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13th Year

Chemical Product (Formulation) Design
Lecture 2

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Problem Definition - 2

Molecular Design

Given: **A set of building blocks for molecules and a set of target (property) function values**

Wanted: **The set of molecules that match the target function values**

Mixture (liquid) Design

Given: **A set of molecules and a set of target (property) function values**

Wanted: **The set of blends (liquid solutions) that match the target function values**

Motivation – I: Chemicals based products

Example-1: Design of a consumer product - an insect repellent lotion

What does it involve? Determine a liquid formualtion that is effective against mosquito, has a pleasant smell, a good skin feeling and is a water-based product (active ingredient, water, solvents, additives)

Properties?The above product attributes, when translated, means that target values on the following properties need to be matched: 90% evaporation time, phase split, solubility, viscosity, molar volume, toxicity, etc., & cost

Formulation design methodology

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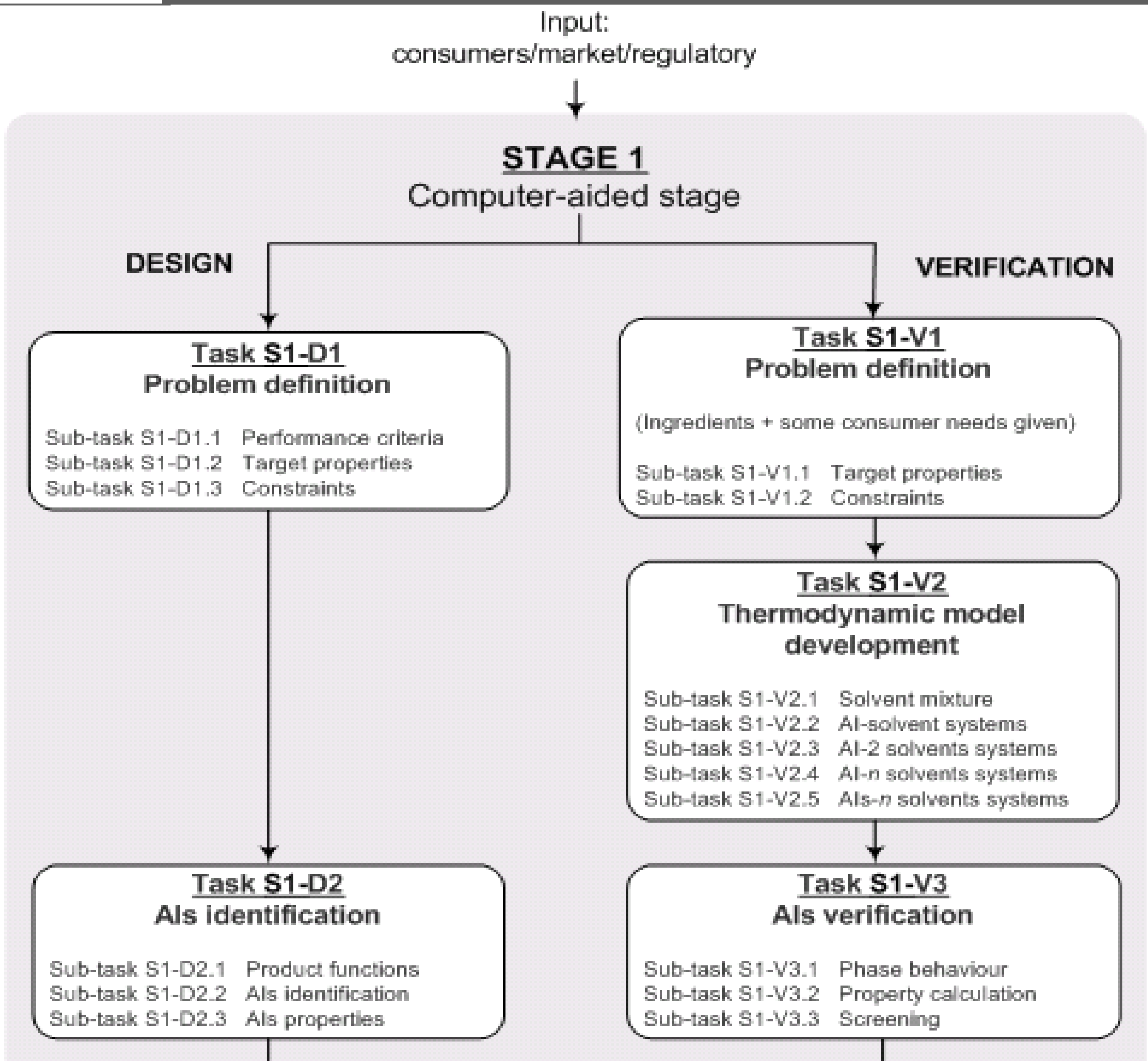

Stage-1: Computer aided methds and tools

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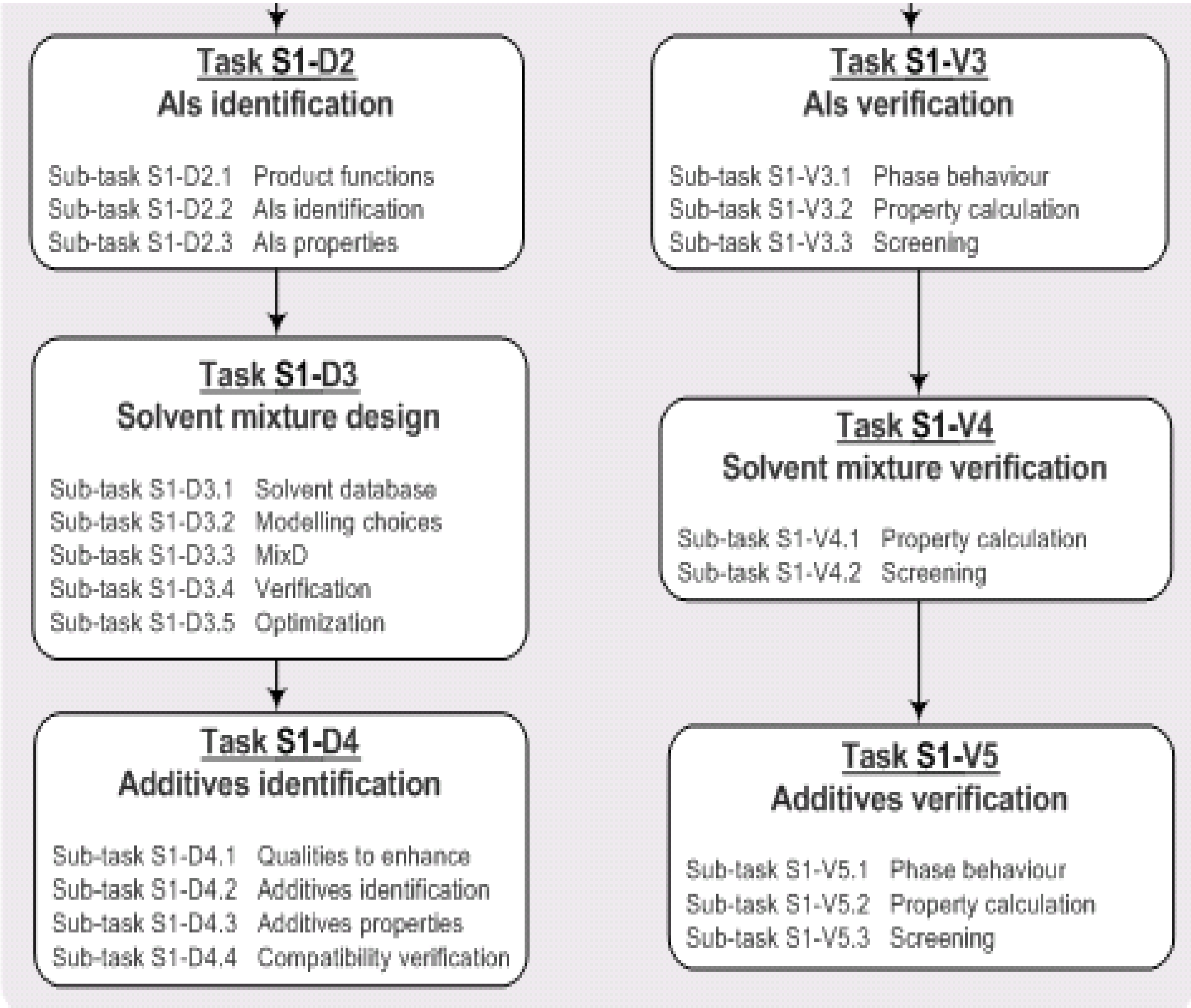
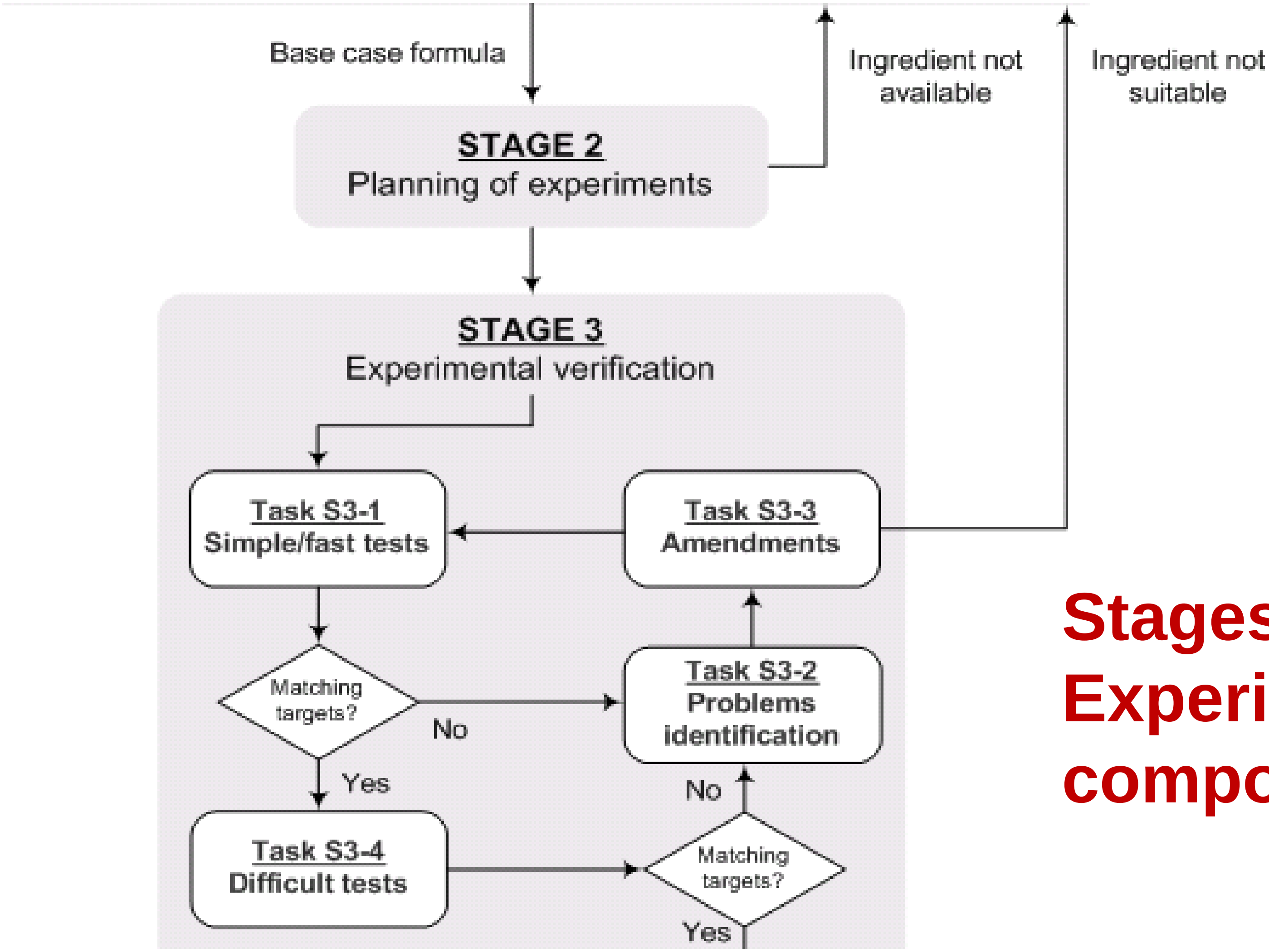


Stage-1: Computer aided methds and tools



Stages 2&3: Experimental component

Algorithm: Mixture design

INPUTS:
1. Database of solvents properties (sub-task 3.1.1)
2. Mixture property models (sub-task 3.1.2)
3. Number of target properties
4. Temperature (K)
5. Information for non-linear models

LEVEL 1
Linear design

Rule 1.1
Screening based on pure components properties
Rule 1.2
Calculation of the composition range for each target property
Rule 1.3
Identification of the overall composition range
Rule 1.4
Identification of the *xi* leading to the cheapest mixture

→ *n* mixtures composition cost

LEVEL 2
Non-linear design

Rule 2.1
Non linear models are solved with *xi* as input
Rule 2.2
m mixture not matching non-linear constraints are rejected

→ *n-m* mixtures composition cost

LEVEL 3
Stability analysis

Rule 3.1
The stability routine is run for each mixture
Rule 3.2
l mixtures showing phase split at *xi* are rejected

→ *n-m-l* mixtures composition cost

A Case Study

Computer-aided…

- Design of a paint for house interiors
- Design of a spray insect repellent
- Design of a spray sunscreen
- Verification of a hair spray (in progress)

Case study considered: spray insect repellent

Experimental…

- Verification of the spray insect repellent
- Verification of the spray sunscreen (in progress)

Task 1: Problem Definition

Main activity:

Performance criteria:

- ❖ **effective against mosquitoes**
- ❖ **long lasting**
- ❖ **low toxicity**
- ❖ **water-based formula**
- ❖ **good material compatibility**
- ❖ **good stability**
- ❖ **spray lotion**
- ❖ **low price**

Qualities to enhance:

- ❖ **pleasant scent**
- ❖ **good skin feeling**

- ❖ **evaporation rate T90**
- ❖ **lethal concentration LC50**
- ❖ **water+water miscible solvents**
- ❖ **non corrosive solvents**
- ❖ **solubility parameter δ, phase stability**
- ❖ **kinematic viscosity ν, molar volume Vm**
- ❖ **cost C**

Constraints:

500	<	$T90$	<	1500	s
0.39	<	$LC50$	<	$+\infty$	mol/m^3
0	<	ν	<	75	cS
21.1	<	δ	<	27.1	$MPa^{1/2}$
20.0	<	Vm	<	50.0	l/kmol

Task 2: AI Identification

DEET:

- ❖ aggressive on surfaces (clothes, plastics,..)
- ❖ high potential of irritating eyes
- ❖ sticky
- ❖ unpleasant odor

Picaridin:

- ❖ higher safety
- ❖ lower toxicity
- ❖ good material compatibility
- ❖ good cosmetic properties
- ❖ low water solubility
- ❖ high alcohol solubility

Natural AIs:

- ❖ low efficiency

Task 3: Mixture Design

Solvent database: water + alcohols

Mixture property models: linear/based on group decomposition

Mixture design routine results:

nº	Mixtures	x_1	δ MPa½	ν cS	ρ kg/l	LC_{50} mol/m³	T_{90} s	Cost $/kg	Phase stability: Stable	Phase stability: Phase split
1	methanol + water	0.32	42.0	0.83	0.89	0.74	819	0.65	X	
2	2-propanol + water	0.24	42.0	1.31	0.87	0.52	661	0.92	X	
3	allyl alcohol + water	0.29	42.0	1.14	0.96	0.52	598	1.10	X	
4	tert-butyl alcohol + water	0.24	42.0	1.49	0.94	0.45	588	1.22		0.02 - 0.44
5	ethanol + water	0.27	42.0	1.01	0.89	0.58	734	1.42	X	
6	2-methyl-1-propanol + water	0.23	42.0	1.66	0.88	0.42	597	1.72		0.02 - 0.46
7	2-butanol + water	0.24	42.0	1.62	0.88	0.41	520	1.81		0.02 - 0.46
8	1-propanol + water	0.25	42.0	1.28	0.88	0.47	628	2.07	X	

Verification results:

nº	Mixtures	ν -linear cS	ν -Cao cS	*RD %*
1	methanol + water	0.83	0.81	2.63
2	2-propanol + water	1.01	0.97	4.60
3	allyl alcohol + water	1.28	1.30	1.04
5	ethanol + water	1.31	1.33	1.57
8	1-propanol + water	1.14	1.06	7.43

Alcohols	δ MPa½
methanol	29.6
2-propanol	23.5
allyl alcohol	27.5
ethanol	26.5
1-propanol	24.5

Optimization:

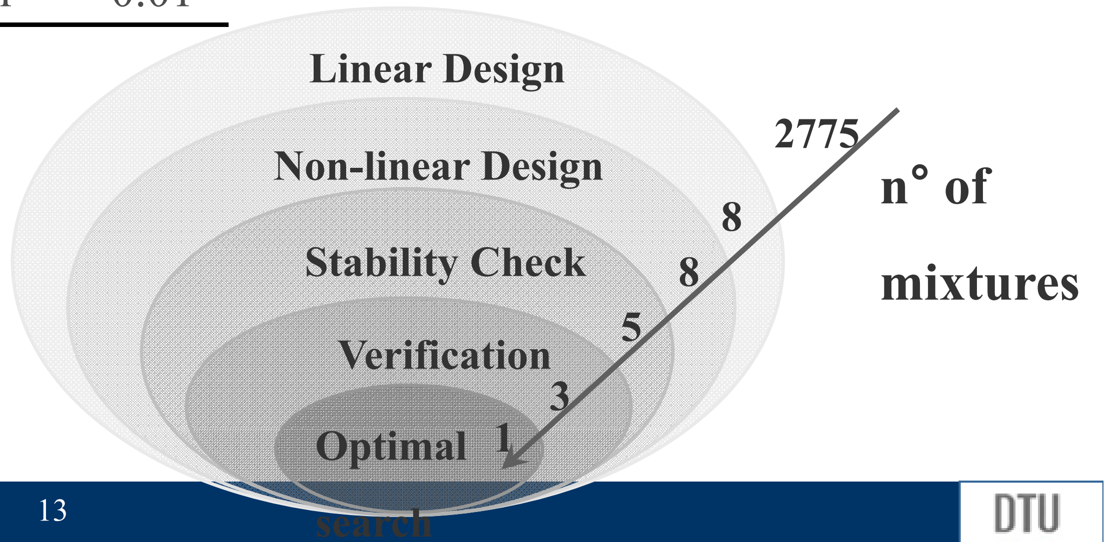
nº	Mixtures	x_1	Cost $/kg
2	2-propanol + water	0.24	0.92
5	ethanol + water	0.27	1.42
8	1-propanol + water	0.25	2.07

Base Case Formula

Aroma compound: Linalool (light and refreshing, floral woody odor)

Base case formula

Family	Chemical	w_i
AI	picaridin	0.10
Solvent mixture	2-propanol	0.39
	water	0.50
Additive	linalool	0.01



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Task 5: Design of Experiment

nº	Test	Experimental set-up
1	solubility limit of picaridin in water	LLE apparatus
2	phase stability of the solvent mixture	3 hours stirring
3	solubility of AI in the solvent mixture	3 hours stirring
4	solubility of additive in the solution AI-solvent mixture	3 hours stirring
5	density of pure compounds, solvent mixture and formula	weight of a known volume of liquid
6	viscosity of pure compounds, solvent mixture and formula	Brookfield viscosimeter
7	evaporation time of pure compounds, solvent mixture and formula	modified standard method ASTM 3539-87
8	spray-ability	commercial spray container is employed
9	appearance (turbidity/colour), odour	observation and sniffing
10	stickiness, greasiness, irritation	application on the skin
11	pH	pH indicator strips
12	stability at different temperatures than 25 °C (5 °C, 45 °C)	one product sample in the refrigerator and another sample in the oven for some weeks
13	shelf life	a product sample is left resting for three months at room temperature

properties that can not be modelled (tests 9–10)

properties not considered during the computer-aided design (tests 11–13)

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Task 6: Experimental Verification

nº	Test	Test results
1	solubility limit of picaridin in water	low solubility (9.3 gr/l @ 25 °C)
2	phase stability of the solvent mixture	successful (homogeneus system)
3	solubility of AI in the solvent mixture	successful
4	solubility of additive in the solution AI-solvent mixture	successful
5	properties of pure compounds	40% of deviation from exp value for predicted viscosity of picaridin
6	properties of solvent mixture	matching constraints
7	properties of formula	still matching constraints
8	spray-ability	successful
9	appearance (turbidity/colour), odour	not satisfactory (too strong scent of picaridin)
10	stickiness, greasiness, irritation	a little bit too sticky
11	pH	not satisfactory
12	stability at different temperatures than 25 °C (5 °C, 45 °C)	successful

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Tasks 7 & 8: Problems Identification and Amendments

Problem	Amendment
The pH of the formula is too high (8.5) for a skin care product which should have a pH between 5 ÷ 7	Addition of a mild acid such as acetic acid to correct the pH. An addition of 0.05 % w. of acetic acid lowers the pH to 5.5 (skin pH)
The scent of the formula is not acceptable since the picaridin odor prevails	Increase of linalool concentration. An addition of 4 % w. of linalool versus the 1 % of the base case improves the scent of the all formula
The product is a little sticky and this is due to the picaridin	Decrease the picaridin concentration, but adding the above compounds will lower the concentration of picaridin in the formula, so no other amendments are planned

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Task 9: Shelf Life Test and Iterations

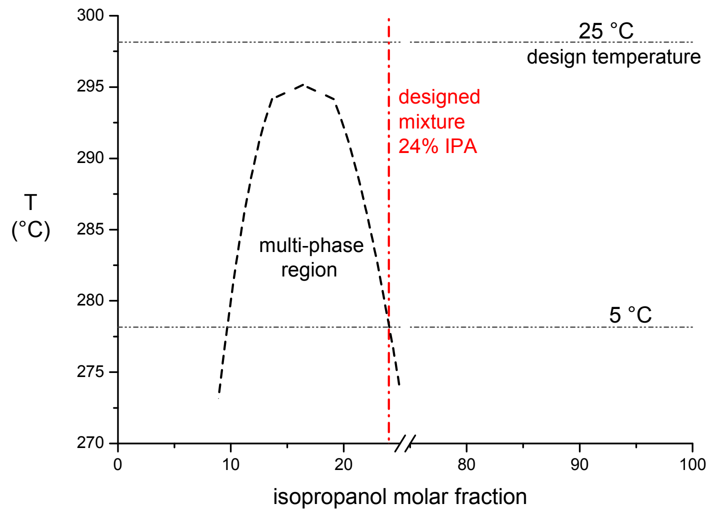
nº	Test	Test results
1	solubility limit of picaridin in water	these tests are performed just in the first iteration (applies to tests 1–6)
2	phase stability of the solvent mixture	
3	solubility of AI in the solvent mixture	
4	solubility of additive in the solution AI-solvent mixture	
5	properties of pure compounds	
6	properties of solvent mixture	
7	properties of formula	still matching constraints
8	spray-ability	successful
9	appearance (turbidity/colour), odour	acceptable
10	stickiness, greasiness, irritation	reduced acceptable stickiness
11	pH	successful
12	stability at different temperatures than 25 °C (5 °C, 45 °C)	successful
13	shelf life test	still in progress (1.5 months left, successful by now)

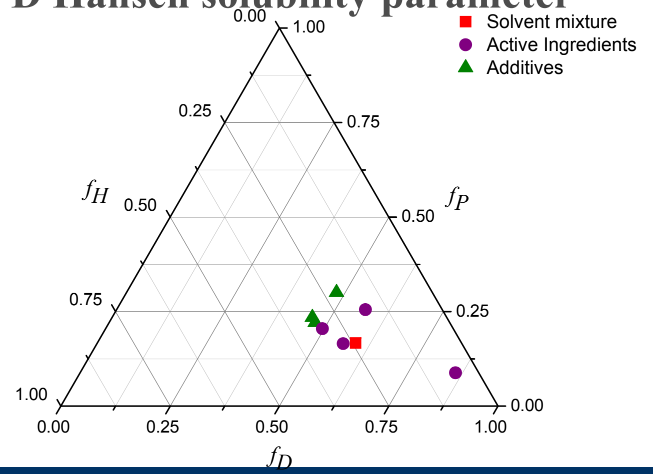
Final Formula

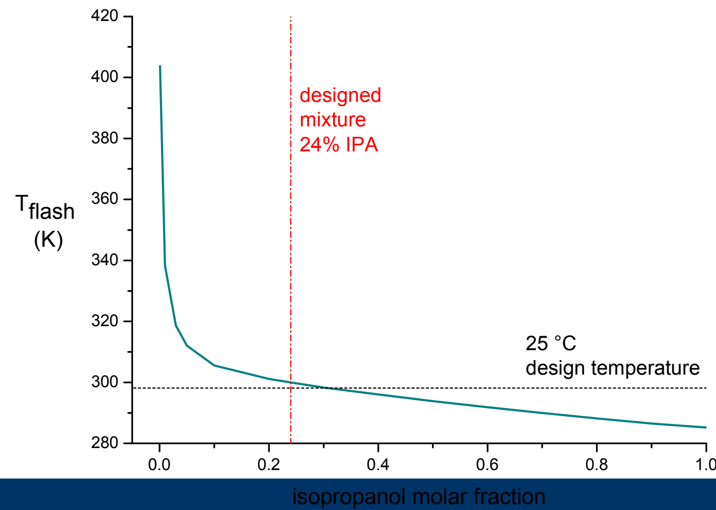
Family	Chemical	W_i %
AI	picaridin	9.70
Solvent mixture	2-propanol	44.25
	water	42.00
Additives	linalool	4.00
	acetic acid	0.05

Modeling Considerations

- The stability of the product at different temperatures should be taken into consideration during the computer-aided design
- The flash point of the mixture should be another constraint to consider during the computer aided design using the model from Liaw et al. (2002)
- The Hildebrand solubility parameter has been shown to be a weak parameter to control the solubility, and we think that it should be replaced by the 3-D Hansen solubility parameter







Remarks

- A hybrid methdology for the design of formulations has been highligthed through a case study
- It has been demonstrated that the screening of alternatives through a computer-aided design can save time and resources and the optimal product candidate can be identified
- Through experimental design, the weak points of computer-aided design have been identified and suggestions for improvement have been made
- Current work is to complete experimental verification of the sunscreen formula, while future work is to complete the new case study on a hair spray product

Use of solvents in product development

Solvent use in different industrial sectors: mostly organic solvents

Reaction/Synthesis
Mixing: mass transport / phases
Selectivity
Reaction rate
Scalability

Isolation/Separation
Solvent extraction
Azeotropic distillation
Cooling crystallisation
Precipitation using an anti-solvent

Product Delivery
Paints, Inks, consumer products
(lotion, hair spray, ...)

Easier operation

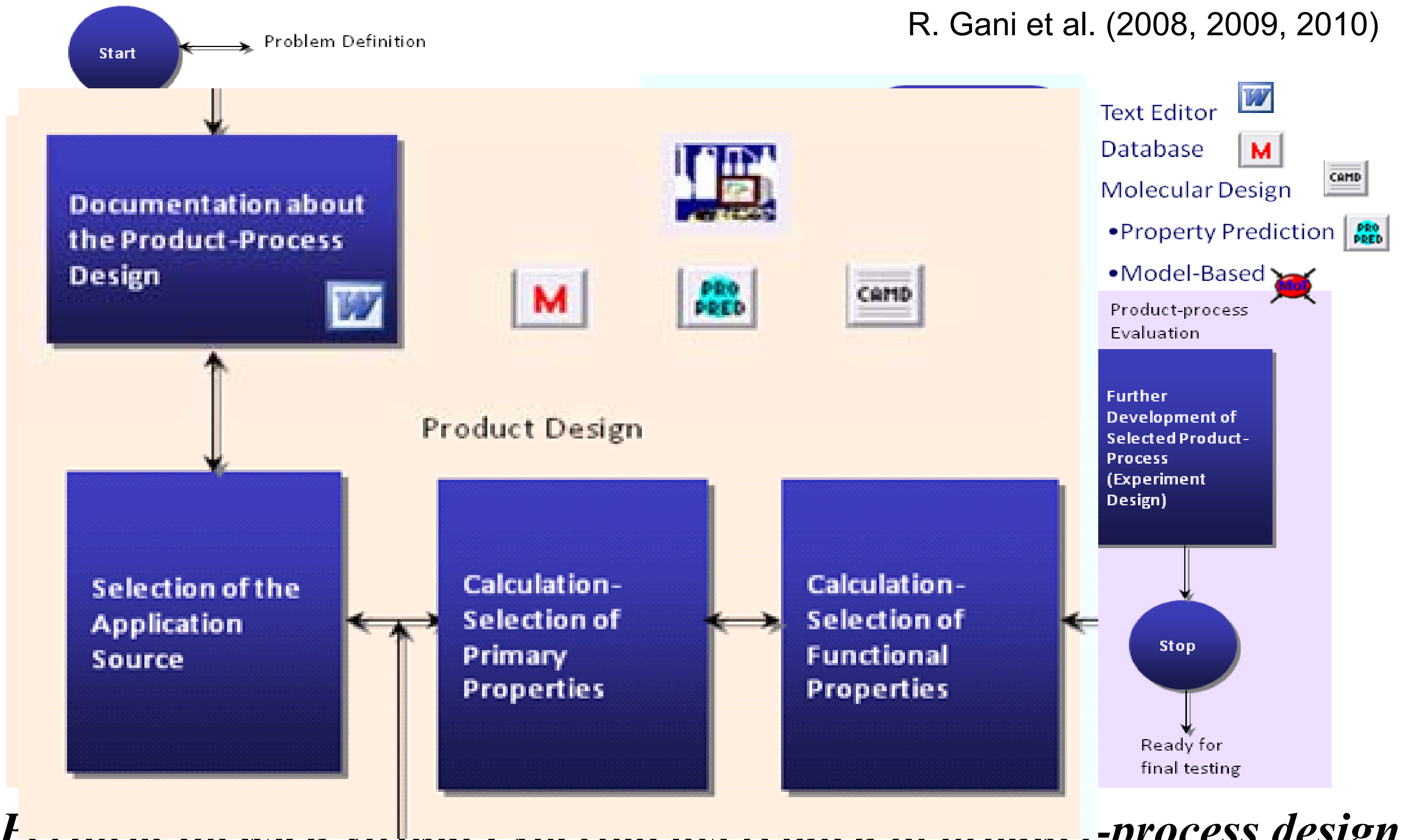
Washing of solid product

Safety
exotherm control

Cleaning

The *Virtual* Process-Product Design Lab

R. Gani et al. (2008, 2009, 2010)



Perform focused virtual experiments related to product-process design

Virtual product-process lab - application

Insect Repellent Formulation Design

Conte et al. 2009

Family	Chemical	w_i
AI	picaridin	0.10
Solvent mixture	2-propanol	0.39
	water	0.50
Additive	linalool	0.01

Main activity:

- effective against mosquitoes

Quality to enhance:

- pleasant scent
- good skin feeling

Target properties:

- evaporation rate T_{90}
- lethal concentration LC_{50}
- water+water miscible solvents
- non corrosive solvents
- solubility parameter δ, phase stability
- kinematic viscosity v, molar volume V_m
- cost C

Perform experiments to verify product performance

Other examples of formulations: Fuel blends 1a

Gasoline blend

Target Property	Target Value	Model
Heating Value (KJ/kg)	> 35 000	$HV_{mix} = \sum x_i HV_i$
Density (kg/m^3)	700 - 790	$\rho_{mix} = \sum x_i \rho_i$
Kinematic Viscosity (mm^2/s)	< 2.41	$\nu_{mix} = \frac{1}{\rho_{mix}} \exp\left(\sum \upsilon_i \ln \eta_i\right)$
Octane Number	> 90	$ON = \sum x_i * ON_i$

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Other examples of formulations: Fuel blends 1b

	Task	Methods & tools	Output
Task1	Identify the important target property	Literature (journals), Blending guideline	List of target properties
	Set the target value for each target property	Literature (journals), Blending regulation, Existing product	List of constraints
Task2	Identify pure property model	Literature, ICAS, calculated directly from chemical structure	Pure property models
	Identify mixture property model	Literature	Mixture property models
Task3	Identify the feasible mixture	ICAS	List of feasible blend compositions
Task4	Generate the possible mixture candidates	GAMS	List of several possible mixture candidates
Task5	Validify the model	Experiment	Rigorous model

Other examples of formulations: Fuel blends 1c

Pure component properties

Component	Gasoline	Ethanol	Butanol	MTHF
Molecule formula	C5 - C12	C_2H_5OH	C_4H_9OH	$C_5H_{10}O$
Molecule weight (g/mole)	115.52	46.05	74.12	86.13
Boiling point (C)	114.52	78.29	117.7	76.74
Flash point (C)	15.02	12.85	28.85	-11.15
Density (kg/m3)	687.94	785.58	805.77	816.06
Viscosity (kg/ms)	0.00091	0.00108	0.00253	0.00029
Heating value (MJ/kg)	48.11	29.74	36.21	36.06
Octane Number	95	110	102.7	112.3

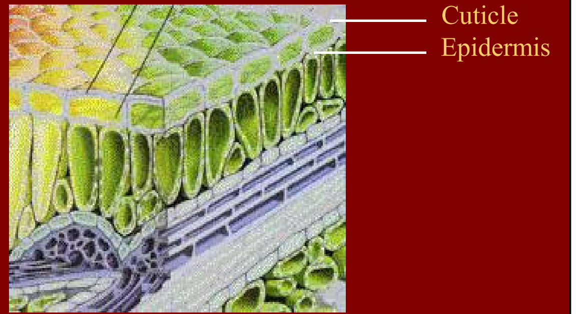
Other examples of formulations: Fuel blends 1d

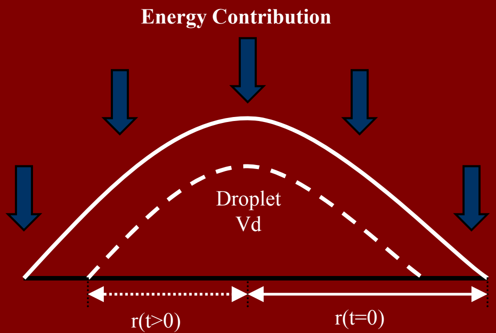
Generated results

Composition	Mix 1	Mix2	Mix3	Mix4	Mix5	Mix6
Gasoline	0.500	0.500	0.610	0.739	0.848	0.90
Ethanol	0.042	0.007				
Butanol	0.378	0.483	0.390	0.261	0.100	0.01
MTHF	0.08	0.010			0.052	
Property						
HV	41.167	41.473	42.779	44.414	45.945	46.746
Density	749.156	749.130	736.186	720.522	707.696	700.000
Viscosity	0.00152	0.00174	0.0016	0.00138	0.00106	0.00109
ON	100	99	98	97	96	95

Pesticide Uptake in a Leaf

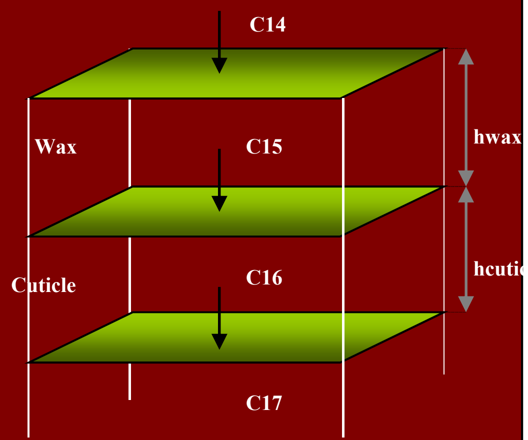
Internal Structure of Leaf





Droplet Evaporation Model

Multilayer Uptake Model



Plant Compartment containing epidermis and the layers beneath.

Challenges and Opportunities – 2

Pesticide Uptake in a Leaf

Diagrammatic representation of Equations used for Active Ingredient & Surfactant in the Model

Droplet

$$\frac{dM_{AI}}{dt} = \frac{-D_{AI} * S * (C1 - C0)}{hwax} + Vd * \frac{dCd_{AI}}{dt}$$

$$\frac{dCd_{AI}}{dt} = 1000 * \left(\frac{MW_{adj}}{MW_{AI}}\right) * \left(\frac{(S_{adj} - S_{water})}{\rho_{adj} * Vd}\right) * \left(Vd * \frac{dCd_{adj}}{dt} + \frac{dM_{adj}}{dt}\right)$$

Plus Surfactant Equations

Layers

0

Wax (hwax)

0: $CO = KwdAI * CdAI$ / Plus Surfactant Equations

1: $\frac{dC1}{dt} = (D_{AI1} * B / h_{wax}^2) * (C2 - 2C1 + C0)$ / $\frac{dC_{adj1}}{dt} = (D_{adj1} * B / h_{wax}^2) * (C_{adj2} - 2 * C_{adj1} + C_{adj0})$

15

Cuticle (hcut)

16: $\frac{dC16}{dt} = ((D_{AI16} * B / h_{cut}^2) * (C17 - C16)) - ((D_{AI15} * B / h_{wax} * h_{cut}) * ((KwcAI * C16) - C15))$ / Plus Surfactant Equations

17: $\frac{dC17}{dt} = (D_{AI17} * B / h_{cut}^2) * (C18 - 2 * C17 + C16)$ / Plus Surfactant Equations

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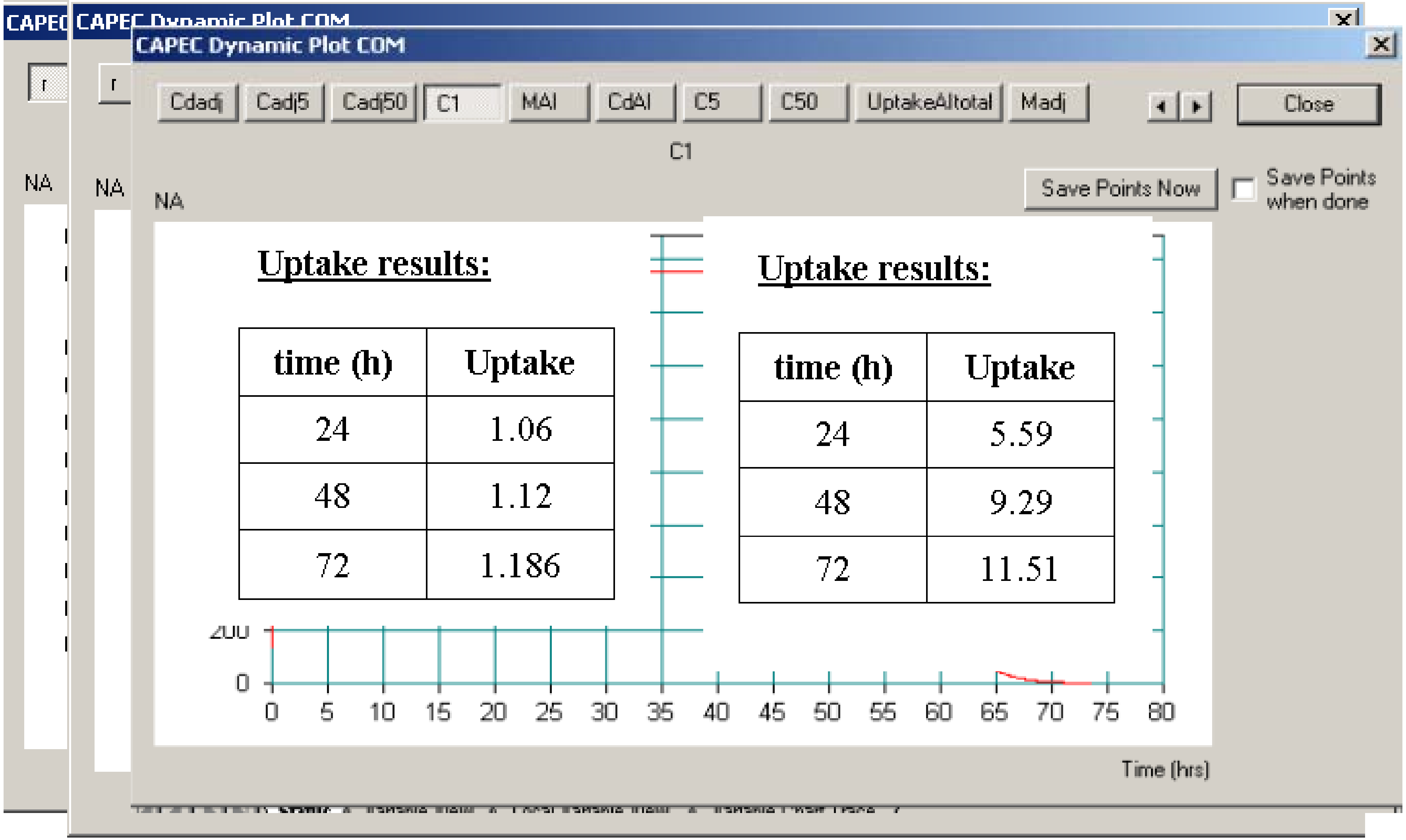
Plant

$CpAI = C30 / KcpAI$ / Plus Surfactant Equations

Verification Through Uptake Model



Uptake results:

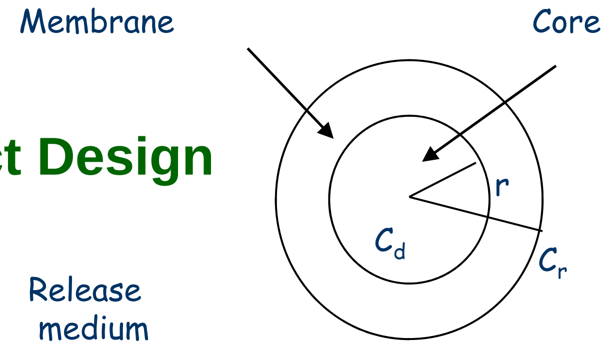
time (h)	Uptake
24	1.06
48	1.12
72	1.186

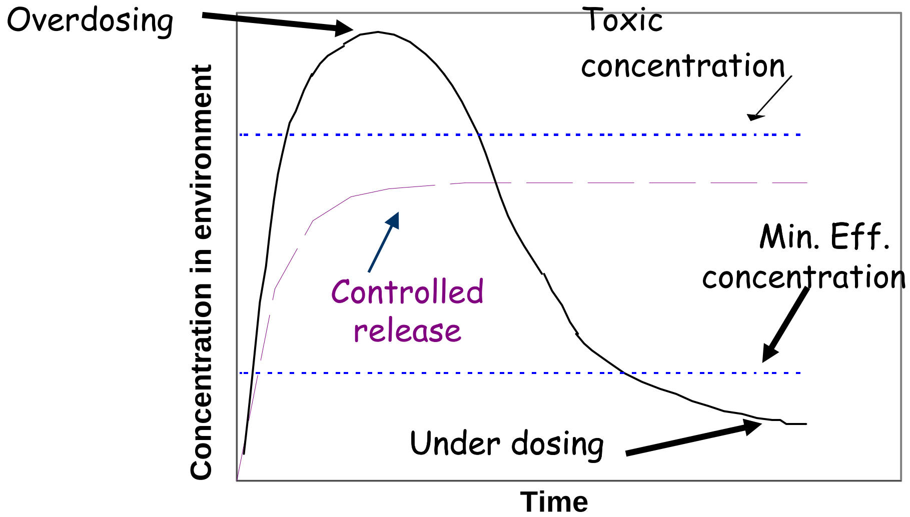
Uptake results:

time (h)	Uptake
24	5.59
48	9.29
72	11.51

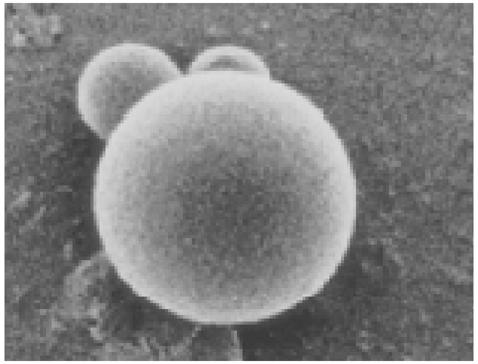
Controlled Release of AIs

I. Product Design





III. Evaluation of performance



II. Process for manufacture of microcapsules

Core: AI solid/liquid, pure/solution (or dispersion) + additives (solvent, emulsifier,...)

Coating: polymer membrane (rate-controlling) porous/non-porous

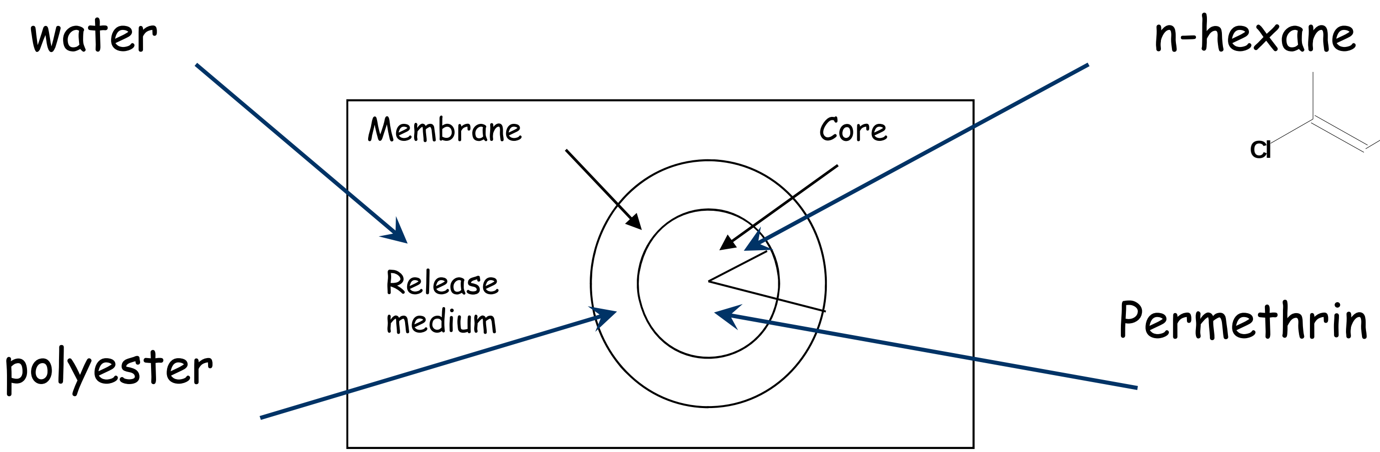
Needed property models develped

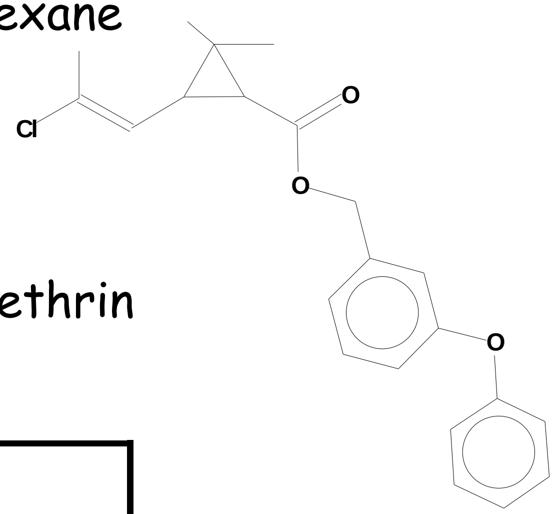
Nuria Muro-Sune, PhD-thesis, 2005

Case study: Permethrin microcapsule

Permethrin microcapsule: Insecticide encapsulated

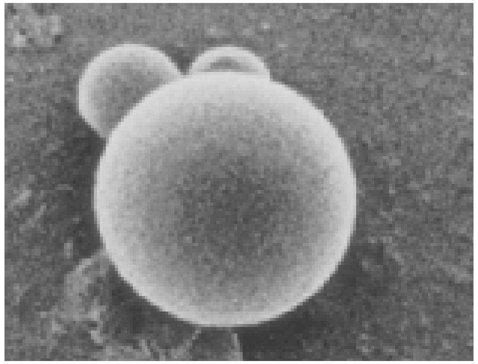
Reduce toxicity & longer bilogical effectivity



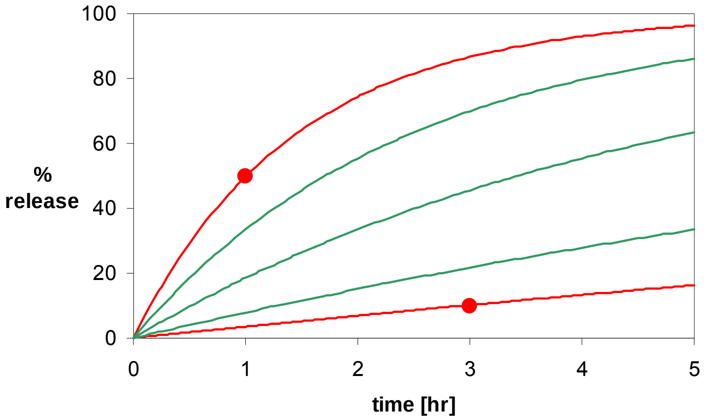


Compound (2)	Function	Solubility of Permethrin in solvent (ppm) [6]	Solubility of Permethrin in solvent (w_1)	Ω_1^{∞}	$K_{p/solv}$
n-Hexane	core solvent	10^6	0.5	2.0	**2.083**
Water	release medium	0.006	$6.0 \cdot 10^{-9}$	$1.66 \cdot 10^8$	**1.73*10^8**
PBMA	polymer wall	-	-	0.96*	

Model based solution strategies: Examples



Controlled release of AI or polymer or microcapsule design?



$K_{m/d}$ = 2.67
$K_{m/r}$ = 0.12
D = 8.9 E-20 ÷ 1.8 E-17 [m^2/s]

δ = 32 $MPa^{1/2}$ **Target property**

Match target

1) Literature search…
2) GC methods
3) Other models

Polymers	δ	T = 310 K	D [cm2/s]
Polyurea	32.76	amorphous	6.9E-17
Polyacrylonitrile	31.50	glassy	
Poly(2-cyanoethyl acrylate)	31.77	amorphous	6.9E-45
Nylon 2I	27.20	glassy	

Conclusions

- Innovative product design needs predictive solution approaches where property models are used (applied) for different roles
- It is necessary to understand the role of the property model and be aware of their limitations
- Use of experimental data in model development, validation and process-product development needs to be carefully planned
- It is necessary to develop predictive models with few additional experimental data (or, use data generated through other means, for example, molecular modelling or models like the PC-SAFT)