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Design of Formulated Products: Experimental Component

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A systematic methodology for the design and verification of chemical-based products is proposed. By integrating modeling, and experiments, the search space is efficiently scanned to identify the feasible product candidates. The product design (or verification) problem consists of three stages: computer-aided design (Stage 1), which generates a list of feasible candidates, experimental planning (Stage 2), which generates a list of experiments and checks the available experimental set-ups, and experimental testing (Stage 3), which measures the necessary data and verifies the desirable attributes of the final product. The first stage (Stage 1) has been covered in previous publications, along with detailed case studies. The development of Stage 2 and Stage 3 is considered in this article and highlighted through two case studies involving the design and validation of an insect repellent lotion and a sunscreen lotion. © 2011 American Institute of Chemical Engineers *AIChE J,* 58: 173–189, 2012
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Introduction

In the last years, the chemical industry has been widening its horizons toward higher value-added materials.[1,2] This change is not simply a change from commodities to specialties, but it signifies a paradigm shift from focus on material purity to material performance. In chemical product design, the problem is to find the most appropriate combination of chemicals and the processing technology that will lead to the desired product attributes set by market demands.

The development of systematic methodologies, tools, and strategies for product design is crucial in a highly competitive commercial environment.[3,4] It is generally agreed that product design is a mix of skills from different disciplines such as business, social sciences, and fine arts, not only chemical sciences and chemical engineering.[5,6]

To meet this need, various attempts have been made to develop systematic methodologies for the design and development of chemical-based products. Cussler and Moggridge[7] suggested a four-step procedure based on needs, ideas, selection, and manufacture. According to the perspective of Gani,[8,9] chemical product design is the discipline that guides the developer in identifying the most appropriate chemical(s) that will exhibit and/or impart the desired behavior. Westerberg and Subrahmanian[5] recommended organizing the design procedure. Wibowo and Ng[10] developed a procedure for the manufacture of creams and pastes, which was subsequently generalized for chemical-based consumer products.[11] Fung and Ng[12] presented a systematic procedure for the manufacture of tablets and capsules. Cheng et al.[13] formulated an approach, which involves business and management decisions in product development.

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Table 1. Comparison Between Model-Based and Experimental-Based Approach for Product Design

	Model-Based	Experimental-Based
Tools	Mathematical predictive models	Knowledge base, experience of few expertises
Objective	Screen numerous candidates—obtain a base case	Manufacture the end-use product
Environment	Virtual reality	Reality
Uncertainty	Models uncertainty, assumptions, hypothesis	No uncertainty
Advantages	Time and resources are spared	Manufacture of end-use products
Disadvantages	High uncertainty, necessity of an experimental validation, some properties can not be modeled (scent, appearance,…), models are limited to some kind of chemical	Long development times, high consumption of resources, necessity of the knowledge base

In addition to the general approaches described above, a large number of computer-aided methods have also been developed. Computer-aided methods have been developed for molecular design,[14] solvent design,[15–18] mixture design,[19] polymer design,[20–23] and refrigerant design.[24,25] The algorithms employed can be classified under the following types: ''generate and test'' algorithm,[15,17,24,26] genetic algorithm,[22] mathematical programing,[16,21] component-less design techniques,[27,28] combinatorial optimization,[29] and hybrid methods.[14]

The design and verification of formulated products

In the chemical industry, several chemicals are often combined in formulations to obtain products with different functions and qualities. Many household products such as cosmetics, pharmaceuticals, and personal care products are formulations. This article focuses on lotions which are formulations in liquid form.

Lotions are usually constituted of one or more active ingredients (AIs) for providing the main product activities, a mixture of solvents serving as the delivery system of the AIs to the desired surface, and additives (usually present in small concentrations, less than 2% in volume) for enhancing the end use product properties. The solvent mixture evaporates after application of the product. Solvent selection and solvent mixture design are key activities in the design of such a product, since many of the end-use product qualities such as drying time, toxicity, product form and so on are closely related to the solvent/solvent mixture present in the product.

A systematic methodology for the design and the verification of formulations with a liquid form has been recently developed,[30,31] design and verification of formulated products are two different scenarios the designer may encounter. When designing a completely new product,[30] the identities of the ingredients of the formula are not known; the objective is to identify the formulation of chemicals that matches the a priori defined criteria. In the verification of formulated products,[31] the identities of most of the chemicals are known, and/or a shortlist of candidate ingredients is given (avoiding thereby the generation/screening of numerous alternatives). The aim here is to verify the (liquid) phase stability of the actual formula and/or to calculate its chemical and physical properties to check the product performance.

The methodology proposed in this work for the design and the verification of formulated products with a liquid delivery system strikes a balance between model-based and experimental approach to product design. Table 1 compares the model-based and experimental approaches in terms of the tools used, objectives, research environment, and uncertainty. The model-based approach aims at screening a large number of product alternatives to identify a small number of candidates (design scenario), or at verifying the mutual solubility and the functions of the chemicals present in a given shortlist (verification scenario) for further testing, validation, and modification through experimental research. The accuracy of predictions depends on the reliability of mathematical models and the assumptions and hypothesis taken. In addition, modeling cannot cover sensorial properties such as the turbidity, color, scent, greasiness, and stickiness of the product although such properties can be easily determined by experiments. Any experiment-based trial-and-error approach is very demanding in terms of time and resources. It also requires experience in the form of heuristics, guidelines, etc., to adjust the product to meet the target values of its attributes.

By combining modeling with experiments, the uncertainties of the model-based approach are compensated by the experimental tests whereas the number of experiments is reduced through model predictions. The proposed methodology based on the integrated approach consists of three stages, as shown in Figure 1. In Stage 1, computer-aided design reduces the search space and provides a list of potential candidates. Stage 2 involves planning for experimental identification of the important product attributes, and to put together the experimental set-up. In Stage 3, experiments are performed. Modifications and improvements of the base case formula are made, if necessary, to meet the target values of the product attributes.

This article deals with the design of formulated products, and attention is focused on Stage 2 and Stage 3 of the formulation design methodology. Stage 1, involving computer-aided liquid formulation design has already been presented in Conte et al.[30] whereas details of computer-aided verification of formulated products can be found in Conte et al.[31] Two case studies are used in this article to illustrate the workflow: the design of formulations for an insect repellent and a water-resistant sunscreen lotion.

An Integrated Methodology for Formulation Design

Before describing Stage 2 and Stage 3 (the focus of this article) of the methodology in detail, Stage 1 related to the design scenario is briefly reviewed below.

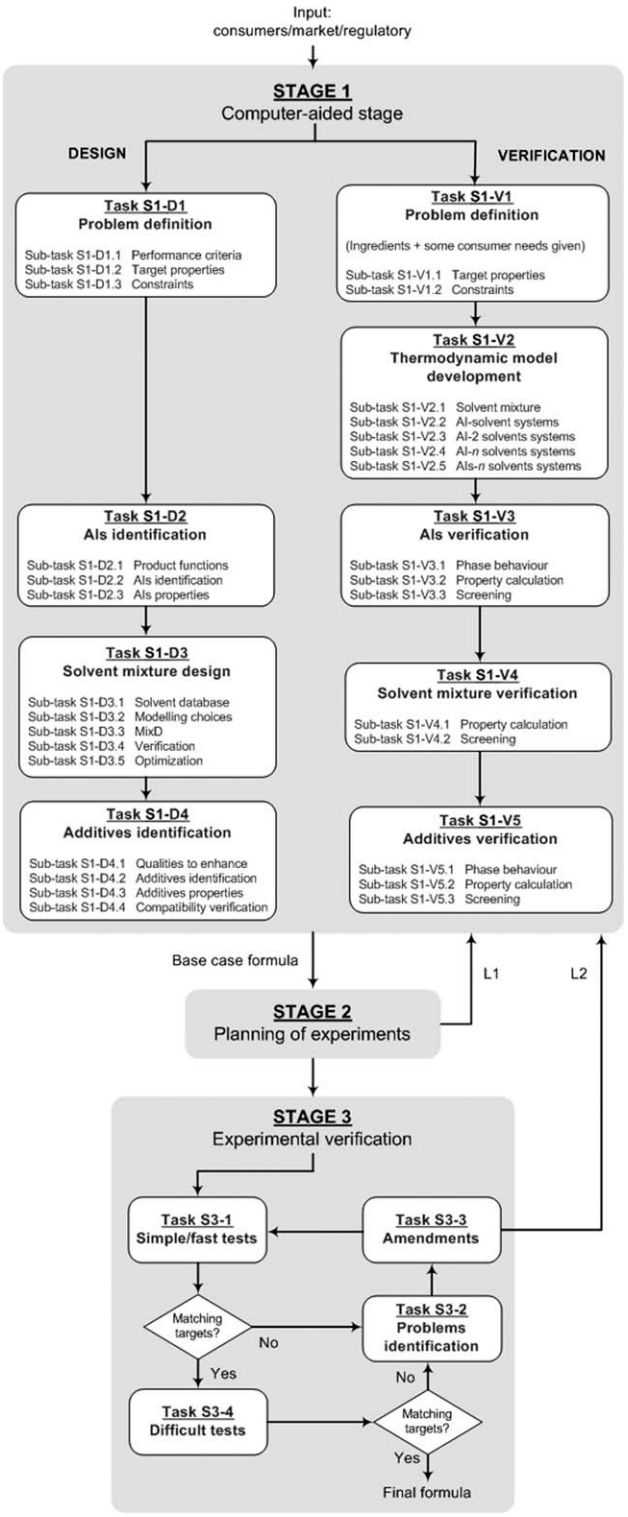

Figure 1. Work-flow diagram for the integrated methodology for formulation design.

Stage 1: Computer-aided design

Stage 1 is based on the reverse design technique[9]: the methodology guides the user through the design of a formulation that matches the a priori defined targets. The targets are set during the problem definition (task S1-D1). AIs are identified (task S1-D2) through database and knowledge base search (patents, literature, company knowledge, and so on). Information about toxicity, efficiency, and concentration that ensures the desired efficacy is also gathered. If measured values of the properties of the AI chemicals are not available, they are predicted through group contribution methods.[32] The identification of the pure solvent or the design of a solvent mixture (task S1-D3) is an important step as it has to guarantee the complete dissolution of the AIs and the phase stability of the formula, in addition to conferring the desired properties to the product. The models used for screening are usually simple linear models, but rigorous models which account for the mixture excess properties can also be employed, if necessary. The design algorithm produces a list of feasible candidate solvent mixtures, but one optimal candidate is identified in the optimization sub-task. In task S1-D4, additives are chosen for the identified base case formula. No iteration is required between the different tasks of Stage 1.

The computer-aided stage produces a base-case formula that serves as the starting point for verification and final selection by experiments. The base-case formula is just an indication of which ingredients should be present in the formulation, and in which ratios, but experiments are extremely important to amend the formula and produce the product prototype.

The computer-aided stage of the methodology has been implemented within a computer-aided framework.[30,31,33] A number of methods and tools, as well as property models, databases, and knowledge base have been included in the framework.[30] The methods (and the associated computer programs) are:

1. The mixture classification algorithm, for the classification of mixture according to hydrogen-bonding properties and, therefore, the contribution of excess properties to the mixing process.
2. The MIXD algorithm, for the design of single liquid phase binary mixtures of solvents. MIXD contains also the STABILITY algorithm.
3. The STABILITY algorithm, for the stability test of binary solvent mixtures.

The developed databases contain data and information for several kinds of AIs, solvents, and additives.

The knowledge base contains data, information, and rules retrieved from literature, patents, patented products, insights, and common sense, which guides the designer through the design (or verification) of formulated products. For instance, the knowledge base contains information on how to identify the performance criteria/consumer needs/product attributes usually required for some specific formulated products, and on how to translate these criteria into technical specifications (target properties and numerical constraints).

As stated in Part I,[30] this work does not aim to determine the compositions of AIs and additives in the formulation, since the necessary models are not available for this task. Instead, values found in the literature (patents) or in real product recipes have been used (knowledge base). Note, however, the amount and compositions of the solvent mixture are calculated.

Stage 2: Experimental planning

Stage 2 serves as the link between the computer-aided screening of alternatives and the experimental validation. Here, the availability of the product ingredients and of the needed experimental set-ups is confirmed. If one of the chemicals is not available, the loop L1 in Figure 1 is followed to find suitable alternative chemicals. For instance, if one of the solvents of the base case formula is not available, the second best solvent mixture identified by the mixture design algorithm could be taken into consideration during experimental planning. If an experimental set-up is not available, alternative solutions need to be found to measure the corresponding property. At the end of Stage 2, a list of experiments that are ready to be performed is produced.

For lotions, the experiments are divided into three levels. First, the AI/AIs should be tested, if necessary, to verify if they possess the needed functional properties for the product. For instance, if an AI is chosen as an insect repellent for tropical areas, it should be proven that it can repel the mosquitoes that are present in tropical areas. The second level involves testing of the solvents and the solvent mixture. The solvents should be able to dissolve the AI/AIs without phase separation. The physical/chemical properties of the solvents/solvent mixture which are considered critical for the product under consideration should be measured as well. Since the additives are present in low concentration, their effect on the final product properties is expected to be negligible. Therefore, they are not tested individually but the effect on the overall formulation is observed in the next level. Availability and price of these materials should also be considered. The third level is the experimentation on the prototypes. For lotions, the production of the prototypes is simply mixing. The overall formula has to meet the a priori defined targets. Spray-ability for the spray products and spread-ability for products such as paints have to be tested. Some tests will include also the validation/measurements of properties that cannot be modeled such as the sensorial factors (color, turbidity, scent, greasiness, etc.), shelf life and pH, and properties such as phase separation at extreme temperatures that have not been considered in the computer-aided design.

All the properties considered during the computer-aided design stage (Stage 1) have to be experimentally verified in Stage 3. In some cases, it is not necessary to measure a particular property, if it is easier to perform a related experiment. For example, instead of measuring the solubility parameters, it is easier to measure solubility and also confirm miscibility. In other cases, it is not possible to perform some experiments due to the lack of experimental set-up and/or chemicals. In this case, substitutive experiments can be performed.

Stage 3: Experimental validation

Stage 3 consists of two iterative loops. In the inner loop, the simple and non time consuming tests are carried out (task S3-1). If not all the tests give satisfactory results, problems are identified (task S3-2) and modifications are made to fix the problems (task S3-3). This loop is iterated until all the simple/fast tests give satisfactory results; that is, when all the a priori defined constraints are satisfied. When this happens, task S3-4, in the outer loop, is performed. Here, all the long time duration and difficult tests are carried out. If any of these tests do not give satisfactory results, the problems are identified and modifications in the formulation are suggested (tasks S3-2 and S3-3). The simple tests may have to be performed again since the modifications could affect the product properties considered in the inner loop (simple tests and measurements). This is continued until a formula that satisfies all the targets has been identified, and process synthesis and scale-up can begin (these two last steps are not considered in this work).

The computer-aided stage and the experimental stage are not independent of each other. Some of the problems found in the experimental stage can be solved by replacing one or more ingredients. Thus, it becomes necessary to go back to the computer-aided stage during task S3-3 (amendments), following the iterative loop L2 (Figure 1), which links Stage 3 back to Stage 1 of the methodology.

Case Studies

Two case studies are presented here to highlight the experimental validation related stages of the integrated methodology workflow: a water-based insect repellent and a waterproof sunscreen, both products in the form of a spray. The development of the base case formula through the computer-aided design stage of the methodology (Stage 1) is not described in detail, since the reader can refer to previous publications[30,34] for more explanations. Instead, only a summary of the results from this stage is reported here.

Design of a water-based insect repellent

The aim of this case study is to design an insect repellent lotion. Water should be one of the formulation ingredients, because of safety and cost concerns. Some well known insect repellents in the spray form are based on water–alcohol mixtures, like the well known product from Bayer, Autan®. The market for consumption is non tropical areas (such as Europe).

Computer-Aided Stage (S1-D). Task S1-D1: Problem definition. 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); a water-based product, for safety and toxicology reasons; 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, such as a spray product; long shelf life. The effectiveness of the product is guaranteed by choosing suitable AIs. Material compatibility is guaranteed by selecting non aggressive and corrosive chemicals. The scent of the product can be improved by adding perfumes (additives). The durability of the product is related to the evaporation time T_{90}; the toxicity is related to the parameter LC_{50}; the stability of the product can be controlled through the solubility parameter δ, the Gibbs energy of mixing and the tangent plane distance[30] (ΔG^{mix}, TPD); the spray-ability is related to the kinematic

Table 2. Target Property Constraints for the Case Studies Under Consideration

Target Property	Symbol	UoM	Insect Repellent		Sunscreen	
			LB	UB	LB	UB
Evaporation time	T_{90}	S	500	1500	700	1300
Lethal concentration	LC_{50}	mol/m^3	$0.39 \cdot \times 10^3$	$+\infty$	3.16	$+\infty$
Solvent mixture solubility parameter	δ	$MPa^{1/2}$	$\delta_{AI} - 3$	$\delta_{AI} + 3$	$\delta_{AI} - 3$	$\delta_{AI} + 3$
Additives solubility parameter	δ_{add}	$MPa^{1/2}$	$\delta_{AI} - 3$	$\delta_{AI} + 3$	$\delta_{AI} - 3$	$\delta_{AI} + 3$
Δ Gibbs energy of mixing	$\Delta G^{mix}/RT$	–	$-\infty$	0	$-\infty$	0
Tangent plane distance	TPD	–	0	$+\infty$	0	$+\infty$
Kinematic viscosity	v	$10^{-6} \cdot m^2/s$	0	75.0	0	75.0
Molar volume	V	$10^{-3} \cdot m^3/kmol$	20.0	50.0	100.0	150.0

LB and UB are the lower and the upper bound for the constraints, respectively.

viscosity v and the density ρ (or molar volume V). Table 2 shows the lower and upper bounds of the constraint values for the target properties described above.

Task S1-D2: AI identification. Only one AI is necessary, since the main function of the product is only one: to repel mosquitoes. DEET,[35,36] natural AIs,[37] and Picaridin[35] are usually employed as AIs in insect repellents. Picaridin was selected because of its superior qualities. Unfortunately, Picaridin has a very low solubility in water (8.6 Kg/m^3 at 273 K) and a second solvent (an alcohol) has to be added to form a solvent mixture which can dissolve Picaridin (Picaridin shows high alcohol solubility). For this reason, it is necessary to verify whether the solubility parameter of the second solvent in the mixture (besides water) is close to that of Picaridin ($\delta_{AI} \pm 3$ $MPa^{1/2}$), substituting the constraint on the solubility parameter of the solvent mixture (see Table 2) with the constraint of Eq. 1.

$$\delta_{AI} - 3.0 \leq \delta_2 \leq \delta_{AI} + 3.0 \qquad 21.1 \leq \delta_2 \leq 27.1 \qquad (1)$$

δ_2 is the solubility parameter of the second solvent present in the solvent mixture (besides water). The Hildebrand solubility parameter of Picaridin (δ_{AI}) corresponds to 24.1 $MPa^{1/2}$, calculated with the M&G GC^+ (Marrero and Gani Group Contribution plus) method.[32]

Task S1-D3: Solvent mixture design. Picaridin is very soluble in alcohols. In addition, the product under development has to contain water. Hence, the database of water soluble alcohols was considered and water was added. The models selected for the mixture target properties are shown in Appendix. The temperature considered in the design was 300 K.

The MIXD algorithm was applied for all the property constraints (see Table 2) excluding the constraints on the solubility parameter of the additive. Results are given in Table 3, where the solvent mixtures are listed in terms of increasing cost. Note that Mixtures 4, 6, and 7 show a phase split in the compositions of interest, so they are rejected.

The remaining mixtures are all mixtures of two polar and non associating fluids (PAS/PAS), therefore, verification with rigorous models is necessary.[30] Viscosity (important property for a spray product) was recalculated using the rigorous model of Cao et al.[38] (see Table 3, last column). A good agreement between predictions from the linear and non linear (rigorous) models is noted and the constraint on the viscosity was not violated.

For the five "feasible" mixtures (Mixtures 1, 2, 3, 5, and 8), the constraint on the solubility parameter of the second solvent in the mixture was now checked. The Hildebrand solubility parameter (δ_2) values for methanol and allyl alcohol do not match the target ($\delta_{Methanol} = 29.6$, $\delta_{allyl\ alcohol} = 27.5$ $MPa^{1/2}$), therefore, the corresponding mixtures (Mixtures 1 and 3) were rejected.

Cost is selected as the only performance index (PI). The isopropanol–water mixture (Mixture 2) is the cheapest among the three remaining mixtures (2, 5, and 8), and it is chosen as the base case formula. Mixture 5 is the one used in the Autan® product, which is a mixture of Picaridin, ethanol–water, and a fragrance. It is interesting to note that the composition of the solvent mixture in Autan® is 28.5% (molar base) of ethanol, which is very close to the composition calculated in this work (see Table 3).

Task S1-D4: Additives identification. The quality to enhance is the scent. Perfumes added to insect repellent lotions also serve as fixatives for the AI, since their large branched molecules lower the vapor pressure of repellents.[37] Two aroma compounds are suitable candidates[39]: α/β-santalol and linalool. Both aroma compounds match the constraint on the additive solubility parameter (Table 2), but linalool is preferred since it is (slightly) soluble in water.

Table 3. Mixtures Matching the Target Properties, Concentration, and Property Values for the Insect Repellent Case Study

No.	Mixtures	x_1	δ	v	ρ	LC_{50}	T_{90}	Cost	Phase split	v-Verification
1	Methanol + water	0.32	42.00	0.83	889.36	744.73	818.7	0.65	Stable	0.81
2	2-Propanol + water	0.24	42.00	1.31	874.84	584.79	660.5	0.92	Stable	0.97
3	Allyl alcohol + water	0.29	42.00	1.14	962.04	472.06	598.0	1.10	Stable	1.30
4	Tert-butyl alcohol + water	0.24	42.00	1.49	941.42	523.60	588.2	1.22	0.02–0.44	–
5	Ethanol + water	0.27	42.00	1.01	893.20	413.05	734.4	1.42	Stable	1.33
6	2-Methyl-1-propanol + water	0.23	42.00	1.66	875.11	419.76	597.0	1.72	0.02–0.46	–
7	2-Butanol + water	0.24	42.00	1.62	879.34	523.60	519.8	1.81	0.02–0.46	–
8	1-Propanol + water	0.25	42.00	1.28	884.90	452.90	628.2	2.07	Stable	1.06

Prediction of viscosity with rigorous models is given in the last column.
Unit of measure: δ ($MPa^{1/2}$), v (10^{-6} m^2/s), ρ (kg/m^3), LC_{50} (mol/m^3), T_{90} (s), and Cost ($/kg).

Table 4. First (Base Case) and Second (Final) Iteration Formulations for the Insect Repellent Case Study

		% w_i	
Family	Chemical	Base Case (First Iteration Formula)	Second Iteration Formula
AI	Picaridin	10.00	9.69
Solvent mixture	2-Propanol	45.65	44.25
	Water	43.35	42.01
Additives	Linalool	1.00	4.00
	Acetic acid	–	0.05

Table 4 gives the details of the base case formula. The suggested composition is calculated taking as reference the values of Frances et al.[40]

Experimental Planning Stage (S2). There is no need to verify the effectiveness of Picaridin which is widely known. However, there is contradiction in the literature about the water solubility of Picaridin. Some documents report that Picaridin is insoluble in water (Autan® report, Picaridin technical fact sheet) whereas other sources state that Picaridin is slightly soluble in water (World Health Organization report). Thus, it was decided to verify Picaridin solubility by experiments. The entire list of experiments that may be performed are given below.

1. Measurement of the solubility limit of Picaridin in water.
2. Verification of phase stability of the solvent mixture.
3. Verification of the solubility of Picaridin and linalool in the solvent mixture.
4. Production of a prototype product based on the formula and verification of its phase stability.
5. ρ and v measurements for pure compounds, solvent mixture, and formulation.
6. T_{90} measurement for the pure solvents (Picaridin and linalool are high boiling and are not supposed to evaporate), solvent mixture, and formulation.
7. Verification of spray-ability through a nozzle.
8. Evaluation of the sensorial factors and cosmetic properties: appearance (turbidity/color), odor, stickiness, greasiness, effect on the skin, irritating power.
9. Measurement of the pH of the formula.
10. Verification of stability at different temperatures than the room temperature.
11. Verification of shelf life.

Table 5 lists the performance criteria for the insect repellent lotion (sub-task S1-D1.1) and the corresponding experiments to be performed (See Table 6). The experiments are listed according to the difficulty and time length: from the simplest and/or fastest to the most difficult and/or time consuming. This is also the order to be employed at Stage 3: Experiments 1–9 belong to the inner loop of Stage 3 (see Figure 1) whereas Experiments 10–11 belong to the outer loop (the stability test at different temperatures requires some days; the shelf life test requires at least two months of time). The list of experiments includes also the verification of those performance criteria that were not included during the computer-aided design stage of the product: in Experiment 8 the sensorial factors/cosmetic properties will be verified (only odor was considered during the computer-aided design stage); in Experiment 9 the pH will be measured to verify if the lotion is compatible with the skin and does not cause irritation (cosmetic products should have a pH close to that of the skin, which is 5.5); in Experiment 10 the stability of the formula at temperatures other than 300 K (design temperature) will be tested, since transportation and storage happen at different temperatures and the product should not decompose or change appearance/odor; in Experiment 11, the product shelf life will be tested.

The parameter LC_{50} was not measured since the values reported in the material safety data sheet (MSDS) for pure compounds are usually employed to calculate the mixture property value with a linear mixing rule (as done in the computer-aided design stage in this work). The solubility parameter is used in the computer-aided design stage to ensure the solubility of Picaridin in the solvent mixture, but through experiments this verification can be performed by observing the actual dissolution process. Therefore, solubility parameter measurements are not necessary.

Picaridin was obtained from Meryer (97 wt %), isopropanol from Mallikckrodt Chemicals (minimum 99.5 wt %); the aroma was natural L-linalool from SAFC (minimum 80 wt %). The water employed was deionized water (DI).

The experimental set-ups were:

- Solubility limit of Picaridin in water: it was measured with an apparatus for liquid-liquid equilibrium. An equilibrium glass vessel (100 ml) with an external jacket for temperature control was employed; 100 ml of DI water was added to the vessel whereas Picaridin was introduced in doses of ~0.1 g/l every day. After 3 h of mixing, the

Table 5. Experiments Employed to Verify the Performance Criteria for the Insect Repellent Lotion

Performance Criteria	Target Property	Considered in Stage 1?	Experiments Planned in Stage 2
Effectiveness	–	Yes	–*
Material compatibility	–	Yes	–
Water based	–	Yes	–
Good sensorial/cosmetic factors	–	Only odor	Exps. 8 and 9
Low priced	–	Yes	–
Durability	T_{90}	Yes	Exp. 6
Toxicity	LC_{50}	Yes	–†
Stability	δ, ΔG^{mix}, TPD	Yes	Exps. 1, 2, 3, 4, and 10‡
Spray ability	v, V	Yes	Exps. 5 and 7
Shelf life	–	No	Exp. 11

*No experimental facility was available.
†Usually, toxicity values are taken from MSDS in experiment-based product design.
‡Experiment 10 verifies stability in a range of temperatures around 300 K, whereas in stage 1 only one temperature was used for the design (300 K).

Table 6. Experimental Results for the Insect Repellent Case Study: First (Base Case) and Second (Final) Iteration

No.	Experiment	Result—First Iteration	Result—Second Iteration
1	Solubility limit of Picaridin in water	Low solubility (9.3 g/l @ 20–23°C)	–
2	Phase stability of the solvent mixture	Successful	–
3	Solubility of AI in the solvent mixture	Successful	–
4	Solubility of linalool in the solution Picaridin + solvent mixture	Successful	–
5	v and ρ of pure solvents, solvent mixture, and formula	Matching a priori defined constraints*	Matching a priori defined constraints
6	T_{90} of pure compounds, solvent mixture, and formula	Satisfactory	Satisfactory
7	Formula spray—ability	Successful	Successful
8	Appearance (turbidity/color), odor, stickiness, greasiness, and irritation	Not satisfactory (too strong scent of Picaridin), too sticky	Reduced acceptable stickiness
9	pH	Not satisfactory	Satisfactory
10	Stability at different temperatures than 300 K (278 and 318 K)	–	Successful
11	Shelf life	–	Successful

*Large deviation between predicted and experimental values for Picaridin viscosity.

solution was left to rest for at least 18 h, to give enough time for a possible phase separation. The experiment was terminated when phase split occurred.

- Other solubility verifications: they were performed by mixing and observing if phase stability occurred.
- Density measurements: a known volume of liquid at 300 K (design temperature) was weighed.
- Viscosity measurements: a Brookfield viscosimeter (model DV-II Pro, adaptor UL/Y, spindle zero) was employed. The temperature was controlled with a thermal bath since the adaptor had a jacket.
- Evaporation time measurements: the T_{90} values (for pure compounds) employed in the computer-aided design were data (or predictions through a correlations based on such data) measured with the shell thin film evaporometer according to the standard method ASTM D3539-87.[41] Such an apparatus was not available in the laboratories where the experiments were performed. An alternative apparatus was used for the T_{90} measurements: a qualitative filter paper (from Advantec) of 7 cm diameter was leaned on a Petri glass dish and introduced in a closed precision digital scale (to exclude any noises affecting evaporation); 0.05 ml of chemical was spread with a syringe on the filter paper, creating a circle of about 2.6 cm of diameter; the weight change was recorded along time. The percentage of weight loss was plotted against the time (seconds) and a trend was generated, from which the T_{90} could be calculated. Since a different apparatus for the T_{90} measurements was employed, results could not be compared with the values predicted during the computer-aided design. But the evaporation trends gave useful information about the way the formulation evaporated and comparison between trends could be performed to understand how the single chemicals affected the formula evaporation.
- Spray-ability verification: this test was performed by spraying the lotion though a nozzle.
- Cosmetic properties verification: greasiness, stickiness, and irritating power of the formula was evaluated by applying the product on the skin.
- pH measurement: indicator strips (Merck) were employed.
- Verification of the stability of the formula at temperatures other than 300 K: this verification was performed by storing one product sample in a fridge at a temperature of 278 K and another sample in an oven at a temperature of 318 K, for at least 1 week.
- Shelf life evaluation: a product sample was left to rest at room temperature for three months and any change in appearance, odor, and consistency, as well as stability of the formula was checked.

Experimental Validation Stage (S3). All results from this stage are summarized in Table 6.

Task S3-1, iteration 1: Simple/fast tests. Experiment 1: The solubility of Picaridin in water was measured to be 9.3 g/l between 273 K and 275 K. This is in reasonable agreement with the literature value of 8.6 g/l at 273 K.

Experiments 2–4: The mixture isopropanol–water was found to be stable; Picaridin, as well as linalool, could be dissolved in the solvent mixture. The product formula was found to be a single liquid phase.

Experiment 5: Table 7 summarizes the values used in the computer-aided design and the measured values for density, molar volume, dynamic viscosity, and kinematic viscosity (the kinematic viscosity was not measured, but calculated using the experimental values of dynamic viscosity and density).

Properties of linalool were not measured because the amount of chemical available was not sufficient and very expensive. The values used for water in the computer-aided design refer to water that was not treated with filters whereas the water used in the experiments was deionized water.

The estimated viscosity of Picaridin was found to be quite different from the experimental value. In fact, the M&G model employed for the estimation of the viscosity[42] had been shown to work very well with small molecules such as solvents but it had not been tested before for multifunctional molecules with complex molecular structures, like Picaridin. Thus, the M&G model parameters need to be fine-tuned for AIs.

The experimentally measured values are reliable since they correspond to values published by others.[43] The fact that the predicted values for the viscosity (see Table 3) is far away from the measured ones is due to the difficulty in predicting the viscosity for alcohol–water mixtures, as already mentioned by Wu,[44] where it was also suggested to fine-tune the UNIFAC-model parameters with viscosity data (this has not been done in this work). It can be noted, however, that the experimentally measured values of the mixture

Table 7. Property Values Used in the Computer-Aided Design (est) and Values Measured with Experiments (exp) for Pure Compounds and Solvent Mixture for the Insect Repellent Case Study

	Picaridin		Isopropanol		DI Water		Solvent Mixture			Formulation	
								est			
Property	exp	est	exp	est	exp	est	exp	lin	rig	Base Case (First Iteration)	Second Iteration
ρ	1066.8	1070.0*	807.4	782.5*	965.4	1000.0*	902.7	874.8	–	952.7	944.7
V	215.0	214.3*	74.4	76.8*	18.6	18.0*	31.13	32.13	–	32.62	33.71
η	76.3	44.60	2.13	2.06*	1.02	0.89*	2.99	1.15	1.16	3.80	4.27
ν	71.5	41.68	2.64	2.63	1.06	0.89	3.31	1.31	1.33	3.99	4.52

Experimental values for the formulations (base case and second iteration) are also shown.
Units of measure: ρ (kg/m^3), V (10^{-3}·m^3/kmol), η (mPa s^{-1}), ν (10^{-6} m^2/s).
"Lin" stands for "linear" model (linear mixing rule) and "rig" for "rigorous" model (viscosity calculation).[38]
*The value used in the calculation was experimental.

viscosities still matched the viscosity constraint, and did not make the product infeasible.

Experiment 6: The evaporation time measurements were performed at room temperature of 295 K and at a humidity of 47%. Figure 2a shows the trends of the percentage of weight lost during the evaporation vs. the time for pure solvents, solvent mixture, and overall formulation (base case). The trends of Figure 2a reveal the reason why existing formulations are not based just on water or do not show high water concentration: the time for complete evaporation of water is too long. The solvent mixture trend is hidden by the formulation trend since they are almost overlapping, but while the solvent mixture reaches 90% of weight loss in around 51 min, the overall formula reaches 90% of weight loss in almost 2.5 h.

The pure compounds show smooth trends and just before reaching the 90% of loss the trends suddenly change their slopes. Instead, the solvent mixture and the formulation trends show quite premature changes in the slopes. Both the solvent mixture and the formulation trends show a clear inflection at around 500 s (40–50% of weight loss): this is the point at which almost all the isopropanol had evaporated. Just after almost all the isopropanol had evaporated the water started to evaporate too. At around 2700 s and 85–90% of weight loss, there is a second inflection in the formulation trend. This is the point at which almost all the solvent mixture had evaporated. The rest of the trend reached the 90% of loss almost asymptotically, employing a very long time, since 11 wt % of the overall formula is constituted of Picaridin and linalool (which have low vapor pressures therefore long evaporation times). After this analysis, it can be concluded that the formulation evaporated as desired: the solvent mixture evaporated at first whereas the AI and the additive stay on the desired surface for longer time, providing the desired activity and a high product durability.

Experiment 7: The formula could be sprayed through a commercial nozzle. Spray-ability was verified.

Experiment 8: The formula was completely transparent. The sensorial feeling on the skin after evaporation was a slight stickiness, caused by Picaridin. No greasiness was felt, nor irritation. The scent was not pleasant since the Picaridin odor was still dominant.

Experiment 9: The pH of the formula was measured. The pH was 8.5, too high for a personal care product (a pH between 5 and 7.5 is preferred, since the skin pH is 5.5) and it could cause irritation to some sensitive skin types.

Tasks S3-2 and S3-3, iteration 1: Problem identification and amendments. The problems encountered were the unpleasant scent of the formula and the high pH value. The modifications suggested were two. At first, linalool

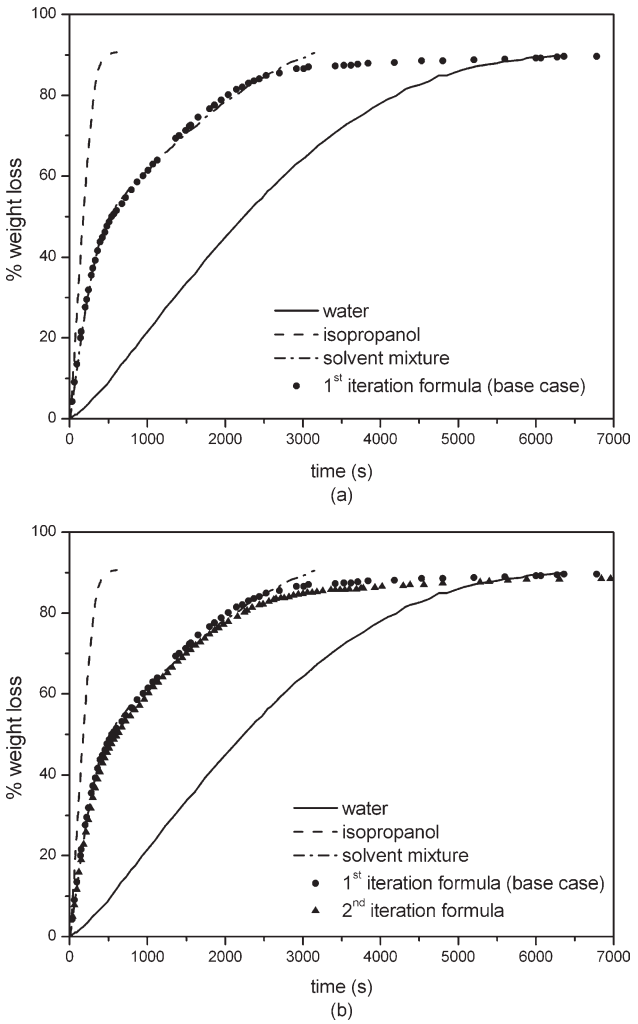

Figure 2. Trends of weight loss (percentage) vs. time (seconds) for pure solvents and solvent mixture. (a) First iteration formula (base case) and (b) second iteration formula (final formula) for the insect repellent lotion.

Table 8. Melting Points (Experimental Data from Databases) and Solubility Parameters of the AIs Chosen for the Sunscreen Lotion (All Predicted with a M&G Method)

Kind of AI	AI	T_m	δ
UV filters	Avobenzone	354–538	23.44
	Octyl salicylate	<298	21.50
Antioxidants	α-Carotene	430*	17.71
	β-Carotene	451–452	17.92
	Vitamin A	334–336	20.69

Unit of measure: T_m (K), δ ($MPa^{1/2}$).
*Predicted with a M&G method.

concentration was increased to improve the scent. Three prototypes were prepared, containing 2, 3, and 4 wt % of linalool, respectively. Only the 4% linalool prototype showed a satisfactory scent after the evaporation of the solvent mixture. The second modification was the addition of a mild acid, such as acetic acid (glacial, 100%, from AnalaR), to correct the pH. Four prototypes were prepared with 0.05, 0.3, 0.5, and 1 wt % of acetic acid, respectively. A concentration of 0.05% brought the pH value to 5.5, which is exactly the skin pH.

Task S3-1, iteration 2: Simple/fast tests. The new product formula (second iteration) is given in Table 4. Experiment 1 did not need to be performed again.

Experiments 2–4: These tests were successful: after the addition of acetic acid, no phase separations were observed.

Experiment 5: The properties (density, viscosity, and evaporation time) of the second iteration product formula were measured and reported in Table 7. The properties did not show drastic changes since the modifications of the product formula were quite small, and they still matched the a priori defined constraints.

Experiment 6: The measurement of the T_{90} was performed again on the new product formula (Figure 2b). The new formulation reached the 90% weight loss in a slightly longer time than the base case formula, due to the increased amount of linalool in the new formulation. The formula still evaporated as desired.

Experiments 7–9: The product formula was still spray-able and the stickiness was reduced (this is maybe due to the lower concentration of Picaridin). The pH was still 5.5 (skin pH).

Task S3-4, iteration 2: Difficult tests. Experiment 10: The test was satisfactory: no phase split was observed and none of the sensorial factors were affected by the temperature changes.

Experiment 11: Also, this test was successful: after resting for two months, the product formula did not show any change.

The second iteration formula (Table 4) is the final product formulation which will undergo the next steps of product development (not taken into consideration in this work).

Design of a water-resistant sunscreen

The aim of this case study is to design a waterproof sunscreen lotion with a sun protection factor (SPF) in the range 10–15.

The sun produces a wide range of electromagnetic radiation. Ultraviolet light (UV-A, B, and C) is responsible for sunburn and suntan and increases the risk of skin cancer. UV-C is stopped by the ozone layer in the upper atmosphere of the earth. Almost all of the UV-A and UV-B rays pass through the ozone layer and cause sunburns, skin aging and skin cancer. One of the defenses of the body against UV radiation is the production of melanin, a pigment that results in darkening of the skin; but this natural defense is not sufficient to avoid severe damages to the skin. Sunscreens are cosmetic formulations that block UV rays.

Computer-Aided Stage (S1-D). Task S1-D1: Problem definition. Consumers want a product which provides: protection from sunburns and the risk of skin cancer (which requires protection against UV-A and UV-B) and prevention of skin aging (main functions of the product); good material compatibility; water-resistance; good cosmetic properties; and sensorial factors (pleasant color and odor, pleasant skin feeling, etc.); low price, long durability (it should not be necessary to apply the lotion several times during the day); low toxicity; good stability; user friendliness, such as a spray product; long shelf life.

Except for the main product activities, a spray sunscreen lotion and a spray insect repellent are quite similar in terms of target properties since they are both personal care spray products. Therefore, the translation of the above performance criteria to the technical specifications is the same as described for the insect repellent. Table 2 gives the constraints and their values for the sunscreen lotion.

Task S1-D2: AI identification. Three main functions of the product were identified in the previous task. Protection from sunburns and prevention of skin cancer can be achieved by providing protection from both UV-A and UV-B rays. A single chemical that provides screening for both types of UV radiations could not be found, therefore, two different AIs were added. The skin aging can be prevented with antioxidants. In addition, inorganic pigments like titanium dioxide or zinc oxide are usually added to formulations, since they are opaque to light and provide a physical barrier for radiations. Since the product should be water-resistant, oil soluble chemicals need to be selected, and the least toxic compounds were preferred. Avobenzone (4-tert-butyl-4′-methoxydibenzoylmethane) was selected as UV-A blockers[45]; octyl salicylate (2-ethylhexyl 2-hydroxybenzoate) was selected as UV-B blocker[45]; α-, β-carotene, and vitamin A were selected as antioxidants[45]; the selected inorganic pigment was titanium dioxide[45] (TiO_2).

The properties (related to solubility) of the AIs (except TiO_2, which cannot be dissolved in the product, but dispersed) are shown in Table 8. The average value of the solubility parameters of the AIs ($\overline{\delta}_{AIs} = 20.3$ $MPa^{1/2}$), inorganic pigment excluded, was used to calculate the numerical values for the upper and lower bounds of the constraints on the solubility parameter of the solvent mixture (δ) and the additives (δ_{add}).

Task S1-D3: Solvent mixture design. The esters database was retrieved from the database library since all the selected AIs are all oil soluble chemicals (except TiO_2, which is insoluble) and the aim of this case study is to design a water-resistant product. In addition, esters are widely used in

Table 9. Mixtures Matching the Target Properties, Their Property Values, and Stability Information for the Sunscreen Case Study

No.	Mixtures	x_1	δ	v	ρ	LC_{50}	T_{90}	C	Phase Split
1	MacAl + 2,2-dimethylpropyl butanoate	0.89	18.95	0.53	832.53	3.63	1017.8	1.40	Stable
2	MacAl + tert-butyl pentan3oate	0.89	18.95	0.53	832.53	3.63	1017.8	1.40	Stable
3	MacAl + isobutyl isopentanoate	0.89	18.93	0.48	830.01	3.65	878.7	1.40	Stable
4	MacAl + 1,1-dimethprop. 3-methbut.	0.91	18.91	0.52	825.23	3.86	846.7	1.41	Stable
5	MacAl + 2,2-dimethprop. 3-methbut.	0.91	18.92	0.53	827.20	3.80	940.2	1.41	Stable
6	MacAl + isobutyl 3,3-dimethbutanoate	0.91	18.92	0.53	827.20	3.80	940.2	1.41	Stable

Unit of measure: δ ($MPa^{1/2}$), v (10^{-6} m^2/s), ρ (kg/m^3), LC_{50} (mol/m^3), T_{90} (s), Cost ($/kg).
"MacAl" stands for "methoxyacetaldehyde" and "dimethprop. 3-methbut" stands for "dimethylpropyl 3-methylbutanoate."

personal care and pharmaceutical applications for their interesting functions (between which, the moisturizing effect). The models selected for the mixture target properties were the same as those selected for the previous case study (Appendix). The temperature considered in the design was 300 K.

The MIXD algorithm was applied for all the property constraints. Results are shown in Table 9. In Mixtures 1, 2, and 3 the second compounds are structural isomers; the same for Mixtures 4, 5, and 6. Isomers can have very similar property values. In fact, the property values of the Mixtures 1, 2, and 3 are close to each other, as well as the property values of the Mixtures 4, 5, and 6. In addition, methoxyacetaldehyde is present in all the mixtures in high concentrations.

The mixture classification algorithm[1] was applied and all the mixtures were found to be of the PNA/PNA type (esters are polar but non associating fluid, PNA). Hence, verification with rigorous models was not necessary.

Toxicity was chosen as the preferred PI. The least toxic mixture is Mixture 4, methoxyacetaldehyde–1,1-dimethylpropyl 3-methylbutanoate (the highest the value of LC_{50}, the least toxic the mixture).

Task S1-D4: Additives identification. According to the performance criteria (task S1-D1), the quality to enhance was the scent. Additional qualities to enhance/augment/add for a sunscreen lotion are the UV filters protection, the stability, and the protection from microbial growth or undesirable chemical changes. Chemicals that can provide these qualities were retrieved from the databases. Aroma compounds were selected (more details on the selection of the aroma compounds can be found in previous publications[30]) to enhance the scent: para-menth-3-yl phenylacetate or iso-propyl salicylate.[39] Octocrylene was selected to augment the UV filters protection and the product stability. Parabens were chosen to prevent the decomposition by microbial growth or by undesirable chemical changes.

The above additives are all esters, as the AIs and the solvents selected in previous tasks. The constraint on the solubility parameter value of the additives (see Table 2) was checked. All the additives matched this constraint, except para-menth-3-yl phenylacetate, which was rejected. Isopropyl salicylate was therefore selected as the aroma compound for the sunscreen lotion.

In Table 10, the details of the base case formula are given, along with the suggested composition. The composition of the AIs in the formulation is a critical parameter since the SPF depends not only on the type of sun blocker compounds selected but also on their composition. The relation between the composition of AIs and the SPF has not been established yet. Cheng et al.[13] showed that with an AIs concentration equal to 9.6 wt %, a SPF of 6.4 is reached. The objective of this case study is to reach a SPF of 10–15, therefore, a total concentration of AIs equal to 20 wt % is proposed.

Table 10. Base Case: First, Second, and Third Iteration Formulations for the Sunscreen Case Study

		% w_i			
Family	Chemical	Base Case	First Iteration Formula	Second Iteration Formula	Third Iteration Formula
AIs	Avobenzone	4.00	4.0	4.0	4.0
	Octyl salicylate	4.00	4.0	4.0	4.0
	α-Carotene	2.00	–	–	–
	β-Carotene	2.00	4.0	–	–
	Vitamin A	4.00	4.0	4.0	4.0
	TiO_2	4.00	–	–	–
	$40\%_w$ ZnO dispersion	–	10.0	10.0	10.0
	Vitamin E acetate	–		4.0	4.0
Solvent mixture	Methoxyacetaldehyde	66.70	–	–	–
	2,2-Dimethylpropyl butanoate	8.20	–	–	–
	Butyl acetate	–	69.0	69.0	69.0
Additives	Octorylene	1.70	1.7	1.7	1.7
	Propyl paraben	1.70	1.7	1.7	1.7
	Iso-propyl salicylate	1.70	–	–	–
	Linalool	–	1.7	1.7	1.7
	Almond oil	–	–	–	2.0

Note that in this case study, the base case formulation does not correspond to the first iteration formulation, due to modifications made during stage 2 (experimental planning stage).

Table 11. Experiments Employed to Verify the Performance Criteria for the Sunscreen Lotion

Performance Criteria	Target Property	Considered in Stage 1?	Experiments Planned in Stage 2
Protection from sunburns	–	Yes	Exp. 11
Prevention of skin cancer	–	Yes	Exp. 11
Prevention of skin aging	–	Yes	–
Material compatibility	–	Yes	–
Water resistance	–	Yes	–
Good sensorial/cosmetic factors	–	Only odor	Exps. 7 and 8
Low priced	–	Yes	–
Durability	T_{90}	Yes	Exp. 5
Toxicity	LC_{50}	Yes	–*
Stability	δ, ΔG^{mix}, TPD	Yes	Exps. 1, 2, 3, and 9†
Spray ability	v, V	Yes	Exps. 4 and 6
Shelf life	–	No	Exp. 10

*Usually, toxicity values are taken from Material Safety Data Sheet in experiment-based product design.
†Experiment 10 verifies stability in a range of temperature around 300 K whereas in stage 1 only one temperature was used for the design (300 K).

Experimental Planning Stage (S2). The following list of experiments was found to be necessary (it resembles the list of the previous case study):

1. Verification of the solubility of every AI in the solvent mixture.
2. Verification of solubility of every additive in the solvent mixture.
3. Production of the prototype formula and verification of its phase stability.
4. ρ, v measurement for pure solvents, solvent mixture, and formulation.
5. T_{90} measurement for pure solvents, solvent mixture, and formulation.
6. Verification of spray-ability through a nozzle.
7. Verification of the sensorial factors and cosmetic properties: appearance (turbidity/color), odor, stickiness, greasiness, irritating power, and soothing effect.
8. Verification of the pH of the formula.
9. Verification of stability at different temperatures than the room temperature.
10. Verification of shelf life.
11. Verification of SPF.

As in the previous case study, Experiments 1–8 are the simple and fast tests whereas Experiments 9–11 are the difficult and time consuming tests. Table 11 lists the performance criteria for the insect repellent lotion (sub-task S1-D1) and the corresponding experiments to be performed.

The list of experiments includes also the verification of those performance criteria that were not included during the computer-aided design stage (Experiments 7–10).

Avobenzone (98 wt %) and octocrylene were obtained from Meryer, octyl salicylate (>99 wt %) from SAFC, natural vitamin A from H^2EI (note that according to the information in Table 8, vitamin A should be solid; instead, vitamin A from H^2EI is liquid). Since α and β-carotene have very similar properties, only β-carotene was purchased (from Wako). Iso-propyl salicylate was not purchased since linalool (from the previous case study) was available (linalool solubility parameter matches the constraint on the solubility parameter, it is therefore compatible with the other ingredients). Nonyl paraben was not found in the market therefore propyl paraben (from Sigma-Aldrich) was purchased.

Methoxyacetaldheyde could not be obtained; therefore, an alternative solvent/solvent mixture needed to be considered. All the other mixtures in Table 9 could not be considered as alternatives, since methoxyacetaldheyde appears in all of them. The opportunity to replace the solvent mixture was investigated by going back to Stage 1 (computer-aided design) following the loop L1 in Figure 1. At task S1-D3 (mixture design task) the constraint on the toxicity parameter LC_{50} was relaxed ($LC_{50} > 0.31$ mol/m^3) and a new simulation was performed. Butyl acetate (>99.5 wt %, Sigma-Aldrich) fulfilled the requirements, and it was chosen since it was available in stock.

Because of the well known toxic properties of small size powders, TiO_2 was replaced by an available suspension of ZnO (ZnO is also used as physical blockers for the UV-radiations in many sunscreen products). This suspension consists of inorganic pigments dispersed in capric/caprylic trygliceride. The solubility of the capric/caprylic trygliceride in the blend constituted of all the other ingredients of the formulation (TiO_2 excluded and butyl acetate instead of the solvent mixture designed in task S1-D3) was checked following the loop L1 of Figure 1 that leads from Stage 2 back to Stage 1 (task S1-D2) of the methodology. The available property models were employed to estimate the trygliceride solubility parameter (17.72 MPa$^{1/2}$), which was found to be very close to the solubility parameters of the other AIs (see Table 8). Therefore, it was decided to use this ZnO dispersion for the experimental validation. After all these considerations, the base case formula changed to the first iteration formula (see Table 10).

The experimental set-ups employed in this case study were the same as the insect repellent example, except for the solubility tests and the SPF test (which was not performed for case study 1):

- Solubility test: since the sunscreen lotion involves numerous AIs and additives, solubility tests were performed separately for each AI and additive in the solvent mixture (in this case pure solvent, butyl acetate) to identify which chemicals cause miscibility problems. The AI (or additive) concentrations in butyl acetate ($w_{AI}|_{AI+but.ac.}$) for the solubility tests were calculated as follows:

$$w_{AI}|_{AI+but.ac.} = \frac{w_{AI}|_{formula}}{(w_{AI} + w_{but.ac})|_{formula}} \tag{2}$$

- w_{AI} and $w_{but.ac.}$ are the concentration of AI and butyl acetate, respectively. The subscript "AI+but.ac." stands for "solution of one AI in the solvent" whereas the subscript

Table 12. Experimental Results for the Sunscreen Case Study: First, Second, and Third Iteration

No.	Experiment	Result: First Iteration	Result: Second Iteration	Result: Third Iteration
1	AIs solubility in the solvent mixture	One AI does not dissolve	Successful	–
2	Additives solubility in the solvent mixture	–	Successful	Successful (performed only for almond oil)
3	Phase stability of the overall formula	–	Successful	Successful
4	v and ρ of pure compounds, solvent mixture, and formula	–	Matching targets*	Matching targets
5	T_{90} of pure solvents, solvent mixture, and formula	–	Satisfactory	Satisfactory
6	Formula spray—ability	–	Successful	Satisfactory
7	Appearance (turbidity/color), odor, stickiness, greasiness, irritation, soothing effect	–	Odor not satisfactory†, soothing effect could be improved	Odor not satisfactory†, soothing effect improved
8	pH	–	Satisfactory	Satisfactory
9	Stability at different temperatures than 300 K (278 and 318 K)	–	–	Not satisfactory
10	Shelf life	–	–	Satisfactory with condition‡
11	SPF	–	–	Not satisfactory

*High deviations of measured viscosity values from predicted values for some AIs viscosity (octyl salicylate and vitamin A).
†The odor is not satisfactory but this factor is taken into consideration for improvements because of chemicals availability issues.
‡The condition is that the product has to be shaken before use.

"formula" means the first iteration formula shown in Table 10. When adding a solid to a liquid it is recommended to stir at a higher temperature (around 313–323 K) than the room temperature, to promote the dissolution process.

• The SPF test follows the guidelines of FDA.[46] An artificial source of light is employed: a solar simulator (Oriel #96000, 150-W) with a total power at the exit port of 8.806 mW/m^2 (UVA: 6.906 mW/m^2; UVB: 1.900 mW/m^2) was used. The test site area is the inner part of the forearm, divided into five test sub site areas of 2.5 cm diameter (each). Each sub site area within a test site area is subjected, for a time interval, to an artificial light source for the determination of the minimal erythematic dose (MED), for a series of time intervals. The rest of the skin around the sub site area is covered. At first, the MED for the unprotected skin (US) is measured in one test site area with the following time interval series: 60, 75, 94, 118, and 146 s (geometric series 1.25^n). The time interval series for the protected skin (PS) test is selected in this way: the MED on unprotected skin is multiplied for the supposed SPF and this time constituted the central time interval of the geometric series. The SPF corresponds to:

$$\text{SPF} = \frac{\text{Exposure time interval MED (PS)}}{\text{Exposure time interval MED(US)}} \tag{3}$$

• Uncertainty of the test is related to the interpretation of test results and depends on the individual perception of the minimal erythematic dose response (the readings can vary of ±20%, different reaction to UV light radiations in different people). Since only one volunteer is to be used for the test (for the SPF determination), the value obtained would be just indicative.

Experimental Validation Stage (S3). All results from this stage are summarized in Table 12.

Task S3-1, iteration 1: Simple/fast tests. Tests 1–8 (simple tests) were here performed.

Experiment 1: The solubility of the AIs and additives in butyl acetate was verified. The composition of the solutions produced for the solubility tests (calculated as in Eq. 2) and the test results are shown in Table 13. All experiments were satisfactory except the solubility test of β-Carotene.

Tasks S3-2 and S3-3, iteration 1: Problem identification and amendments. β-Carotene was found to be not soluble in butyl acetate. Since only one AI out of five was found to have miscibility problems with the solvent, it was decided to substitute it with another ingredient (instead of modifying the solvent mixture, pure solvent in this case study). Therefore, the loop L2 in Figure 1 for not suitable ingredients (linking task S3-D3 with actions in Stage 1) was followed. The antioxidants database was searched and vitamin E acetate was chosen as a replacement of β-Carotene. Vitamin E acetate is a form of powdered vitamin E that is naturally converted by the body to vitamin E. It is an ester and its solubility parameter (16.91 MPa$^{1/2}$) is close enough to the solubility parameters of the other AIs. Vitamin E acetate was purchased from Opal.

The composition of the second iteration formula is shown in Table 10, and compared with the base case and the first iteration product formulations.

Task S3-1, iteration 2: Simple/fast tests. Experiment 1: The solubility test on the new AI (vitamin E acetate) was performed. Vitamin E acetate was found to be soluble in the solvent.

Experiments 2–3: The solubility tests of the additives in the solvent (Experiment 2) did not need to be performed again.

Table 13. Concentration of the Solutions AI/Additive in Butyl Acetate for the Solubility Tests of the Sunscreen Lotion (Test Results are Also Shown)

AI	% w_i	Result
Avobenzone	5.5	Successful
Octyl salicylate	5.5	Successful
β-Carotene	5.5	Failed
Vitamin A	5.5	Successful
ZnO dispersion	12.7	Successful
Octocrylene	2.4	Successful
Propyl paraben	2.4	Successful
Linalool	2.4	Successful

Table 14. Property Values Used in the Computer-Aided Design (est) and Values Measured with Experiments (exp) for the Pure Compounds and the Solvent Mixture for the Sunscreen Case Study

	Butyl Acetate		Octyl Salicylate		Vitamin A		Formulation	
Property	exp	est	exp	est	exp	est	Second Iteration	Third Iteration
ρ	929.4	919.6	1052.1	1014.0*	978.4	934.9	995.4	1038.8
V	125.0	126.3	237.9	246.9	292.8	306.4	136.9	133.0
η	0.85	0.65	9.60	92.86	91.70	12.13	3.20	3.20
v	0.91	0.71	9.12	91.58	93.72	12.97	3.21	3.08

Experimental values of the second and third iteration formulation are also shown.
Units of measure: ρ (kg/m^3), V (10^{-6} m^3/kmol), η (mPa s^{-1}), v (10^{-6} m^2/s).
*The value used in the calculation is experimental.

According to Experiment 3, the prototype of the overall formulation was produced and no phase split was observed.

Experiment 4: Density and viscosity of the pure compounds, solvent mixture, and formulation were measured. Table 14 shows the calculated and experimental values for density and viscosity. No density or viscosity measurements could be performed for the solid ingredients and additives.

There is a significant disagreement between the predicted and the measured values for the viscosity of the AIs, like for Picaridin in the previous case study whereas there is a good agreement between predictions and measurements for the solvent. This shows once again that the M&G GC$^+$ model for the prediction of the viscosity finds difficulties in predicting the properties of large and multifunctional molecules such as the AI molecules. But these disagreements do not make the formula infeasible: molar volume and viscosity of the formulation still matched the a priori defined targets.

Experiment 5: The weight loss during evaporation (Figure 3) for the solvent and the formulation (second iteration formula) was measured at the following conditions: 294–295.5 K, 47% of humidity.

The evaporation trend of the formulation did not reach the 90% of evaporation and a sharp change in the slope could be observed between 500 and 800 s. After all the butyl acetate had evaporated (69% of weight loss), no evaporation was observed any more since 31 wt % of the formulation is composed of AIs and additives that do not evaporate in a relatively short time due to their low vapor pressure. The evaporation trend of the formulation revealed that the formula behaved as desired: the solvent evaporated almost completely after AIs and additives had been delivered on the surface (skin), providing thereby the desired activities. The formulation evaporated as expected, therefore, the experiment was successful.

Experiment 6: The formula could be sprayed through a commercial nozzle.

Experiment 7: The product had a milky appearance since it was white and opaque due to the presence of the inorganic pigment. The scent of the overall formula was not satisfactory. When the product was sprayed on the skin, the smell of butyl acetate (sweet and fruity) was very strong but after evaporation (<4 min) no residual smell of the solvent was left on the skin, and the pleasant scent of linalool could be noticed. The sensation on the skin after spraying was good, no stickiness or greasiness was detected and the skin did not show any irritation. The soothing capacity could actually be improved.

Tasks S3-2 and S3-3, iteration 2: Problem identification and amendments. The main problem was the scent of the formula, related to the solvent. But it was decided not to focus on this issue since the solvent was chosen because of its availability rather than for its characteristics. The improvement of the soothing effect was instead taken into consideration: an emollient needed to be added to the formulation. The loop L2 of Figure 1 that connects the experimental validation with the computer-aided design stage (S1) was followed, the database of moisturizing agents was searched and almond oil was found to be a feasible candidate. This oil is a blend of different fatty acids (oleic, linoleic, palmitic, and stearic acid) and is well-known as emollient in personal care products. Its Hildebrand solubility parameter was calculated as an average of the single fatty acid parameters weighted on their molar fractions, and it was found to be 17.61 MPa$^{1/2}$, which matches the constraint on the additive solubility parameter (see Table 2). Usually, for an emollient, a concentration between 2 and 5 wt % is employed. Two prototypes were produced, one with a concentration of 2% and another with a concentration of 4%. It was found that a concentration of 2% was sufficient to give the desired effect on the skin. The composition of the new formula (third iteration formula) is shown in Table 10 and compared with the previous formulations.

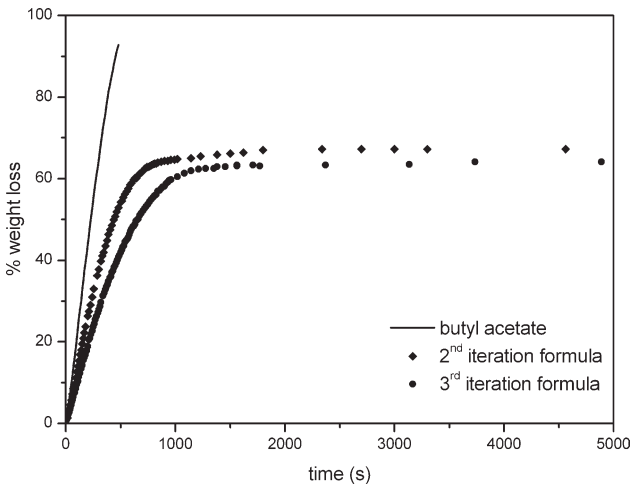

Figure 3. Trends of weight loss (percentage) vs. time (seconds) trends for butyl acetate. Second and third iteration formula for the sunscreen case study.

Table 15. Hansen Solubility Parameters for the Ingredients of the Sunscreen Formulation (Except Inorganic Pigment)

AI	$\ddot{a}_D$	$\ddot{a}_P$	$\ddot{a}_H$
Butyl acetate	15.55	4.4	6.38
Avobenzone	21.48	9.64	6.61
Octyl salicylate	17.92	7.41	10.80
β-Carotene	39.46	4.05	2.42
Vitamin A	27.89	8.19	13.42
Octocrylene	16.05	11.00	6.35
Methyl paraben	17.92	9.82	12.74
Linalool	15.45	7.24	10.06

Task S3-1, iteration 3: Simple/fast tests. Experiment 1 did not need to be performed again.

Experiments 2–3: It was verified that almond oil is soluble in butyl acetate. The third iteration formula prototype was produced and almond oil was found to be compatible with the other ingredients (no phase split was observed).

Experiment 4: Since almond oil looked very viscous, its viscosity was measured to understand the impact of an addition of 2 wt % to the formulation. The dynamic viscosity was found to be 61.70 cP (v = 65.9 cS). The properties of the formula at the third iteration loop were measured too. Table 14 shows the experimental values. Even though almond oil was highly viscous, a concentration of 2 wt % in the overall formula did not affect the formula viscosity. The formula property values still matched the constraints.

Experiment 5: The evaporation time of the third iteration formula was measured (Figure 3). The evaporation trend is slightly different from the previous formula trend, due to the addition of an extra compound with low vapor pressure: the evaporation was slowed down at the beginning and the asymptotic value of weight loss reached was even lower than the one reached by the second iteration formula since the total amount of AIs and additives in the formula increased from 31 wt % to 33 wt %. But the formula still evaporated as desired.

Experiments 6–8: The product is spray-able. The formula appeared white and opaque and with the same strong scent as before. The product was not sticky or greasy and it did not cause irritation. The pH of the formula was still 5.5 (skin pH).

Task S3-4, iteration 3: Difficult tests. The experimental iterative loop for the simple and fast tests was successfully completed (except for the scent of the formula). Therefore, the difficult and time consuming experiments could be performed.

Experiment 9: At first, the stability test at different temperatures was performed. Deposition of the zinc oxide was observed at 318 K, along with a mild change in the color of the formula, which appeared slightly yellow after the test. It is important that all the inorganic pigment is dispersed in the lotion to ensure the specified SPF. The inorganic pigment could be dispersed by briefly shaking the sample.

No changes were observed for the sample of the test performed at 278 K.

Experiment 10: The shelf life test revealed a partial deposition of ZnO. Also, in this case, the inorganic pigment could be dispersed by briefly shaking the sample. The shelf life could be considered satisfactory under the condition the product is shaken before use (and this condition has to be specified upfront, for instance, on the product container).

Experiment 11: The SPF test was now performed. The MED-US (unprotected skin) for the volunteer was recorded at 118 s. The sunscreen lotion was estimated to have a SPF around 8, to be precautionary. Therefore, erythema on the volunteer should have be recorded at 8·118 s, which corresponds to 944 s (15 min and 44 s). Therefore, the time sequence chosen for the test was: 531, 708, 944, 1180, and 1475 s. The MED-PS (protected skin) was detected at 708 s, leading to a SPF value of 6, which did not match the target (10–15).

Task S3-2, iteration 3: Problem identification. The test at 45°C was not completely satisfactory since the product changed color. The SPF did not match the targets. Further modifications were necessary. However, since the workflow had been clearly demonstrated at this point, the experiments were stopped.

Summary of experimental validation. Solubility issues: In this study, the mutual solubility between chemicals has been controlled constraining the Hildebrand solubility parameter. This constraint has been effective, except in the sunscreen study where β-carotene was found to be insoluble in butyl acetate. Solubility investigations have been carried out using the Hansen solubility parameters.[47] Table 15 shows the Hansen solubility parameter values for the sunscreen formula ingredients. Measured values of properties not available in the literature have been calculated through the Marrero and Gani group contribution methods.[48] The accuracy of this method might be poor if the melting temperature of the chemical is far above 298 K, and this is the case for β-carotene, which is also solid at room temperature. The position of the sunscreen lotion ingredients (AIs, solvent, and additive) in the ternary triangular diagram of Figure 4 is determined according to the fractional values of the dispersive, polar, and hydrogen-bonding contribution of the Hansen solubility parameters. In Figure 4, all the ingredients are gathered in the same area, except β-carotene, which is the

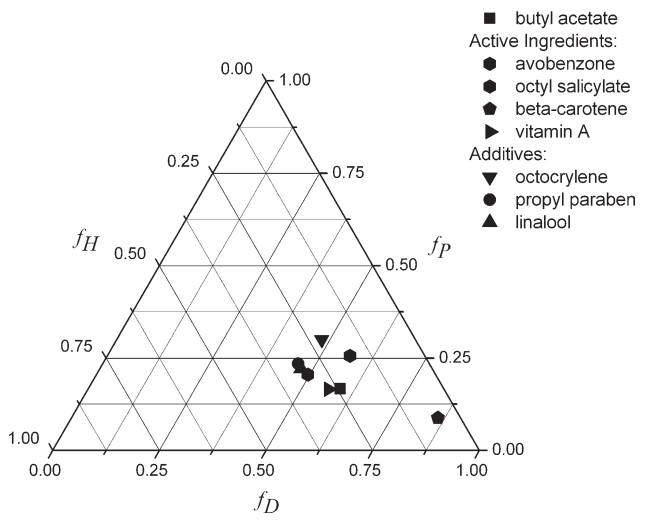

Figure 4. Position of all ingredients of the sunscreen lotion according to the fractional Hansen solubility parameter values.

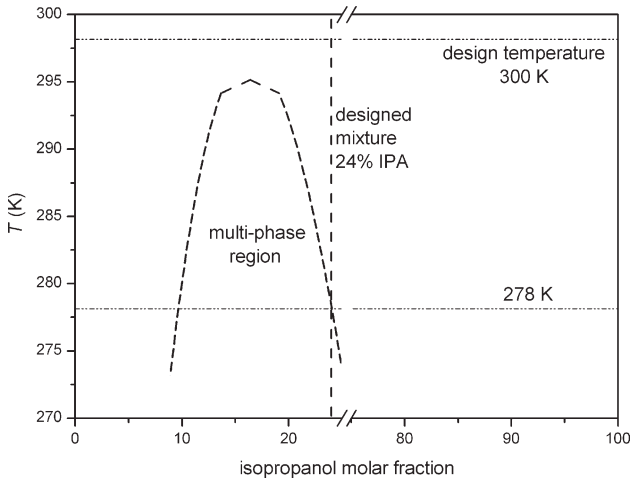

Figure 5. Phase equilibrium for the mixture isopropanol–water (24% molar of isopropanol) and relative position of the designed solvent mixture for the insect repellent lotion.

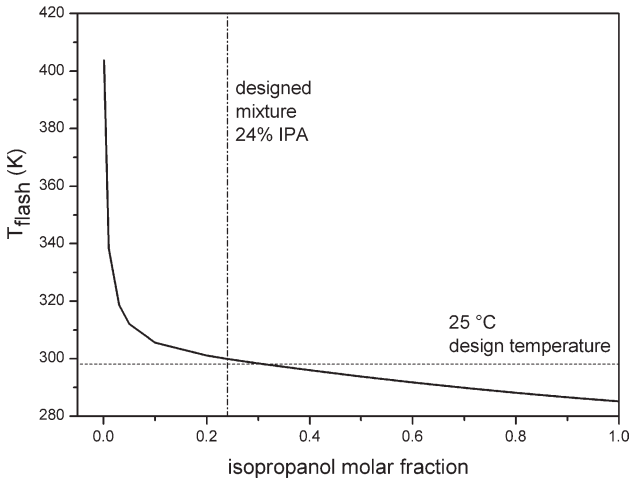

Figure 6. Flash point vs. isopropanol composition for the mixture isopropanol–water (insect repellent lotion).

only ingredient that had solubility issues. It can, therefore, be concluded that the screening of ingredients based on Hansen solubility parameters is more effective than the one based on the Hildebrand solubility parameter.

It should be noted, however, that β-carotene is not an ester whereas all the other AIs and additives in the sunscreen lotion are esters (except linalool, the aroma compound). Therefore, the empirical rule ''similar dissolves similar'' has been shown to be successful once again.

Resistance to temperature changes: Products in general should have resistance to temperature changes, a condition which can easily happen during transportation or storage of the product. The reaction of the product to changes in temperature can be predicted through solubility models. For example, activity coefficient models such as UNIQUAC, NRTL (or UNIFAC) can be used to estimate the phase behavior of the solvent mixture at different temperatures. In the insect repellent case study, the mixture of isopropanol–water was selected. Figure 5 shows the phase equilibrium isopropanol–water and the relative position of the mixture used in the final product.

Figure 5 confirms that the designed mixture is stable at the designed temperature since it is far away from the two phase region, but at 278 K the mixture hits the boundaries of the unstable region. The final product (solvent mixture plus AI and additives) was tested for stability at a temperature of 278 K, and the test revealed the formula was stable. Temperature vs. liquid miscibility investigation like the one highlighted through Figure 5 could have been useful during the computer-aided stage of product design. The second best

Table 16. Relation Problem-Cause and Suggested Modification, Achieved Through the Case Studies in This Study

Problem	Cause	Amendment
Insolubility of AI in a formula with a single AI	Solvent mixture not adequate	Pick another solvent mixture from the list of task S1-D3.3
Insolubility of one AI in a formula with several AIs	AI not adequate	Change the AI showing problems
Insolubility of several AIs (multiple AIs formula)	Solvent mixture not adequate	Pick another solvent mixture from the list of task S1-D3.3
Solubility of one or more additives	Additive/additives not adequate	Replace the additive/additives
The formula cannot be sprayed	Viscosity and/or density are too high	Try to replace the solvent mixture otherwise the product form need to be changed (cream for instance)
The product has an unpleasant color or is turbid	One of the ingredients affects this quality factor	Identify ingredients giving problems and replace it or lower its concentration
The product has an unpleasant scent	The aroma concentration is too low	Increase the aroma concentration or change the aroma
	The solvent mixture has a strong smell	Substitute the solvent mixture
The product is sticky or greasy	Type of the ingredients and (maybe) their viscosity	Identify AI or additives causing the problem and amend their concentration (if this affect the product activity, replace AI)
The product is not stable at room temperature or other temperatures	Solvent mixture splits	Pick another solvent mixture from task S1-D3.3
	The AI/additive is not soluble at different temperatures	
Appearance/flavor/odor changes after some months	Photochemical reaction	Augment stabilizer concentration
	Bacteria growth	Augment preservatives concentration

solvent mixture resulting from task S1-D3 (mixture design task) is ethanol–water and this mixture does not have any miscibility issues in the liquid phase for a temperature range wider than the one explored. Taking into consideration the mixture stability as a function of temperature during the computer-aided design stage would have driven the product developer to choose the ethanol–water mixture for the final product formula, which happens to be exactly the mixture employed by Bayer in Autan®.

Flammability issues: The flash point of the solvent mixture was not considered during the computer-aided design stage. This factor is extremely important since solvents are flammable chemicals and affects the product safety. The solvent mixture should have a flash point, which is at least higher than the room temperature (considering that in the formulation the solvent mixture is diluted by AIs and additives which are usually not highly flammable chemicals). Models are available for the prediction of the flash point of mixtures, such as the model of Liaw et al.[49] Using this model, the flash point of the mixture isopropanol–water (insect repellent formulation) can be predicted as function of composition, as shown in Figure 6. The designed mixture is just above the constraint limit of 278 K even when the water mole fraction is as high as 76%. The formula flash point is just above the tolerance, that is, a safer mixture could have been chosen.

Shelf life: Accelerated testing for shelf life verification would shorten the experimental waiting time and cut down the resources.

Conclusions

A methodology for formulation design and verification which integrates computer-aided tools and experimental testing has been illustrated. Details on the computer-aided algorithm can be found in previous publications.[30,31] The application of the integrated work-flow (Figure 1) has been highlighted through two case studies dealing with personal care products.

The integration of computer-aided design and experiments is essential for product design. It is true that many properties such as sensorial factors and shelf life cannot be modeled or cannot be accurately modeled. Yet, computer-aided design can narrow down the search space to minimize the experiment work. In some cases, such as the flash temperature, the parameter can be predicted using models, thereby avoiding dangerous experiments. In addition, models are expected to reveal the causes of problems encountered in product design and suggest changes to correct those problems. Table 16 summarizes some of the rules for lotions.

The development of predictive models for products with multiple phases, structures, and solids such as ice creams, pharmaceutical dosage forms, air-purifiers, batteries, solar cells, etc., is highly challenging. It calls for significant advances in thermodynamics and transport models that can predict the performance of such products with accuracy. In addition, experiments that can isolate the model parameters and product attributes in a systematic way are needed. It is expected that the experimental component will play a more dominant role for highly complex products. An integrated design procedure with a proper balance between modeling and experiments executed in a timely manner can lead to the best product in the shortest time. Efforts in these directions are in progress.

Notation

C = cost ($/kg)
f = fraction
LC_{50} = measure of toxicity (mol/m^3)
T = temperature (K)
T_m = melting temperature (K)
T_f = flash temperature (K)
T_{90} = time for 90 wt % evaporation (s)
TPD = tangent plane distance
V = molar volume ($10^{-3}\cdot$m^3/kmol)
x_i = composition of compound i, mole fraction
w_i = composition of compound iI, weight fraction
ΔG^{mix} = excess Gibbs energy of mixing (J/kmol)

Greek letters

δ = Hildebrand solubility parameter (Hansen solubility parameter when subscripts D/P/H are present) (MPa$^{1/2}$)
$\overline{\delta}$ = average solubility parameter (MPa$^{1/2}$)
η = dynamic viscosity (cP)
ν = kinematic viscosity (cS)
ρ = density (kg/m^3)

Superscripts

rig = rigorous
lin = linear

Subscript

i = compound i in mixture
1, 2, ... = compound index (in mixture)
add = additive
AI = active Ingredient
D = dispersive attractions
P = polar attractions
H = hydrogen-bonding attractions
formula = formulation, product
but. ac. = butyl acetate

Abbreviations

AI = active ingredient
MED = minimum erythematic dose
MIXD = mixture design algorithm
PAS = polar associating
PI = performance index
PNA = polar non-associating
SPF = sun protection factor
UV = ultra violet

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Appendix: Modeling Choices

The models selected for the estimation of mixture properties in the MIXD routine are shown in Table A.

Table A1. Models Selected for the Calculation of the Mixture Target Properties for Both the Case Studies Considered

Target Property	Symbol	Mixture Model
Evaporation time	T_{90}	Ref. 50
Lethal concentration	LC_{50}	Linear mixing rule
Solubility parameters	δ, δ_{add}	Linear mixing rule
Ä Gibbs energy of mixing	$\Delta G^{mix}/RT$	UNIFAC-LLE
Tangent plane distance	TPD	UNIFAC-LLE
Kinematic viscosity	v	Linear mixing rule
Molar volume	V	Linear mixing rule

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