A Systematic Testing Strategy In Performing A Successful Chemical Characterization At Medtronic

- How Industry May Be Performing Chemical Characterization Differently Than FDA Preferences and Why

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Disclaimer

The views and opinions expressed in this presentation are those of the presenter and do not necessarily reflect the view of Medtronic

Discussion Topics Today

1. *Analytical Testing Strategy and Requirements*
2. *Solvent Selection*
3. *Solvent Polarity Scale and Its Significance (ISO10993-18)*
4. *Number of Solvents Required for Extractions (Exhaustive or Exaggerated)*
5. *Difference between Semipolar and Nonpolar Solvents in Extraction*
6. *Significance of Extraction Processes (ISO10993-12)*
7. *Critical Assessment of Use of NVR Test*
8. *Summary and General Analytical "Specifications"*

The Physical Processes

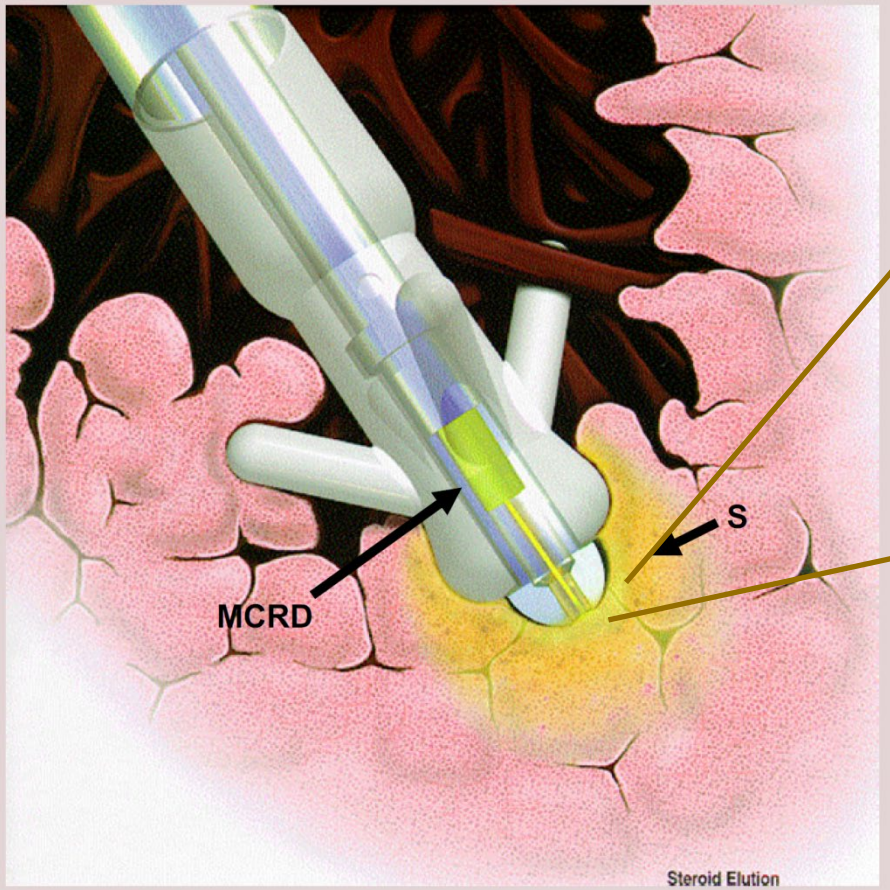
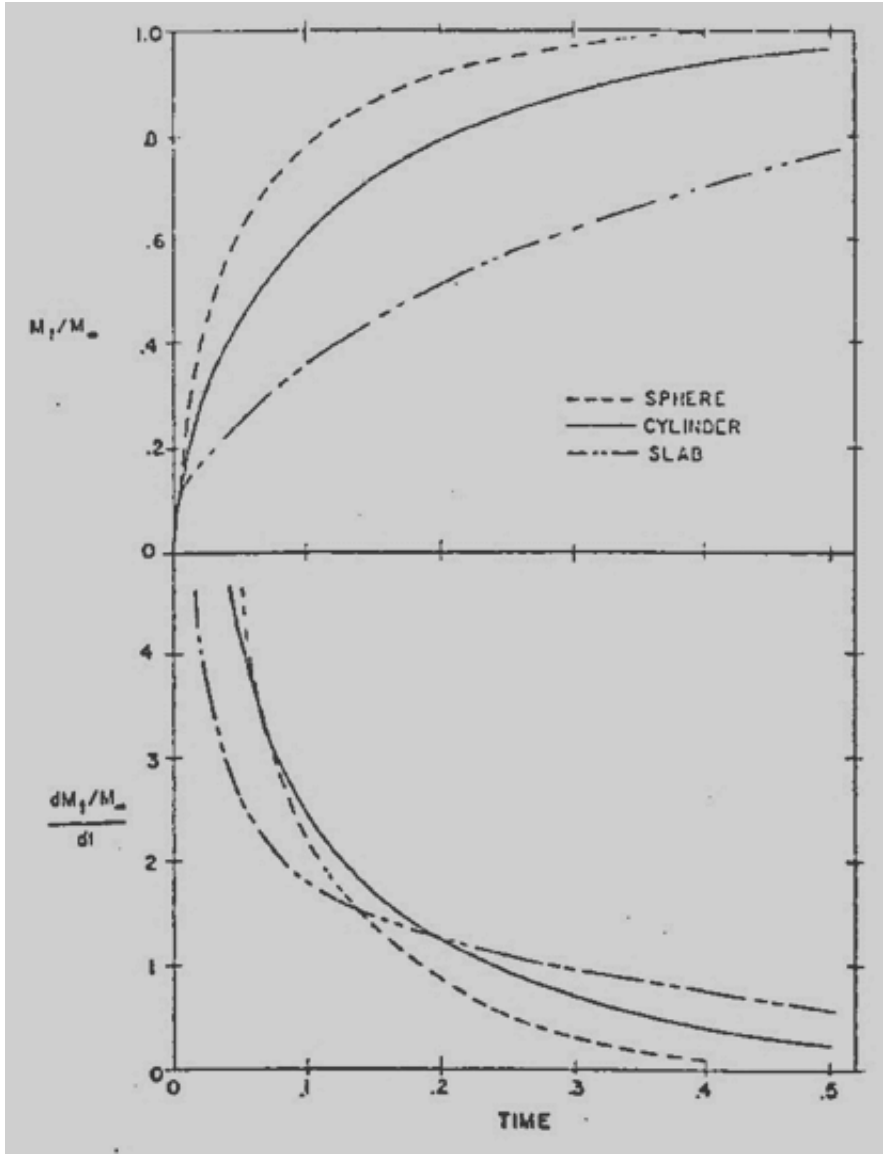


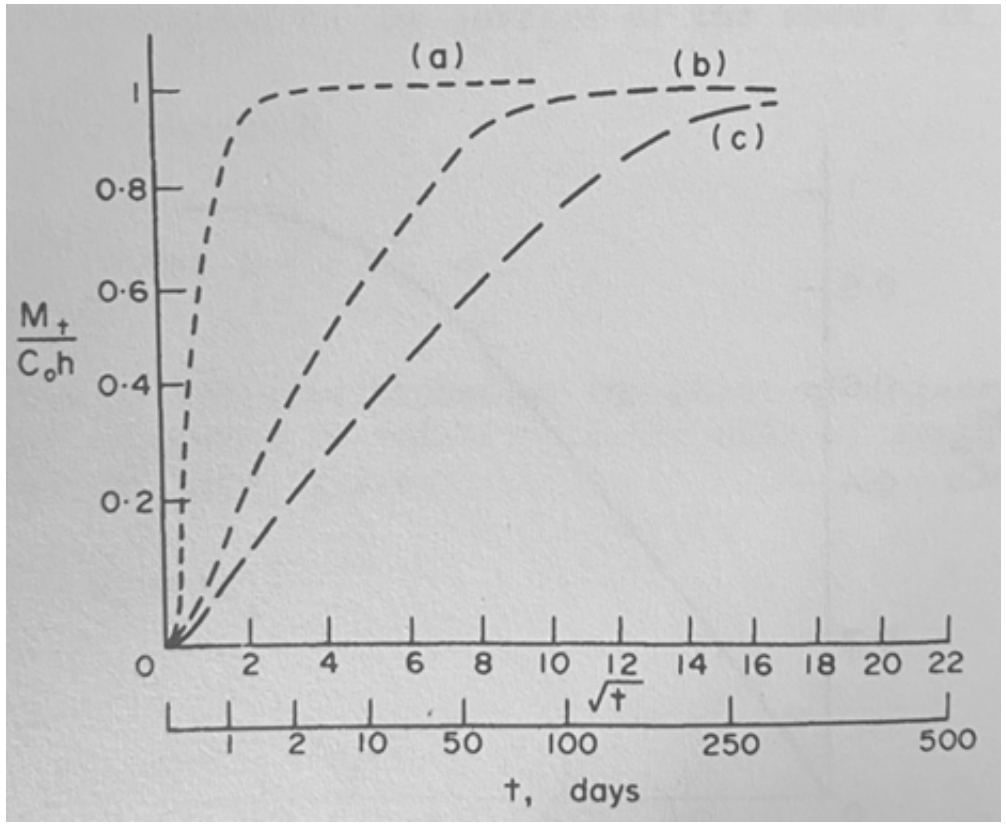
FIGURE II.3.3.8 Depiction of a tyned steroid-eluting pacing lead electrode positioned against cardiac tissue. The yellow zone represents steroid (S) eluting into the local tissue from a monolithic controlled release depot (MCRD) consisting of drug in a silicone matrix.

Physical Process: Diffusion/Migration

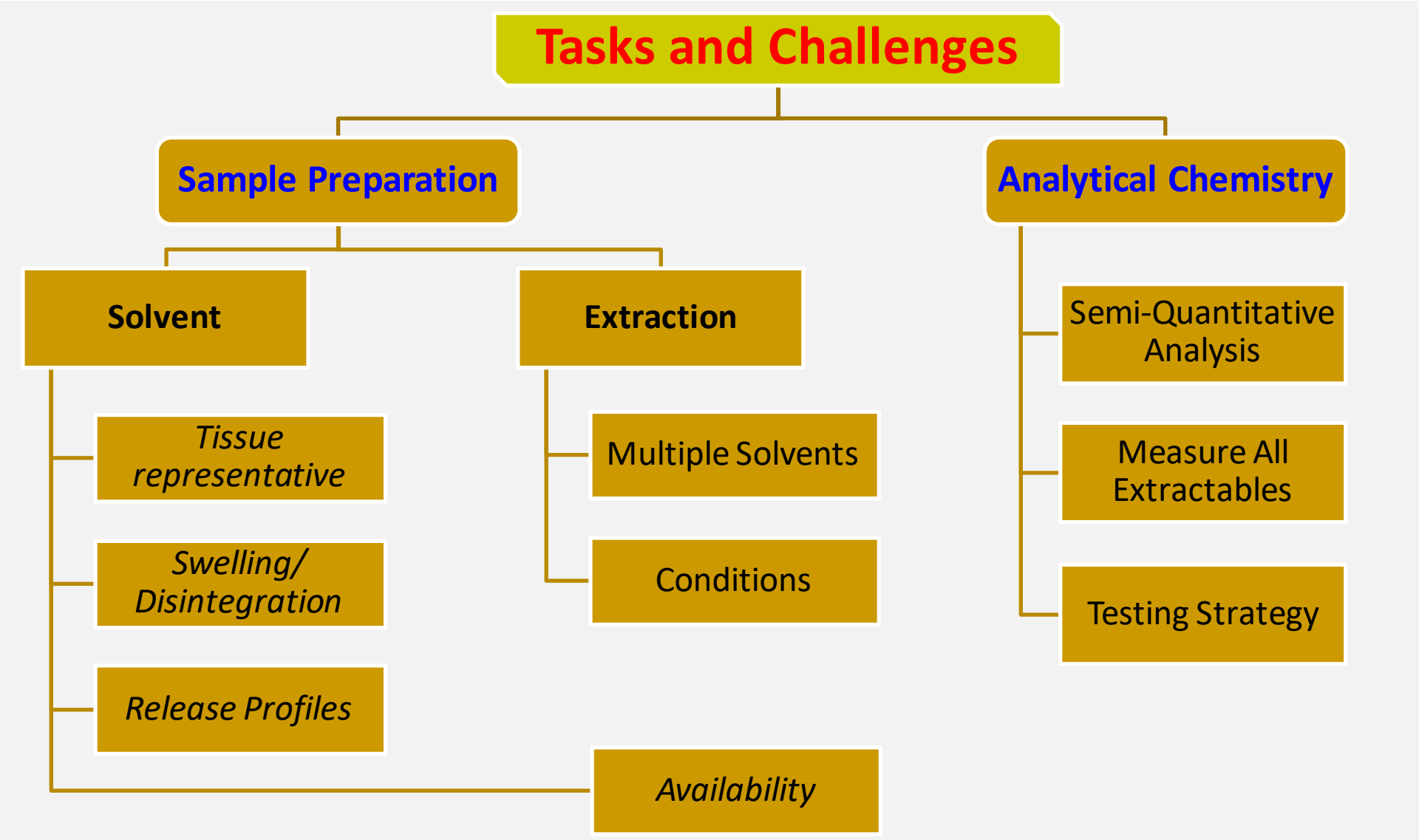
Biocompatibility: *What and Amount*

Extractables Release Profiles





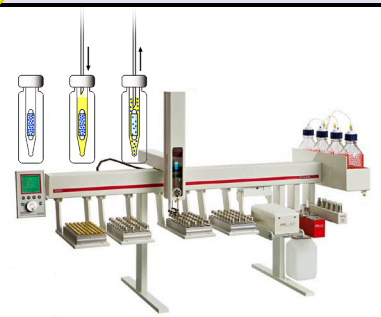
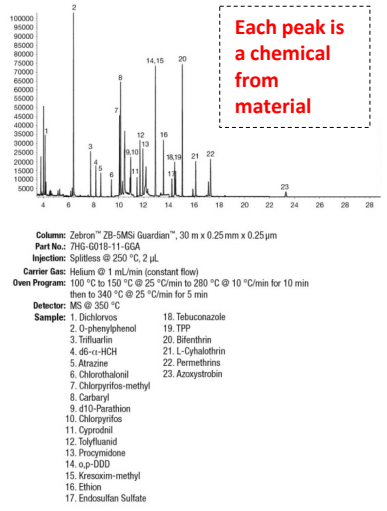
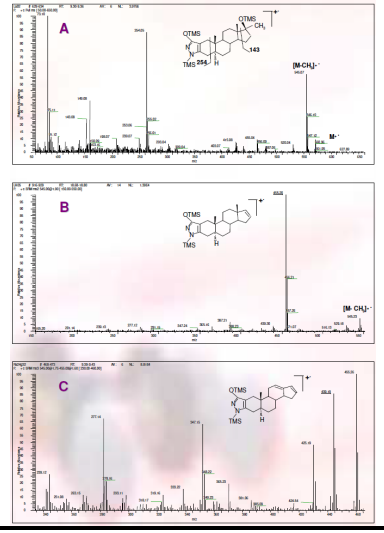
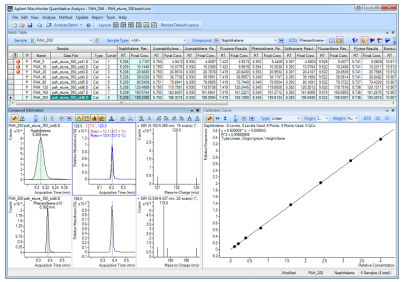
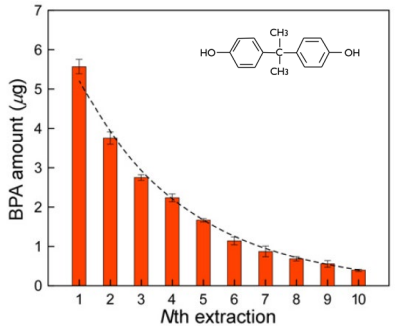
Analytical Tasks and Challenges



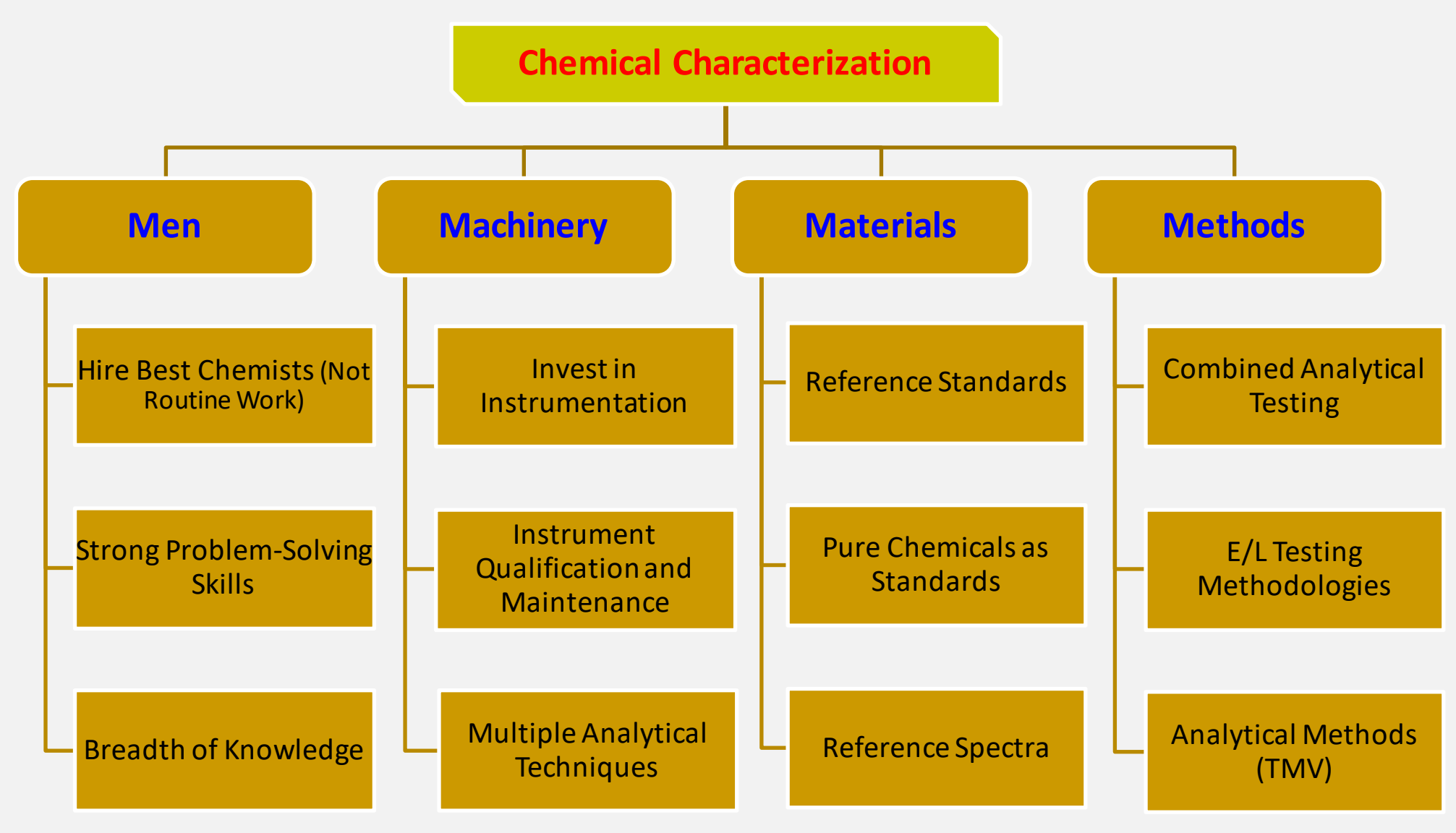
Chemical Characterization (ISO10993-18) Flow

ISO10993-Part 12

Extraction Study

Sample Selection	Sample Preparation	Extraction	Test Extracts
			
Qualitative Analysis	**Identification**	**Quantitative Analysis**	**E/L Profiles**
			

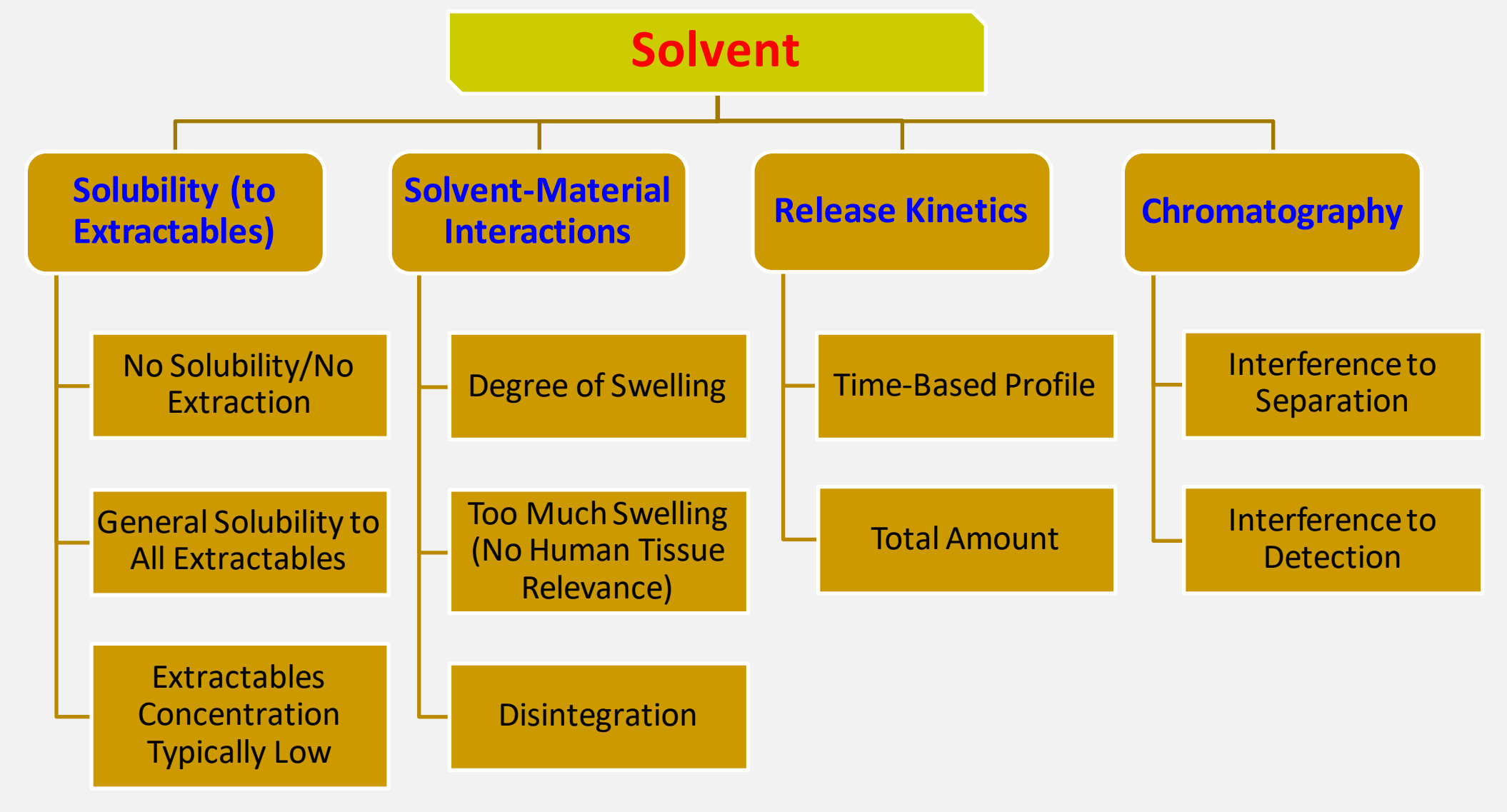
Successful Chemical Characterization Program



Analytical Strategy and Requirements

1. *Extraction Solvents and Conditions to achieve desired outcomes*
2. *Analytical Methods*
   - ✓ *Detection comprehensiveness (cover extractables in 3D of MW, hydrophobicity, and volatility)*
   - ✓ *Apply to solvents of varying polarity*
   - ✓ *High peak capacity*
   - ✓ *Signal consistency (low UF)*
   - ✓ *Sensitivity*
   - ✓ *Standard selections*
   - ✓ *Validation considerations*

Solvents-So Critical



Solvent Selection/Requirements

- ✓ *Similar to human tissue environment in solvation/extraction strength*
- ✓ *Commercially available as highly pure chemicals*
- ✓ *Low toxicity*
- ✓ *Adequate physical properties such as polarity, boiling point, UV absorbance, viscosity, etc.*
- ✓ *We can do chromatography*
- ✓ *Solvent-extractables interactions, recovery, interference, sample stability, LOQ, etc.*
- ✓ *Solvent-material interaction (release profiles)*

Solvent Polarity Scale (ISO10993-18)

Solvent	Polarity Index (p1)	Boiling Point (°C)	Viscosity 20°C (cP)
Pentane	–	36,1	0,23
Tetrachloroethylene	–	121,2	0,93
2,2,4 Trimethylpentane	0,1	99,2	0,51
Heptane	0,1	94-97,5	0,41
Hexane	0,1	67-69,5	0,31
Cyclohexane	0,2	80,7	1.00
1-Chlorobutane	1.0	78,4	0,45
Carbon tetrachloride	1,6	76,8	0,97
Toluene	2,4	110,6	0,59
Methyl-tert-butyl ether	2,5	55,3	0,27
Benzene	2,7	80,1	0,65
Diethyl ether	2,8	34,5	0,23
Dichloromethane	3,1	39,7	0,43
Octan-1-ol	3,4	195,2	10,64 approx
1,2 Dichloroethane	3,5	83,5	0,79
Propan-2-ol	3,9	82,3	2,3
Propan-1-ol	4.0	97,2	2,26
Tetrahydrofuran	4.0	66.0	0,55
Chloroform	4,1	61,7	0,57
Ethanol, absolute	4,3	78.00	1,2
Ethyl acetate	4,4	77,1	0,45
1,4 Dioxane	4,8	101,1	1,54
Acetone	5,1	56,2	0,32
Methanol	5,1	64,7	0,55
Pyridine	5,3	115,3	0,95
2-Methoxyethanol	5,5	124,6	1,72
Acetonitrile	5,8	81,6	0,36
Dimethylformamide	6,4	153.00	0,85
Dimethylsulfoxide	7,2	189.00	2,24
Water	10,2	100.00	1.00

Snyder solvent scale is more a solvent selectivity scale in chromatography than a polarity scale. It is mostly for small molecules (not polymers).

The Kamlet-Taft scale is really a better useful scale of solvent polarity.

Ref: Classification of the Solvent Properties of Common Liquids by L.R. Snyder, *Journal of Chromatography*, 92 (1978) 223-234.

Correlation of Polarity to Physical Properties, Swelling

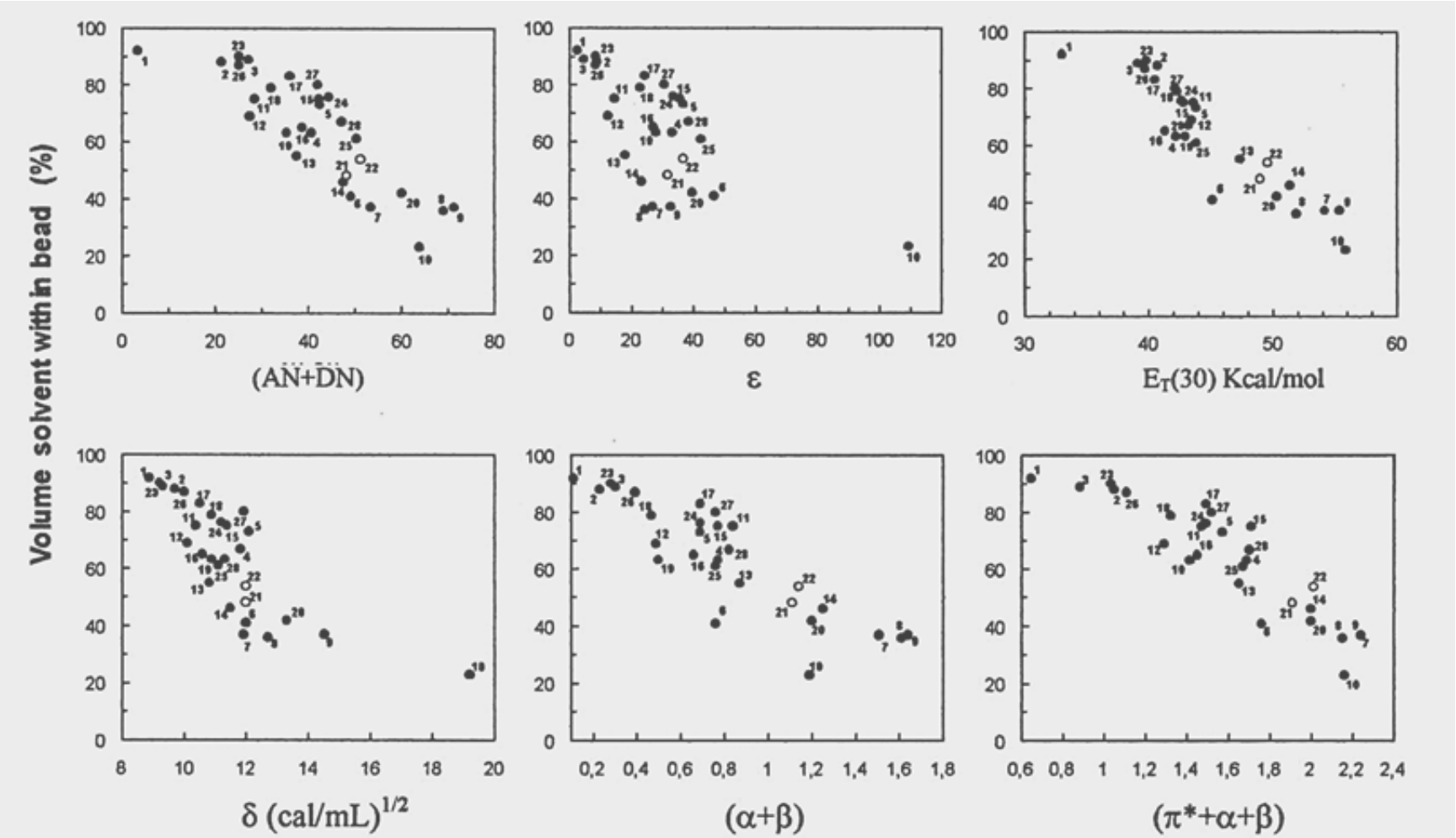
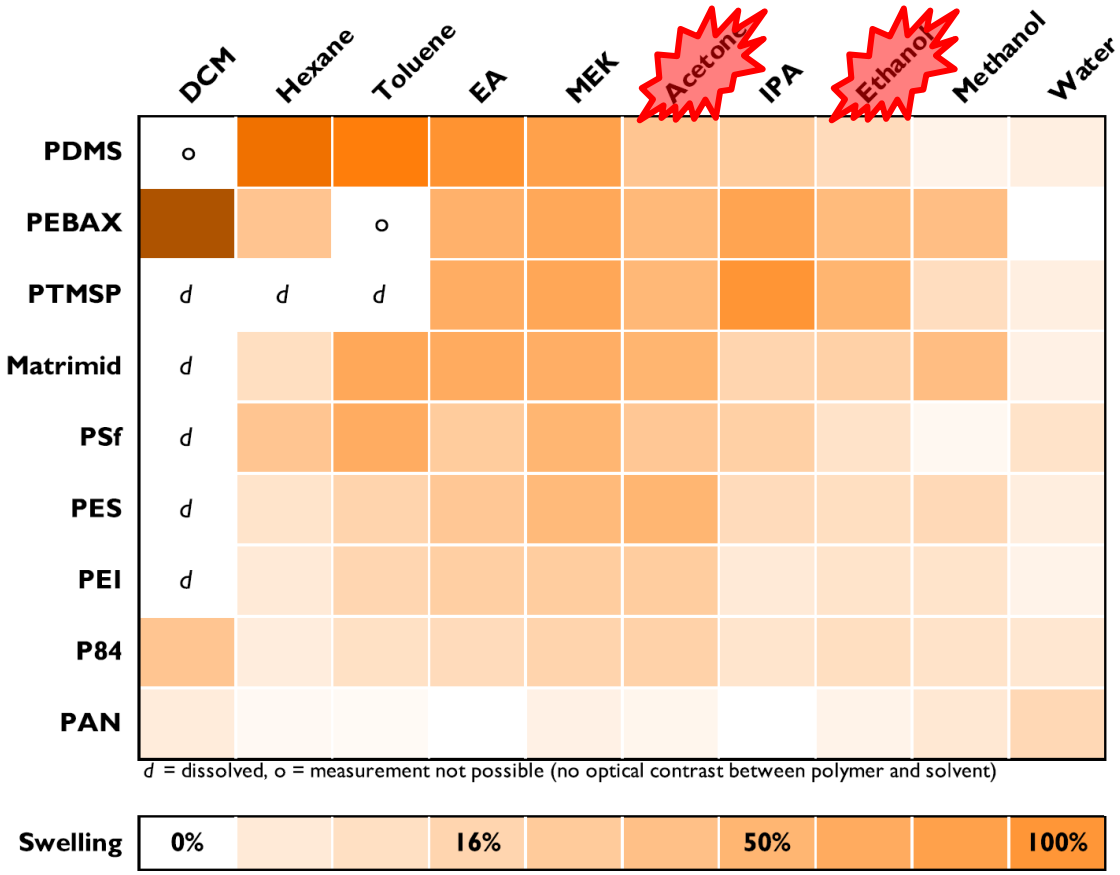


Figure 2. Swelling of resin (2), PS–DVB as a function of solvent (AN+DN), ε, $E_T(30)$, δ, (α+β) and (π^*+α+β) values.

Solvent-Polymer Interaction as Indicated by Swelling



PAN=poly(acrylonitrile)

PSF=poly(sulfone)

PES=poly(ether sulfone)

PDMS=Polydimethylsiloxane

PEI=poly(ether imide)

PEBAX=Poly (ether block amide)

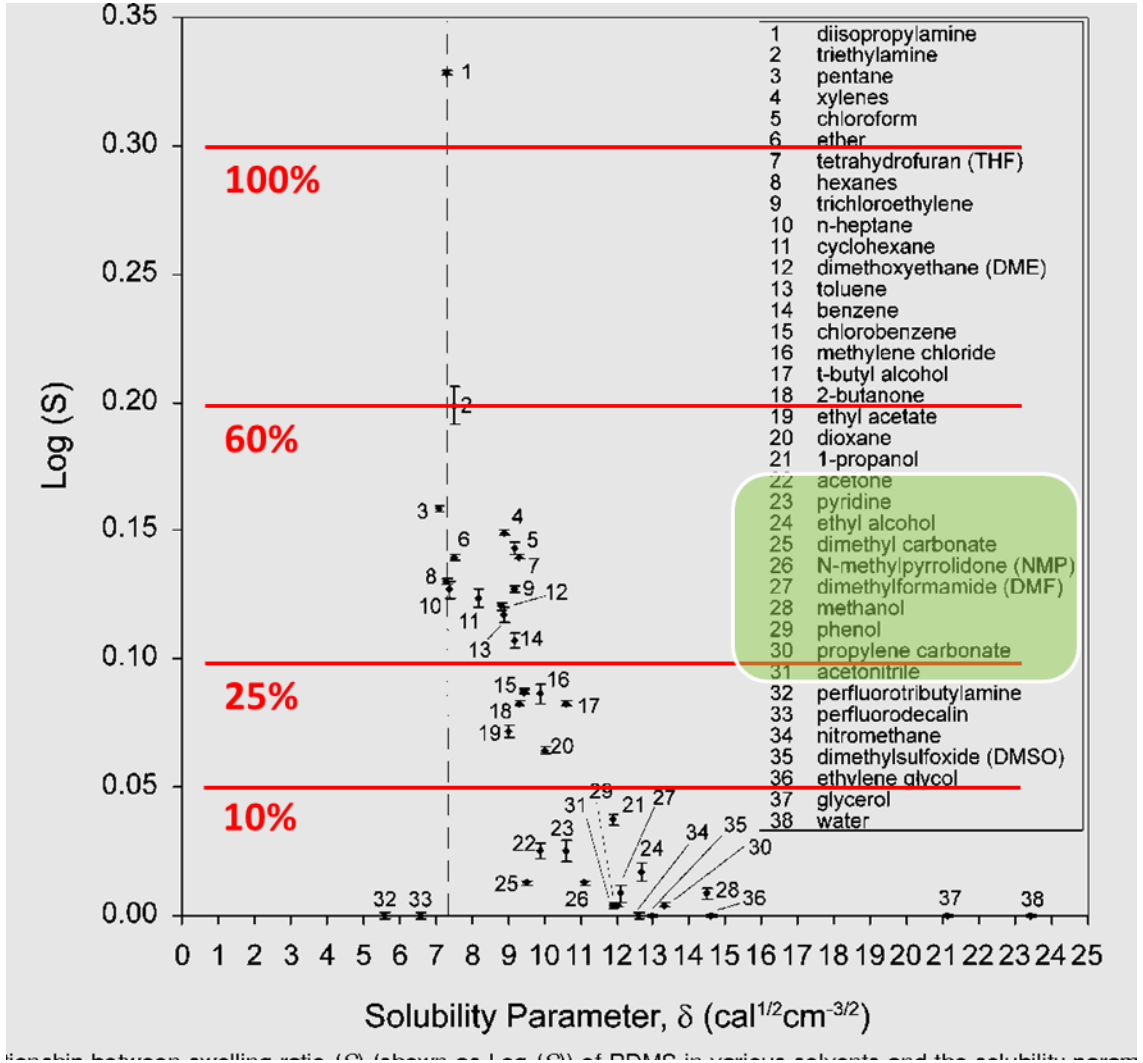
P84 and **Matrimid**=poly(imide)

PTMSP=poly[1-(trimethylsilyl)-1-propyne]

Fig. 22. Overview of all swelling degrees measured after long-term exposure to the respective solvents. For each polymer-solvent combination, the last measured data point was taken. 'o' indicates absence of a measurement due to lack of optical contrast, 'd' indicates dissolution of the polymer in the solvent.

Ref: Swelling of 9 polymers commonly employed for solvent-resistant nanofiltration membranes

Solvent-Polymer Interaction as Indicated by Swelling (Silicone)



Swelling 60-120%

- Silicone-based devices can be “damaged” by many solvents
- Solvents not swelling silicone, still nonpolar, are hard to find
- Smipolar solvents can be important to compensate

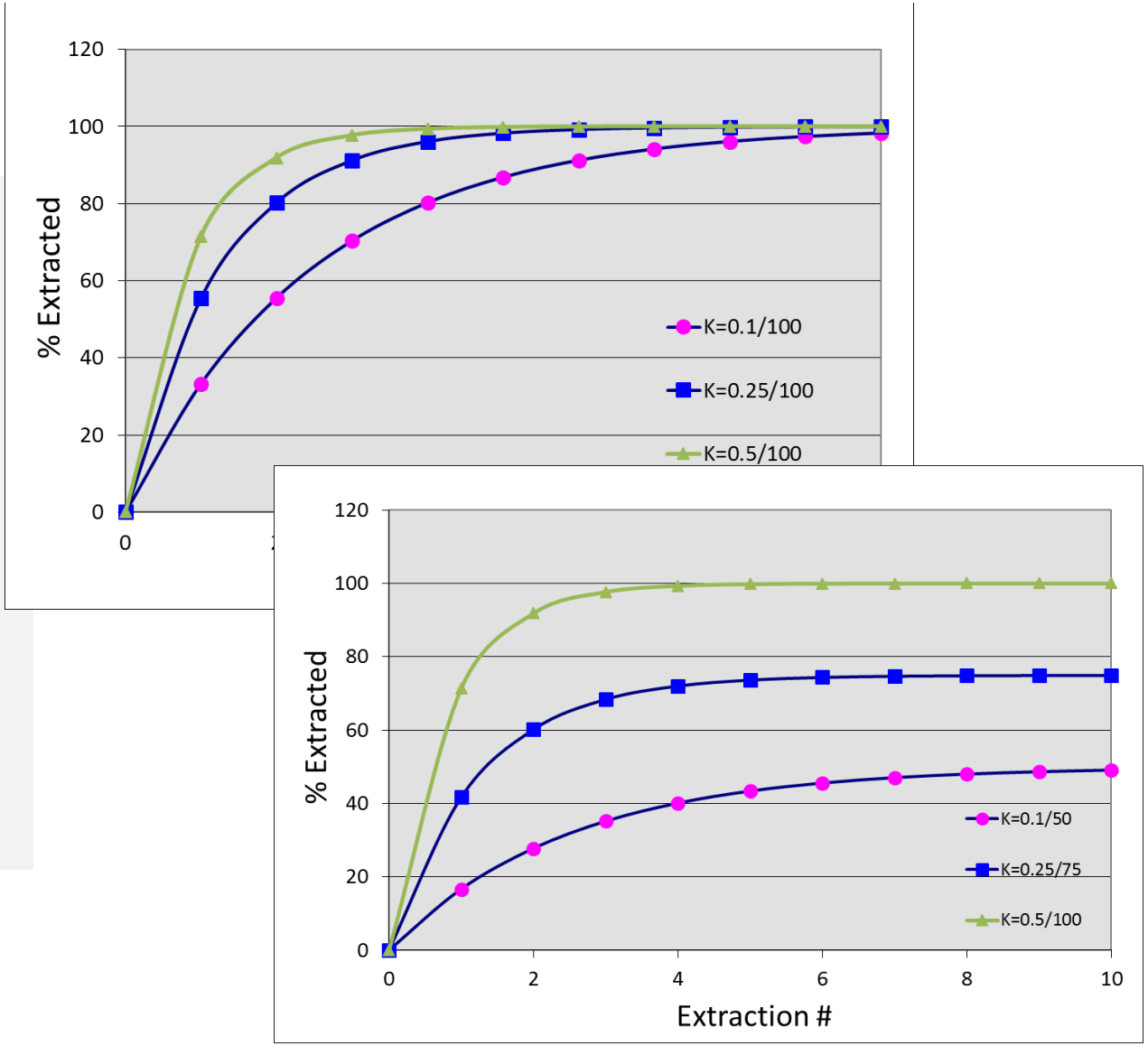
Ref: Solvent Compatibility of Poly(dimethylsiloxane)-Based Microfluidic Devices

How Many Can Be Used for Extractions?

	KT/ET(30)	Snyder	AN (Acceptor #)	DN (Donor #)	(AN+DN)	Hildebrand Sol. Parameter	Dipole Moment
Carbon tetrachloride	32.4	1.6	8.6	0	8.6	8.6	2.2
Toluene	33	2.4	3.3	0.1	3.4	8.9	2.4
Dichloromethane	40.7	3.1	20.4	1	21.4	9.7	8.9
1,2-Dichloroethane	41.3	3.5	16.7	0	16.7	9.9	10.1
Propanol	48.4	3.9	33.5	36	69.5	11.4	18.3
THF	37.4	4.0	8	20	28	9.1	7.5
EtOH	51.9	4.3	37.1	32	69.1	12.7	24.3
Ethyl acetate	38.1	4.4	9.3	17.1	26.4	9	6
Acetone	42.2	5.1	12.5	17	29.5	9.6	20.7
MeOH	55.4	5.1	41.3	30	71.3	14.5	32.6
Acetonitrile	45.6	5.8	18.9	14.1	33	11.9	36
Dimethylformamide	43.8	6.4	16	26.6	42.6	12.1	36.7
Dimethylacetamide	42.9	6.5	13.6	27.8	41.4	10.8	37.8
Methylpyrrolidone	42.2	6.7	13.3	27.3	40.6	11.3	33
Dimethyl sulfoxide	45.1	7.2	19.3	29.8	49.1	12	46.7

Differences Among Solvents-Extraction Alone

- ✓ *Solvation, polar or hydrogen bonding (ACN or methanol, ethanol, etc.)*
- ✓ *Solubility*
- ✓ *Thermodynamics-Amount of extraction*
- ✓ *Kinetics-Speed of release*
- ✓ *How to achieve exhaustive?*

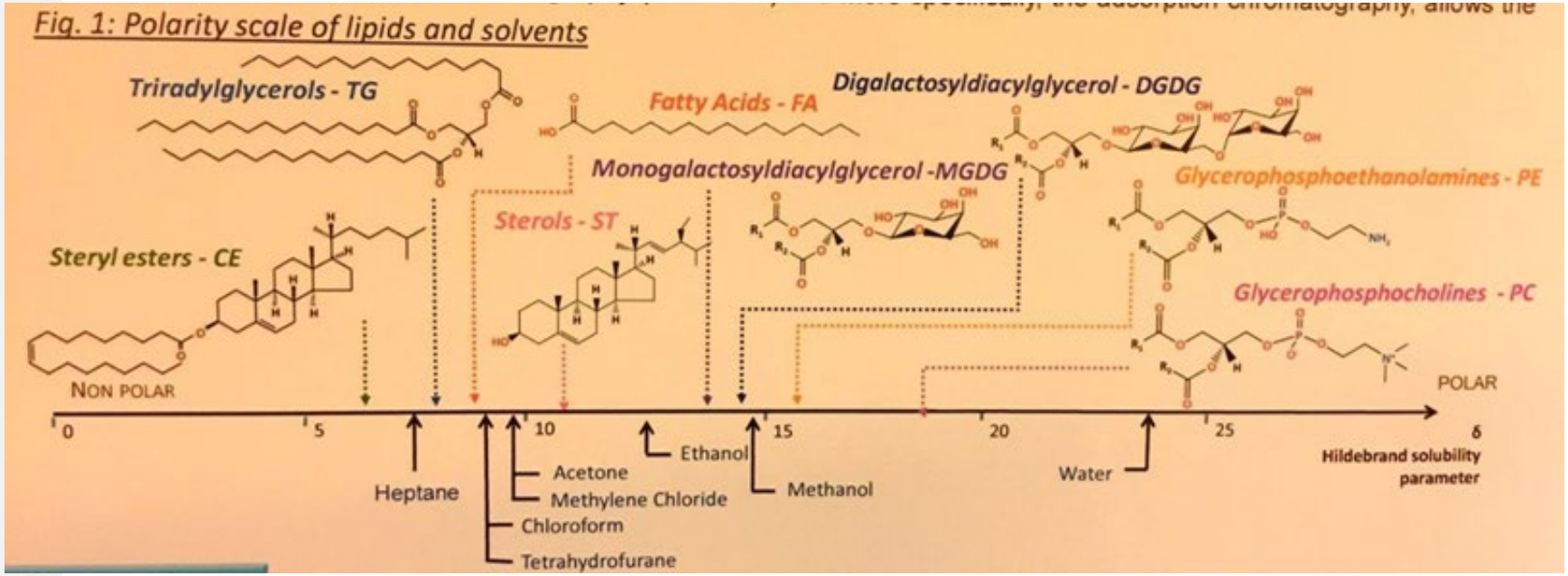


Solvents Required for Exhaustive Extractions-Tissue Polarity

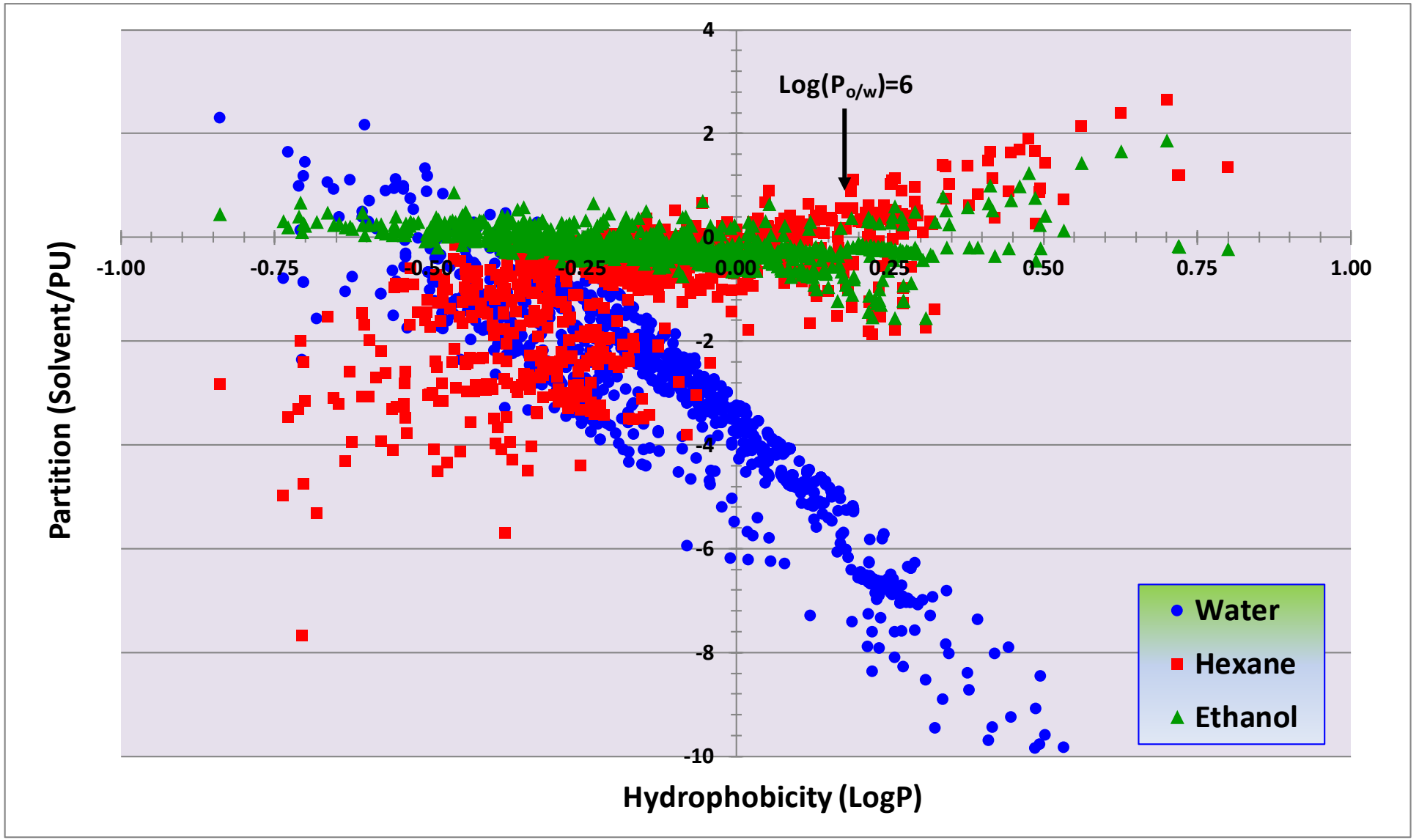
LEAST POLAR

Saturated hydrocarbons
Unsaturated hydrocarbons
Wax esters
Steryl esters
Long chain aldehydes
Triacylglycerols
Long chain alcohols
Free fatty acids
Quinones
Sterols
Diacylglycerols
Monoacylglycerols
Cerebrosides
Glycosyl diacylglycerols
Sulpholipids
Acid glycerophosphatides
Phosphatidyl ethanolamine
Lecithin
Sphingomyelin
Lysolecithin

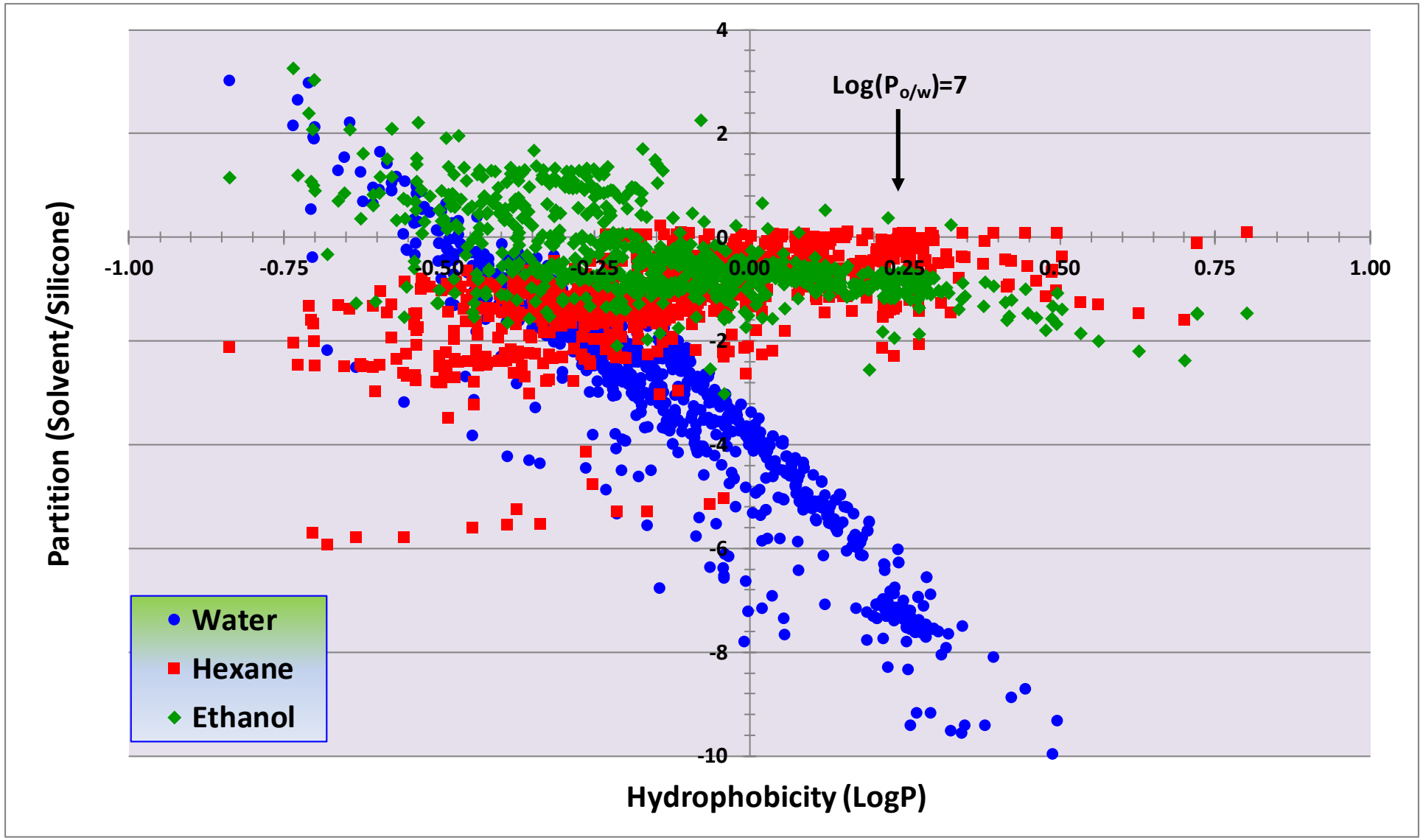
MOST POLAR



Solvent Extraction Efficiency from "Polyurethane" Material



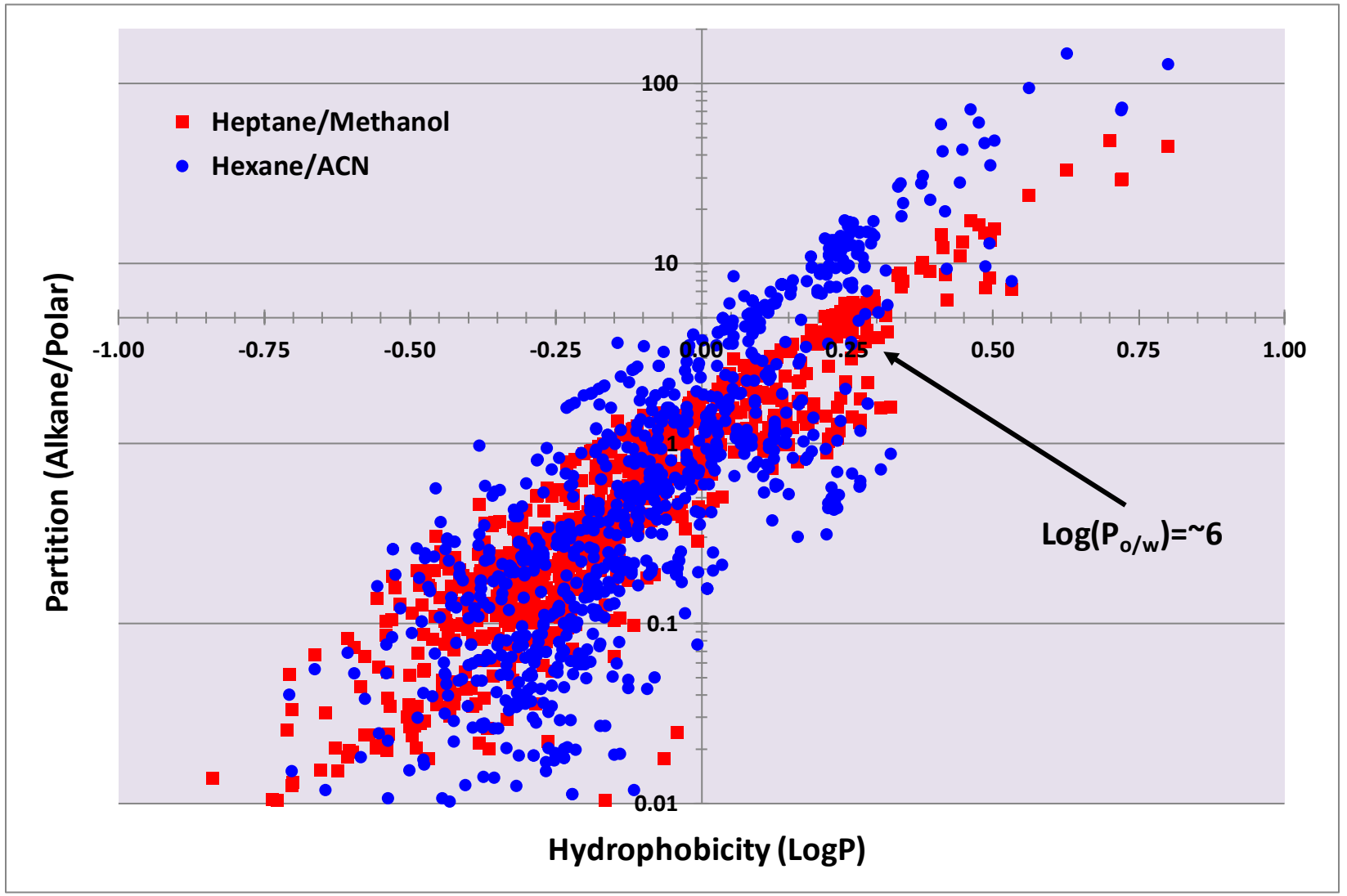
Solvent Extraction Efficiency from "Silicone" Material



Benefits of Use of Multiple Solvents

- ✓ *Help achieve exhaustive extraction*
- ✓ *Solvent alone is not a guarantee for exhaustive extraction*
- ✓ *If a nonpolar solvent destroys device, can we use a semipolar solvent to cover the extractables by nonpolar solvent*
- ✓ *Look at the fundamental, solvent differences*

Difference between Nonpolar and Semipolar Solvents



- ✓ Similar for hexane/ethanol
- ✓ Not solubility limited
- ✓ Nonpolar solvents important after Log($P_{o/w}$) > ~6

Solvent -Material Interactions: Thermodynamics

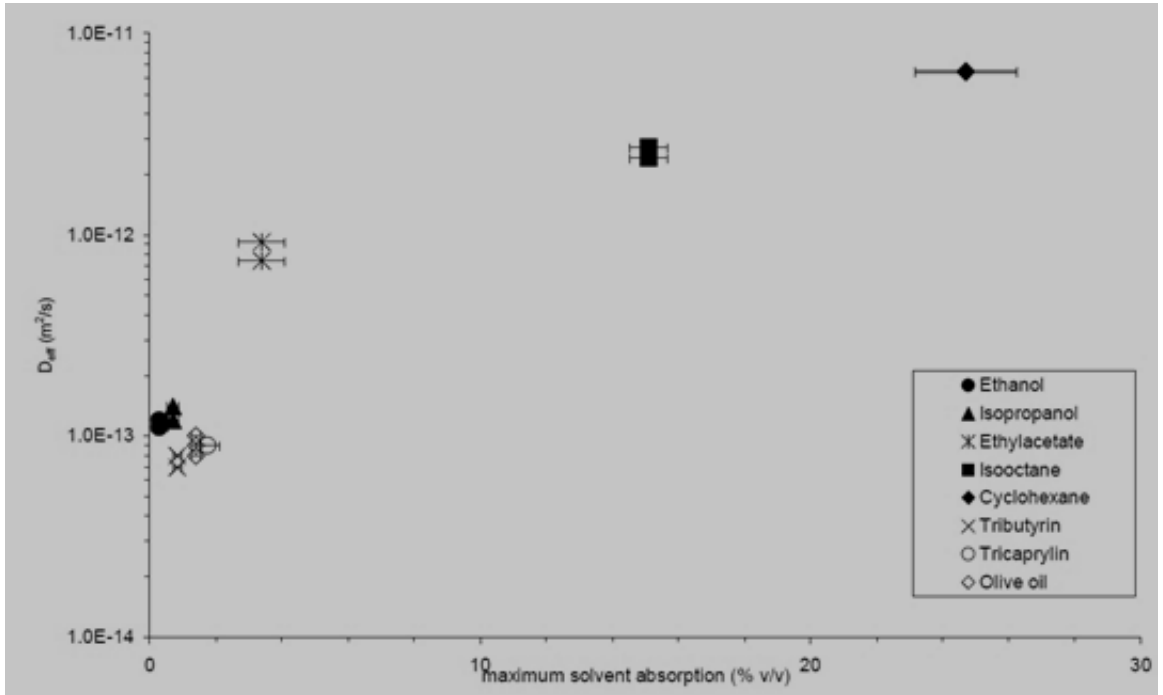


Figure 4.2 Effective diffusion coefficient of Irganox 1076 as a function of maximum solvent absorption. Errorbars are the SD for the determination of solvent absorption obtained for at least 5 measurements at equilibrium.

Table 4.1 Effective diffusion coefficients (D) and partition coefficients (K) of Irganox 1076 migrating from LDPE to the test solvents at 40°C (duplicate or triplicate values).

Solvent	D ($m^2 s^{-1}$) $\times 10^{13}$	K ($m^3 m^{-3}$)
Tributyrin	0.8	11
	0.7	11
Tricaprylin	0.9	5
	0.9	6
Olive oil	0.8	n.d.
	0.9	n.d.
	1.0	n.d.
Ethanol	1.0	0.3
	1.2	3
Isopropanol	1.2	3
	1.4	2
Ethylacetate	7.4	4
	9.3	11
Isooctane	24	4
	27	7
Cyclohexane	64	4
	65	9

n.d., No data.

Ref: Release of additives from packaging plastics

Solvent-Material Interactions: Kinetics

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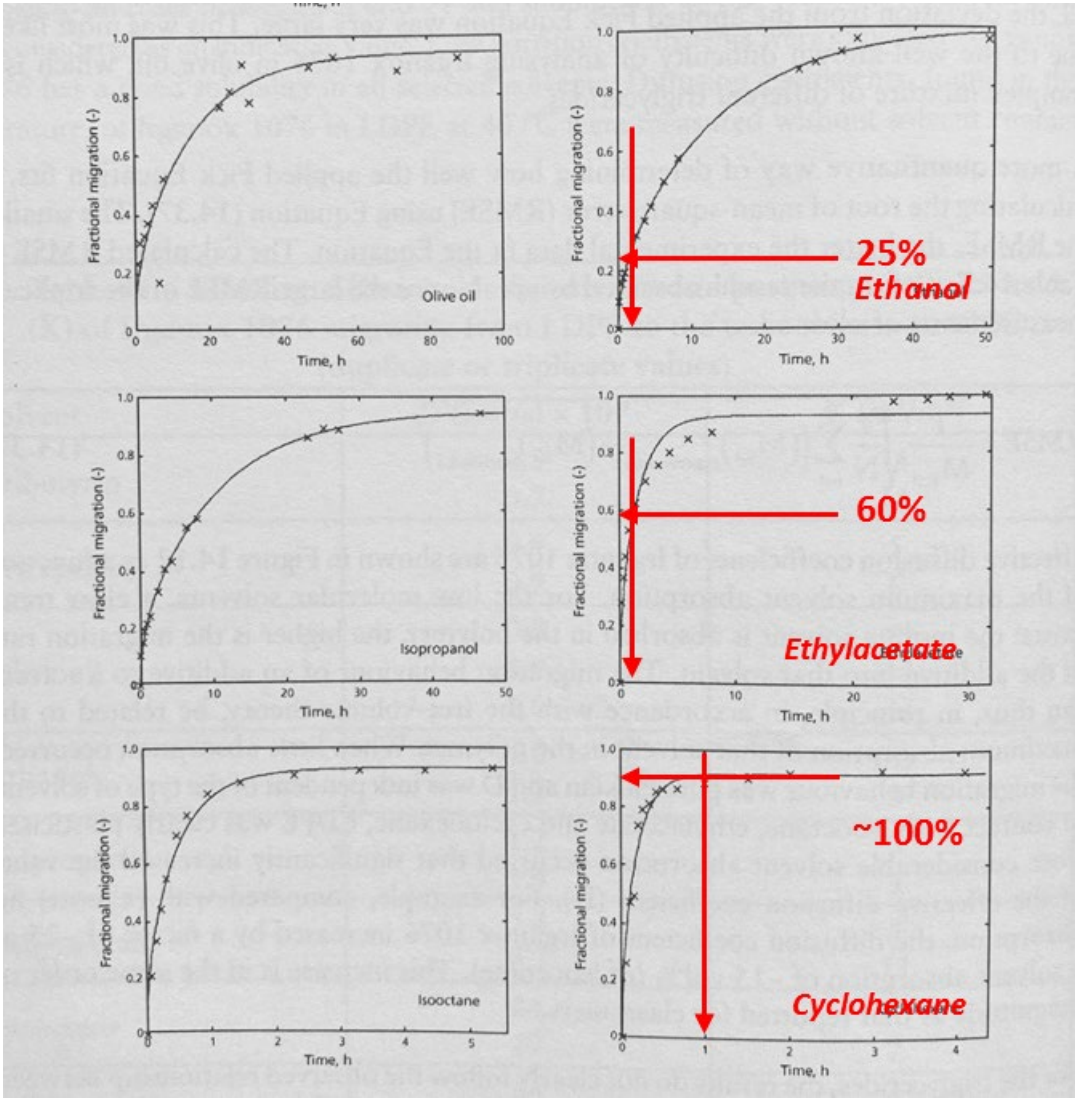
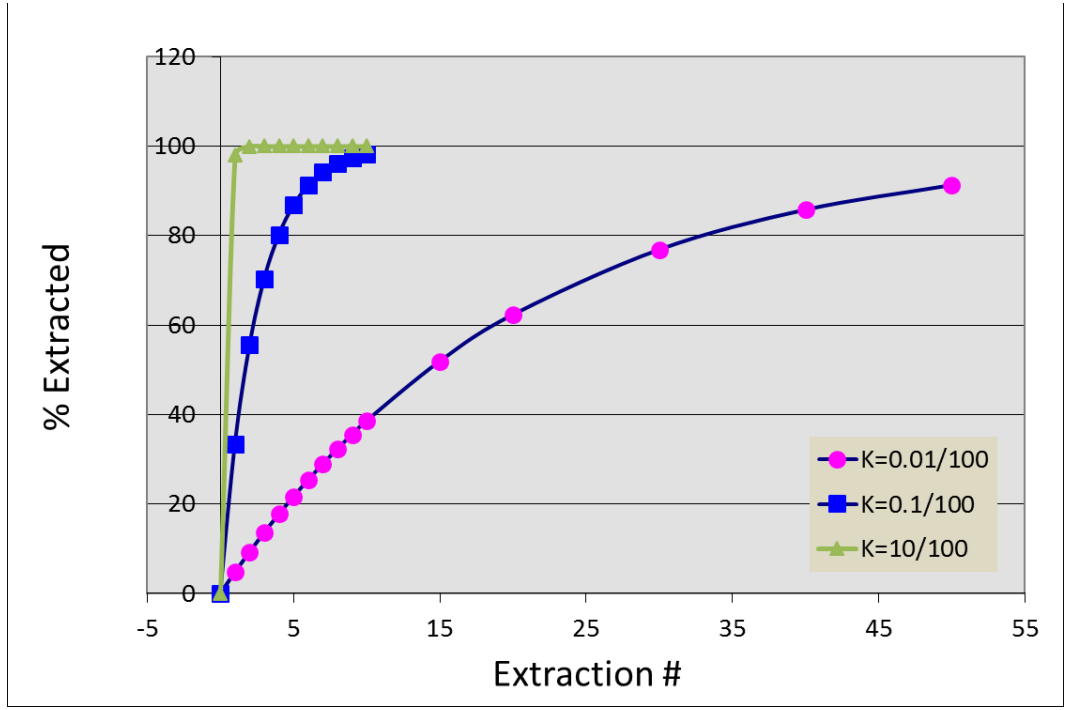
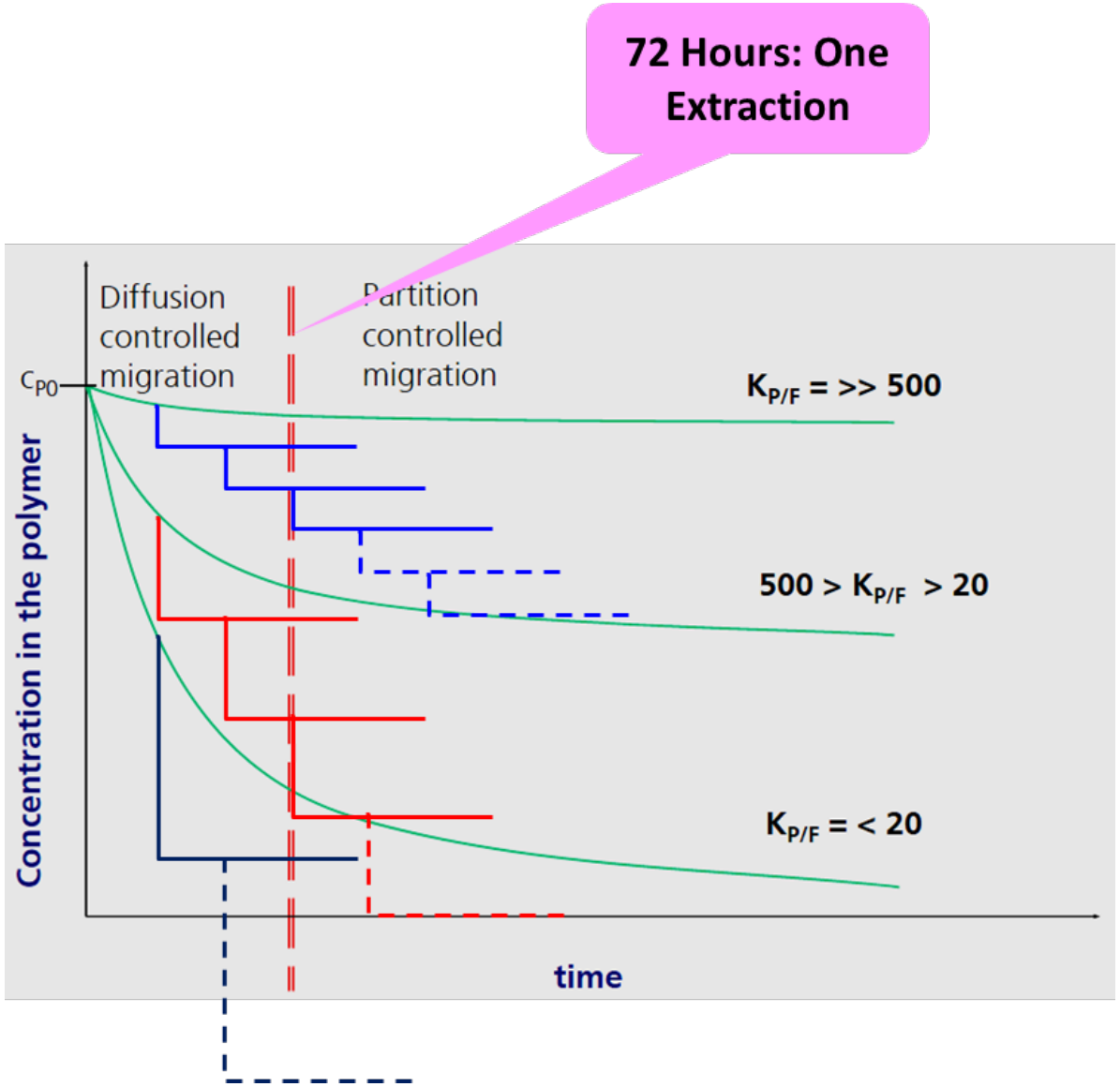


Sequential (Repeated) Extractions

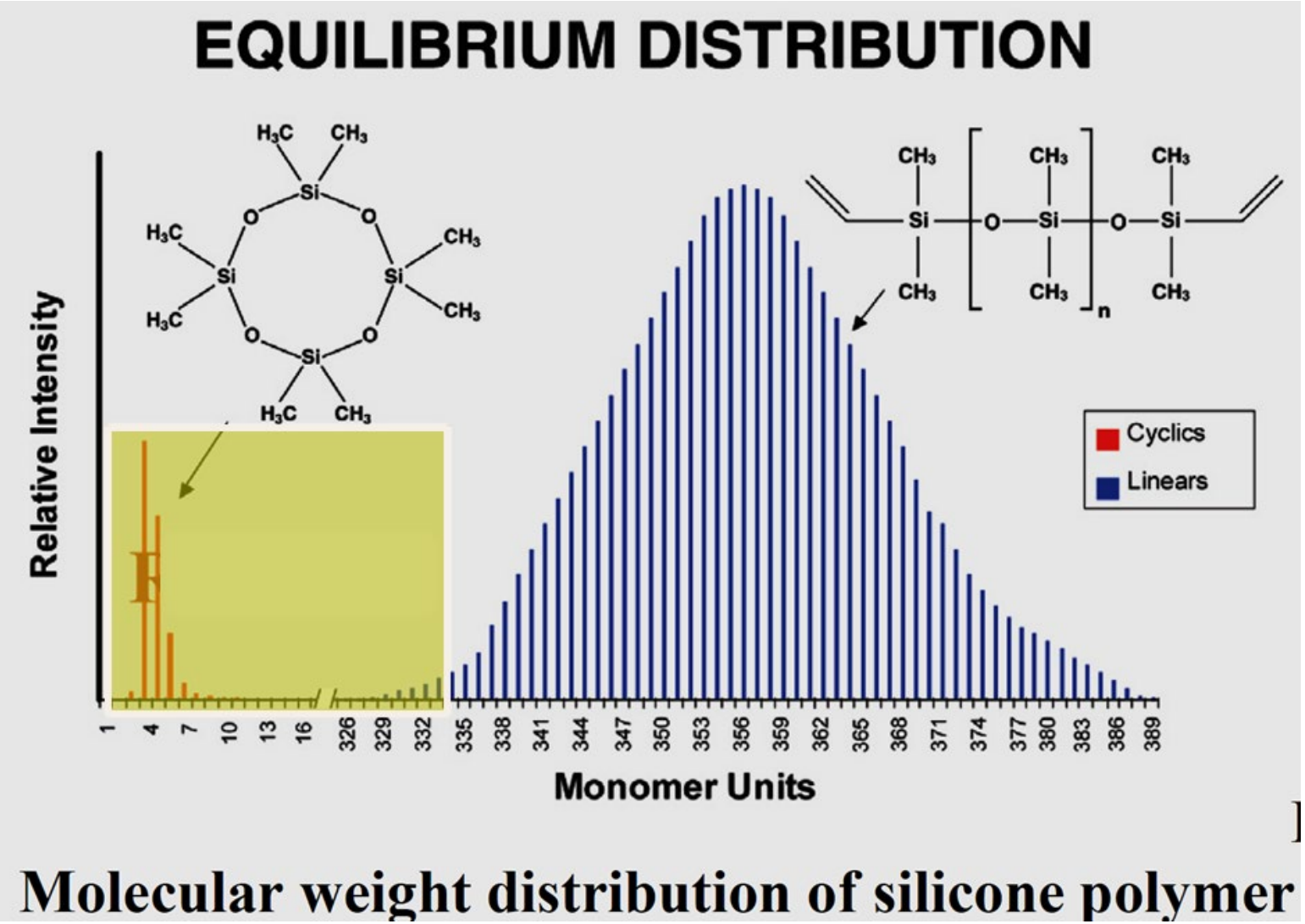




Advantages of Sequential (Repeated) Extractions

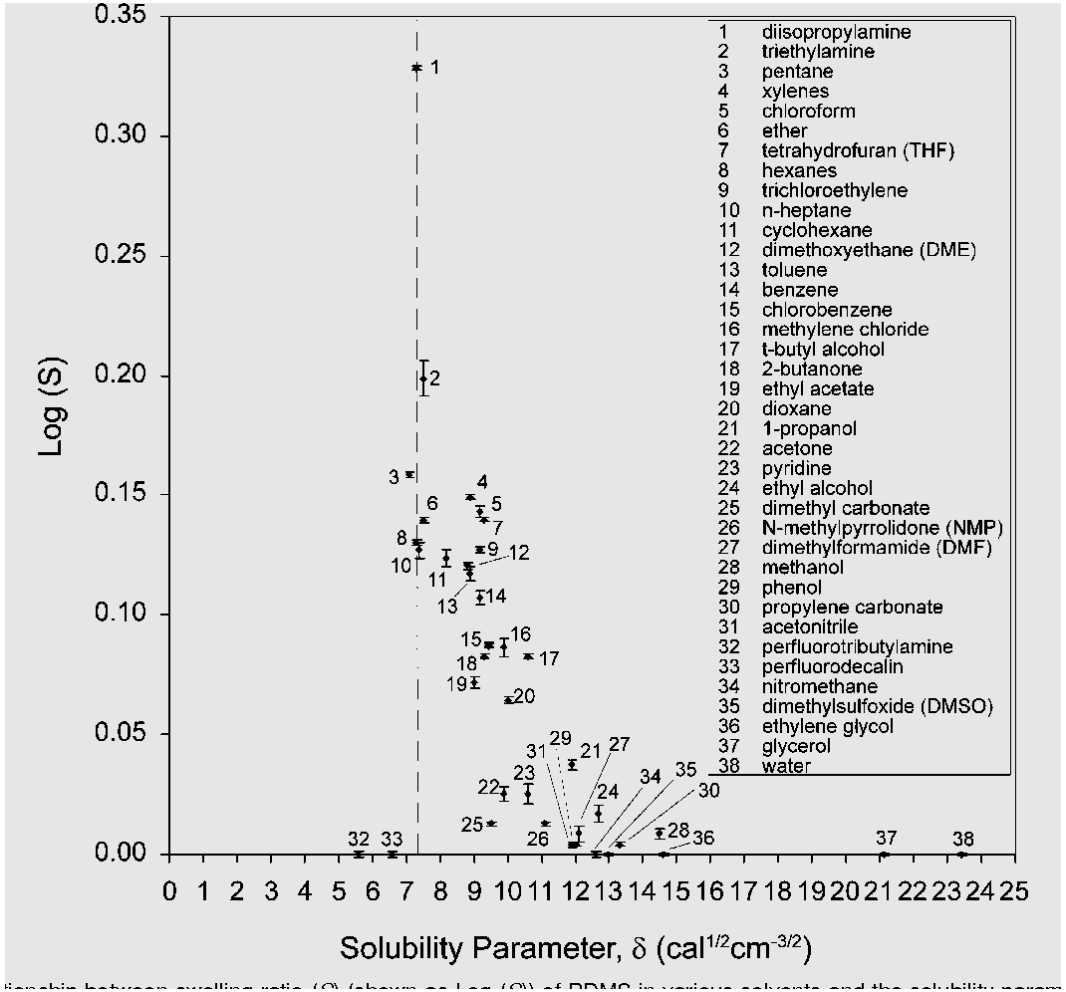
- ✓ *Compensate on multiple solvents*
- ✓ *Compensate on different extractables*
- ✓ *Compensate different partition coefficients (thermodynamics)*
- ✓ *Do repeated consecutive extractions (daily)*
- ✓ *ISO10993-12 needs an major update (72 hours)*
- ✓ *Not dissolution-based release profiles*

NVR (Nonvolatile Residue) Test



Molecular weight distribution of silicone polymer

NVR (Nonvolatile Residue) Test: Silicone



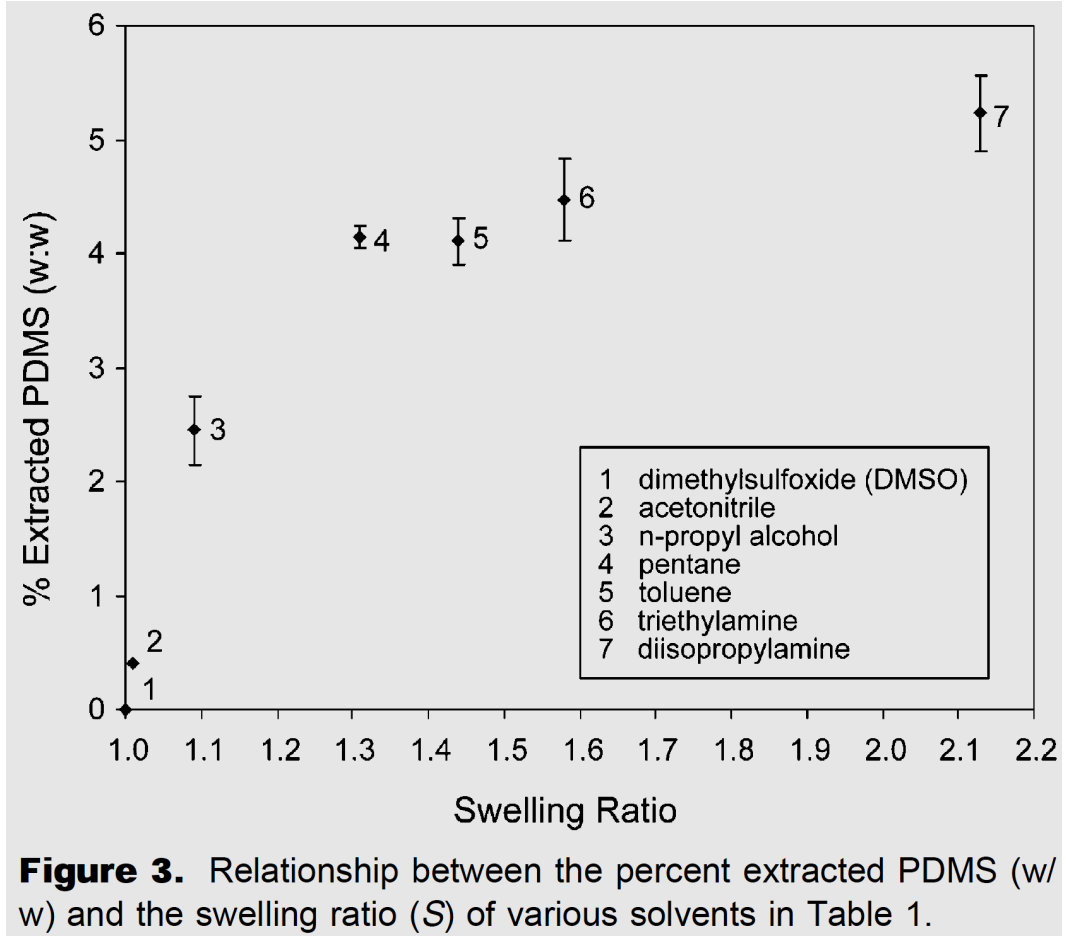
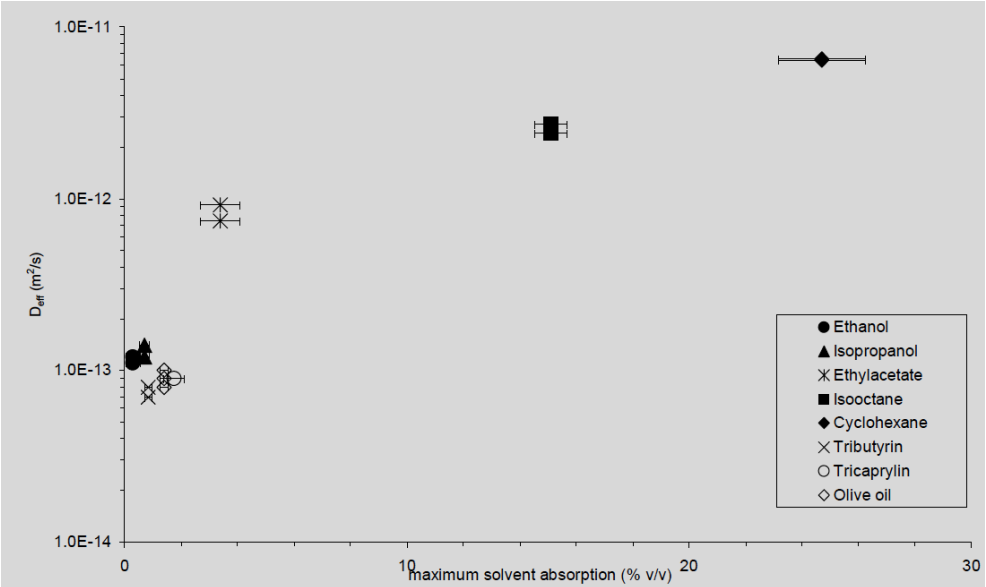


Figure 3. Relationship between the percent extracted PDMS (w/w) and the swelling ratio (*S*) of various solvents in Table 1.

Ref: Solvent Compatibility of Poly(dimethylsiloxane)-Based Microfluidic Devices

NVR (Nonvolatile Residue) Test: LDPE



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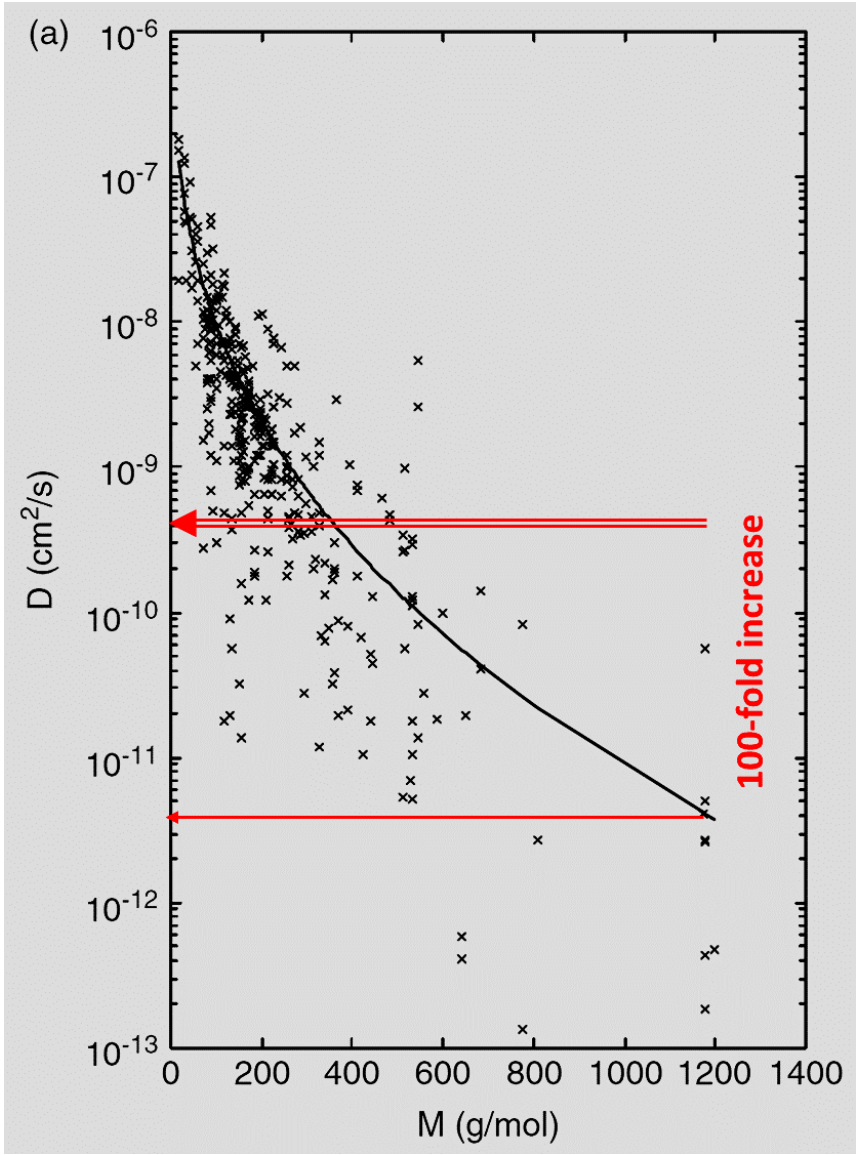
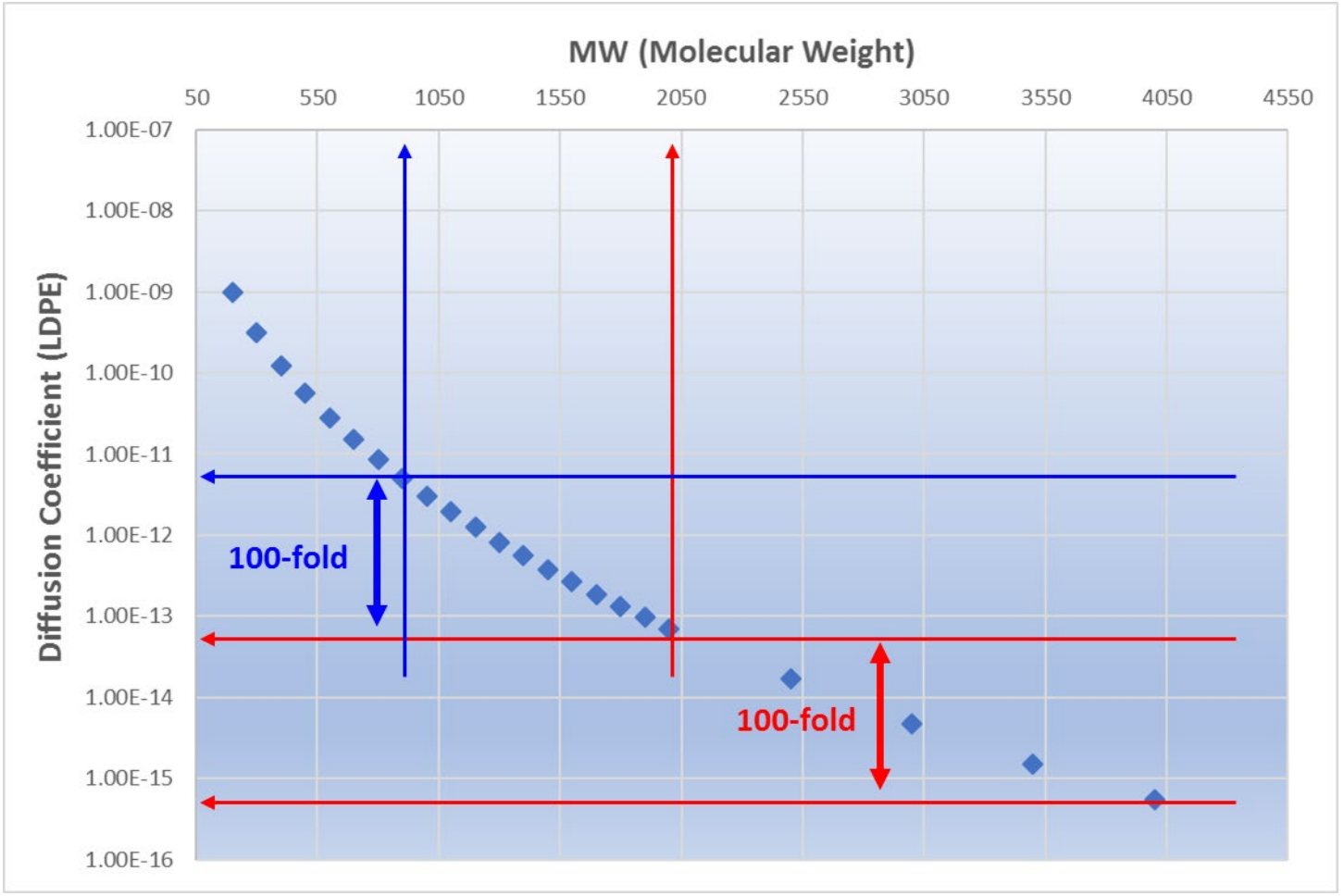


Ref: Diffusion rate can increase up to 100-fold for high MW extractables, making them detectable by NVR

NVR (Nonvolatile Residue) Test



Ref: Release of additives from packaging plastics

NVR (Nonvolatile Residue) Test: PE

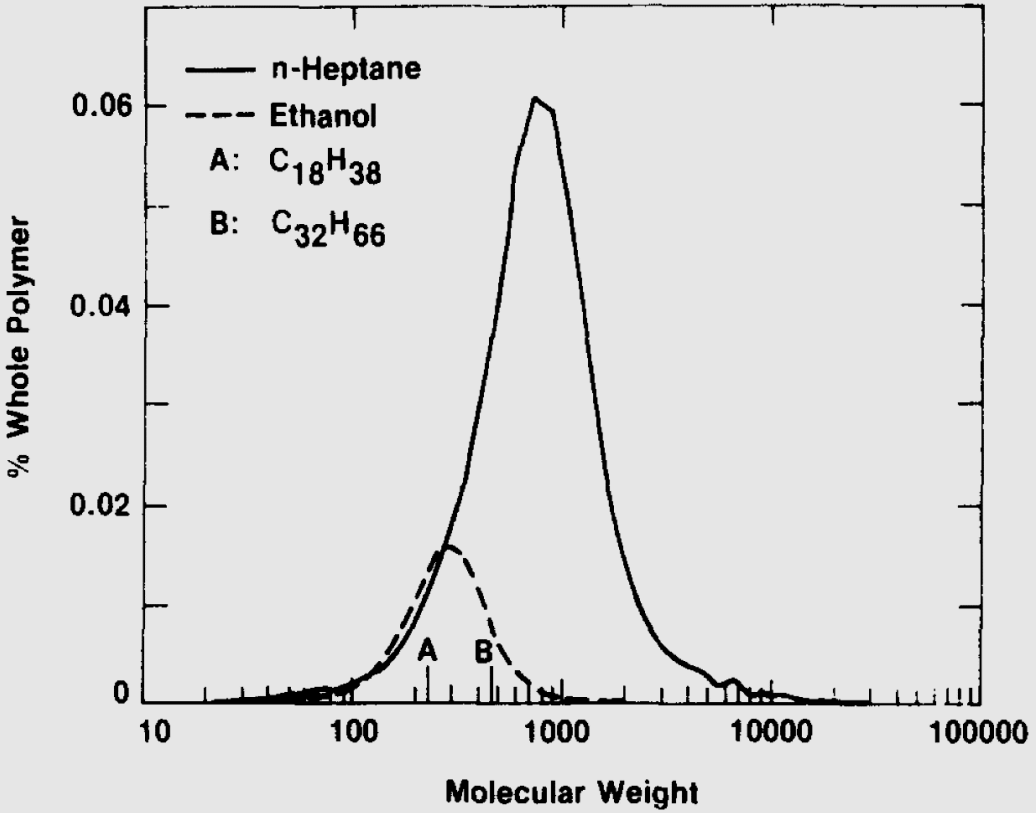


Figure 3 Molecular weight distribution of 70°C ethanol (– – –) and n-heptane (————) extracts of linear polyethylene

Table 5 Extractions of polyethylenes by ethanol and n-Heptane at 70°C for 160 days

	Amount extracted (wt%)	
Solvent	LPE (SRM 1475)	BPE (SRM 1476)
Ethanol	0.08	0.23
n-Heptane	0.47	1.8

Table 6 Molecular weight distributions of ethanol and n-Heptane extract of polyethylenes

	M_n:M_w	
Solvent	LPE (SRM 1475)	BPE (SRM 1476)
Ethanol	250:310	310:410
n-Heptane	560:1020	620:3000

NVR (Nonvolatile Residue) Test (Silicone)

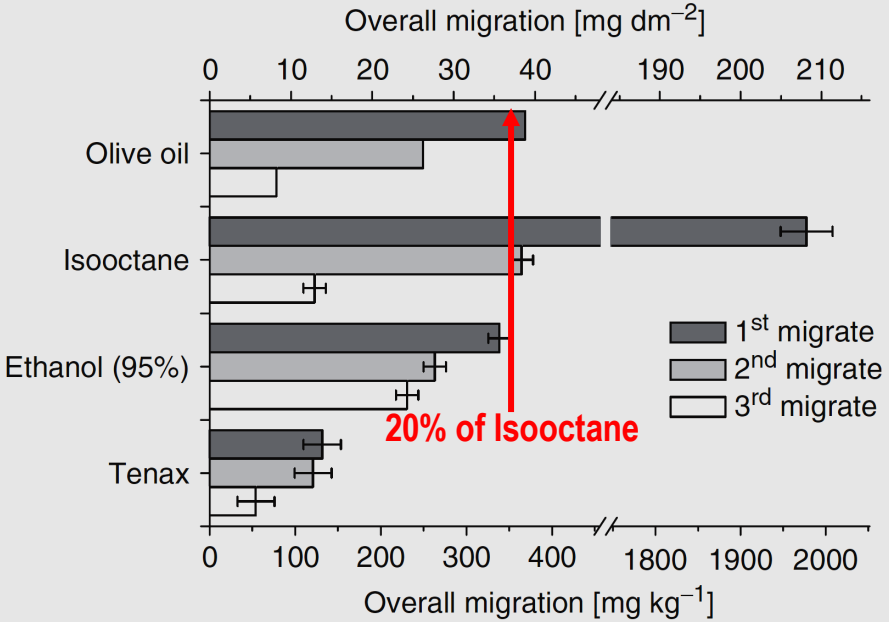


Figure 6. Overall migration into simulants (after gravimetric determination according to EN 1186:2002). Data shown: mean ± confidence interval ($\alpha = 0.05$), threefold determination (olive oil: single determination).

Table 2. Overall migration into isooctane and ethanol (95%) determined by ^{1}H-NMR and gravimetry. Data shows mean ± confidence interval ($\alpha = 0.05$) of threefold determination.

Simulant	Migrate	^{1}H-NMR w_A [mg dm^{-2}]	Gravimetry w_B [mg dm^{-2}]	Ratio w_A/w_B
Isooctane	1st	166.7 ± 10.6	208.1 ± 3.2	0.83
	2nd	33.3 ± 1.2	38.4 ± 2.3	0.87
	3rd	10.7 ± 2.9	12.9 ± 3.2	0.83
Ethanol (95%)	1st	30.2 ± 1.4	35.6 ± 1.3	0.85
	2nd	24.7 ± 3.1	27.7 ± 3.1	0.89
	3rd	21.1 ± 3.9	24.3 ± 2.9	0.87

Ref: Determination of the overall migration from silicone baking molds into simulants and food using 1H-NMR techniques

Presentation Summary

- *Solvent selection is "limited", considering all factors*
- *Three extraction solvents can be beneficial to achieve exhaustive extractions, not a guarantee*
- *The semipolar solvent can be more important than nonpolar solvent*
- *Repeated (sequential) extractions (daily, not 72 hours) can compensate difference in solvents to achieve exhaustive extraction and to generate extractables release profiles*
- *NVR is sometimes questionable as a reliable test for exhaustive extraction. Analytical on individual extractables is much more sensitive and reliable.*
- *Mass balance between NVR and analytical can be difficult to achieve*

Method "Specifications"

- *Solvents and methods can cover many materials and device types*
- *Repeated (sequential) extractions (daily, not 72 hours)*
- *Analytical comprehensiveness (MW range; hydrophobicity range; Volatility range)*
- *High peak capacity (hundreds)*
- *Apply to varying solvent polarity*
- *Sensitivity: the sensitive the better*
- *Validated*
- *Standard selections for a low uncertainty factor (UF)*

End of Presentation