Design of Formulated Products: A Systematic Methodology

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In chemical product design one tries to find a product which exhibits the desired (target) behavior specified a priori. *The identity of the ingredients of chemical-based products maybe unknown at the start, but some of their desired qualities and functions are usually known. A systematic model-based computer-aided methodology for design and verification of a class of chemical-based products (liquid formulations) is presented. This methodology is part of an integrated three-stage approach for design/verification of liquid formulations where stage-1 generates a list of feasible product candidates and/or verifies a specified set through a sequence of predefined activities (work-flow). Stage-2 and stage-3 (not presented here) deal with the planning and execution of experiments, for product validation. Four case studies have been developed to test the methodology. The computer-aided design (stage-1) of a paint formulation and an insect repellent lotion are presented.* © 2011 American Institute of Chemical Engineers *AIChE J,* 57: 2431–2449, 2011
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Introduction

In (chemical) product design, the aim is to find a product that exhibits certain desirable or specified behavior.[1] That is, while the identity of the final product is unknown, how the product must perform, is known. The chemical product (formulation) design problem can be defined in generic terms as: given a set of desired (target) product attributes, determine a set of chemicals blends (a mixture of compounds) that satisfy the desired attributes, and, from them, select the most appropriate candidates for final validation[2] by experiments.

One way to solve the aforementioned product design problem is to employ a systematic methodology consisting of a sequence of activities (work-flow) that guides the developer through an integrated set of decisions and/or calculations. Cussler and Moggridge[3] suggested four steps in the search for a solution to product design problems: define the needs, generate ideas to meet the needs, select among the ideas and, finally, manufacture the product. Ng, Gani and Dam-Johansen[4] on the other hand, identified the following three approaches for product design, which are classified in terms of their solution strategies:

1. Experiment-based trial-and-error approach: a large number of consumer products are developed through trial-and-error experiments. Because the desired properties need to be measured, not many candidate products are normally considered. Past knowledge and experience are crucial in this approach.

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2. Model-based approach: when validated mathematical models for the estimation of the (target) properties are available, a list of feasible candidates is generated and tested. This approach is able to efficiently find feasible candidates within the application range of the models.

3. Integrated experiment-modeling approach: this approach is based on the decomposition of the design problem into a hierarchical sequence of subproblems (levels). At the outer level, predictive models with wide application are employed. As one goes from the outer levels to the inner levels, the number of candidates decreases. The inner levels employ special correlations, rigorous models and/or experiments.

By far, the largest number of chemical-based products is designed through some form of the integrated experiment-modeling approach,[4] employing one or more of the four design steps of Cussler and Moggridge.[3] The integrated approach is the most convenient, because time and resources could be saved (compared to approach 1) and more reliable results could be obtained (compared to approach 2).

Many chemical-based personal care products of everyday life such as sun lotions, shower creams, insect repellents, etc., are liquid formulations. Other examples of chemical-based liquid formulated products are paints, pesticides and drugs. Formulations can be classified as "consumer-oriented products"[5–7] because it is the consumers who specify their "wants" and/or "needs". Therefore, for these formulations to be commercially successful products, they must satisfy the multiple consumer needs. An insect repellent, for instance, must provide effective protection against mosquito bites, as well as being long lasting, safe, easily applicable, nonsticky, and having a pleasant smell.[8] Formulations can also have other physical forms.[9] For example, suspensions contain insoluble chemicals dispersed in the liquid with the help of a dispersant; creams[10–11] are emulsions where solid constituents have been emulsified through selected emulsifiers together with solvents and additives; solid products such as pharmaceutical tablets[12] or soap bars are at the solid state. Because a single chemical (molecule) is unlikely to satisfy the multiple needs, a blend of several chemicals is usually sought. Consequently, a formulation may contain materials from different classes of chemicals, for example, insecticides, pigments, solvents, polymers, propellants, aromas, and others.

This article focuses on liquid formulations. Unless otherwise mentioned, the term product will be used in this article to mean liquid formulations.

The chemicals present in liquid formulations can be classified as follows:

1. Active ingredient (AI): every formulation has at least one active ingredient. This substance is the most important chemical in the formulation because it defines the function of the product. For example, the function of an insect repellent is to repel insects; a sunscreen lotion provides protection against the UV radiations and prevention of skin aging; paint formulations provide the desired color and protection of surfaces.

2. Solvent mixture: it is usually present in high concentrations and has the important functions of dissolving the AI and other additives, ensuring that the end-use product has a single-liquid phase, and of delivering the product to an application site. The solvent mixture evaporates after application.

3. Additives: they are usually present in low concentrations (<2% by volume), and they are responsible for enhancing the end-use product properties. Additives may only cause small modifications of the qualities of the final product.

The preferred and most common approach for the design of liquid formulations is the experiment-based trial-and-error approach. Experiments are usually performed in all steps during the development of a formulation. Obviously, this approach requires a large amount of resources and a long time for product development. Also, there is no guarantee that the optimal product would be found. Therefore, it would be beneficial if the number of feasible candidates could somehow be reduced and the experimental resources applied only to test and improve the likely best solution.

In recent years, various attempts have been made to develop systematic methodologies for the design and development of chemicals-based products. Computer-aided methods have been developed for solvent design,[13] mixture design[14] and general molecular design.[15] Liquid formulations, however, involve very different chemicals that form complex liquid mixtures/blends, and, therefore, pose a more challenging modeling task. With the availability of appropriate models, it is possible to develop systematic methodologies for the development of products by efficiently managing the associated complexities.

In this work, the integrated approach[4] is employed and the goal is to combine computer-aided model-based techniques with heuristic based experimental testing and improvement of designs of liquid formulated products. This approach has the following three stages:

1. Stage-1: Computer-aided design/verification based on "define target - match target" (design scenario: the search space is reduced and a list of potential product candidates is provided; verification scenario: few product candidates are verified against the targets or the best performing ingredients are selected from shortlists of candidates).

2. Stage-2: Planning of experiments (identifies the product attributes that need to be experimentally validated).

3. Stage-3: Experimental testing (measures and evaluates the needed properties of the pure compounds and/or mixtures), and design modification (amends the formulation to improve specific functions, if necessary).

Four case studies have been developed for testing the 3-stages approach: the design of a white waterproof paint formulation for the finishing of surfaces; the design of a spray insect repellent lotion (both an alcohol-based and a water-based product have been considered); and, the design of a waterproof sunscreen lotion. Also, the modeling issues for verification of a hair spray product has been reported by Conte et al.[16] The paint and the alcohol-based insect repellent case studies are presented in this work to highlight the work-flow of the computer-aided stage (stage-1) of the methodology (design scenario). The experimental validation of the designs of the water-based insect repellent and the sunscreen lotion are presented in an upcoming publication.[17] That is, this article highlights the computer-aided design issues, and the second article highlights the experiment-based trial-and-error approach for product validation and modification (Figure 1).

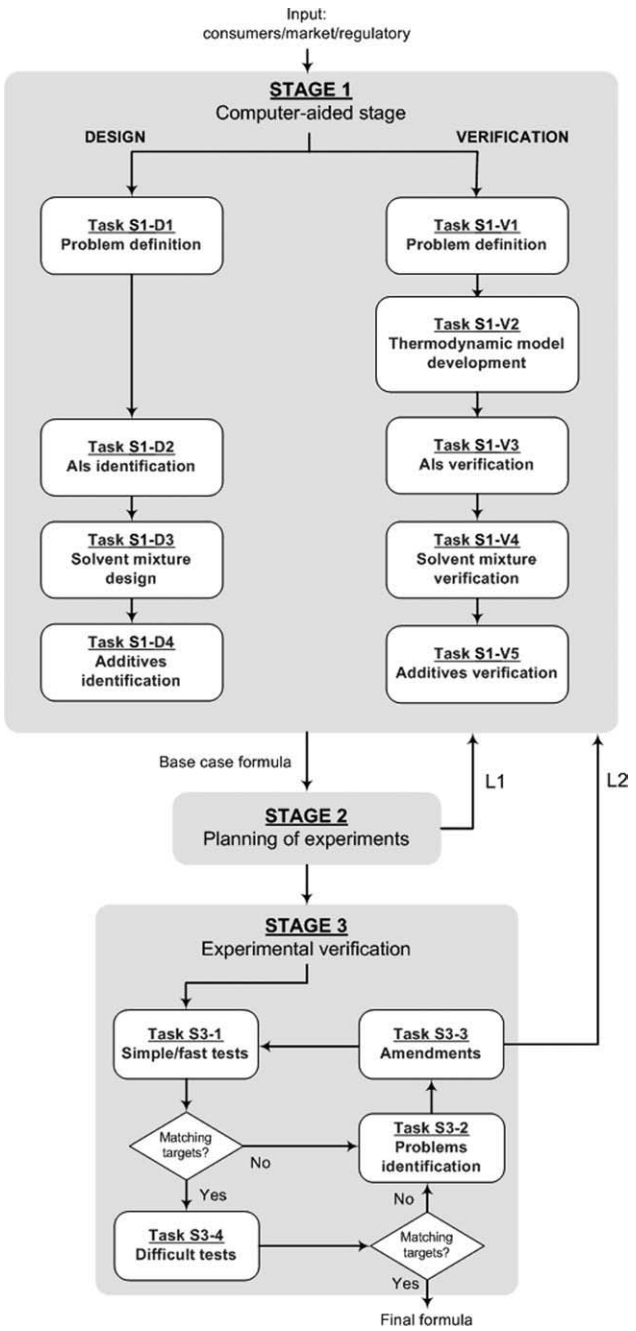

Figure 1. Work-flow diagram for the integrated methodology for formulation design.

The methodology employs the ''reverse design'' technique,[1,14] which is ideally suited to handle problems of the ''define target and match target'' type. Here, thousands of alternatives need to be generated and screened, systematically and efficiently. Posed as a reverse design problem, the target properties for the product become the known variables, and, therefore, input for the property models. Appropriate property models[18–22] are employed to estimate the target properties of the candidates so that they may be accepted or rejected. At the same time the mixture compositions that satisfy all the constraints are determined. In this way, the repetitions are avoided. Note also that all the product candidates satisfying the constraints are found in only one pass of the work-flow, and from this, the optimal is identified.

The methodology has been tested on several case studies from the coating and personal care industries. Two of these case studies are highlighted here.

Design of Liquid Formulated Products

The integrated modeling-experiment based approach divides the computer-aided liquid formulation design problem into four tasks (tasks S1-1 to S1-4), with each task having a number of subtasks, as shown in Figure 2. Table 1 provides a list of the data-flow (as input and output), the activities and the models for each of the subtasks of stage-1.

Task S1-D1: Problem definition

Activity: Identify the performance criteria (consumer needs, product attributes); translate the product attributes/needs into a set of physicochemical properties (target properties); set constraint values for the set of target properties.

Subtask S1-D1.1: Performance Criteria. Activity: Identify a set of performance criteria $(\underline{\psi})$ for the product to be designed using the knowledge base.[23]

Note A: The most important consumer need is the principal product function: it is the main reason for which consumers buy the product. For instance, for an insect repellent, the principal function is to repel mosquitoes. Consumer oriented chemical-based products can also have more than one principal function. For instance, a sunscreen lotion has to protect the skin from ultraviolet radiation of type A and type B, and it also has to prevent skin aging. For this reason, there are at least three active ingredients in a sunscreen lotion: a UV-A filter, a UV-B filter and an antioxidant. Other performance criteria are related to the form of the product (liquid, solid, powder, spray, etc.), safety, drying time (if part of the product has to evaporate after application), cosmetic properties (if the product is to be applied on the body), and so on. For instance, if the product is a body lotion, consumers do not generally want a sticky product or a product with a bad scent that may be unpleasant.

Note B: Some of the performance criteria will not be taken into consideration at this stage of the design (computer-aided), but only in the experimental planning and experimental validation. These properties are, for instance, the cosmetic and sensorial factors and the shelf life. These properties are actually difficult to define through the target properties but quite easy and fast to test through experiments.

Subtask S1-D1.2: Target Properties. Activity: Translate the performance criteria set $(\underline{\psi})$ into a set of target properties $(\underline{\zeta_i})$ using the knowledge base.

Note A: The target properties are classified in terms of:

1. $\underline{\zeta_1}$ properties that determine the product main functions. These properties are related exclusively to the choice of the AIs.
2. $\underline{\zeta_2}$ properties that determine the product performance. They are the physicochemical properties, which are mainly related to the solvent mixtures and they can mainly be enhanced or corrected by the additives.

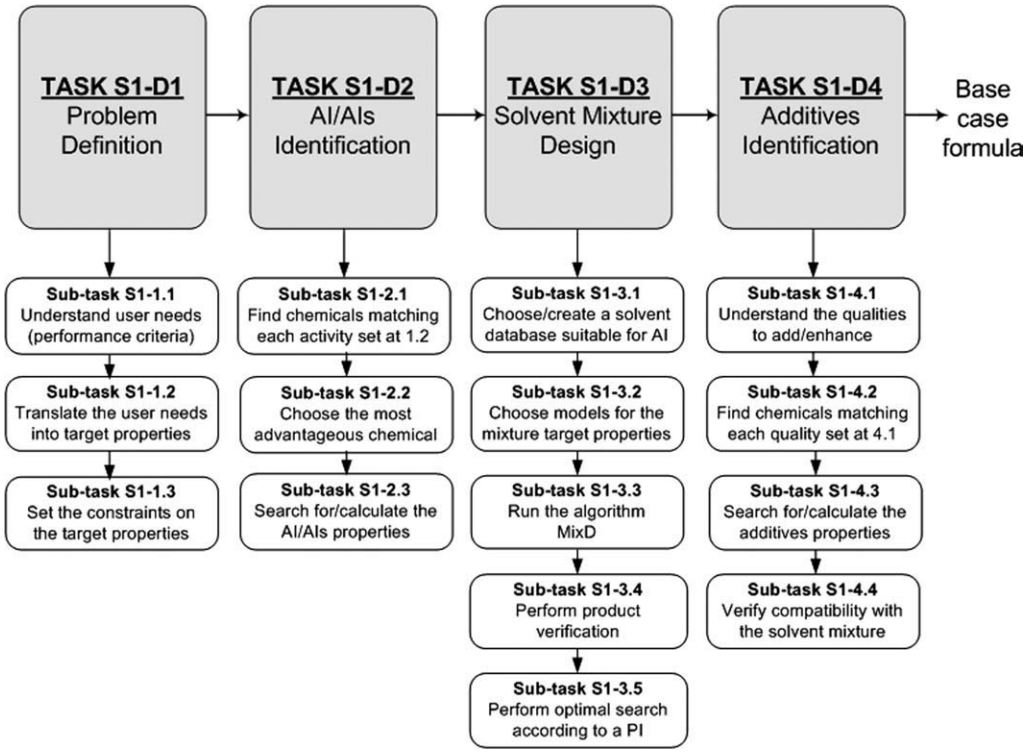

Figure 2. Work-flow diagram for the stage one of the integrated methodology.

Table 1. Data flows, Method and Tools used in the Computer-Aided Stage of the Integrated Methodology

Sub-task	Input	Action Performed	Methods & Tools	Output
S1-1.1	Information about the product	Understand user needs	Literature, knowledge base, statistics[1]	List of product attributes
S1-1.2	List of product attributes	Translate the user needs into target properties	Knowledge base[1]	List of target properties
S1-1.3	List of target properties	Set the constraints on the target properties	Knowledge base[1]	List of constraints
S1-2.1	Product function (from 1.1)	Find chemicals matching the function set at 1.2	Literature, knowledge base[1]	List of feasible AIs
S1-2.2	List of feasible AIs, PI	Choose the most advantageous chemical	Optimization methods	One AI for each product function
S1-2.3	One AI for each product function	Search/calculate AI properties	Literature, M&G GC+ models[2]	Solubility par., target properties, solubility info.
S1-3.1	Solubility par., target properties, solubility info.	Choose/create a solvents database suitable for the AI	Literature, M&G GC+ models[2], STABILITY algorithm	Suitable property database
S1-3.2	List of target properties (from 1.2)	Choose the models for the mixture target properties	Linear/ non-linear models for mixture properties[3]	Mixture property models
S1-3.3	Database, models, constraint n° and value, temperature	Run the algorithm MIXD	MIXD algorithm	*n* mixtures, properties, cost, composition
S1-3.4	*n* mixtures, properties, cost, composition, target properties to verify	Perform product verification	H-B classification ± rigorous mixture property models	(*n-m*) mixtures, properties, cost, composition
S1-3.5	(*n-m*) mixtures, properties, cost, composition, PI	Perform optimal search according to a PI	Optimization methods[2]	One optimal solvent mixture
S1-4.1	One optimal solvent mixture	Understand the qualities to add/enhance	Literature, knowledge base, statistics[1]	List of properties to enhance
S1-4.2	List of properties to enhance	Choose at least one chemical for each quality	Literature, databases[1]	List of possible additives
S1-4.3	List of possible additives	Search for/calculate the additives properties	Literature, M&G GC+ models[2]	Solubility par., target properties, solubility info.
S1-4.4	Solubility par., target properties, solubility info.	Verify compatibility with the solvent mixture	STABILITY algorithm	List of additives to add to the formulation

[1]CAPEC database.
[2]ProPred and property package.
[3]MoT.

Table 2. Performance Criteria Employed in this Work for the Design and Verification of the Products Considered and Translation of the Performance Criteria into Target Properties

Performance Criteria	Target Properties
spray-ability	η, σ, ρ
spray-ability	ν, ρ
drying time	T_{90}
flammability	T_f
toxicity	LC_{50}
conductivity	ε
cost	C
solubility	δ/δ_D, δ_P, $\delta_H/\Delta G^{\text{mix}}$

3. $\underline{\zeta_3}$ properties that determine the phase stability. They are the phase equilibria related properties. The stability of a liquid phase is controlled through the following conditions:

- Condition 1: the AI/AIs must be dissolved in the solvent mixture;
- Condition 2: the solvent mixture must be a single-liquid phase;
- Condition 3: the additives must be soluble in the solvent mixture.

Note B: It may not be possible to directly translate some performance criteria into chemical/physical properties even though they affect the design choices made later. For instance, the material compatibility with fabrics, metals and plastics is not translated into target properties, but it affects the selection of a specific section of a solvent database (see subtask S1-D3.1) employed for the design of the solvent mixture.

Note C: One performance criterion could be affected by more than one target property.

Note D: Table 2 shows the translation of the performance criteria into target properties employed in this work for the products under consideration (information contained in the knowledge base).

Subtask S1-D1.3: Constraints. Activity: Set numerical constraints $\underline{\zeta_i^{LB}}, \underline{\zeta_i^{UB}}$ on the set of target properties using the knowledge base (if necessary)

$$\underline{\zeta_i^{LB}} \le \underline{\zeta_i} \le \underline{\zeta_i^{UB}} \qquad \text{with } i = 1, 3 \tag{1}$$

Assumption: Compounds having similar solubility parameters are miscible with each other.[24]

The assumption of Hancock et al.[24] is employed to set (some of) the constraints for $\underline{\zeta_3}$ applied to conditions 1 and 3 (see subtask S1-D1.2)

$$\delta_{AI} - 3 \le \delta \le \delta_{AI} + 3 \tag{2}$$

$$\delta_{AI} - 3 \le \delta_{add} \le \delta_{AI} + 3 \tag{3}$$

δ is the solubility parameter of the solvent mixture, δ_{AI} is the solubility parameter of the AI (or average of the AIs solubility parameters, if more than one AI is present in the product), while δ_{add} is the solubility parameter of each additive. Eq. 2 corresponds to condition 1, while Eq. 3 corresponds to condition 3. To evaluate condition 2, the following constraints are introduced

$$\frac{\Delta G^{\text{mix}}}{RT} < 0 \tag{4}$$

$$TPD \ge 0 \tag{5}$$

Equations 4 and 5 are considered by the stability algorithm (see the related section).

Note: When fixing the numerical constraints for a parameter, at first information found in literature, patents, existing products, and websites (all information contained in the knowledge base) are consulted. If no information/data are available in the knowledge base, trial-and error-procedure is employed to find a feasible solution to the design problem. For instance, if no solution is found for a set of constraints, one constraint is relaxed and the MIXD algorithm is run once again. If still no solution is found, the same constraint is relaxed even more or another constraint is taken into consideration and relaxed.

Task S1-D2: AIs identification

Activity: Retrieve from databases[23] the chemicals that are able to satisfy the product functions $\underline{\zeta_1}$ defined in subtask S1-D1.2; select the best performing chemicals in the list; retrieve from databases[23] and/or calculate through appropriate property models[18–22] the needed properties.

Subtask S1-D2.1: Product Functions. Activity: For each of the desired main activities identified in subtask S1-D1.2, generate a list of chemicals (AIs) by consulting the AIs databases.

Assumption: The important hypothesis made here is that the AI/AIs are considered to be responsible only for the principal product functions $\underline{\zeta_1}$, and that they do not strongly affect the performance criteria $\underline{\zeta_2}$. This assumption is not valid if the AI/AIs are present in high concentrations or if the AI/AIs have a large contribution to one of the target properties. In this case, the selected AI may affect other product qualities and this should be taken into consideration in the design. For instance, if the selected AI/AIs are highly viscous (honey-like), and viscosity is one of the target properties, the AI concentration will affect this constraint. In this case, it would be better to define the constraint on the mixture viscosity taking into account the contribution of the AI/AIs.

For the kind of products (liquid formulations) considered in this work, the aforementioned assumption is very close to reality because in liquid formulations, the solvent mixture is usually present in high concentrations. Hence, the solvent mixture usually affects the other product properties with the largest contribution, while the AI/AIs affect mainly the product function, due to their low concentrations.

Subtask S1-D2.2: AIs Selection. Activity: Select at least one chemical from each of the lists generated in subtask S1-D2.1.

Note: The selection is done on the basis of one or more of the following criteria: effectiveness (the most effective chemical is selected); cost (the cheapest chemical is selected); safety and hazards (the safest chemical is selected); environment

(the most environmentally friendly chemical is selected); legislation (in some cases legislations need to be examined because some chemicals may be allowed for some applications and/or there may be regulations on the allowed concentration limits of the AI in the product); others not listed before and/or combination of the aforementioned criteria.

With multicriteria optimization, in principle, Pareto curves can be generated and analyzed to find the optimal trade-off solution. However, an easier option is to try different weights and obtain a weighted solution. The later option has been used in this work.

Subtask S1-D2.3: AIs Properties. Activity: For each of the AIs selected in subtask S1-D2.2, collect the necessary information/properties employing the databases[23] or calculate them by employing appropriate property models.[18–22]

Assumption: Like dissolves like.[25]

Note: The necessary information/properties to be collected in this subtask are:

- Information about the solubility in solvents (alcohol solubility, water solubility, etc.). This information is necessary when selecting the solvents for the solvent mixture design task (see task S1-D3). For instance, if the AI/AIs are water-soluble, only water-soluble solvents need to be considered for solvent mixture design.
- The (Hildebrand/Hansen) solubility parameter. The solubility parameter is employed to set the upper and lower bounds for the constraints of Eqs. 2 and 3, related to the product phase stability ζ_3.

Task S1-D3: Solvent mixture design

Activity: Determine (design) a set of candidate solvent mixtures that matches constraints on ζ_2 and ζ_3.

Note: If additional (rigorous) verifications of the mixtures are considered to be necessary, they would also be performed here. In the final step of this task, the optimal solvent mixture is determined for a specified performance index (PI).

Subtask S1-D3.1: Solvent Database. Activity: Select one or more solvent databases (consisting of solvents of a specific type and their properties) from the database library by employing the identified performance criteria from subtask S1-D1.1.

Assumption: Like dissolves like.[25]

Note: Because the solvent mixture should dissolve the AIs, solvents with solubility characteristics similar to those of the selected AIs have to be considered. For example, if the AI is well-known to be soluble in alcohols, the alcohols database is selected. In this way, it is likely that the solvent mixtures to be designed (in subtask S1-D3.3) will dissolve the AI and also remain in a single-liquid phase.

Subtask S1-D3.2: Modeling Choices. Activity: Select the property models needed for predicting the pure compound and mixture target properties from the model library.[18–22]

Note: For properties such as viscosity and surface tension, the available models are pure compound property[22] based linear models, or rigorous models.[26,27] The later are based on the group contribution concept (viscosity[26] and surface tension[27]). In the MIXD algorithm the models usually employed for the estimation of mixture viscosity and surface tension are linear models, because the rigorous models of Cao et al.[26] and Suarez et al.[27] are computationally expensive. The rigorous models are used, instead, in the verification subtask S1-D3.4 on the mixtures resulting from the MIXD algorithm.

Subtask S1-D3.3: MIXD (Solvent Mixture Design). Activity: Apply the MIXD algorithm to design the solvent mixtures matching the constraints of Eq. 1 on ζ_2 and ζ_3 (defined in subtask S1-D1.3).

Assumption: As a result of the assumptions made in subtask S1-D2.1, all the constraints defined in subtask S1-D1.3 on ζ_2 and ζ_3 must be satisfied by the solvent mixture, with the exception of the constraint of Eq. 3 that is considered in task S1-D4 (when selecting additives).

Note: The mixtures matching the targets, their composition, cost, target property values and stability information are the output of the MIXD algorithm.

Subtask S1-D3.4: Verification. Activity: Apply the mixture classification algorithm (see related section) and verify if the target properties of the candidate mixtures estimated with rigorous models also satisfy the constraints on ζ_2 and ζ_3. If not, reject these mixtures.

Subtask S1-D3.5: Optimization. Activity: Define a PI and determine the optimal solvent mixture by ordering all the feasible mixtures in terms of the PI value. For multiple PIs, determine optimal solutions for each PI, than rank and weight the mixtures to identify the best ''trade-off'' solution.

Note A: At this stage a short-list of feasible candidates (solvent mixtures) is available; therefore, it is a simple task to order the feasible candidates according to a specific PI to find the optimal selection. Note that when all the target properties can be explicitly modeled, a purely mathematical programming based solution can also be obtained (Pareto curves can be generated and analyzed also in this subtask).

Note B: The hierarchy of activities in subtasks S1-D3.3 to S1-D3.5 reduces the number of feasible solvent mixtures. Every level employs a different set of constraints:

1. Linear design level (performed in the MIXD algorithm): linear property models are employed for mixture design and the mixtures that do not match the constraints on the corresponding target properties are rejected.
2. Nonlinear design level (performed in the MIXD algorithm): simple nonlinear property models are employed using the list of feasible mixtures from the linear design level. The mixtures that do not match the constraints on the corresponding target properties are rejected.
3. Stability test level (performed in the STABILITY algorithm, which is part of MIXD): mixtures that show phase split at the compositions of interest are rejected.
4. Verification level: rigorous models (or measured data) are employed, if necessary, to verify if mixture properties predicted with linear models (in level 1) are correct, and mixtures whose property values do not now match the specified target values are rejected.
5. Optimization level: the optimal solvent mixture is selected according to any specific performance index PI (or a combination of PIs).

Task S1-D4: Additives identification

Activity: Add the final set of additives to the blend of AIs and solvents resulting from task S1-D3.

Subtask S1-D4.1: Qualities to Enhance. Activity: Identify the qualities to enhance or add to the formulation from the list available in the knowledge base.[23]

Note: It could be necessary, for instance, to: enhance the dispersion of solids; promote the solubilization of the AIs; ensure the product stability; enhance the spread-ability on surfaces; avoid microbial growth or undesirable chemical changes; enhance the sensorial factors and the cosmetic properties for products to apply on the body.

Subtask S1-D4.2: Additives Selection. Activity: Identify a short-list of candidate chemicals for each of the qualities that have to be enhanced/added/promoted from the additives databases.

Subtask S1-D4.3: Additives Properties. Activity: Retrieve from the additives databases[23] the properties of the additives in each short-list.

Assumption: Like dissolves like.[25]

Note: The necessary information/properties to be retrieved in this subtask are:

- Information about the solubility in solvents (alcohol solubility, water solubility, etc.). For instance, if the additives are alcohol soluble, and the solvent mixture designed in task S1-D3 was a mixture of alcohols, the additives are more likely to be able to dissolve in the solvent mixture.
- The (Hildebrand/Hansen) solubility parameter. The solubility parameter of the additive is necessary for the next subtask S1-D4.4, where Eq. 3 is applied.

Subtask S1-D4.4: Compatibility Verification. Activity: Apply the constraint of Eq. 3 and reject the additives that do not match this constraint.

Implementation of the Methodology

The methodology (see also Figure 2 and Table 1) described earlier has been implemented within a computer-aided framework.[28] A number of new tools/algorithms[28] as well as existing tools[29,30] have been necessary to obtain a working version of the implemented formulation design methodology. As listed in Table 1, among the methods/tools needed for liquid formulation design by the systematic methodology, the following have been developed in this work and described here: databases of solvents, additives, AIs and aroma compounds;[23] a knowledge base with the consumer needs for different formulated products, the translation to target properties, the setting of the constraint and so on;[23] the mixture classification algorithm; the mixture design algorithm (MIXD); the stability test algorithm (STABILITY).

The Mixture Classification Algorithm

This algorithm has been developed to quickly determine which mixtures are likely to have negligible excess properties of mixing, so that, time-consuming and tedious calculations with rigorous models can be avoided. Here, organic chemicals are classified in terms of hydrogen bonding (HB) properties into three kinds of fluids;[29] normal (NF), polar no associating (PNA), and polar associating (PAS). To form binary mixtures, these fluids can be combined in six different ways (NF/NF, PNA/PNA, PAS/PAS, NF/PNA, NF/PAS, PNA/PAS). In Figure 3 plots of excess properties for more than 130 binary mixtures of solvents are shown. It can be noted that mixtures of two similar fluids, especially of two normal fluids and polar non associating fluids, fall in the region where the excess property contributions can be neglected. Therefore, for these mixtures the use of linear models for the calculation of the corresponding mixture properties may be assumed to be acceptable.

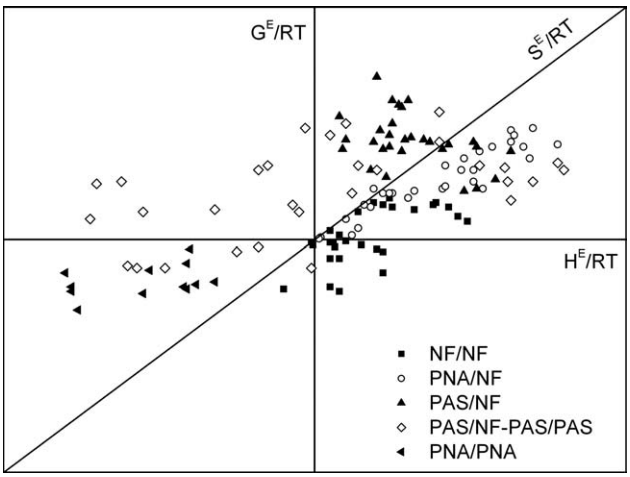

Figure 3. Equimolar excess properties for more than 130 mixtures at 298.15 K. G^E, H^E and S^E are the excess Gibbs energy, the excess enthalpy and the excess entropy, respectively.

The mixtures are represented according to the hydrogen bonding concept.

The MIXD Algorithm

This algorithm employs a decomposition based solution strategy[31] where the number of feasible mixtures is systematically decreased in subsequent levels (arranged in a hierarchy of calculations of increasing complexity). Four levels are involved, as highlighted in Figure 4. Each level is related to a subset of target properties for the desired mixture. The target properties are classified as linear (if linear models are used) and nonlinear (if simple nonlinear models are used). In addition, a rigorous stability test is performed to ensure the stability for the liquid mixture. The algorithm is described and highlighted for binary mixtures, but can easily be extended to multicomponent mixtures.

The input information to the algorithm is a solvent database[23] where the necessary pure compound properties are stored, the kind of property models[18–22] for the description of necessary properties (linear/nonlinear), the constraints on the target properties, the design temperature and information for the nonlinear models employed.

The algorithm returns, as output, the mixtures matching the constraints, their composition, values of the target properties, cost, and information about the phase stability.

The constraints on the generic target property ζ^k can be of the following types:

- Perfect match ($\zeta^{k,PM}$) constraints

$$\zeta^k = \zeta^{k,PM} \tag{6}$$

When perfect match problems need to be solved, a slack of 0.5% is applied on the value $\zeta^{k,PM}$ to find the solutions as

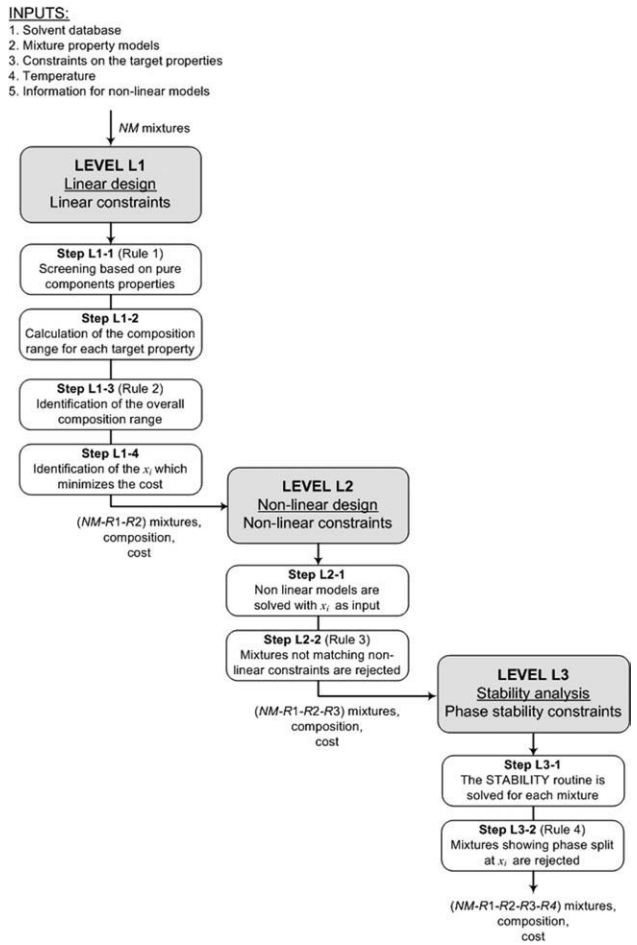

Figure 4. Flow-diagram of the MIXD algorithm used for the design of solvent mixtures (.vsd).

close as possible to the desired value. Hence, the equality constraints of Eq. 6 are transformed to inequality constraints of the type

$$(0.995)\cdot\zeta^{k,PM} \le \zeta^{k} \le (1.005)\cdot\zeta^{k,PM} \tag{7}$$

- Upper ($\zeta^{k,UB}$) and lower ($\zeta^{k,LB}$) bound constraints

$$\zeta^{k,LB} \le \zeta^{k} \le \zeta^{k,UB} \tag{8}$$

- Lower or upper bound constraints

$$\zeta^{k} \ge \zeta^{k,LB} \tag{9}$$

$$\zeta^{k} \le \zeta^{k,UB} \tag{10}$$

In the last case, the upper bound in Eq. 9 is set to a very large positive value, and the lower bound in Eq. 10 is set to a very large negative value.

It has to be underlined that, in a mixture design problem, there is a set of target properties ($\underline{\zeta}$) for each of the mixtures under consideration. Therefore, the vector $\underline{\zeta}$ becomes a matrix, where each row represents a target property and each column a mixture. The matrix $\zeta(k \times m)$ is defined as shown in Eq. 11

$$\zeta(k\times m) = \begin{vmatrix} \zeta^{1,1} & \zeta^{1,2} \\ \zeta^{2,1} & \zeta^{2,2} \\ & \cdots \end{vmatrix} \qquad \text{with } k = 1, NP; m = 1, NM \tag{11}$$

NP is the total number of target properties and *NM* the total number of mixtures (resulting from the combination of all the solvents in the database).

The element $\zeta^{1,2}$ is, for instance, the mixture property number 1 for mixture number 2.

Level L1

The screening of the mixtures starts at this level, in which linear constraints for the target properties are considered. Linear constraints are related to the properties described by linear models. For a binary mixture, the generic form of the linear model is

$$\zeta^{k,m} = \sum_{i=1}^{NC} x_i \cdot \zeta_i^{k,m} = x_1 \cdot \zeta_1^{k,m} + (1 - x_1)\cdot\zeta_2^{k,m} \tag{12}$$

The subscripts 1 and 2 indicate compounds 1 and 2 in the binary mixture; $\zeta_i^{k,m}$ is the pure compound property k of compound i in mixture m; x_i is the mole fraction of compound i.

Step L1.1. Rule 1: Reject a binary mixture if the pure component property values of both compounds in the mixture are either lower than the lower-bound values $\underline{\zeta LB}$ ($\zeta_1^{k,m} < \zeta^{k,LB}$ and $\zeta_2^{k,m} < \zeta^{k,LB}$), or greater than the upper-bound values $\underline{\zeta UB}$ ($\zeta_1^{k,m} > \zeta UB^{k}$ and $\zeta_2^{k,m} > \zeta UB^{k}$) of the target properties. $\underline{\zeta LB}$ and $\underline{\zeta UB}$ are vectors of dimension k.

Note: With $R1$ being the number of mixtures rejected after the application of Rule 1, the total number of feasible mixture has been reduced to (NM-$R1$).

Step L1.2. Activity: Calculate the composition boundaries for each of the target properties considered in the design.

Note: For a general binary mixture m, the mixing process with respect to the general property k (ζ^{k}-axis), can be represented as shown in Figure 5. Solvents 1 and 2 involved in the mixture have a position in the ζ^{k}-axis according to their pure component property values ($\zeta_1^{k,m}$ and $\zeta_2^{k,m}$); in Figure 5, the case in which $\zeta_1^{k,m} < \zeta_2^{k,m}$ is shown. The target region is represented by the dashed line, and corresponds to the segment between the lower bound (ζLB^{k}), and the upper bound (ζUB^{k}). The mixture property must lie in the target region to match the design target: in Figure 5a possible solution is represented. According to the lever rule, the composition of the mixture ($x_1^{k,m}$, because it is relative to the k-property and the m-mixture) can be calculated as follows

$$x_1^{k,m} = \frac{\left(\zeta_2^{k,m} - \zeta^{k,m}\right)}{\left(\zeta_1^{k,m} - \zeta_2^{k,m}\right)} \tag{13}$$

$\underline{x_1}$ is a matrix: $x_1(k\times m)$.

When, instead of a single target value, bounds are given, Eq. 13 is substituted by Eqs. 14 and 15

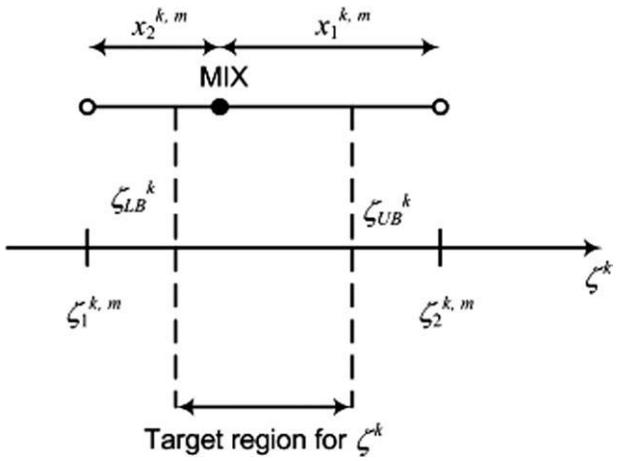

Figure 5. Representation of a binary mixing process with respect to the property ζ^k.

$$xLB_1^{k,m} = \frac{\left(\zeta_2^{k,m} - \zeta UB^k\right)}{\left(\zeta_1^{k,m} - \zeta_2^{k,m}\right)} \qquad \text{with } k = 1, NP; m = 1, NM - R1 \tag{14}$$

$$xUB_1^{k,m} = \frac{\left(\zeta_2^{k,m} - \zeta LB^k\right)}{\left(\zeta_1^{k,m} - \zeta_2^{k,m}\right)} \qquad \text{with } k = 1, NP; m = 1, NM - R1 \tag{15}$$

$xLB_1(k\times m)$ and $xUB_1(k\times m)$ are matrices containing the lower and upper bound values (respectively) of compositions calculated for all the target properties k and the mixture m

$$xLB_1^{k,m} \le x_1^{k,m} \le xUB_1^{k,m}, \qquad \text{with } k = 1, NP; m = 1, NM - R1 \tag{16}$$

Equations 14 and 15 have to be solved for NP properties and (NM-$R1$) mixtures. From Figure 5 it can be observed that the lowest value (xLB_1^k) that x_1^k can assume to have the property ζ^k still matching the targets is where $\zeta^{k,m} = \zeta UB^k$. The highest value (xUB_1^k) that $x_1^{k,m}$ can assume to have the property ζ^k still matching the targets is where $\zeta^{k,m} = \zeta LB^k$.

Step L1.3. Activity: Identify the overall composition range for each mixture.

Note A: The strictest condition for the composition must be identified for each mixture. That is, for each column of the matrix xLB_1 the maximum value has to be selected, while within each column of the matrix xUB_1 the minimum value has to be chosen, as shown in Eqs. 17 and 18

$$xL_1^m = \max_{k=1}^{NP}(xLB_1^{k,m}) \qquad m = 1, NM - R1 \tag{17}$$

$$xU_1^m = \min_{k=1}^{NP}(xUB_1^{k,m}) \qquad m = 1, NM - R1 \tag{18}$$

$\underline{xL_1}$ and $\underline{xU_1}$ are vectors of dimension m. The overall composition range (for all the mixtures) can be written using vectors

$$\underline{xL_1} \le \underline{x_1} \le \underline{xU_1} \tag{19}$$

Three different types of binary solvent mixtures can be classified according to the composition range evaluated at this step:

1. Type 1: binary mixtures for which the composition range of Eq. 19 is feasible, because $\underline{xL_1} \le \underline{xU_1}$.
2. Type 2: binary mixtures for which the composition range of Eq. 19 is not feasible, because $\underline{xL_1} > \underline{xU_1}$.
3. Type 3: binary mixtures for which the composition ranges of Eq. 19 cannot be identified; this happens when the ranges defined by the different properties do not overlap. Consider, for example, that only two target properties are involved and that, for the mixture m, the first property constraint on $\zeta^{1,m}$ sets a composition range [0.2, 0.3], while the second property constraint on $\zeta^{2,m}$ sets a composition range [0.5, 0.7]: these two ranges do not overlap and no common composition range can be identified.

Rule 2: Reject mixtures of types 2 and 3.

Note B: The composition range in which all the possible values of composition lead to a mixture of solvents that matches the design constraints has been identified at the end of step L1-3. With $R2$ being the number of mixtures rejected after the application of rule 2, the total number of feasible mixture has been reduced to (NM-$R1$-$R2$).

Step L1.4. Activity: Calculate the composition value that leads to the cheapest mixture, for all the mixtures that were not rejected with step L1-3.

Note: In the case of a binary mixture, the solution of this problem is straightforward. If, for mixture m, solvent 1 is the cheapest among solvents 1 and 2, then the cheapest mixture is the one with the composition equal to xU_1^m, which is the maximum value of x_1^m (while still matching the constraints); and *vice versa* if solvent 2 is the cheapest.

Level L2

At the end of level 1, (NM-$R1$-$R2$) binary mixtures matching the linear constraints, together with their compositions and costs have been determined. In this second level nonlinear constraints are applied for further screening of the mixtures.

Step L2.1. Activity: Solve the nonlinear models for each of the (NM-$R1$-$R2$) mixtures designed in level 1.

Note: The new mixture properties are now calculated employing the composition values determined in the previous level.

Step L2.2. Rule 3: Reject the mixtures for which the calculated property values do not match the nonlinear property constraints.

Note: With $R3$ being the number of mixtures rejected after the application of rule 3, the total number of feasible mixture has been reduced to (NM-$R1$-$R2$-$R3$).

Level L3

At the end of level 2, ($R1$+$R2$+$R3$) mixtures have been rejected. Only (NM-$R1$-$R2$-$R3$) mixtures match the nonlinear as well as the linear constraints. Only these mixtures are now considered in level 3, for the stability test by applying the STABILITY algorithm (see the following section). Phase split should not occur for the feasible binary mixtures.

Step L3.1. Activity: Apply the STABILITY algorithm on all the (*NM*-*R*1-*R*2-*R*3) feasible mixtures.

Step L3.2. Rule 4: Reject the mixtures showing phase split at the design composition x_1.

Note: With *R*4 being the number of mixtures rejected after the application of rule 4, the total number of feasible mixture has been reduced to (*NM*-*R*1-*R*2-*R*3-*R*4).

The STABILITY algorithm

The STABILITY algorithm checks the phase stability of a binary liquid mixture. The stability test is based on the trend of the Gibbs energy function of mixing ($\Delta G^{\text{mix}}/RT$) and its first and second derivatives as a function of composition. The Gibbs energy of mixing is calculated as follows

$$\frac{\Delta G^{\text{mix}}}{RT} = \frac{G^E}{RT} + \sum_{i=1}^{NC} x_i \cdot ln(x_i) \tag{20}$$

G^E is the excess Gibbs energy of mixing that is calculated from

$$\frac{G^E}{RT} = \sum_{i=1}^{NC} x_i \cdot ln(\gamma_i) \tag{21}$$

Figure 6 represents the four most common types of plots of $\Delta G^{\text{mix}}/RT$ as a function of x_i:

1. Mixtures of type *a* are completely immiscible in the composition range [0,1], and they can be recognized from the positive value of the function $\Delta G^{\text{mix}}/RT$ in the entire composition range [0,1].

2. Mixtures of type b_1 show a phase split in the composition range where the function $\Delta G^{\text{mix}}/RT$ is positive; the two liquid phase region corresponds to the region in which the $\Delta G^{\text{mix}}/RT$ is positive. The compositions of the two liquid phases are identified by the points in which the function $\Delta G^{\text{mix}}/RT$ is zero, at the extremities of the immiscibility gap.

3. Mixtures of type *c* are one phase in the entire composition range and they have negative values of the function $\Delta G^{\text{mix}}/RT$ and positive values of its second-order derivative in entire the composition range.

4. Mixtures of type b_2 are more complex: here, $\Delta G^{\text{mix}}/RT$ is negative and its second-order derivative is negative between the compositions x_1^{δ} and x_1^{ϵ} (δ and ϵ are the wrong phases in equilibrium). These mixtures show a miscibility gap, but the compositions of the two liquid phases are not identified by the points in which the second derivative of $\Delta G^{\text{mix}}/RT$ changes its sign (x_1^{δ} and x_1^{ϵ}), because these points do not correspond to the composition at which the total Gibbs energy is at its global minimum. To identify the composition of the two liquid phases in equilibrium the tangent plane condition[32–34] has to be employed.

The fact that the second derivative of the function $\Delta G^{\text{mix}}/RT$ does not identify the "real" immiscibility gap, where as the tangent plane condition does, is explained in Appendix A.

Figure 7 shows the work-flow of the STABILITY algorithm. The algorithm consists of three levels of screening. The UNIFAC model[19] with the LLE group representations and contributions[35] have been chosen to describe the binary chemical systems.

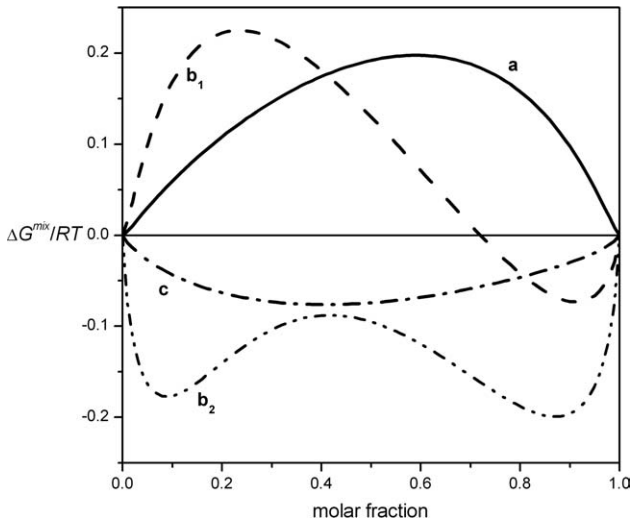

Figure 6. The most common shapes for the function $\Delta G^{mix}/RT$.

The algorithm needs the following information as input: the UNIFAC-LLE group representation of the chemicals involved in the mixtures under evaluation, and the temperature at which the stability test has to be performed.

The algorithm returns, as output, the stability information about the solvent mixtures (total miscibility, partial miscibility, total immiscibility), and, in case of partially miscible mixtures, the compositions of the two phases in equilibrium are also given.

Level L1

Activity: Calculate the function $\Delta G^{\text{mix}}/RT$ and identify all the mixtures of type *a* and b_1. For mixtures of type b_1, calculate the immiscibility range $[x_1^{\alpha}, x_1^{\beta}]$ (it corresponds to the region in which the function $\Delta G^{\text{mix}}/RT$ is positive).

Level L2

Activity: Calculate the second derivative of the function $\Delta G^{\text{mix}}/RT$ and identify mixtures of type *c* (immiscible in all the composition range [0, 1]) and b_2.

Level L3

Activity: For the mixtures of type b_2, employ the tangent plane condition[32–34] to identify the immiscibility range $[x_1^{\alpha}, x_1^{\beta}]$.

Computer-Aided Framework

The work-flow of stage-1 of the systematic methodology together with the associated algorithms (mixture design, molecular design, mixture classification, etc.), and the associated tools (databases, model library, modeling tool-box, etc.) have been included in a computer-aided framework, called the virtual product-process design lab[28] (vPPD-laboratory). In addition to the tools developed in this work, tools available in the ICAS software,[30] such as ProPred (pure compound property prediction), ProCAMD (computer-aided

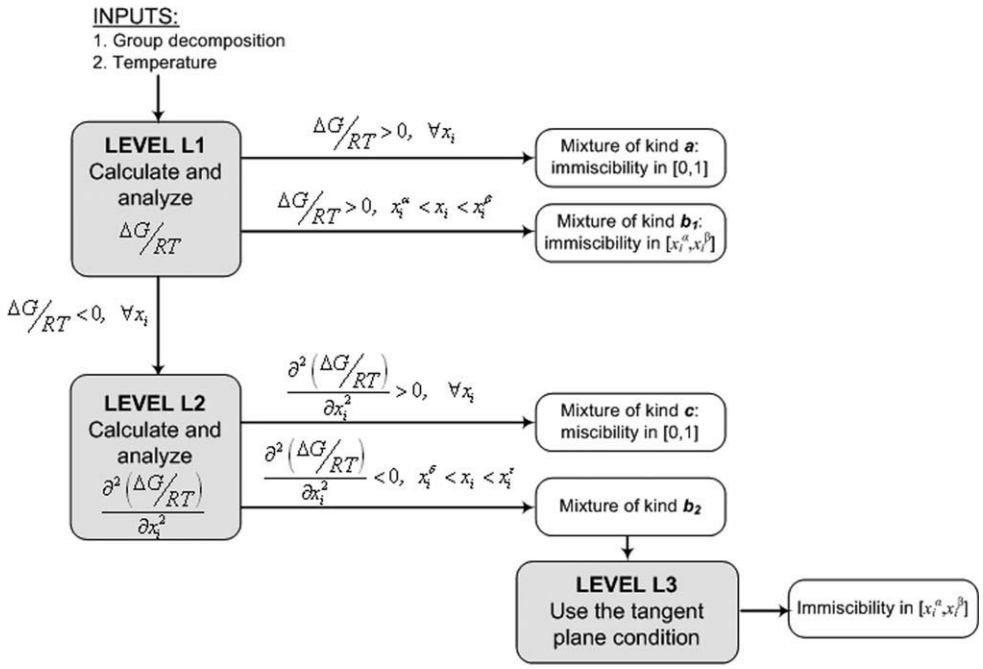

Figure 7. Work-flow diagram of the STABILITY algorithm.

molecular design) and MoT (modeling toolbox), are also available in vPPD-laboratory. The property models[18–22,26,27] are available in the property model library, and the database library[23] has been updated with solvents, AIs and additives databases. Through the vPPD-laboratory, the product design problems are solved as if they are focused virtual experimentations, guiding the user through the established work-flow (see Figures 1 and 2).

Case Studies

The formulation design methodology and its implementation have been applied and tested on several case studies; two are being highlighted here: a white paint/coating for house interiors; a spray insect repellent lotion (alcohol-based formulation). For both case studies, the results have been obtained through the vPPD-laboratory software.

Design of a Paint Formulation

The aim of this case study is to design a white waterproof (for exterior) paint formulation, to employ for the finishing of surfaces. For this product, the stages of experimental planning (stage-2), and validation (stage-3) were not performed, and, therefore, results only from the computer-aided design methodology (stage-1) are reported here.

A paint formulation is constituted of a pigment conferring the particular color, a binder with the function of binding the insoluble pigment particles and providing the surface coating, a solvent or a mixture of solvents whose function is to deliver the paint on a surface (when it is applied) and then vaporize out. Additives may be added to give the paint formulation a particular appearance or to enhance its spreadability on surfaces during application and so on.[36]

Task S1-D1: Problem definition

Subtask S1-D1.1: Performance Criteria. From the knowledge base it resulted that consumers want a product with the following characteristics: the surface color and coating should be white; the paint should be water-proof; low-price; short drying time; low toxicity; good spread-ability on surfaces; good stability (no separation of phases).

Subtask S1-D1.2: Target Properties. According to the knowledge base, the target properties/choices affecting the above performance criteria are:

- color/coating: choice of AI/AIs;
- water-proof: choice of all oil-soluble ingredients;
- price: cost, (C);
- drying time: evaporation time, (T_{90});
- toxicity: toxicity parameter, (LC_{50});
- spread-ability: dynamic viscosity (η), surface tension (σ), density (ρ);
- stability: Hildebrand solubility parameter (δ), Gibbs energy of mixing (ΔG^{mix}, TPD) for stability test.

Subtask S1-D1.3: Constraints. Consulting the knowledge base, the constraints corresponding to the target properties defined in the previous subtask were set (the symbols for the target properties as well as unit of measure for the constraints can be found in the notation):

1. Color/coating: (AI/AIs) no constraints
2. Water-proof: (ingredients) no constraints
3. Price: (C) minimized in MIXD
4. Drying time: (T_{90})

$$255 \leq T_{90} \leq 450 \tag{22}$$

5. Toxicity (LC_{50})

$$LC_{50} \geq 0.40 \tag{23}$$

6. Spray-ability

$$\eta: \quad 0.6 \leq \eta \leq 0.9 \tag{24}$$

$$\sigma: \quad 26.5 \leq \sigma \leq 29.5 \tag{25}$$

$$\rho(V): \quad 100 \leq V \leq 130 \tag{26}$$

7. Stability

$$\delta: \quad \delta_{AI} - 3 \leq \delta \leq \delta_{AI} + 3 \tag{27}$$

$$\delta_{AI} - 3 \leq \delta_{add} \leq \delta_{AI} + 3 \tag{28}$$

$$\Delta G^{\text{mix}}: \quad \frac{\Delta G^{\text{mix}}}{RT} < 0 \tag{29}$$

$$TPD: \quad TPD \geq 0 \tag{30}$$

Regarding the drying time, it is important that the paint formulation does not dry too slowly. For safety and environmental reasons also a lower bound for the drying time is desirable. It has to be underlined that, instead of the density, molar volume is considered for the constraint setting ($V = M_w/\rho$). In fact, volume is additive while density is not, and additivity is important when employing linear mixing rules for the estimation of mixture properties (see subtask S1-D3.2). The cost is minimized when calculating the solvent mixture composition.

Task S1-D2: AI identification

Subtask S1-D2.1: Product Functions. The function of the paint formulation is to provide the desired color (white), and a protecting coating (water resistant) on the surface.

Subtask S1-D2.2: AIs Selection. From the knowledge base it was found that pigments are used for coloring paint, ink, plastic, fabric, cosmetics, food and other materials. The pigment particles are insoluble, so a binder is needed to bind together and to provide the protective coating on the surface. Polymers are common binders for pigments. From the pigments and polymers databases, the following chemicals were retrieved:

- Pigment database: titanium dioxide (TiO_2). It is a common white pigment, which is normally insoluble and precipitates.
- Polymers database: polyesters such as poly(3-hydroxylalkanoates) (PHAs). They constitute a family of biodegradable polymers frequently used in paints, which are also able to bind the TiO_2 particles. In this case study, the simplest polymer from the family of PHAs (see Figure 8) is considered.

Subtask S1-D2.3: AIs Properties. The AIs properties are retrieved from the databases and/or calculated with the models in the model library when not available:

- Solubility information: TiO_2 is insoluble in most solvents. PHAs are polyesters, therefore, they are water-insoluble and they can be employed for the paint formulation being designed in this case study, which has to be a waterproof product.
- Hildebrand solubility parameter: the needed solubility parameter is the one of the polymer, which binds the pigment and has to be dissolved in the binary solvent mixture. The polymer solubility parameter is calculated to be 19.92 $MPa^{1/2}$.

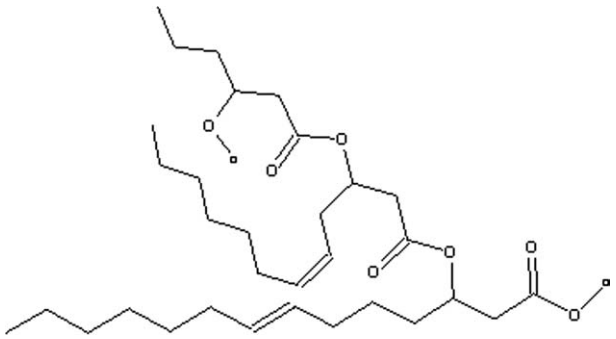

Figure 8. The simplest polymer from the family of the poly(3-hydroxylalkanoates).

The constraints on the mixture solubility parameter δ (Eq. 27), and the additives solubility parameters (Eq. 28), therefore, become

$$\delta_{Pol} - 3.0 \leq \delta \leq \delta_{Pol} + 3.0 \qquad 17.0 \leq \delta \leq 23.0 \tag{31}$$

$$\delta_{Pol} - 3.0 \leq \delta_{add} \leq \delta_{Pol} + 3.0 \qquad 17.0 \leq \delta_{add} \leq 23.0 \tag{32}$$

δ_{pol} is the solubility parameter of the polymer, which is the AI that has to be dissolved by the binary solvent mixture.

Task S1-D3: Solvent mixture design

Subtask S1-D3.1: solvent database. The paint formulation under development has to be water-insoluble. Hence, the database of water-insoluble solvents usually employed for paint formulations is retrieved from the database.

Subtask S1-D3.2: modeling choices. The mixture property models selected from the model library for the calculation of target properties are listed in Table 3. The temperature considered is 300 K.

Subtask S1-D3.3: MIXD. The MIXD algorithm was applied for all the property constraints excluding the constraints on the solubility parameter of the additive. Results are given in Table 4, where the solvent mixtures are listed in terms of increasing cost. Note that mixture 10 is the only mixture showing miscibility problems (see the last column of Table 4), but at the designed molar fraction of 0.90 the mixture is in a single liquid phase. Therefore, this mixture was not rejected.

Subtask S1-D3.4: Verification. The mixture classification algorithm was applied. Mixtures 4, 5 and 8 are mixtures of two normal fluids (hydrocarbons, cyclohydrocarbons and derivates). These mixtures do not need verification with rigorous models, and they were not therefore considered in this subtask. For all the other mixtures, the HB classification is reported in Table 5. Viscosity and surface tension are critical parameters for a product that has to be spread on a surface; therefore, verification was performed using the model of Cao et al.[26] for viscosity and the model of Suarez et al.[27] for surface tension. Table 5 lists the results of these calculations.

The definitions of relative error RD (%), and average absolute error AAD (%) are reported

Table 3. List of Target Properties and Models used for the Two Case Studies

Paint Formulation Case Study			Insect Repellent Case Study		
Target Property	Symbol	Mixture Model	Target Property	Symbol	Mixture Model
evaporation time	T_{90}	Klein *et al.*[42]	evaporation time	T_{90}	Klein *et al.*[42]
lethal concentration	LC_{50}	linear mixing rule	lethal concentration	LC_{50}	linear mixing rule
dynamic viscosity	η	linear mixing rule	solubility parameters	δ, δ_{add}	linear mixing rule
surface tension	σ	linear mixing rule	Δ Gibbs energy of mixing	$\Delta G^{mix}/RT$	UNIFAC-LLE
molar volume	V	linear mixing rule	tangent plane distance	TPD	UNIFAC-LLE
solubility parameter	δ, δ_{add}	linear mixing rule	kinematic viscosity	v	linear mixing rule
Δ Gibbs energy of mixing	$\Delta G^{mix}/RT$	UNIFAC-LLE	molar volume	V	linear mixing rule

$$RD(\%) = \frac{\left|\zeta_i^{rig} - \zeta_i^{lin}\right|}{\zeta_i^{rig}} \cdot 100 \tag{33}$$

$$AARD(\%) = \frac{\sum \left|\zeta_i^{rig} - \zeta_i^{lin}\right|}{NMV} \tag{34}$$

NMV is the number of mixtures considered in the verification step. Mixtures 3 and 6 did not match the target on viscosity ($0.6 < \mu < 0.9$), while mixtures 6 and 7 did not match the target on surface tension ($26.5 < \sigma < 29.5$), therefore, mixtures 3, 6 and 7 were rejected and not considered in the subsequent subtasks. The mixtures considered in the next subtask were: mixture 1, 2, 4, 5, 8, 9, 10 and 11.

Subtask S1-D3.5: Optimization. Cost was selected as the only performance index PI. To determine the optimal mixture requires only a check of the last column of Table 4: mixture 1 is found to be the cheapest. It is a mixture of diethylene glycol ethyl ether + toluene, and is selected as the solvent mixture for the paint formulation. Figure 9a shows the reduction of the number of feasible solvent mixtures through subtasks S1-D3.3 to S1-D3.5.

Task S1-D4: Additives identification

Subtask S1-D4.1: Qualities to Enhance. Form the knowledge base it was found that the spread-ability on surfaces is a very important quality for paint formulations. Hence, it was decided to look for additives that could enhance this property.

Subtask S1-D4.2: Additives Selection. Wetting agents lower the surface tension of the blend they are added to, and they are used to enhance the spread-ability of paint formulations. Two additives were retrieved from the wetting agents database: sodium dioctyl sulfosuccinate (Aerosol OT); acetylenic surfactant (Surfynol™ 104). They are both powerful wetting agents because the presence of the polar group (between the surfactant chains) provides sufficient spacing for the solvent to reach the surface of the pigment particle.

Subtask S1-D4.3: Additives Properties. The following information were retrieved from the wetting agents database and/or calculated through the models contained in the model library:

1. Sodium dioctyl sulfosuccinate (Aerosol OT): it is water-insoluble and has a solubility parameter of 22.95 $MPa^{1/2}$. It is found that sodium dioctyl sulfosuccinate also promotes the solubilization and the dispersion of the pigment solid particles.

2. Acetylenic surfactant (Surfynol™ 104): it is biodegradable and has a solubility parameter of 23.95 $MPa^{1/2}$.

Subtask S1-D4.4: Compatibility Verification. The constraint of Eq. 32 was applied here to verify the compatibility of the selected additive with the designed solvent mixture and the selected AIs. Sodium dioctyl sulfosuccinate solubility parameter matches Eq. 32, while the acetylenic surfactant solubility parameter does not match Eq. 32. Hence, sodium dioctyl sulfosuccinate was selected a wetting agent for the paint formulation designed in this case study.

In Table 6 the base case formulation for a white and water-insoluble paint for finishing of exteriors is shown. The suggested composition was calculated taking values from literature as reference.[37]

Design of an Insect Repellent Lotion

The aim of this case study was to design an insect repellent lotion. The market for consumption is non tropical areas, for example, Europe.

Table 4. Mixtures Matching the Target Properties and Property Values (Paint Case Study)

n°	Mixtures	x_1	δ	μ	σ	ρ	LC_{50}	T_{90}	Cost	Stability
1	DEGEE + toluene	0.05	18.35	0.71	28.63	869.33	0.40	256.1	1.35	Yes
2	toluene + cyclohexanone	0.95	18.24	0.63	28.80	861.55	0.40	256.4	1.37	Yes
3	toluene + butyrolactone	0.96	18.49	0.60	28.65	861.12	0.43	255.6	1.60	Yes
4	toluene + ethylbenzene	0.56	18.03	0.60	28.41	864.27	0.40	345.8	2.49	Yes
5	ethylbenzene + heptane	0.62	17.67	0.67	26.93	835.53	0.40	448.0	3.51	Yes
6	ethylbenzene + ethyl acetate	0.87	17.46	0.60	26.94	837.47	0.52	437.4	3.67	Yes
7	ethylbenzene + butyl acetate	0.87	17.42	0.60	26.50	868.96	0.46	436.1	3.70	Yes
8	ethylbenzene + hexane	0.77	17.92	0.60	27.18	867.54	0.69	403.8	3.72	Yes
9	ethylbenzene + butanone	0.80	18.09	0.60	27.56	852.74	1.02	427.2	3.72	Yes
10	ethylbenzene + dichloromethane	0.90	18.11	0.60	28.19	843.68	0.62	449.7	3.85	LLE: $x_1 = 0.0$-0.71
11	ethylbenzene + isopropylacetone	0.72	17.54	0.62	26.50	888.88	0.84	418.2	3.91	Yes

Unit of measure: δ [$MPa^{1/2}$], μ [mPa·s], σ [mN/m], ρ [kg/m^3], LC_{50} [mol/m^3], T_{90} [s], Cost [$/kg]. DEGEE stands for diethylenglycol ethyl ether.
In the last column the compositions of the first compound in the two liquid phases are reported for mixtures showing partial miscibility at 300 K.

Table 5. Results from the Verification Subtask: Prediction of Viscosity and Surface Tension with Rigorous Models (Paint Case Study)

			μ-prediction			σ-prediction		
n°	x_1	H-B	linear	Cao	RD(%)	linear	Suarez	RD(%)
1	0.05	PA-NF	0.71	0.62	14.02	28.63	28.61	0.05
2	0.95	NF-PNA	0.63	0.60	5.66	28.80	28.70	0.35
3	0.96	NF-PNA	0.60	0.58	3.71	28.65	28.60	0.20
6	0.87	NF-PNA	0.60	0.59	2.10	27.00	25.48	5.98
7	0.87	NF-PNA	0.61	0.61	1.34	27.00	24.94	8.28
9	0.80	NF-PNA	0.60	0.60	0.10	27.56	27.53	0.12
10	0.90	NF-PNA	0.60	0.60	0.25	28.19	28.22	0.12
11	0.72	NF-PNA	0.63	0.63	0.76	27.00	26.58	1.59
	AAD(%)				2.65			1.68

An insect repellent lotion is usually constituted of the AI/AIs, with the function of repelling mosquitoes, a binary solvent mixture whose function is to deliver the AI/AIs on the skin and vaporize after application. Additives are usually perfumes, moisturizing agents, and so on.

Task S1-D1: Problem definition

Subtask S1-D1.1: Performance Criteria. From the knowledge base it resulted that consumers want a product with the following characteristics: high effectiveness against mosquitoes (the main function of the product); high compatibility with other materials (fabrics, plastics, etc); good sensorial factors and cosmetic properties (that is, nice odor, appearance and good skin feeling); low-price; long durability (it should not be needed to apply the product often during exposure to mosquitoes), low toxicity; high stability (no separation of phases); good user friendliness (a spray product); long shelf life.

Subtask S1-D1.2: Target Properties. According to the knowledge base, the target properties/choices affecting the above performance criteria are:

- effectiveness: choice of the AI/AIs;
- material compatibility: choice of the solvent database;
- cosmetic properties: choice of additives for odour;
- price: cost, (C);
- durability: evaporation time, (T_{90});
- toxicity: toxicity parameter, (LC_{50});
- stability: Hildebrand solubility parameter (δ), Gibbs energy of mixing (ΔG^{mix}, TPD), for stability test;
- spray-ability: kinematic viscosity (v), density (ρ)).

The other cosmetic properties, sensorial factors (except odour) and shelf-life could not be considered in stage-1 because of lack of model or data. However, as they are easy to measure, they can be validated[2] in stage-3 of the methodology (see Figure 1).

Subtask S1-D1.3: Constraint. Consulting the knowledge base, the constraints corresponding to the target properties defined in the previous subtask were set:

1. Effectiveness: (AI/AIs) no constraints
2. Material compatibility: (solvents) no constraints
3. Odor: (additives) no constraints
4. Price (C) minimized in MIXD
5. Durability (T_{90})

$$500 \leq T_{90} \leq 1500 \tag{35}$$

6. Toxicity (LC_{50})

$$LC_{50} \geq 50.0 \tag{36}$$

7. Stability

$$\delta: \quad \delta_{AI} - 3 \leq \delta \leq \delta_{AI} + 3 \tag{37}$$

$$\delta_{AI} - 3 \leq \delta_{add} \leq \delta_{AI} + 3 \tag{38}$$

$$\Delta G^{mix}: \quad \frac{\Delta G^{mix}}{RT} < 0 \tag{39}$$

$$TPD: \quad TPD \geq 0 \tag{40}$$

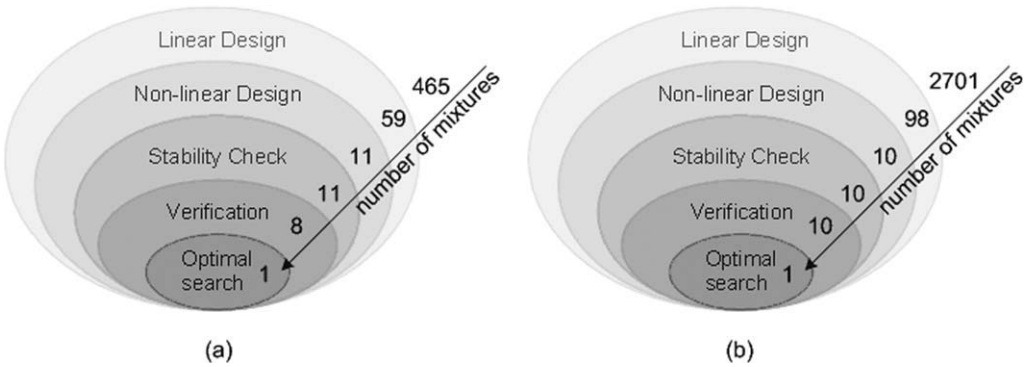

Figure 9. Reduction of the number of feasible solvent mixtures through subtasks S1-D3.3 to S1-D3.5.

(a) Paint formulation case study, and (b) insect repellent lotion case study.

Table 6. Base Case Formulation for the Paint (Case Study 1), and the Insect Repellent (Case Study 2)

	Paint		Insect Repellent	
	Ingredient	% x_i	Ingredient	% x_i
AI	TiO_2	6.04	Picaridin	2.90
	PHAs	0.04		
Solvent mixture	DEGEE	2.96	Methanol	32.20
	toluene	90.62	1-butanol	64.70
Additives	sodium dioctyl sulfosuccinate	0.34	α/β-santalol	0.30

8. Spray-ability

$$v: \quad v \leq 75 \tag{41}$$

$$\rho(V): \quad 75 \leq V \leq 100 \tag{42}$$

The AIs used for insect repellent are usually volatile, so temperature, humidity, wind, perspiration and abrasion affect longevity; usually the high losses of repellent due to evaporation are overcome with high concentration of active ingredient, leading to high absorption on the skin, with all the safety concerns this involves.[38] To increase repellent longevity without increasing the active ingredient concentration the evaporation rate of the solvent mixture has to be a reasonable compromise: if the evaporation of the solvent mixture is too fast there is the risk that part of the AI evaporates too. On the other hand if the solvent mixture evaporates too slowly, high amount of solvents and AI can be absorbed by the skin, which should to be avoided for health reasons.

Task S1-D2: AI identification

Subtask S1-D2.1: Product Functions. Only one AI is necessary, because the main function of the product is only one: to repel mosquitoes.

Subtask S1-D2.2: AIs Selection. Three alternatives were retrieved from the database of AIs for insect repellents:

1. DEET: it is the active ingredient traditionally used in insect repellents, due to its high efficiency and durability. DEET has been shown to be aggressive on clothes, plastics, glasses, and to have a high potential to irritate eyes and skin.[39] It has also been blamed to be sticky, greasy and with an unpleasant odor. Finally, it causes systemic and local toxicities.[40]

2. Natural AIs, such as essential oils from plants (citronella, camphor, paraffin): they are safe but have limited duration.[38]

3. Picaridin: it has been recently discovered. It is far superior to DEET in terms of safety, toxicology, material compatibility and cosmetic properties.[39]

Picaridin was selected as the AI in this formulated product.

Subtask S1-D2.3: AIs properties. Picaridin properties were retrieved from the database and/or calculated with the property models in the model library when not available:

- Solubility information: according to Bayer (Autan®, www.autan.co.uk), picaridin has a very low solubility in water (8.6 g/L at 293 K), but a good solubility in alcohols such as ethanol and 2-propanol (www.autan.co.uk).
- Hildebrand solubility parameter (δ_{AI}) was calculated to be 24.1 $MPa^{1/2}$.

The constraints on the solubility parameter of the solvent mixture (Eqs. 37 and 38) could now be set

$$\delta_{AI} - 3.0 \leq \delta \leq \delta_{AI} + 3.0 \qquad 21.1 \leq \delta \leq 27.1 \tag{43}$$

$$\delta_{AI} - 3.0 \leq \delta_{add} \leq \delta_{AI} + 3.0 \qquad 21.1 \leq \delta_{add} \leq 27.1 \tag{44}$$

Task S1-D3: solvent mixture design

Subtask S1-D3.1: Solvent Database. Because picaridin is very soluble in alcohols, the alcohols database was retrieved.

Subtask S1-D3.2: Modeling Choices. The mixture property models selected from the model library for the calculation of the target properties are listed in Table 3. The temperature considered in the design was 300 K.

Subtask S1-D3.3: MIXD. The MIXD algorithm was applied for all the property constraints excluding the constraint on the solubility parameter of the additive. Results are shown in Table 7. The mixtures are listed for increasing cost values. Also information about the phase stability is shown, in the last column.

Subtask S1-D3.4: Verification. The mixture classification algorithm was applied. All the mixtures were found to be of the type PAS/PAS, as shown in Table 8. Verification with rigorous models was therefore necessary. Because viscosity is an important target property for the product being designed, viscosity was recalculated using the rigorous model of Cao et al.[26] Table 8 compares the results of the prediction with linear and rigorous models. A good agreement between predictions from the linear and nonlinear (rigorous) models can be noted and the constraint on the viscosity (Eq. 41) was not violated.

Table 7. Mixtures Matching the Target Properties and their Property Values (Alcohol Based Insect Repellent)

n°	Mixtures	x_1	δ	v	ρ	LC_{50}	T_{90}	Cost	Stability
1	methanol + 1-butanol	0.33	24.89	2.42	801.99	50.70	772.5	1.74	Yes
2	2,2,3-trimethyl-3-pentanol + allyl alcohol	0.16	26.41	2.89	793.02	63.83	886.5	1.77	Yes
3	methanol + 2,2-dimethyl-1-butanol	0.55	26.33	2.60	844.11	53.83	805.2	1.78	Yes
4	methanol + 2-methyl-2-heptanol	0.70	26.96	2.85	817.52	56.62	1096.2	1.79	Yes
5	2-methyl-2-heptanol + allyl alcohol	0.14	26.54	2.61	834.18	51.17	663.0	1.81	Yes
6	ethanol + 2,2-dimethyl-1-butanol	0.71	25.27	2.40	816.25	52.48	630.9	2.30	Yes
7	ethanol + 2,2,3-trimethyl-3-pentanol	0.79	25.34	2.90	845.43	52.12	1083.8	2.31	Yes
8	ethanol + 2-methyl-2-heptanol	0.82	25.47	2.52	910.30	50.47	755.2	2.40	Yes
9	methanol + 2-methyl-1-propanol	0.35	25.13	2.98	906.19	51.29	527.9	2.44	Yes
10	2,2-dimethyl-1-butanol + allyl alcohol	0.23	26.26	2.51	926.55	51.05	597.7	2.75	Yes

The unit of measure for the properties reported in the table above are: δ [$MPa^{1/2}$], v [$10^{-6}m^2/s$], ρ [kg/m^3], LC_{50} [mol/m^3], T_{90} [s], Cost [$/kg].

Table 8. Results Form the Verification Subtask for the Insect Repellent Case Study: Prediction of Viscosity with Rigorous Models

			v-prediction		
n°	x_1	H-B	linear	Cao	RD(%)
1	0.33	PAS-PAS	2.42	2.31	4.48
2	0.16	PAS-PAS	2.89	2.77	4.52
3	0.55	PAS-PAS	2.60	2.43	6.75
4	0.70	PAS-PAS	2.85	2.60	9.37
5	0.14	PAS-PAS	2.61	2.53	3.13
6	0.71	PAS-PAS	2.40	2.31	4.27
7	0.79	PAS-PAS	2.90	2.61	11.08
8	0.82	PAS-PAS	2.52	2.33	8.29
9	0.35	PAS-PAS	2.98	2.80	6.45
10	0.23	PAS-PAS	2.51	2.49	0.77
	AAD(%)			10.14	

The kinematic viscosity is obtained from the ratio of dynamic viscosity and density.

Subtask S1-D3.5: Optimization The selected performance index PI was the cost. The cheapest mixture was found to be the mixture of methanol + 1-butanol (see Table 7). Figure 9b shows the reduction of the number of feasible solvent mixtures through subtasks S1-D3.3 to S1-D3.5.

Task S1-D4: Additives identification

Subtask S1-D4.1: Qualities to Enhance. The quality to enhance was the scent. Perfumes are added to insect repellent lotions also as fixatives for the AI, because their large branched molecules lower the vapor pressure of repellents. Tibetene and Vanillin were used as fixatives in the formulations containing DEET and they increased the longevity of 29 and 95%, respectively, when used with a ratio 1:1 with DEET.[38]

Subtask S1-D4.2: Additives Selection. Two aroma compounds were retrieved from the aroma database:

1. α/β-santalol: they are usually not found as a single aroma compound, because they are very difficult to separate. They have a sweet, woody and tenacious odor, but α-santalol also shows a very rich warm-woody odor.

2. Linalool: it has a light, refreshing, floral woody odor with a faintly citrusy note.

Subtask S1-D4.3: Additives Properties. The additives properties were retrieved from the aroma database and/or calculated with the models in the model library when not available:

1. α/β-santalol: they are almost colorless alcohols, slightly viscous, and with a very high-boiling point. They are soluble in alcohols and oils, but insoluble in water. The solubility parameter values were calculated to be: 22.34 $MPa^{1/2}$ for α-santalol, 21.09 $MPa^{1/2}$ for β-santalol, for an average value of 21.72 $MPa^{1/2}$.

2. Linalool: it is an alcohol slightly soluble in water. It also has a high-boiling point and its solubility parameter was calculated to be 21.67 $MPa^{1/2}$.

Subtask S1-D4.4: Compatibility Verification. Equation 44 (constraint on the solubility parameter value of the additives) was checked here. Both aroma compounds were found to match the constraint. α/β-santalol was selected as it was reported to be the nicest of the two fragrances. Table 6 gives the details of the base case formula (chemicals and their compositions), which was calculated taking as reference, the values in the knowledge base.[41] A modification of this base case formula has been experimentally validated and further improved.[17]

Conclusions

A systematic model-based computer-aided methodology for liquid formulated product design has been presented and its application highlighted through two case studies from the paint and personal care industries. The methodology is part of an integrated 3-stages chemicals-based product design approach, where the goal of the computer-aided stage is to quickly and reliably reduce the search space and within it, to identify a set of promising candidates. The goals of the second- and third-stages are to experimentally validate the product designs from the first stage, and if necessary, to make minor adjustments for further improvement.

An important advantage, highlighted through this work, is the opportunity to perform focussed virtual experimentation through the vPPD-laboratory, which provided the computer-aided framework for implementation of the systematic methodology. In this way, valuable time and resources can be saved during the initial stages of chemicals-based product design. The vPPD-laboratory framework had been earlier tested for product analysis from the agrochemical and pharmaceutical industries. The results from the second- and third-stages are reported in the second part of this article.[17] Because of the nature of the design problem and the current availability of data and models, the decomposition based solution strategy was found to be useful and flexible in managing the associated complexities. It is well suited to problems of the type "define target — match target".

The methodology presented in this work shows also some limitations and leaves room for future improvements and modifications.

One of the major limitations of this work is that only one particular type of formulations has been taken into consideration, formulations with a liquid delivery system. However, many more types of formulated product exists, such as emulsions (creams, dilute emulsions, etc.), or solid products (tablets, pastes, powders, granules, etc.), foams, aerosols, and so on.[7] These products are more challenging from the modeling point of view because they involve microstructures (dispersion of phases in emulsions, crystalline structure for powders and granules, etc.) which are determined not only by the physical and chemical properties, but also by the processing conditions (T, P, etc.). Procedures to systematize the design and the verification of these kinds of products should also be developed. Current and future work is further extending the methodology and its implementation in vPPD-laboratory to more products from the consumer, pharmaceutical, agrochemical and energy sectors. In each case, first the workflow for each product design is developed and then the associated models and data are added and/or implemented to the vPPD-laboratory. Some of the challenges to address are modeling of emulsions, defining the target properties of fuels, predicting the solubility properties of complex solids representing the AIs. This not only shows the need for a systems approach to chemicals-based product design, but also the need for efficient and reliable strategies for managing the

associated complexities, such as, multidisciplinary problem, multiscale models, multicriteria optimization, multiple sources of data and many more.

The set of performance criteria employed in this work could be expanded, for instance, human toxicity should be considered together with the ecotoxicity (LC_{50}), and flammability issues should also be taken into consideration to ensure product safety.[16]

Sensorial factors and cosmetic properties (appearance, turbidity, odor, skin feeling, stickiness, etc.) are very important for the type of products considered in this work, and they are of major importance for the success of the product on the market. It is still not clear how these factors are related to physical and chemical properties, therefore, it is still not possible to consider them during the stage of computer-aided design of formulated products. However, they can be validated by experiment in stage-3 of the methodology.[17] Additional efforts should be focused in tracing the relation between these factors and the target properties, because their inclusion in the computer-aided design could spare time and resources during the experimental validation.

The relation between the product main functions (to repel the mosquitoes for an insect repellent, to block the UV radiations and/or reduce the risk of skin cancer for a sunscreen, etc.), and the concentration of the AIs in the formulation is another point on which future research could focus.

Notation

at = intercept of TPD
bt = slope of TPD
C = cost, $\$\cdot kg^{-1}$
ER = evaporation, s
G = Gibbs energy, $J\cdot kmol^{-1}$
H = enthalpy, $J\cdot kmol^{-1}$
LC_{50} = ecotoxicity parameter: aqueous concentration required to cause death in 50% of a fathead minnow population after 96 h, $mol\cdot m^{-3}$]
M_w = molecular weight
N = number of data points
NC = number of compounds in mixture
NM = number of mixtures
NMV = number of mixtures considered in the subtask S1-D3.4
NP = number of properties
P^{sat} = vapor pressure, Pa
R = universal gas constant, $J\cdot K^{-1}\cdot mol^{-1}$
T = temperature, K
T_{90} = time for 90 wt % evaporation, s
TPD = tangent plane distance
V = molar volume, $10^{-3}\cdot m^3\cdot kmol^{-1}$
x_i = composition of compound i, mole fraction
S = entropy, $J\cdot K^{-1}\cdot kmol^{-1}$
ΔG^{mix} = excess Gibbs energy of mixing, $J\cdot kmol^{-1}$

Greek letters

α, β = Phases in equilibrium
γ_i = activity coefficient of compound i
δ = Hildebrand solubility parameter, $MPa^{1/2}$
ξ_i = generic target property
$\underline{\zeta_i}$ = vector of target properties
η = dynamic viscosity, mPa·s
v = kinematic viscosity, $10^{-6}\cdot m^2\cdot s^{-1}$
ρ = density, $kg\cdot m^{-3}$
σ = surface tension [$mN\cdot m^{-1}$

Superscripts

E = excess property
k = property k
LB, L = lower bound
m = mixture m
PM = perfect match
UB, U = Upper bound

Subscript

i = constraints set or compound i in mixture
1, 2,… = constraint index or compound index (in mixture)
add = additive
AI = active Ingredient
pol = Polymer

Abbreviations

AI = active ingredient
HB = hydrogen Bonding
MIXD = mixture design algorithm
NF = normal fluid
PAS = polar associating
PHA = poly(3-hydroxylalkanoate)
PI = performance index
PNA = polar nonassociating
STABILITY = stability test algorithm
UV = Ultraviolet

Literature Cited

1. Gani R. Chemical product design: challenges and opportunities. *Comput Chem Eng*. 2004;28(12):2441–2457.
2. Gani R. Computer-aided methods and tools for chemical product design. *Chem Eng Res Des*. 2004;82(A11):1494–1504.
3. Cussler EL, Moggridge GD. *Chemical Product Design*. New York: Cambridge University Press; 2001.
4. Ng KM, Gani R, Dam-Johansen K. *Chemical Product Design - Towards a Perspective through Case Studies*. The Netherlands: Elsevier; 2007.
5. Charpentier JC. Among the trends for a modern chemical engineering, the third paradigm: the time and length multiscale approach as an efficient tool for process intensification and product design and engineering. *Chem Eng Res Des*. 2001;88:248–254.
6. Hill M. Product and process design for structured products. *AIChE J*. 2004;8(50):1656–1661.
7. Costa R, Moggridge GD, Saraiva PM. Chemical product engineering: an emerging paradigm within chemical engineering. *AIChE J*. 2006;52(6):1976–1986.
8. Bagajewicz MJ. On the role of microeconomics, planning, and finances in product design. *AIChE J*. 2007;53(12):3155–3170.
9. Wibowo C and Ng KM. Product-centered processing: manufacture of chemical-based consumer products. *AIChE J*. 2002;48:1212–1230.
10. Cheng YS, Lam KW, Ng KM, Ko RKM andWibowo C. An integrative approach to product development-A skin-care cream. *Comput Chem Eng*. 2009;33:1097–1113.
11. Wibowo C, Ng KM. Product-oriented process synthesis and development: cream and pastes. *AIChE J*. 2001;48:1212–1230.
12. Fung KY, Ng KM. Product-centered processing: pharmaceutical tablets and capsules. *AIChE J*. 2003;49(5):1193–1215.
13. Gani R, Jimenez-Gonzalez Constable DJC. Method for selection of solvents for promotion of organic reactions. *Comput Chem Eng*. 2005;29:1661–1676.
14. Eden MR, Jørgensen SB, Gani R, El-Halwagi MM. A novel framework for simultaneous separation process and product design. *Chem Eng Process*. 2004;43:595–608.
15. Harper PM, Gani R. A multi-step and multi-level approach for computer-aided molecular design. *Comput Chem Eng*. 2000;24:677–683.
16. Conte E, Gani R, Malik TI. The virtual product-process design laboratory to manage the complexity in the verification of formulated products. *Fluid Phase Equilibria*. 2010; doi: 10.1016/j.fluid.2010.09.031.

17. Conte E, Gani R, Cheng YS, Ng KM. Design of formulated products: experimental component. *AIChE J*. 2010; submitted.
18. Marrero J, Gani R. Group-contribution based estimation of pure component properties. *Fluid Phase Equilibria*. 2001;183–184: 183–208.
19. Fredenslund Aa, Jones RL, Prausnitz AM. Group-contribution estimation of activity coefficient in non ideal mixtures. *AIChE J*. 1975; 21(6):1086–1099.
20. Bogdanic G, Vidal J. A segmental interaction model for liquid-liquid equilibrium calculations for polymer solutions. *Fluid Phase Equilibria*. 2000;173:241–252.
21. Modarresi H, Conte E, Abildskov J, Gani R, Crafts P. Model-based calculation of solid solubility for solvent selection - A review. *Ind Eng Chem Res*. 2008;47(15):5234–5242.
22. Conte E, Martinho A, Matos HA, Gani R. Combined group-contribution and atom connectivity index-based methods for estimation of surface tension and viscosity. *Ind Eng Chem Res*. 2008;47(20): 7940–7954.
23. Nielsen TL, Abildskov J, Harper PM, Papaeconomou I, Gani R. The CAPEC database. *J Chem Eng Data*. 2001;46:1041–1044.
24. Hancock BC, York P, Rowe RC. The use of solubility parameters in pharmaceutical dosage form design. *Int J Pharm*. 1997; 148:1–21.
25. Williamson KJ. *Macroscale and Microscale Organic Experiments*. Lexington, MA: D. C. Heath; 1994.
26. Cao W, Knudsen K, Fredenslund A, Rasmussen P. Group-contribution viscosity predictions of liquid mixtures using UNIFAC-VLE parameters. *Ind Eng Chem Res*. 1993;32:2088–2092.
27. Suarez JT, Torres-Marchal C, Rasmussen P. Prediction of surface tensions of nonelectrolyte solutions. *Chem Eng Sci*. 1989;44(3): 782–786.
28. Conte E, Morales-Rodriguez R, Gani R. The virtual product-process design laboratory for design and analysis of formulations. *Computer Aided Chemical Engineering*. 2009;27:825–830.
29. Smith JM, Van Ness HC, Abbott MM. *Introduction to Chemical Engineering Thermodynamics*. New York: McGraw-Hill; 2001.
30. ICAS Documentation. Internal report, CAPEC, KT-DTU, Lyngby, Denmark,2003.
31. Karunanithi AT, Achenie L, Gani R. A new decomposition-based computer-aided molecular/mixture design methodology for the design of optimal solvents and solvent mixtures. *Ind Eng Chem Res*. 2005;44:4785–4797.
32. Baker LE, Pierce AC, Luks KD. Gibbs energy analysis of phase equilibria. *J Petrol Sci Eng. AIME*. 1982;22(5):731–738.
33. Michelsen ML. The isothermal flash problem. Part I. Stability. *Fluid Phase Equilibria*. 1982;9:1–19.
34. Michelsen ML, Mollerup JM. *Thermodynamic Models: Fundamentals and Computational Aspects*. 2nd ed. Denmark: Tie-Line Publications;2007.
35. Magnussen T, Rasmussen P, Fredenslund Aa. UNIFAC parameter table for prediction of liquid-liquid equilibria. *Ind Eng Chem Process Des Develop*. 1981;20:331–339.
36. Van der Walle GAM, Buisman GJH, Weusthuis RA, Gerrit E. Development of environmentally friendly coatings and paints using medium-chain-length poly(3-hydroxyalkanoates) as the polymer binder. *Int J Biol Macromol*. 1999;25:123–128.
37. Tarng M-R, Minamyer M, Pham A, Brownell S, Pham A, Alexander A, Shah D, Nguyen KL, Pham ML, Maxey S. Exterior paint formulation. US Patent 7642309, 2010.
38. Debboun M, Frances SP, Strickman D. *Insect Repellents: Principles, Methods, and Use*. New York, NY: CRC Press; 2006.
39. Badolo A, Ilboudo-Sanogo E, Patoin Ouédraogo A, Costantini C. Evaluation of the sensitivity of Aedes aegypti and Anopheles gambiae complex mosquitoes to two insect repellents: DEET and KBR 3023. *Am J Trop Med Hyg*. 2004;9(3):330–334.
40. Qui H, Jun HW, Dzimianski M, McCall J. Reduced transdermal absorption of *N,N*-diethyl-m-toluamide from a new topical insect repellent formulation. *Pharm Dev Technol*. 1997;2(1): 33–42.
41. Frances SP, Marlow RM, Jansen CC, Huggins RL, Cooper RD. Laboratory and field evaluation of commercial repellent formulations against mosquitoes (Diptera: Culicidae) in Queensland, Australia. *Aust J Entomol*. 2005;44:431–436.
42. Klein JA, Wu DT, Gani R. Computer aided mixture design with specified property constraints. *Comput Chem Eng*. 1992;16(S): 229–236.

Appendix A: Miscibility Gap Identification

Figure A1a shows the plot of $\Delta G^{\mathrm{mix}}/RT$ and its first and second derivatives for the system ethanol + hexadecane (the system chosen for purpose of illustration). The second derivative becomes zero for $x_1^{\delta} = 0.62$ and $x_1^{\epsilon} = 0.92$, but this range is not the "real" two-phase region, because the metastable regions (where the mixture is not stable) are not included in this range. Figure A1b shows the plot $\Delta G^{\mathrm{mix}}/RT$ and the metastable regions, as well as the "real" miscibility gap and the "apparent" miscibility gap (the one identified

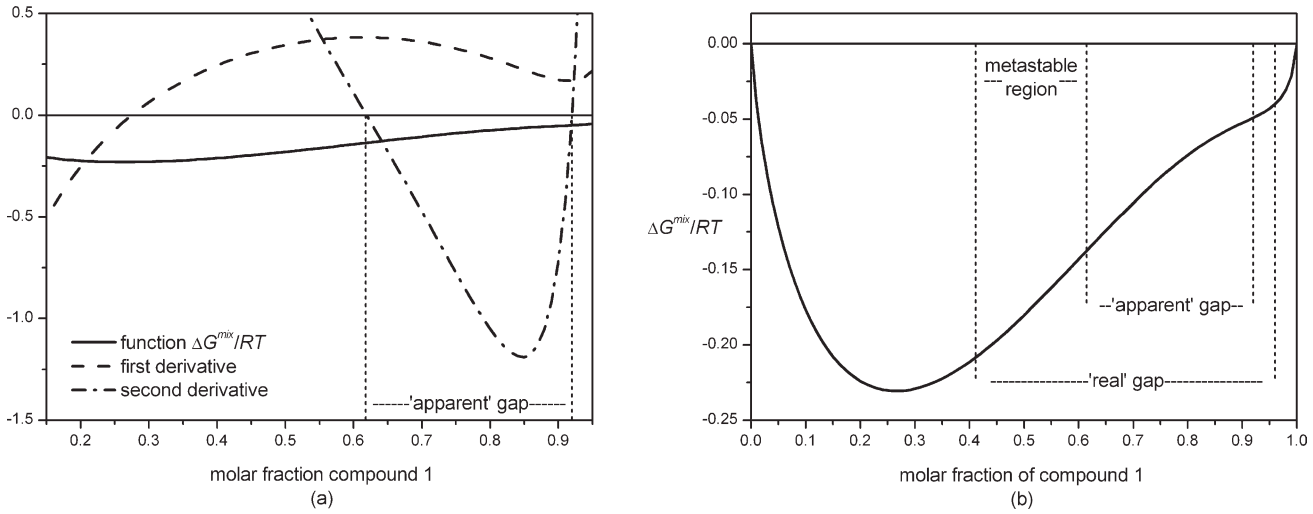

Figure A1. (a) Function $\Delta G/RT$ and its first and second derivative for the system ethanol(1) + hexadecane(2), at 298.15 K, and (b) function $\Delta G/RT$, "real" immiscibility gap, "apparent" immiscibility gap and metastable regions for the same system.

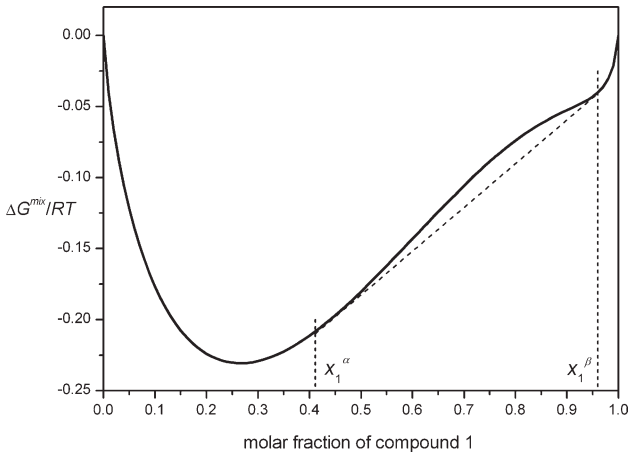

Figure A2. Real immiscibility gap graphically identified by the tangent plane condition, for the system ethanol(1) + hexadecane(2), at 298.15 K.

analyzing the sign of the second derivative of the function $\Delta G^{\text{mix}}/RT$).

The points defining the "real" immiscibility gap can be graphically illustrated as shown in Figure A2, and they correspond to the tangent points found by drawing a tangent line ($y = at \cdot x_1 + bt$, with at and bt the slope and the intercept, respectively) to the $\Delta G^{\text{mix}}/RT$ surface, which has also to lie under the same $\Delta G^{\text{mix}}/RT$ surface. The mathematical expression for this condition is

$$TPD = \frac{\Delta G^{\text{mix}}}{RT} - (at \cdot x_1 + bt) \geq 0 \quad \forall x_1 \tag{47}$$

where TPD is the tangent plane distance, which corresponds to the distance between the function $\Delta G^{\text{mix}}/RT$ and its tangent at every trial compositions.

The interpretation of this graphical solution from a thermodynamic point of view is the following: all the feed compositions z_1 between the immiscibility gap $[x_1^{\alpha}, x_1^{\beta}]$ will split into two different phases of compositions x_1^{α} and x_1^{β} (α and β are the right phases in equilibrium) because the value of the Gibbs energy of mixing of the two phases is lower than the value at the feed composition z_1.

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