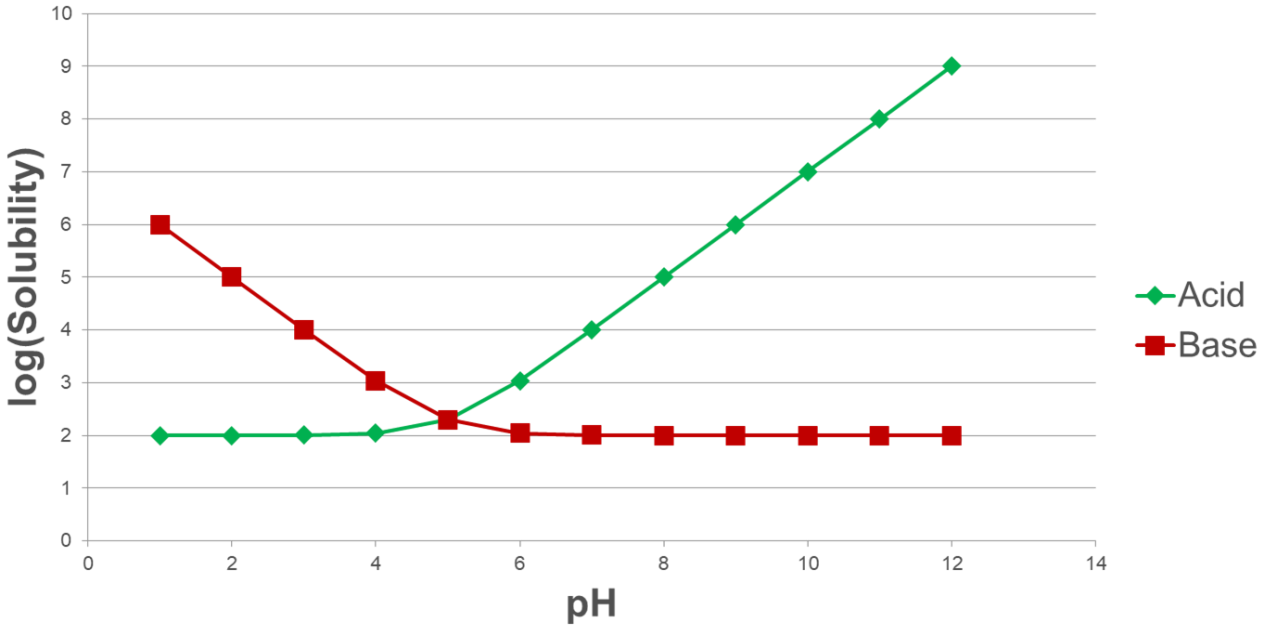
Addressing Solution pH

- A leachable will accumulate in a drug product to a level dictated by its solubility in the drug product.
- The solubility of an acidic or basic leachable will depend on the acid/base dissociation constant (pK_a) of the leachable and the pH of the drug product.



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Simulating pH

- **Most common acidic leachables have a pK_a of 7 or less.**
- **Most common basic leachables have a pK_a of 3 or more.**
- **Most aqueous drug products have a pH between 3 and 9.**

Therefore:

- Two simulating solvents, one prepared at pH 3 and one prepared at pH 10, reasonably bracket the universe of leachables and drug products, although acceptions may require more extreme pH values.
- There is little or no value in using a simulating solvent with an intermediate pH.
- If your drug product(s) have a more narrow pH range, then use a range that is more appropriate.

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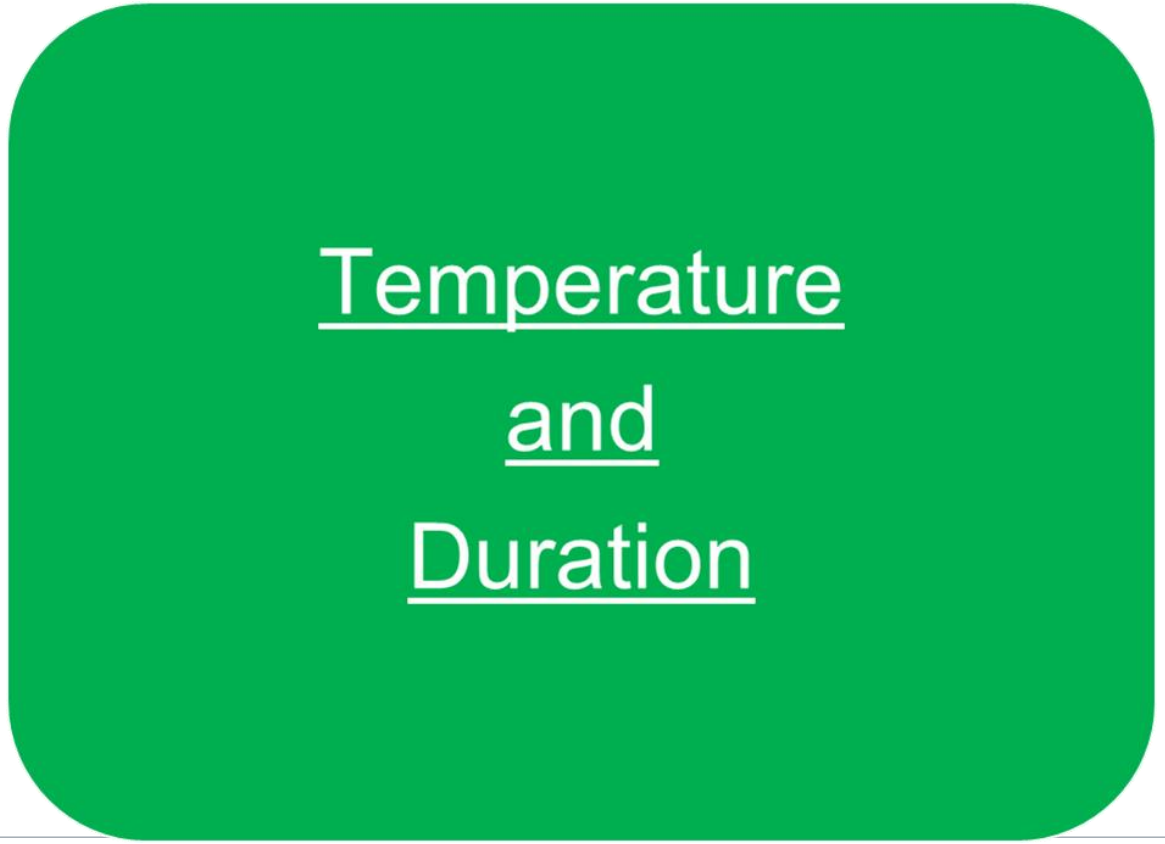
Accelerating Shelf-life:
Temperature and Duration



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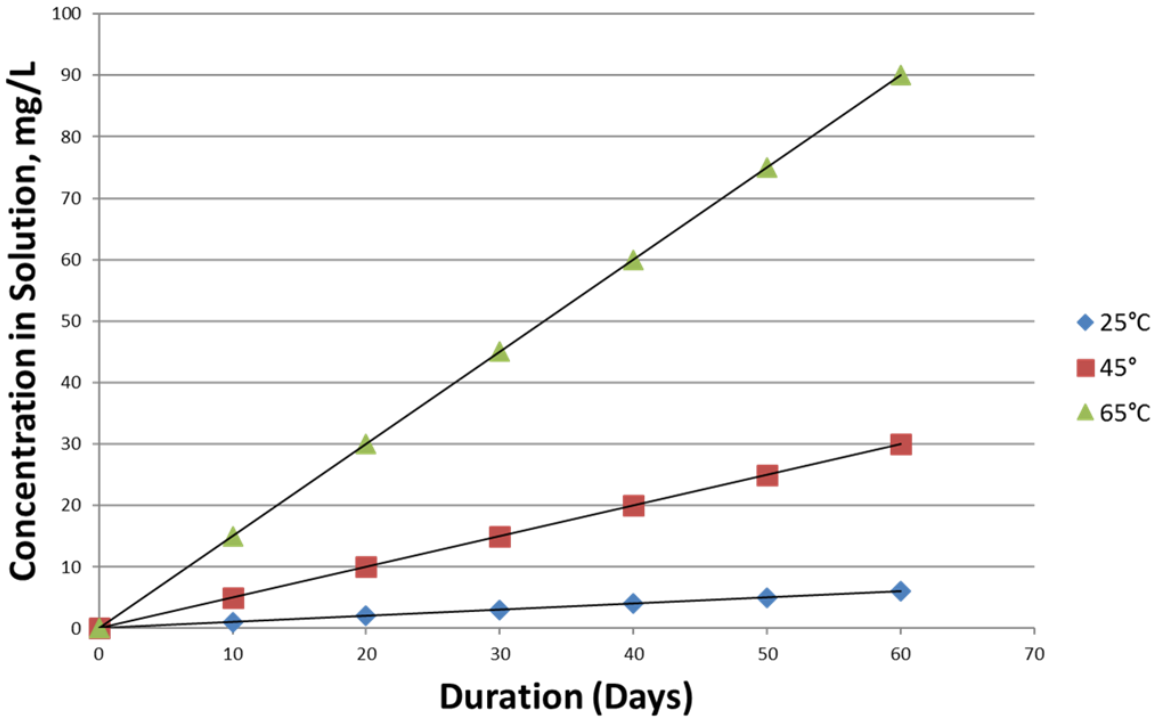
Accelerating an Extraction

The higher the temperature, the longer the extraction and the larger the diffusion coefficient:

1. The larger will be the leachable's concentration in the drug product.
2. The more likely an equilibrium leachable concentration will be achieved.



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Estimating Accelerated Conditions (1)

1. **ASTM F1980-16**: Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices.

Accelerated Aging Time at T2 = Actual Aging Time at T1 ÷ C

$$C = Q_{10}^{[(T2 - T1)/10]}$$

where Q_{10} = 10°C Reaction Rate Constant
T2 = accelerating temperature (°C)
T1 = actual temperature of contact (°C)

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Estimating Accelerated Conditions (2)

2. "Factor 10 Rule"[1]: This factor 10 rule is based on the observation that activation energies for migrating substances in polymers relevant to packaging are typically in the range of 80 to 100 kJ/mole. In such a circumstance, the diffusion coefficient increases by roughly an order of magnitude for every 20°C increase in contact temperature. Thus for example, the migration rate at 40°C is ten times faster than the migration rate at 20°C.

Accelerated Aging Time at T2 = Actual Aging Time at T1 ÷ C

$$C = 10^{[(T2 - T1)/20]}$$

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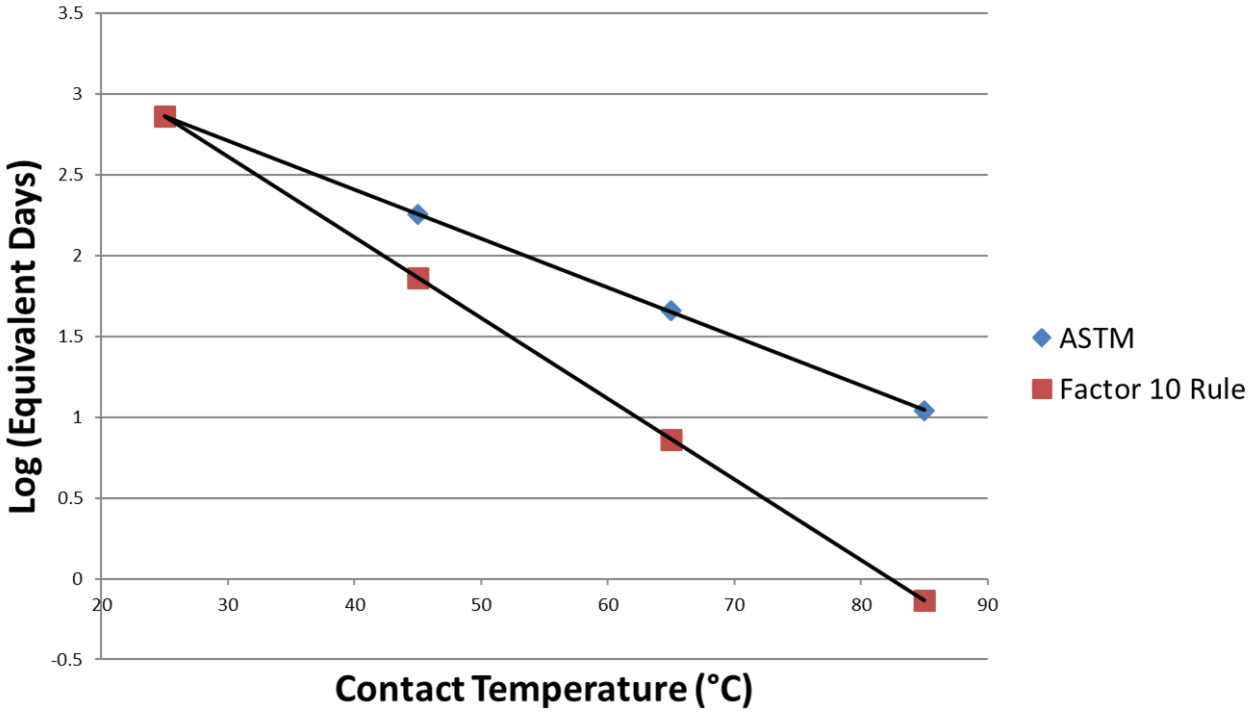
[1]R. Franz, A. Stormer. Migration of Plastic Constituents. In Plastic Packaging: Interactions with Foods and Pharmaceuticals. Wiley-VCH; Second Edition, 2008, pp. 368.

Which Approach to Use?

Acceleration of a Two-Year (730 days) Ambient Temperature Shelf-life



The ASTM approach produces the longest duration is thus **is the most conservative**.

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Example Acceleration Calculation

The time (t_2) required for an extractable to reach a certain concentration at a temperature T2 can be estimated from the time (t_1) required for the same extractable to reach the same concentration at a reference temperature T1 using the following equation, although exceptions will occur:

$$t_2 = t_1 \div 10^{[(T2-T1)/20]}$$

For example, if the time it takes for an extractable to achieve a concentration of 2.0 mg/L at 25°C is 10 hours, the time it takes for the same extractable to achieved the same concentration of 2.0 mg/L at 45°C will be:

$$t_{45} = t_{25} \div 10^{[(45-25)/20]}$$

$$t_{45} = 10 \text{ hours} \div 10^{1}$$

$$t_{45} = 1 \text{ hour}$$

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Extraction Stoichiometry

Stoichiometry

1. Surface area/Solution volume
2. Material weight/Solution volume

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Stoichiometry Fallacies:

1. **Its all about surface area.**

   In fact, what is generally attributed to surface area effects is actually due to changes in the amount (mass) of the extracted item.

2. **As the surface area to solution volume ratio increases, the concentration of extractables will increase in the same linear and 1 to 1 manner for all extractables.**

   In fact, the relationship between the ratio and the concentration depends on the plastic/solution partition coefficient of the extractables in question.

   - **"Solution-loving" extractables' concentrations will increase in proportion to increased ratio (but not 1 to 1)**
   - **"Plastic-loving" extractables' concentration will change very little as the ratio increases.**

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The Stoichiometry Equation

$$C_{l,e} = m_{l,e}/V_l = m_{p,o}/[V_l + (k_{p/l} \times SA_p \times t_p)]$$

Where C is the extractable's concentration,

- m is the mass of the extractable in either phase,
- SA is the surface area of the sample being extracted,
- t is the thickness of the sample being extracted,
- $k_{p/l}$ is the extractable's plastic/solution partition coefficient,
- V is the volume of either phase, and
- the subscripts p, l, e and o refer to the plastic phase, the liquid phase, equilibrium and original respectively

R. Franz, A. Stormer. Migration of Plastic Constituents. In Plastic Packaging: Interactions with Foods and Pharmaceuticals. Wiley-VCH; Second Edition, 2008, pp. 370.

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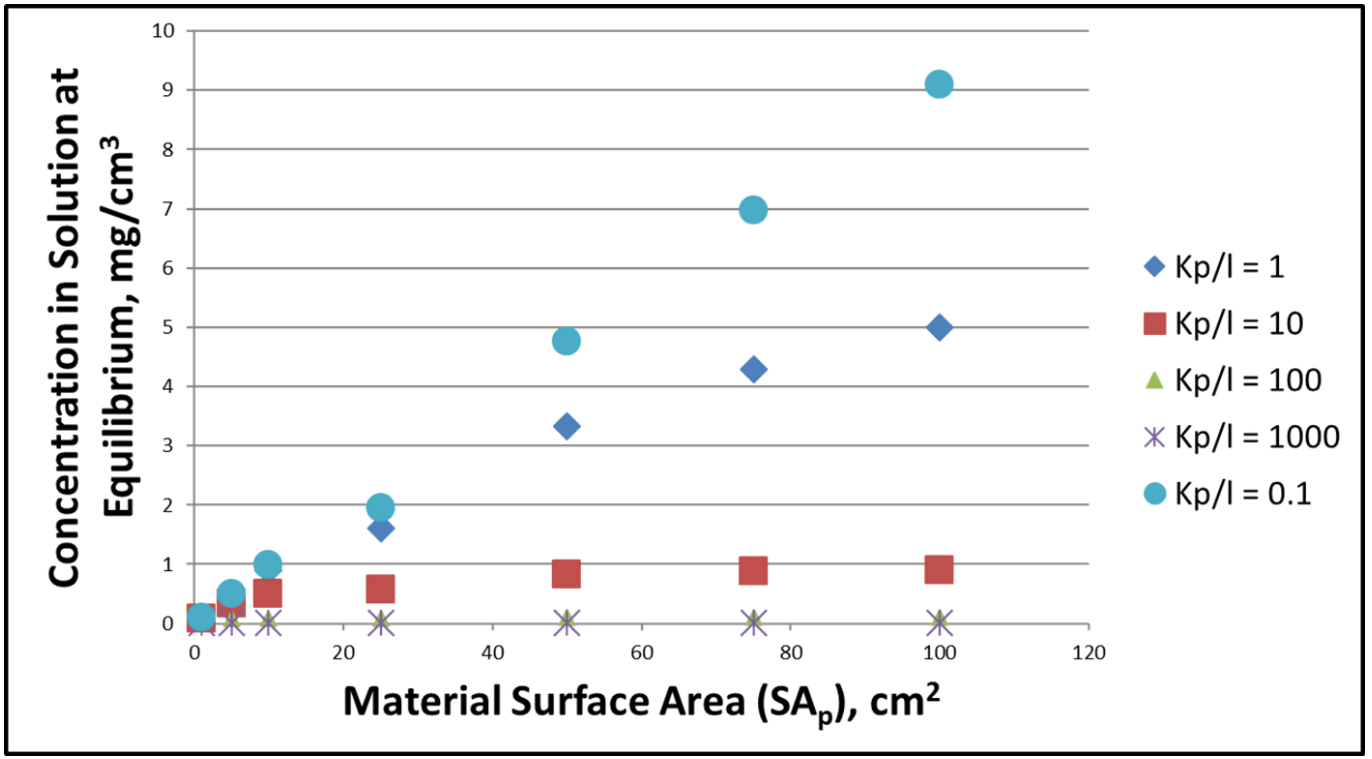
The Real Effect of SA/V:

Theoretical Relationship between the Material Surface Area and the Concentration of an Extractable in an Extracting Solution at a Constant Extracting Solution Volume.



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This is not a Simulated Extraction!

Once the scaling factor of a simulated extraction versus commercial drug product exceeds 3, then the effect of the partition coefficient is so great that the scaling factor cannot be used to extrapolate simulated extraction data to the commercial drug product.

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In Review

- An LVP is an injected dosage form with a high unit volume and frequently complicated composition.
- A properly designed and implemented extractables simulation study produces an extractables profile that is equal to or slightly exaggerated than the leachables profile for a packaged drug product.
- Critical design parameters for a simulation study include:
    - Solution Composition
    - Temperature and Duration
    - Stoichiometry
- In considering Solution Composition, the aspects of “polarity”, pH and “reactivity” should be considered. Of these three, “polarity” and pH are relatively straightforward, while “reactivity” needs further consideration.
- In considering Temperature and Duration, certain mathematical conventions can be quite useful in terms of accelerating leaching.
- In considering Stoichiometry, it is noted that in many cases the surface area to solution volume ratio is just another way of saying material weight to solution volume. More importantly, the assumption of a linear relationship between stoichiometry and leachables accumulation may or may not be true.

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Key References

1. <1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems. USP 38 – NF 33 (First Supplement), pp. 7181 – 7193. August 1, 2015.
2. Jenke, D.; Liu, N.; Hua, Y.; Swanson, S.; Bogseth, R. A means of establishing and justifying binary ethanol/water mixtures as simulating solvents in extractables studies. *PDA J Pharm Sci Technol.* 69(3): 366-38 2(2015).
3. Jenke, D. Establishing the proper pH of simulating solvents used in organic extractables assessments for packaging systems and their materials of construction used with aqueous parenteral drug products. *Pharm Outsourcing.* 15(4):20, 22, 24-27 (2014).
4. ASTM F1980-07 (Reapproved 2016): Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices.
5. R. Franz, A. Stormer. Migration of Plastic Constituents. In Plastic Packaging: Interactions with Foods and Pharmaceuticals. Wiley-VCH; Second Edition, 2008, pp. 368.
6. R. Franz, A. Stormer. Migration of Plastic Constituents. In Plastic Packaging: Interactions with Foods and Pharmaceuticals. Wiley-VCH; Second Edition, 2008, pp. 370.
7. Jenke, D; Rabinow, B. Proper accounting for surface area to solution volume ratios in exaggerated extractions. *PDA J Pharm Sci Technol.* 71(3): 225-233 (2017).
8. Jenke, D. Application of Arrhenius Kinetics to Acceleration of Controlled Extraction Studies. *PDA J Pharm Sci Technol.* 73(2): 135-168 (2019).

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Q&A

Thank you!

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