Computer-aided design of optimal environmentally benign solvent-based adhesive products

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Abstract

The manufacture of improved adhesive products that meet specified target properties has attracted increasing interest over the last decades. In this work, a general systematic methodology for the design of optimal adhesive products with low environmental impact is presented. The proposed approach integrates computer aided design tools and Generalised Disjunctive Programming (GDP), a logic-based framework, to formulate and solve the product design problem. Key design decisions in product design (i.e., how many components should be included in the final product, which active ingredients and solvents compounds should be used and in what proportions) are optimised simultaneously. This methodology is applied to the design of solvent-based acrylic adhesives, which are commonly used in construction. First, optimal product formulations are determined with the aim to minimize toxicity. This reveals that number of components in the product formulation does not correlate with performance and that high performance can be achieved by investigating different number of components as well as by optimising all ingredients simultaneously rather than sequentially. The relation between two competing objectives (product toxicity and concentration of the active ingredient) is then explored by obtaining a set of Pareto optimal solutions. This leads to significant trade-offs and large areas of discontinuity driven by discrete changes in the list of optimal ingredients in the product.

Keywords: Solvent-based Adhesives; Chemical Product Design; Computer-Aided Methods; Generalized Disjunctive Programming; Minimise Toxicity

1. Introduction

While the manufacturing of new processing materials and high-value chemicals is essential for the well-being of modern societies, our understanding of the negative

impacts of many chemicals and their manufacturing processes on the environment has increased substantially over the last few years. As a result, there has been a growing focus on developing methods and tools that integrate green chemistry into the manufacturing of better materials and improve product-process sustainability. The design of new and sustainable chemical products, however, remains challenging as it requires (i) the combination of a large number of ingredients to obtain product formulations with desired functionalities and qualities (e.g., 10-30 ingredients are used to formulate a typical paint or shampoo with specific colour, sticking/cleaning power, etc. (Nicks & Ryan, 1975; Trüeb, 2007)) and (ii) taking into account economic, environmental and health/safety aspects. In current industrial practice, methods for identifying suitable chemicals and the corresponding processing technology are mainly empirical or based on database searches. This results in relatively small search spaces due to large cost of experimental investigations and the finite time and resources available. Clearly, we need to develop systematic methodologies and tools that combine predictive property models within a computer-assisted search for chemical product design to transform trial-and-error practice into an efficient search through the large space of possible blends. In this context, computer-aided product design (CAPD) has emerged as a promising tool for identifying suitable blends that meet predefined target properties and maximise/minimise a given performance measure (Achenie et al., 2003; Gani, 2004a, 2004b).

Several methods based on a CAPD framework for the design of mixtures and products have been applied to specific problems of relevance to today's industries (Gani & Ng, 2015). Among the previous studies, substantial work has been conducted on the design of optimal processing materials, such as solvent mixtures used in separation processes and chemical reactions (Austin et al., 2017; Gopinath et al., 2016; Jonuzaj et al., 2018; Karunanithi et al., 2005; Scheffczyk et al., 2017; Siougkrou et al., 2014), refrigerant and polymer blends (Duvedi & Achenie, 1997; Solvason et al., 2009; Cignitti et al., 2015; Vaidyaraman & Maranas, 2002), working fluid mixtures for Organic Ranking Cycles (ORCs) (Lampe et al., 2014; Lee & Mitsos, 2017; Mavrou et al., 2015; Oyewunmi et al., 2016; Papadopoulos et al., 2013; White et al., 2017) and carbon dioxide capture solvents (Papadopoulos et al., 2016; Zarogiannis et al., 2016). An extended review of existing computer-aided methodologies for designing process-centered chemical blends is given by Jonuzaj (2017). In the area of chemical products (i.e., product-centered formulations), several studies reported in the literature have focused on the design of health-care and personal-care products (such as cosmetic creams and gels, detergent powders and liquids, etc.) (Arrieta-Escobar et al., 2018;

Conte et al., 2012; Fung et al. 2016; Kontogeorgis et al., 2018; Mattei et al., 2012, 2014; Zhang et al. 2017), tailor-made fuel blends and lubricants (Kalakul et al., 2018; Liu et al., 2019; Yunus et al., 2013, 2014; Zhang et al., 2018) and bio-based blends derived from biomass (Dahmen & Marquardt, 2017; Hernández et al., 2017; Mah et al., 2019; Ng et al., 2015). Several interesting reviews on computer-aided methodologies for chemical product design and their applications have been published in the last few years. Gani & Ng (2015) classified chemical products into molecular products, formulated products, functional products and devices, and reviewed the different product categories focusing on their conceptualization. Zhang et al. (2016, 2017) provided an overview of chemical product design and process synthesis methodologies, where they compared different methods and tools and discussed challenges and future perspectives of the field.

The choice of chemicals has a major impact on the environmental and health-and-safety performance of a process or product. Hence, important efforts have been made over the last decade towards minimizing the environmental footprint of chemical products and processes in fine-chemical and pharmaceutical production (Capello, Fischer & Hungerbuhler, 2007). Several studies in the literature have been focused on incorporating environmental impact constraints in the computer-aided design framework. Khor et al. (2017) developed a decomposition-based computer-aided methodology to design an optimal solvent for extracting oil from pressed palm fibre. Their proposed approach considers solvent physical properties along with health-and-safety indexes (e.g., toxicity, flammability, volatility) in a multiobjective optimization problem. In a similar computer-aided design framework, Ooi et al. (2018a, 2018b) presented a multiobjective optimization method for the design of an extractive solvent, taking into account environmental concerns during the solvent recovery process. A two-stage multiobjective optimisation method was recently proposed by Neoh et al. (2019), where first an optimal additive (solvent) was determined to upgrade bio-oil, and next the environmental impact of the solvent-oil blend was minimised. Ten et al. (2017) have also focused on integrating health-and-safety parameters with physicochemical properties design criteria into a computer-aided optimization problem. Most approaches proposed to date are applicable to the design of pure chemicals (mainly solvents) that are used in separation processes or chemical product formulations. Further research efforts are required to extend these approaches to the design of multicomponent chemical blends and formulated products.

Thus, in spite of advances in the area of chemical product design, there remains significant scope for further improvement and innovation in this field. Formulating and

solving product design problems without restricting the design space has proved challenging. This is because product formulations contain blends of ingredients from different chemical/functional categories (e.g., polymers, solvents or solvent mixtures and aromas). It is often difficult to determine simultaneously the optimal compound(s) for each aspect of the product's function due to the combinatorial explosion in the problem size that arises from the many possible combinations of chemicals. Thus, a restricted version of the problem is often posed and solved. Most existing methodologies follow a hierarchical design approach, where one or more ingredients of each type are determined in sequential steps (Conte et al., 2011; Mattei et al., 2014). Thus, within the decomposition-based methods smaller sequential subproblems are usually solved, where the active ingredient is first determined, and then a solvent or a binary solvent mixture and additives are identified. However, questions such as how many components participate in a chemical product and in what proportions, or what are the best active ingredients and solvents to achieve specific product attributes cannot be answered in isolation. These answers depend on physical/chemical properties of the different chemicals in the final product. There have been a few recent publications investigating the design of mixtures where the number of components is not defined *a priori.* In previous work from our group (Jonuzaj et al., 2016, 2018; Jonuzaj & Adjiman, 2017), a formulation based on Generalized disjunctive programming (GDP) (Grossmann & Trespalacios, 2013; Raman & Grossmann, 1994) has been developed for computer-aided molecular/blend design, to explore simultaneously the choice of number of components, component identities and mole fractions. A feature of this approach is that it avoids the numerical difficulties that arise in many models (e.g., phase equilibrium) if the absence of some components is modelled by setting their mole fractions to zero. The OptCAMD framework of Liu et al. (2019) is also applicable to mixtures with an unknown number of components but this is achieved via mixed-integer constraints that force the mole fractions of non-selected components to zero.

In this work, we extend the comprehensive CAPD method for the design of solvent-based acrylic adhesives proposed in our previous work (Cui et al., 2018), avoiding the sequential restricted designs. We develop a generic methodology in which the number of components, the identities and compositions of product ingredients (active ingredient and solvents) are optimized simultaneously to maximize the performance objective. The optimal active ingredient and solvent mixtures are selected from given lists of candidate compounds. Generalized disjunctive programming (GDP) is again employed to formulate the main design decisions of the problem (i.e., how many

ingredients should be included, which active ingredients and solvents compounds should be used and in what proportions). The GDP product design problem is converted into mixed integer form using the big-M approach (Nemhauser & Wolsey, 1999). The design methodology is applied successfully to the design of optimal solvent-based acrylic putty (adhesive) with low toxicity. A set of solutions with different blends is generated by including integer cuts to the general model and the trade-offs between product toxicity and the solubility (concentration) of the active ingredient in the solvent mixture are explored by obtaining a set of Pareto-optimal solutions.

The paper is organized as follows. In Section 2, a brief overview of adhesive products and the GDP and MINLP formulations of the general product design problem are presented. In Section 3 the proposed approach is applied to the case study, followed by the discussion of the results in Section 4. Finally, the main conclusions of this work are summarized in Section 5.

2. Adhesive product design

2.1. Adhesive products

Adhesives are formulated products that can join materials together when applied to their surfaces. They are widely used in consumer goods, dental composite restoration, wood processing, and in the paper and packaging, construction, and transportation industries (Ebnesajjad & Landrock, 2015; Kinloch, 1987). According to a recent analysis of the global adhesives market (Ceresana Market Research, 2019), nearly 14 million tonnes of adhesives are used worldwide and market demand is expected to increase in the next few years, resulting in a revenue increase of 3.6 % per year. In the context of this highly competitive field, the ability to design environmentally benign adhesive products at minimum cost and time can be an important advantage.

Although extended work has been conducted on the design of several chemical-based products that are used in many aspects of human life, only a few model-based approaches have been developed for the design of adhesive products (Abedin et al., 2016, 2017; Fung et al., 2016; Spencer et al., 2010). In particular, the design of dental adhesives using computer-aided tools was investigated in the works of Spencer et al. (2010) and Abedin et al. (2016, 2017). Within their proposed computational approach, suitable water compatible visible light photosensitizers were identified in order to improve the photo-polymerization of the hydrophilic-rich phase and avoid phase separation of dental adhesive resins during infiltration. Fung et al. (2016) studied the design of die attach adhesives using a grand product design (GPD) model. In the GPD

framework, the design of optimal chemical products (such as die attach adhesives) was considered from a technical and cost perspective.

2.2. Problem definition

The CAPD problem involves the generic formulation of the product design problem where the optimal number of components, the optimal identities of all ingredients and their proportions are determined, such that all given constraints are satisfied and the performance objective is optimised. The solvent-based adhesives to be designed consist of three main chemical classes (Ebnesajjad & Landrock, 2015), the active ingredient (AI), solvent mixtures and additives. The AI, which is usually a polymer in certain types of adhesives (e.g., in acrylics), defines the main function of the product; the solvent mixtures are usually in high concentration and are used to dissolve the AI and additives; finally the additives are included in small concentrations to enhance the quality and attributes of the final product. Due to the small amount (traces) of additives in the product, we assume that they do not affect the main properties of the blend considered here and thus, they are not included in the proposed design formulation. They can be considered in the post design/verification phase of the proposed approach, where suitable molecules can be added to the final blend to improve certain desired qualities.

In order to derive the product design formulation, the following index sets need to be defined. First, the user provides the sets $A = \{1, \dots, N_a\}$ and $S = \{1, \dots, N_s\}$ whose elements are compounds and from which the active ingredient and solvent(s) are chosen, respectively. The set $N = \{1, \dots, N_{max}\}$ is the set of possible values for N_c, which is the number of components or ingredients in the optimal adhesive mixture. The components that are present in the adhesive product are represented with the set $I = \{1, \dots, N_{max}\}$. In general, the first few elements of set I represent the active ingredients (denoted by subset J), while the rest of the elements, denoted by subset II, represent the solvent molecules in the blend, with $I = J \cup II$ and $J \cap II = \emptyset$. In the CAPD considered here, we will assume that there is a single active ingredient present, i.e., only one element in J. Throughout this paper, the term “component" refers to an ingredient that is selected to participate in the product blend (i.e., in the set I) and the term “compound" refers to the elements of the sets A and S.

For the purpose of property prediction, each compound is built from functional groups (such as CH_3, COO, OH) that are used in the calculation of relevant pure component and mixture properties, and the groups are represented by the set $G = \{1, \dots, N_g\}$.

2.3. GDP formulation of the CAPD problem

The GDP methodology for the formulation of mixture design problems and different solution relaxation techniques were recently employed by Jonuzaj et al. (2016) and Jonuzaj & Adjiman (2017). Here, we derive the GDP formulation for the general product design problem.

First we define appropriate Boolean variables. The assignments of compounds from the candidate lists (A and S) to the components in the mixture are determined through Boolean variables $\hat{Y}_{1,a},\ a \in A$ and $Y_{i,s},\ i \in II, s \in S$ (i.e., an active ingredient a is assigned to component 1 in the mixture if $\hat{Y}_{1,a}$ is True and a solvent compound s is assigned to component i in the mixture if the $Y_{i,s}$ is True. The number of components in the product is defined via Boolean variable $\tilde{Y}_n,\ n \in N$ such that if $\tilde{Y}_n$ is True, there is a total of n components in the mixture.

The general formulation is then given by:

$$\min_{x,p,Y} \quad f(x,p)$$

$$\text{s.t.} \quad g(x,p) \le 0$$

$$\bigvee_{a \in A} \begin{bmatrix} \hat{Y}_{1,a} \\ r_{1,a}(x,p) \le 0 \end{bmatrix}$$

$$\underline{\bigvee}_{a \in A} \ \hat{Y}_{1,a}$$

$$\underline{\bigvee}_{s \in S} \ Y_{2,s}$$

$$\bigvee_{n \in N\backslash\{1\}} \begin{bmatrix} \tilde{Y}_n \\ \tilde{F}_n(x,p) \le 0 \\ x_i \ge x_i^L, i = 3, \dots, n \\ x_i = 0, i = n+1, \dots, N_{max} \\ \bigvee_{s \in S} \begin{bmatrix} Y_{i,s} \\ h_{i,s}(x,p) \le 0 \end{bmatrix}, i = 2, \dots, n \\ Y_{i,s} = \mathrm{False}, i = n+1, \dots, N_{max}, s \in S \end{bmatrix}$$

$$\underline{\bigvee}_{n \in N} \ \tilde{Y}_n$$

$$\tilde{Y}_1 = \mathrm{False}$$

$$\Omega\left(\hat{Y}_1, Y, \tilde{Y}\right) = \mathrm{True}$$

$$x \in [0,1] \subset \mathbb{R}^{N_{max}}, p \in [p^L, p^U] \subset \ \mathbb{R}^{m_p}$$

$$\widehat{Y}_1, Y, \tilde{Y} \in \{\text{False}, \text{True}\}^q \qquad (GDP)$$

where x is the vector of mole fractions for the components in the mixture (dimension N_{max}), p is the vector of other continuous variables (dimension m_p), $q = N_a + N_s + N_{max}$ is the total number of Boolean variables, f is the objective function to be optimised (e.g., minimise cost or environmental impact) and $g(x,p) \leq 0$ represents general constraints that must hold regardless of the logical decisions made. Three different disjunctive sets are included in the general model, corresponding to the three types of Boolean variables. The first two sets involve disjunctions for assigning an active ingredient a from the list A and a solvent s from the list S to components i in the product formulation. The presence of an active ingredient and at least one solvent compound as the first and second designed components $(i = 1,2)$ in the blend is represented through the exclusive OR disjunctions $\left(\underset{a \in A}{\veebar} \widehat{Y}_{1,a}\right)$ and $\left(\underset{s \in S}{\veebar} Y_{2,s}\right)$, respectively (Grossmann & Trespalacios, 2013), which means that one active ingredient and at least one solvent should be present in the formulation. The sets of inequalities $r_{1,a}(x,v) \leq 0$ and $h_{i,s}(x,p) \leq 0$ represent conditional constraints and they are active when the corresponding Boolean variables $\widehat{Y}_{1,a}$ and $Y_{i,s}$ are true, respectively. The third set of disjunctions includes constraints, $\tilde{F}_n(x,p) \leq 0$, that depend on the number of product ingredients and are active when the Boolean variable $\tilde{Y}_n$ is True. Common examples of these constraints include mixture property constraints, such as phase equilibrium relations (e.g., solid-liquid and liquid-liquid equilibrium) and phase stability functions (e.g., miscibility constraint to ensure that the designed mixture is in a single liquid phase at given temperature and pressure). The mole fraction, x_i, of a component i is greater than a user-specified threshold value x_i^L if the component is present in the product formulation and is zero otherwise. It is noted that the mole fractions of the active ingredient and the first solvent component are always strictly greater than zero $(x_i > 0, i = 1,2)$. They do not depend on the discrete choices but are treated as general constraints (i.e., included in set $g(x,p) \leq 0$). Exactly one disjunction (i.e., exclusive OR disjunctions) for the number of designed components must be active, which is ensured by the expression $\left(\underset{n \in N}{\veebar} \tilde{Y}_n\right)$. The logic propositions, $\Omega\left(\widehat{Y}_1, Y, \tilde{Y}\right) = \text{True}$, involve Boolean and auxiliary variables and express the relationships between the disjunctive sets. A set of logic conditions is derived to avoid degenerate solutions by ensuring that no two identical components are designed in the blend. Additional logic propositions are included in the formulation to relate the Boolean variables for the number of components, $\tilde{Y}_n$, to the Boolean variables for the

identity of the active ingredient, $\hat{Y}_1$, and the solvent molecules, Y, in the final product. A detailed description of the logic relations is given in Jonuzaj et al. (2016). The GDP formulation is converted into an MINLP problem by replacing the Boolean variables $(\hat{Y}_1, Y, \tilde{Y})$ with binary ones $(\hat{y}_1, y, \tilde{y})$ and transforming the logic propositions into linear algebraic inequalities (by applying Boolean algebra rules (Raman & Grossmann, 1991)). Conditional constraints inside the disjunctions are formulated using the big-M (BM) approach as described in the following section.

2.4. Reformulation of the GDP problem as an MINLP via the big-M approach

The big-M formulation is the simplest representation of a GDP problem in a mixed-integer form and it has a one-to-one correspondence with model (GDP), so that both formulations have the same global and local solutions (Raman & Grossmann, 1994). The general GDP product design problem is converted into mixed integer form as follows:

$$
\begin{aligned}
\min_{x,p,Y} \quad & f(x,p) \\
\text{s.t.} \quad & g(x,p) \le 0 \\
& r_{1,a}(x,p) \le M_{r_{1,a}}\left(1-\hat{y}_{1,a}\right), a \in A \\
& h_{i,s}(x,p) \le M_{h_{i,s}}\left(1-y_{i,s}\right), i \in II \ ; s \in S \\
& \tilde{F}_n(x,p) \le M_{\tilde{F}_n}(1-\tilde{y}_n), n = 1,\dots,N_{max} \\
& x_i^L \tilde{y}_n \le x_i \le x_i^U \tilde{y}_n, i = 3,\dots,N_c;\ n = 1,\dots,N_{max} \\
& \sum_{a \in A} \hat{y}_{1,a} = 1 \\
& \sum_{s \in S} y_{2,s} = 1 \\
& \sum_{n \in N} \tilde{y}_n = 1 \\
& A\hat{y}_1 + By + C\tilde{y} \le d \\
& x \in [x^L, x^U] \subset \mathbb{R}^{m_x} ; p \in [p^L, p^U]^{m_p} \\
& \hat{y}_1, y, \tilde{y} \in \{0,1\} \qquad (MINLP)
\end{aligned}
$$

where $A\hat{y}_1 + By + C\tilde{y} \le d$ is a set of linear inequalities resulting from the logic relations, $\Omega\left(\hat{Y}_1, Y, \tilde{Y}\right) = \text{True}$. Valid upper bounds are derived for the big-M parameters

$\left(M_{r_{1,a}}, M_{h_{i,s}}, M_{\tilde{F}_n}\right)$ such that when the binary variables $\hat{y}_1, y$ and $\tilde{y}$ are zero the constraints are always satisfied. We note that the big-M parameter values for the nonlinear functions are chosen to be relaxed bounds rather than exact ones, so that numerical difficulties arising from tight bounds and machine precision are avoided. As shown in model (MINLP), exact bounds x_i^L and x_i^U are however used as big-M parameter values for the mole fractions of all components in the mixture.

3. Case study: the design of solvent-based acrylic putty with low toxicity

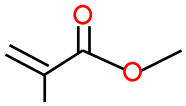
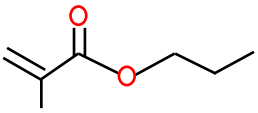
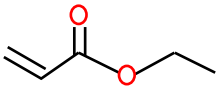
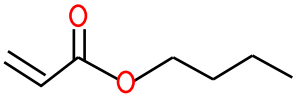
3.1. Problem description

Acrylic adhesives play an important role in a large section of modern industry with a significant commercial use in construction and in paper and packing applications. Common acrylic adhesives are water- or solvent-based, where the liquid carrier is water or a solvent, respectively. While water-based adhesives represent the largest segment of the acrylic adhesives market due to their low cost and low health-and-safety risks, a market shift towards solvent-based adhesives has been observed over the last few years, as they offer high peel and shear strength, faster drying, and better resistance to other chemicals and water. Clearly, the use of suitable solvents can improve the product attributes, but identifying suitable compounds to formulate acrylic blends with desired qualities can be challenging, due to the need to ensure high performance and to meet environmental and safety regulations (REACH, 2017).

In this case study, an optimal solvent-based acrylic putty that meets specific property and environmental constraints is identified. Acrylic putty is a typical acrylic adhesive mainly employed for interior and exterior use in construction (3M Industrial Adhesives and Tapes, 2015; Oil and Colour Chemists' Association, 1993). Its formulation consists of (i) an active ingredient (usually a polymer), (ii) a solvent or solvent mixture that dissolves the active ingredient and (iii) additives that enhance the final qualities of the product (e.g., reduce drying time and improve durability). The objective of the design problem is to choose the best combination of active ingredient and solvent or solvent mixture that leads to the minimum product toxicity, while maximizing the AI concentration in the blend. As a first illustrative problem, we consider a single objective optimisation formulation, where we minimize product toxicity and place a constraint on the solubility of the active ingredient in the solvent mixture. The trade-off between the different performance objectives is then explored in a multi-objective optimisation problem by maximising the solubility of AI and minimising the toxicity of the adhesive.

The active ingredients and the solvent components are selected from lists of 4 and 14 candidate compounds, respectively, derived from the literature on adhesives (Ebnesajjad & Landrock, 2015; Kinloch, 1987) and presented in Table 1. The candidate polymers employed in this work are oligomers that consist of monomer repeat units commonly used in formulating acrylic adhesives, whereas the solvent molecules in the list were chosen based on their low environmental/economic metrics and on their liquid range, ensuring that they are liquid at ambient conditions ($T = 300\ \mathrm{K}$ and $P = 1\ \mathrm{atm}$) (Ebnesajjad & Landrock, 2015; Kinloch, 1987). The polymer structures and the solvent molecules are built from a set of atom groups (functional groups) and the number of occurrences of a group g in each polymer a ($u_{a,g}$) and in each solvent compound s ($v_{s,g}$) is given in Appendix A in Tables A.1 and A.2, respectively.

Table 1: Lists of candidate polymers (active ingredients, a, set A) and solvent compounds, s (set S).

a	**Active ingredient (polymer)**	**Monomer structure**
1	3 units of methyl methacrylate (3MMA)	
2	3 units of propyl methacrylate (3PMA)	
3	4 units of ethyl acrylate (4EA)	
4	3 units of butyl acrylate (3BA)	

s	**Solvent compound**	s	**Solvent compound**
1	Acetone	8	Toluene
2	Butanone	9	Xylene
3	Hexane	10	Ethyl acetate
4	Heptane	11	Propyl acetate
5	Ethanol	12	Butyl acetate
6	2-propanol	13	Ethyl benzene
7	Butanol	14	Propyl benzene

The toxicity, τ, of the final product that needs to be minimised is approximated as shown below (Conte et al., 2011):

$$\tau = \sum_{i \in I} x_i \tau_i \tag{1}$$

where τ_i and x_i are the toxicity and the mole fraction of each component (active ingredient and solvents) in the blend, respectively. It is noted that $\tau_1 = \sum_{a \in A} \hat{y}_{1,a}\, \tau_a$ and $\tau_i = \sum_{s \in S} y_{i,s}\, \tau_s,\ \ i = 2, \dots, N_{max}$. The toxicity, τ_s (or τ_a), of the pure compounds is calculated based on the 96-h LC_{50} acute toxicity of a fish population (fathead minnow) as follows (Martin & Young, 2001):

$$\tau_{s\ (\text{or } a)} = -\log(\mathrm{LC}_{50})_{s\ (\text{or } a)}, s \in S\ (\text{or } a \in A) \tag{2}$$

where LC_{50} is the aqueous concentration (in mol/L) that causes 50% mortality in the fathead minnow. Experimental measurements are used, when available, for the acute toxicity (96-h LC_{50}) of the solvent compounds, whereas the toxicity of the active ingredients is predicted using the following group contribution method (Gao et al., 1992; Martin & Young, 2001) due to the lack of experimental data for the polymers employed in this case study:

$$\tau_a = \sum_{g \in G} u_{a,g} \acute{t}_{a,g}, a \in A \tag{3}$$

where $u_{a,g}$ and $\acute{t}_{a,g}$ are the number of occurrences and toxicity contribution of group g in the active ingredient a. Apart from low toxicity, the product to be designed should have some additional characteristics, such as good spreadability on the applied surface, strong adhesion and short drying time (Ebnesajjad & Landrock, 2015). The target properties affecting these performance criteria are the dynamic viscosity ($\eta\ [\mathrm{mPa \cdot s}]$), surface tension ($\sigma\ [\mathrm{mN/m}]$) and evaporation time ($T^{90}\ [\mathrm{s}]$) of the solvent mixture (Conte et al., 2011; Ebnesajjad & Landrock, 2015). In order to achieve good spread- and sticking-ability, the values of the dynamic viscosity and surface tension need to be within the following limits, which were adapted from the work of Conte et al. (2011) who designed paint formulations:

$$0.5 \leq \eta \leq 1.0 \tag{4}$$

$$26 \leq \sigma \leq 30 \tag{5}$$

In order to ensure the fast drying of the adhesive, the evaporation time of the solvent mixture (i.e., the time needed to evaporate 90 wt% of the solvents) is bounded as follows:

$$250 \leq T^{90} \leq 500 \tag{6}$$

We note that slightly relaxed bounds are used in equations (4), (5) and (6) compared to previous work (Cui et al., 2018), in order to avoid over-restricting the design space and to explore a wide range of blends. The dynamic viscosity, surface tension and evaporation time of the blend are calculated under the assumption of ideal mixing, as represented by the following linear mixing rule (Conte et al., 2012):

$$\xi = \sum_{i \in I} x_i \xi_i \tag{7}$$

where the variable ξ_i and ξ represent the dynamic viscosity, surface tension and evaporation time of component i in the blend $\left(\xi_i \equiv \eta_i, \sigma_i, T_i^{90}\right)$ and of the overall blend $(\xi \equiv \eta, \sigma, T^{90})$, respectively. Through equations similar to those used for toxicity, appropriate assignments are made between mixture components and solvents: $\eta_i = \eta_s,\ \sigma_i = \sigma_s$ and $T_i^{90} = T_s^{90}$, if the compound s is assigned to component i in the mixture. The values of η_s and σ_s are evaluated using experimental data (NIST, 2019; PubChem, 2019) or group contribution methods (Conte et al., 2008) when no experimental property values exist. T_s^{90} is calculated using the following equation (Conte et al., 2011; Klein et al., 1992):

$$\ln(T_s^{90}) = -0.793 \times \ln(P_s) + 12.416 \tag{8}$$

where P_s (Pa) is the vapour pressure of candidate compound s at the operating temperature $T = 300\text{K}$ and it is calculated using a group contribution method (Tu, 1994). The experimental and predicted data for the properties of pure candidate compounds are included in Table A.3 in Appendix A.

The active ingredient needs to be dissolved in the solvent mixture. It has been assigned to component 1 in the mixture and thus, the following solid-liquid equilibrium relation is used to evaluate the solubility of the polymer in solution:

$$\ln x_1 + \ln \gamma_1 = \frac{\Delta H_{fus,1}}{R}\left[\frac{1}{T_{m,1}} - \frac{1}{T}\right] \tag{9}$$

where x_1 is the mole fraction of the active ingredient (polymer) in the solvent mixture; γ_1 is the liquid phase activity coefficient of the active ingredient at composition x, temperature T and pressure P; $\Delta H_{fus,1}$ is the enthalpy of fusion of active ingredient at temperature ; R is the gas constant; and $T_{m,1}$ is the normal melting point of the active ingredient, and T is the mixture temperature (300 K). The pressure is assumed to be ambient. The enthalpy of fusion and the normal melting point are calculated using group contribution methods (Marrero & Gani, 2001). The following constraint is imposed to set a lower bound on the mole fraction of active ingredient in the mixture to achieve a functionality that surpasses a set threshold:

$$x_1 \geq x_1^L \tag{10}.$$

In order to ensure that the designed blend is stable and it does not undergo phase separation, a multi-component phase stability calculation should be embedded in the formulation. A more computationally-tractable approach consists in ensuring the miscibility of all binary pairs of solvent molecules. To this end, the following miscibility function is employed (Smith et al., 2001):

$$\frac{\partial \ln \gamma_i^{i,\check{\imath}}}{\partial x_i^{i,\check{\imath}}} + \frac{1}{x_i^{i,\check{\imath}}} \geq 0, i = 2, \dots, N_c - 1;\ \check{\imath} = i + 1, \dots, N_c \qquad (11)$$

where $\gamma_i^{i,\check{\imath}}$ is the activity coefficient of solvent component i in a binary solvent mixture of i and $\check{\imath}$, at temperature T and pressure P and $x_i^{i,\check{\imath}}$ is the mole fraction of component i in a mixture of i and $\check{\imath}$, where the ratio of the two components has been preserved. The mole fraction can be calculated as $x_i^{i,\check{\imath}} = x_i/(x_i + x_{\check{\imath}})$, with x_i and $x_{\check{\imath}}$ being the mole fractions of components i and $\check{\imath}$, respectively, in the multi-component mixture.

The activity coefficient of each designed component (active ingredient and solvents) is evaluated using the UNIFAC (Fredenslund et al., 1975) group contribution method and the model proposed by Smith et al. (2001), which is presented in a form convenient for programming, is employed in this work. These equations are presented in our earlier work (Jonuzaj et al., 2016).

The application of the proposed CAPD methodology to the design of acrylic putty is presented in the following section. All the design sets used in the formulations of this case study are shown in Table 2.

Table 2: Indices and sets for the case study.

Description	**Index**	**Set**	**Value range**
Total components in the formulation	$i, \check{\imath}$	$I, \check{I}$	$c_1, c_2, c_3, c_4, c_5, c_6$
Active ingredient in the mixture	j	J	c_1
Solvent components in the mixture	ii	II	c_2, c_3, c_4, c_5, c_6
Candidate active ingredients	a	A	$1, \dots, 4$
Pure candidate solvents	s	S	$1, \dots, 14$
Number of ingredients in the formulation	n	N	$1, \dots, 6$
Functional groups	g, k	G	$1, \dots, 11$

3.2. Problem formulation

In order to compare the proposed general methodology with the hierarchical decomposition approaches often used in the design of formulated products, two different scenarios are considered: (i) sequential design, where the active ingredient is optimised first and only the design of the corresponding solvent mixtures is investigated; and (ii) integrated design, where both active ingredient and solvent mixture are designed simultaneously. In addition, the number of components in the mixture is treated in two ways. We consider restricted design problems where we fix the number of ingredients in the blend and general design problems where the number of components is a design variable which is bounded by an upper limit. In the restricted sequential design approach, the active ingredient and the number of solvents are fixed and we design mixtures with one, two, three, four and five solvents (instances M1-M5); in the general sequential design with unknown number of solvent components, we design mixtures with a fixed active ingredient and up to five solvents (instance M6). Similarly, the integrated design includes a restricted product problem with fixed number of ingredients, where blends with one (unknown) active ingredient and one, two, three, four and five solvents are designed (instances P1-P5); and a general product problem where the number of components is a decision variable and products with one active ingredient and up to five solvent components are formulated (instance P6).

The restricted problem of the sequential design includes only disjunctions for assigning each solvent s from the given list to components i in the mixture and thus, the set of conditional constraints $h_{i,s}(x,p) \leq 0$ is formulated via the big-M approach. Here, conditional constraints represent the identity of the selected solvent, so that $n'_{ii,g}$, the number of occurrences of group g $(g \in G)$ in component ii $(ii \in II)$ is set to the corresponding value, $v_{s,g}$, in solvent s assigned to ii. Similarly, the toxicity, $\tau_{ii}, ii \in II$, viscosity, $\eta_{ii}, ii \in II$, surface tension, $\sigma_{ii}, ii \in II$ and evaporation time, $T_{ii}^{90}, ii \in II$, the molecular van der Waals volume, $r_{ii}, ii \in II$, and the molecular surface area, $q_{ii}, ii \in II$ required in the UNIFAC model, are assigned to the values for the selected solvent compound. The above linear constraints can be expressed algebraically by using the binary variable $y_{ii,s}$ and forming their convex hull (Jonuzaj & Adjiman, 2017) as follows:

$$n'_{ii,g} = \sum_{s \in S} v_{s,g}\, y_{ii,s}, ii \in II; g \in G \tag{12}$$

$$\tau_{ii} = \sum_{s \in S} \tau_s\, y_{ii,s}, ii \in II \tag{13}$$

$$\eta_{ii} = \sum_{s \in S} \eta_s\, y_{ii,s}, ii \in II \tag{14}$$

$$\sigma_{ii} = \sum_{s \in S} \sigma_s \, y_{ii,s}, ii \in II \quad (15)$$

$$T_{ii}^{90} = \sum_{s \in S} T_s^{90} \, y_{ii,s}, ii \in II \quad (16)$$

$$r_{ii} = \sum_{s \in S} r_s \, y_{ii,s}, ii \in II \quad (17)$$

$$q_{ii} = \sum_{s \in S} q_s \, y_{ii,s}, ii \in II \quad (18)$$

In the above relations the use of large big-M parameter which may lead to poor relaxations (Grossmann & Trespalacios, 2013), is avoided.

The general formulation of the sequential design (M6) consists of disjunctions for the identity and number of solvents in the mixture. The conditional constraints included in the former disjunctions are converted into mixed-integer form as described in the restricted problem of the first scenario. The conditional constraints $\tilde{F}_n(x,p) \leq 0$ included in the second set of disjunctions represent all the relevant functions that depend on the number of mixture ingredients, such as solvent property constraints (τ_{ii}, η_{ii}, σ_{ii} and T_{ii}^{90}), miscibility function (eq. (11)), UNIFAC terms to predict the activity coefficient (e.g., r_{ii} , q_{ii}), and the mole fractions (x_{ii}) of the solvents in the blend, and they are converted into mixed-integer form using the big-M approach. In the sequential design, notice that the solubility function (eq. (9)) is expressed in terms of the fixed active ingredient and thus, it does not depend on the discrete decisions.

In the integrated design (scenario (ii)), the active ingredient and the solvent mixture are determined simultaneously and thus, additional disjunctive constraints that depend on the identity of the AI are included in the restricted and general formulations of this scenario. In particular, the restricted problem consists of disjunctions for the identities of the active ingredients and the solvent molecules, whereas the general problem includes all three types of disjunctive sets (identity of the AI, identity of the solvents and number of ingredients in the blend). The conditional constraints that depend on the identity of solvents and the number of components in the mixture are converted into mixed-integer form via the big-M approach as described in the first scenario (sequential design). Similarly, disjunctive constraints for the assignment of the active ingredients in the blend include pure component property functions and UNIFAC model equations which are expressed algebraically using the binary variable $\hat{y}_{1,a}$, as described in equations (12)-(18).

All MINLP models for both scenarios (sequential and integrated design) can be found at https://zenodo.org/record/3332758, where the big-M parameter values for all

constraints, the variable bounds and the UNIFAC interaction parameters are presented in detail.

4. Results and discussion

All models for the sequential (M1-M6) and the integrated design (P1-P6) were implemented and solved in GAMS (GAMS Development Corporation) version 25.0.3, running on a single core of a dual 8 core Intel(R) Xeon(R) CPU E5-2650 machine at 3.52 GHz with 125GB of memory. SBB (Bussieck and Drud, 2001), a local branch-and-bound MINLP solver, was used to solve all problem cases and the results are discussed in the following sections.

The lower bounds on the active ingredient and solvent mole fractions in the mixture are set to $x_1^L = 0.08$ and $x_{ii}^L = 0.01, ii = 2, \dots, N_{max}$, respectively.

4.1. Sequential design

In the sequential design the problem is decomposed into smaller subproblems, where the active ingredient of the product is first defined based on performance criteria and then optimal solvent mixtures are determined. Here, the toxicity of the polymers is used as performance measure to rank the candidate active ingredients and the compound with the lowest toxicity is selected to participate in the final blend. The toxicity values, estimated using a group contribution method (Martin & Young, 2001), are 7.32, 10.00, 10.43 and 10.50 for 3MMA, 3PMA, 4EA and 3BA, respectively. Hence, the active ingredient of acrylic putty formulation is fixed to 3MMA (polymer with the lowest toxicity) when employing the sequential design approach. The results obtained when solving problems M1-M6 are summarized in Table 3.

In the restricted problem of the sequential design (M1-M5), an optimal solvent mixture with four solvent components (M4) yields the lowest product toxicity with a value of 3.078, where acetone, butanol, toluene and propyl benzene are selected as the optimal solvents that satisfy the property constraints and dissolve a sufficient amount of 3MMA. The same optimal mixture is identified in the general model (M6), confirming that the lowest toxicity is obtained with a mixture of four solvents. It can be observed that different optimal mixtures (with different solvent molecules) are identified in models with small number of components (M1-M2) compared to blends with a larger number of ingredients (M3-M6), showing the benefits of designing large general systems where different blends with improved performance can be determined.

In the restricted formulation of the sequential approach, the computational time increases with the number of components due to the increased number of variables

and equations, and in particular due to the combinatorial nature of the number of binary miscibility functions (Eq. (11)). The general model M6 requires a larger solution time compared to the restricted problems M1-M5, due to the fact that in formulation MG the number of ingredients is a decision variable and thus extra degrees of freedom are introduced to the system. However, the computational performance analysis cannot be conclusive as the models were run with a local solver and thus, the CPU times depend on the initial guesses given to each problem. Global solutions are required in order to compare the overall computational cost of all models. A global branch-and-bound algorithm, BARON version 19.3.24 (Kilinc and Sahinidis, 2018; Tawarmalani and Sahinidis, 2005), was used to achieve global solutions, but only the smallest model (M1), where one solvent is determined, was solved to global optimality. The results confirm that the optimal solution obtained with the SBB MINLP solver is a global solution. Convergence to global optimality was not reached in 86,400 CPU seconds (24 CPU hours) when larger problems (M2-M6) were solved, and no superior solutions where found in that time relative to the SBB solutions.

Table 3: Optimal product toxicity (τ), identities of the product components and their mole fractions (x_i), obtained when solving the restricted and generalised problems of formulations MR and MG. The identity of the active ingredient is chosen in advance and it is fixed to poly methyl methacrylate (3MMA).

Problem	$\boldsymbol{\tau}$	**Ingredients**	**Components**	$\boldsymbol{x_i}$	**CPU (s)**	$\boldsymbol{N^o_=}$ **of nodes**
M1 ($\boldsymbol{N_c}$=2)	4.395	c_1	3MMA	0.250	0.10	12
		c_2	Toluene	0.750		
M2 ($\boldsymbol{N_c}$=3)	3.372	c_1	3MMA	0.246	0.68	98
		c_2	Ethyl benzene	0.384		
		c_3	Ethanol	0.370		
M3 ($\boldsymbol{N_c}$=4)	3.092	c_1	3MMA	0.237	4.73	327
		c_2	Acetone	0.355		
		c_3	Ethyl benzene	0.204		
		c_4	Butanol	0.204		
M4 ($\boldsymbol{N_c}$=5)	**3.078**	c_1	3MMA	0.238	24.58	659
		c_2	Acetone	0.357		
		c_3	Butanol	0.204		
		c_4	Toluene	0.137		
		c_5	Propyl benzene	0.064		

M5 (N_c=6)	3.079	c_1	3MMA	0.238	53.62	673
		c_2	Acetone	0.356		
		c_3	Butanol	0.204		
		c_4	Toluene	0.131		
		c_5	Propyl benzene	0.061		
		c_6	Ethyl benzene	0.010		
M6 ($N_c \leq$6)	**3.078**	c_1	3MMA	0.238	681.32	3841
		c_2	Acetone	0.357		
		c_3	Butanol	0.204		
		c_4	Toluene	0.137		
		c_5	Propyl benzene	0.064		

4.2. Integrated design

In the integrated design, the identity of the active ingredient is not fixed but optimised simultaneously with the solvent mixture. Once again, we consider a restricted product design problem with fixed number of ingredients, where optimal blends with one AI and one, two, three, four and five solvents are designed (models P1-P5); and a general formulation with a variable number of ingredients, where an acrylic putty with one AI and up to five solvent components is identified (model P6). Locally optimal solutions were obtained with SBB for all problem cases and the results are presented in Table 4. Overall, the optimal product with the lowest toxicity is found in models P4 and P6, and consists of poly-propyl-methacrylate (3PMA) and 4 solvents (toluene, acetone, ethanol and xylene). The use of a solvent mixture, rather than a single solvent, leads to a product with comparatively low toxicity. It can be observed that the optimal active ingredient found in the integrated design approach is a different polymer than the one selected in the first step of the hierarchical (sequential) approach. This is because product formulations with 3PMA and solvent mixtures yield lower toxicity values than product blends where the active ingredient is fixed to 3MMA. A comparison of the different blends found in the sequential and integrated designs is presented in Figure 1, with the latter always resulting in better product performance. This behaviour is of course expected when a global solver is used since the integrated design contains additional degrees of freedom. It is encouraging that the local solver also leads to better solutions. This comparison makes it possible to quantify the benefits derived from optimising all decision variables in general product design problems compared to

the traditional decomposition-based approaches where the AI is fixed *a priori*. The reduction in toxicity observed ranges from 8 to 12%, depending on the number of components. Compounded with decrease observed when varying the total number of components, the best adhesive formulation (integrated design with 5 components) is nearly 40% less toxic than the best two-component, sequentially-designed formulation.

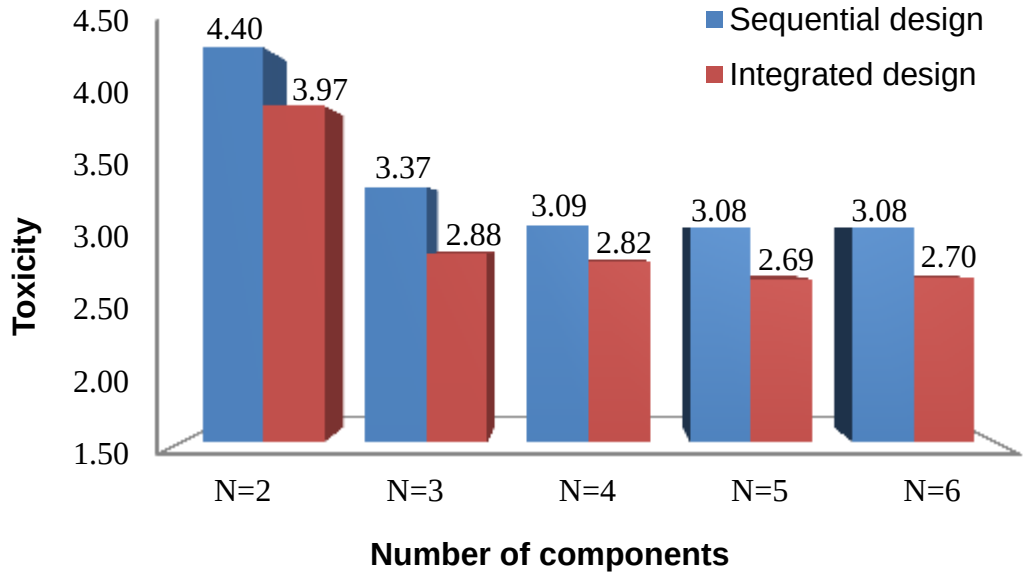


Figure 1: Toxicity of adhesive products with different number of ingredients. Different product formulations are obtained when using integrated and sequential design approaches.

Similar to the sequential design, the CPU time increases when more ingredients are added to the blend (i.e., problem size increases). The restricted models, P1-P5, require less computational time than the general problem P6. In practice, however, formulating a single generic problem (P6) requires less user input than formulating and solving a series of restricted problems. BARON version 19.3.24 (Kilinc and Sahinidis, 2018; Tawarmalani and Sahinidis, 2005) is also used here to obtain global solutions. The smallest problem (P1), where one active ingredient and one solvent are determined, is solved and the results verify the global optimality of the solution obtained with the local MINLP solver. Problems P2-P6 did not converge to global optimality in 86,400 CPU seconds (24 CPU hours), but no improved solution was found during this time.

Table 4: Optimal product toxicity (τ), identities and composition (x_i) of AI and solvent mixtures, obtained when solving the restricted and general integrated design problems.

Problem	τ	**Ingredients**	**Components**	x_i	**CPU (s)**	$N_{=}^{o}$ **of nodes**
P1 (N_c=2)	3.966	c_1	3PMA	0.083	0.16	38
		c_2	Toluene	0.917		
P2 (N_c=3)	2.882	c_1	3PMA	0.082	2.93	476
		c_2	Toluene	0.546		
		c_3	Ethanol	0.372		
P3 (N_c=4)	2.822	c_1	3PMA	0.082	18.11	1279
		c_2	Toluene	0.517		
		c_3	Ethanol	0.327		
		c_4	Acetone	0.074		
P4 (N_c=5)	**2.692**	c_1	3PMA	0.082	129.57	3816
		c_2	Toluene	0.357		
		c_3	Acetone	0.374		
		c_4	Ethanol	0.115		
		c_5	Xylene	0.071		
P5 (N_c=6)	2.701	c_1	3PMA	0.082	709.59	9712
		c_2	Toluene	0.362		
		c_3	Acetone	0.364		
		c_4	Ethanol	0.120		
		c_5	Xylene	0.062		
		c_6	Ethyl benzene	0.010		
P6 ($N_c \leq$6)	**2.692**	c_1	3PMA	0.082	2706.70	12008
		c_2	Toluene	0.357		
		c_3	Acetone	0.374		
		c_4	Ethanol	0.115		
		c_5	Xylene	0.071		

4.3. List of optimal solutions

The design of blends with multiple components and the use of integrated general models is characterized by large design spaces. For instance, there are 8,008 combinations of possible blends (at one composition) when we design an acrylic putty with one active ingredient selected from a list of 4 polymers and five solvent components chosen from a list of 14 candidates. Hence, high performance or desired product attributes can be achieved with different combinations of blends. To identify multiple high-performance blends for the formulation of an acrylic putty with low toxicity values, the following integer cut (Sahinidis et al., 2003) is introduced in the general problem P6:

$$\sum_{i\in I}\sum_{g\in G}\left|\acute{n}_{i,g}-\acute{n}_{i,g,l}^{sol}\right|\geq 1, l=1,\ldots,N_l \tag{19}$$

where $\acute{n}_{i,g,l}^{sol}$ is the optimal number of occurrences of group g in component i generated in previous solutions $l=1,\ldots,N_l$. The twenty best solutions obtained with the general models of the integrated design are ranked in ascending order and presented in Table 5.

A diverse list of optimal blends with different number, identity and composition of ingredients is obtained. Most optimal formulations that yield the lowest toxicity values consist of 3PMA and various solvent mixtures with one, two, three or four solvent components. 3MMA is identified as the optimal active ingredients in three blends, whereas blends with 3BA or 4EA yield higher toxicity values than the ones presented in the first 20 solutions. The optimal blends of 3PMA and 1, 2, 3, and 4 solvents (obtained in models P1 - P4) and the blend of 3MMA and 2 solvents (obtained in model M2) are also generated with integer cuts in the general model P6 (positions 1, 7, 11, 20 and 15 in Table 5, respectively). However, optimal product formulations obtained in models M3 - M5 and P5, which have toxicity values falling within the range values included in Table 5, were not found in the first 20 runs of the general problem when introducing integer cuts. This indicates that on at least four occasions, the SBB solver converged to a local solution.

Table 5: Ranking of optimal solutions generated with integer cuts. Optimal product toxicity (τ), optimal number, identities and composition (x_i) of product ingredients, and optimal proportion of solvent mixture ($\%\, s_{ii}$) obtained for the general mixture problem (P6) of case study when including integer cuts.

Rank	**Blend**	τ	**AI**	x_{c_1}	**Solvents**	x_{ii}	$\%\, s_{ii}$
1	1 AI + 4 solvents	2.692	3PMA	0.082	Toluene	0.357	38.93
					Acetone	0.374	40.79
					Ethanol	0.115	12.54
					Xylene	0.071	7.74
2	1 AI + 4 solvents	2.719	3PMA	0.082	Toluene	0.425	46.30
					Acetone	0.317	34.53
					Ethanol	0.150	16.34
					Propyl benzene	0.026	2.83
3	1 AI + 4 solvents	2.750	3PMA	0.082	Toluene	0.399	43.46
					Acetone	0.275	29.96
					Ethanol	0.177	19.28
					Ethyl benzene	0.067	7.30
4	1 AI + 4 solvents	2.773	3PMA	0.082	Acetone	0.444	48.37
					Toluene	0.365	39.76
					Xylene	0.080	8.71
					2-propanol	0.029	3.16
5	1 AI + 4 solvents	2.779	3PMA	0.082	Toluene	0.469	51.09
					Acetone	0.250	27.23
					Ethanol	0.163	17.76
					Butanol	0.036	3.92
6	1 AI + 4 solvents	2.807	3PMA	0.082	Acetone	0.442	48.15
					Toluene	0.401	43.68
					Xylene	0.054	5.88
					Butanol	0.021	2.29
7	1 AI + 3 solvents	2.822	3PMA	0.082	Toluene	0.517	56.32
					Ethanol	0.327	35.62
					Acetone	0.074	8.06
8	1 AI + 3 solvents	2.861	3PMA	0.082	Toluene	0.474	51.63
					Acetone	0.387	42.16
					Butanol	0.057	6.21

Rank	Blend	τ	AI	x_{c_1}	Solvents	x_{ii}	% s_{ii}
9	1 AI + 3 solvents	2.875	3PMA	0.082	Toluene	0.510	55.56
					Ethanol	0.369	40.20
					Hexane	0.039	4.25
10	1 AI + 3 solvents	2.882	3PMA	0.082	Toluene	0.540	58.82
					Ethanol	0.357	38.89
					Butanone	0.021	2.29
11	1 AI + 2 solvents	2.882	3PMA	0.082	Toluene	0.546	59.48
					Ethanol	0.372	40.52
12	1 AI + 3 solvents	2.887	3PMA	0.082	Toluene	0.537	58.50
					Ethanol	0.371	40.41
					Xylene	0.010	1.09
13	1 AI + 2 solvents	3.330	3PMA	0.088	Toluene	0.658	72.15
					2-propanol	0.254	27.85
14	1 AI + 2 solvents	3.366	3PMA	0.085	Toluene	0.675	73.77
					Acetone	0.240	26.23
15	1 AI + 2 solvents	3.372	3MMA	0.246	Ethyl benzene	0.384	50.93
					Ethanol	0.370	49.07
16	1 AI + 2 solvents	3.496	3MMA	0.233	Butanone	0.429	55.93
					Ethyl benzene	0.338	44.07
17	1 AI + 2 solvents	3.546	3MMA	0.241	Ethyl benzene	0.415	54.68
					Acetone	0.344	45.32
18	1 AI + 2 solvents	3.592	3PMA	0.082	Toluene	0.740	80.61
					Butanone	0.178	19.39
19	1 AI + 2 solvents	3.630	3PMA	0.082	Ethyl acetate	0.562	61.22
					Xylene	0.356	38.78
20	1 AI + 1 solvent	3.966	3PMA	0.083	Toluene	0.917	100.00

4.4. Pareto optimal solutions

The design of environmentally benign acrylic adhesives with respect to one individual performance measure (minimizing toxicity) does not always lead to blends with optimal overall performance. By minimizing the toxicity of the designed blend we obtain product formulations with low concentrations of the active ingredient, as the relative amounts of polymer and solvents in the blend affect the toxicity level. Hence, it is

important to explore the trade-offs between the two competing performance objectives of maximizing solubility while minimizing toxicity (i.e., $\max x_1$, $\min \tau$) in order to obtain optimal blends with low toxicity values and high content of active ingredient. This can be achieved through a multiobjective optimization formulation of the product design problem, which makes it possible to identify a set of Pareto optimal solutions (Chankong & Haimes, 1983; Erfani & Utyuzhnikov, 2011; Papadopoulos et al., 2013). Here, a set of Pareto optimum blends is obtained using the ε-constrained method (Chankong & Haimes, 1983), where one objective is optimised and the other one(s) are bounded by given target values. Hence, the objective function of the general model P6 is modified to maximize the solubility of the active ingredient (i.e., $\max x_1$) while constraining the toxicity of the product with varying upper bounds. The upper limit on the product toxicity is varied from 2.5 to 7 with a step-size of 0.2. The SBB solver is once again used to compute the solutions, so we note that the Pareto front obtained is a pessimistic approximation of the trade-off for any point that is a local but not global solution. The Pareto front solutions (trade-off curve) are shown in Figure 2 and the list of optimal blends (15 blends with one optimal AI and various solvent mixtures) is presented in Table 6.

The (approximate) set of Pareto optimal solutions shown in Figure 2 highlights the trade-offs between the two competing objectives, since we observe that a decrease in product toxicity is directly connected to a decline in the solubility of the active ingredient in the solvent mixture. The results reveal that there are discrete changes in the list of optimal blends (different active ingredients, solvent compounds, number of components and their composition in the product blend), which leads to large areas of discontinuity in the Pareto front. Three main areas of optimal solutions with distinct active ingredients can be observed, where optimal formulations of 3PMA (Region 1), 3MMA (Region 2) and 3BA (Region 3) and different solvent mixtures yield low, medium and high toxicity and solubility values, respectively (cf. Figure 2). Therefore, the optimal solutions of the second region (blends of 3MMA and different solvent mixtures) seem to represent the best compromise between the two objectives. As seen in Table 6, optimal product blends with multiple ingredients are identified in the first and second regions (products with 3PMA and 3MMA, respectively). This agrees with the results of single-objective approach, where lower toxicity is achieved with multicomponent blends of 4, 5 and 6 ingredients. Furthermore, the same optimal solvent molecules are identified with both single and multiobjective approaches.

Comparing the computational performance of the two approaches, the general problem of the multiobjective formulation, where the solubility is maximized and toxicity is constrained, appears to be more effective than the general model P6 of the single

objective problem. In addition, CPU time decreases dramatically when moving from region one to regions two and three. We note, however, that this analysis is based on local solutions and global solutions are required in order to compare the overall computational cost of all models.

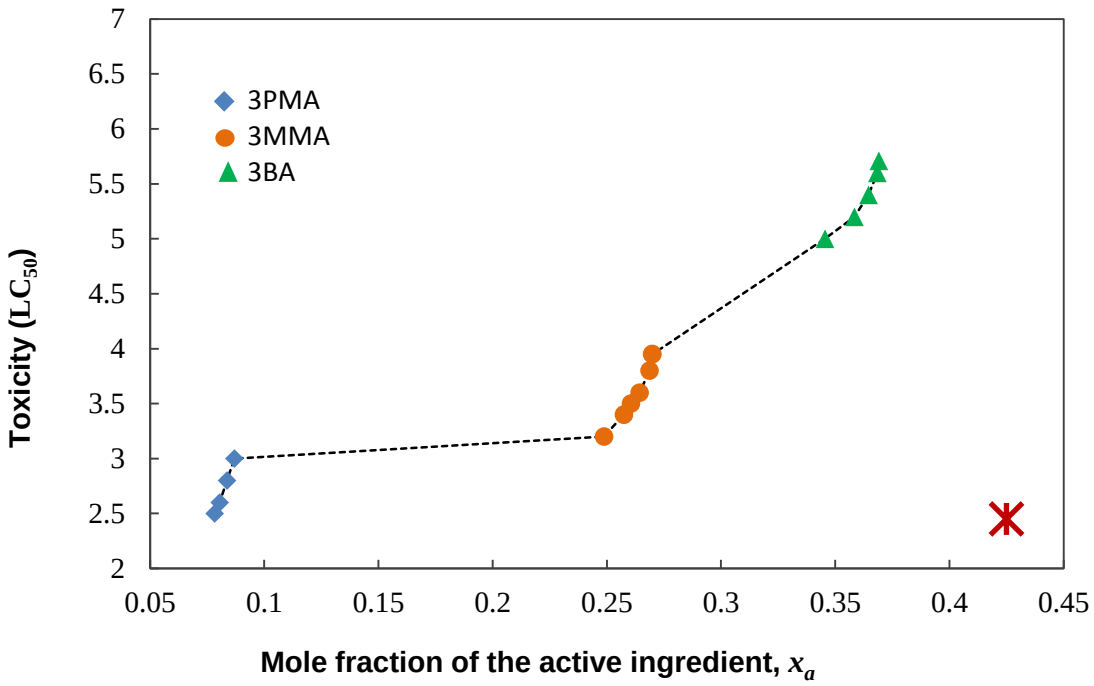


Figure 2: Pareto optimal solutions obtained by when solving the general integrated design problem with two competing objectives, product toxicity and solubility of the active ingredient. The dashed line is shown to aid visualization while the star indicates the most desirable area, where AI solubility is maximized and product toxicity is minimized. Region 1 corresponds to solutions containing 3PMA (diamonds), Region 2 to solutions containing 3MMA (circles) and Region 3 to solutions containing 3BA (triangles).

Table 6 - Pareto optimal solutions obtained by when solving the general integrated design problem with two competing objectives, product toxicity and solubility of the active ingredient. Optimal product toxicity (τ), solubility of the active ingredient (x_1) in the solvent mixture, optimal identities of active ingredient and solvents, optimal composition (x_i) of product ingredients, and optimal proportion of solvent mixture ($\%\ s_{ii}$) obtained when solving the general problem of the integrated design.

Blend	τ	x_1	AI	Solvents	x_{ii}	$\%\ s_{ii}$	CPU (s)
N_c=6	2.500	0.078	3PMA	Acetone	0.495	53.75	642.15
				Toluene	0.261	28.34	

				Xylene	0.091	9.88	
				Ethanol	0.059	6.41	
				Butanol	0.015	1.63	
N_c=5	2.600	0.081	3PMA	Acetone	0.435	47.33	949.98
				Toluene	0.303	32.97	
				Ethanol	0.092	10.01	
				Xylene	0.089	9.68	
N_c=6	2.800	0.084	3PMA	Toluene	0.420	45.85	491.04
				Acetone	0.302	32.97	
				Ethanol	0.143	15.61	
				Xylene	0.050	5.46	
				Hexane	0.001	0.11	
N_c=5	3.000	0.087	3PMA	Toluene	0.540	59.15	230.34
				Ethanol	0.196	21.47	
				Acetone	0.167	18.29	
				Xylene	0.010	1.10	
N_c=4	3.200	0.249	3MMA	Acetone	0.406	54.06	34.28
				Toluene	0.264	35.15	
				Butanol	0.081	10.79	
N_c=4	3.400	0.257	3MMA	Toluene	0.386	51.95	51.85
				Ethanol	0.330	44.41	
				Acetone	0.027	3.63	
N_c=3	3.500	0.261	3MMA	Toluene	0.416	56.29	17.76
				Ethanol	0.323	43.71	
N_c=4	3.600	0.264	3MMA	Toluene	0.436	59.24	19.19
				Ethanol	0.245	33.29	
				Acetone	0.055	7.47	
N_c=3	3.800	0.269	3MMA	Toluene	0.501	68.54	0.83
				Ethanol	0.230	31.46	
N_c=3	3.950	0.270	3MMA	Toluene	0.550	75.34	23.87
				Ethanol	0.180	24.66	
N_c=3	5.000	0.345	3BA	Ethanol	0.319	48.70	18.53
				Ethyl benzene	0.336	51.30	
N_c=3	5.200	0.358	3BA	Toluene	0.380	59.19	9.26
				Ethanol	0.262	40.81	
N_c=3	5.400	0.365	3BA	Toluene	0.428	67.30	1.77
				Ethanol	0.208	32.70	
N_c=3	5.600	0.369	3BA	Toluene	0.483	76.55	22.30
				Ethanol	0.148	23.45	
N_c=3	5.710	0.369	3BA	Toluene	0.519	82.25	9.05
				Ethanol	0.112	17.75	

5. Conclusions

A general and comprehensive mathematical formulation for the design of environmentally benign solvent-based adhesive products based on a computer aided product design (CAPD) framework has been presented in this work. Within this systematic approach, the number of product constituents, the identities of the components (i.e., active ingredients and solvents) and their compositions were determined simultaneously. Generalized disjunctive programming was employed to formulate the discrete decisions in the problem. A general integrated design formulation was developed to make it possible to identify the best combination of AI and the solvent mixture, alleviating the need to decompose the problem in sequential steps in order to specify the identity of each type of chemical.

The general methodology was applied successfully to the design of acrylic adhesives, where optimal acrylic putty formulations with one active ingredient and up to 5 solvents were determined. The results showed that better performance was achieved with multicomponent formulations (blends with one active ingredient and solvent mixtures with four components). In addition, comparison of the proposed integrated design problem and the traditional hierarchical approach (sequential design) enable the quantification of the benefits of undertaking a simultaneous design of the AI and solvent mixtures. Reductions of 8 to 12% in toxicity were achieved compared to the adhesive products obtained when fixing the active ingredient *a priori*. Importantly, high-performing products with a different AI were identified with the integrated approach. A ranked list of promising designs, which can serve as a guide to experiments, was generated by adding integer cuts to the general integrated formulation, showing that the top-ranked products are diverse in terms of the number of mixture ingredients, the identity of the solvents and their composition. Finally, significant trade-offs between competing performance objectives were highlighted through a set of Pareto optimal solutions, where different blends were evaluated based on toxicity and active ingredient solubility values.

Given the insights and varied solutions generated by the proposed integrated design framework, future efforts will be directed at extending the applicability and reliability of the approach. First, the group contribution methods employed to predict pure component and mixture properties are subject to uncertainty, with the potential to over- or under-estimate the predicted performance of the formulated products. Therefore, future work will focus on conducting uncertainty analysis of the product design

formulation in order to achieve more robust designs. Furthermore, a post-design verification phase should be investigated, where the performance of the final product with all ingredients (including additives) is evaluated. Finally, the development of suitable algorithms and solution strategies to achieve global solutions should be considered, as should the case of multiobjective optimisation problems with more than two objectives (Papadopoulos et al., 2016, Lee et al. 2019).

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Appendix

Appendix A. Functional groups and solvent properties used in the design of the acrylic putty

Table A.1: $u_{a,g}$ number of group of type g in an active ingredient a.

$u_{a,g}$	CH_3	CH_2	CH	C	COO
3MMA	6	3		3	3
3PMA	6	9		3	3

4EA	4	8	4		4
3BA	3	12	3		3

Table A.2: $v_{s,g}$ number of group of type g in a solvent s.

$v_{s,g}$	CH_3	CH_2	CH	aCH	$aCCH_3$	$aCCH_2$	CH_3COO	OH	CH_3CO
Hexane	2	4							
Heptane	2	5							
Ethylacetate	1	1					1		
Butylacetate	1	3					1		
Toluene				5	1				
Xylene				4	2				
Ethyl benzene	1			5		1			
Propyl benzene	1	1		5		1			
Ethanol	1	1						1	
2-propanol	2		1					1	
Butanol	1	3						1	
Acetone	1								1
Butanone	1	1							1
Propyl acetate	1	2					1		

Table A.3: Experimental and calculated solvent property values. The units of measure are: τ_s [mol/L], η_s [mPa · s], σ_s [mN/m] and T_s^{90} [s].

Solvents	$\boldsymbol{\tau_s}$	$\boldsymbol{\eta_s}$	$\boldsymbol{\sigma_s}$	$\boldsymbol{T_s^{90}}$
Hexane	3.02*	0.33	17.89	89.05
Heptane	3.50	0.37*	19.66	187.98

Ethyl acetate	2.58	0.42	24.00	136.43
Butyl acetate	3.81	0.69	24.71	561.54
Toluene	3.42	0.60	27.73	316.55
Xylene	3.81	0.62*	28.08*	1001.37
Ethyl benzene	3.59	0.67	27.93*	790.15
Propyl benzene	3.76*	0.85*	28.55*	1834.97
Ethanol	0.52	1.07	21.97	187.20
2-propanol	0.78	2.04	20.93	224.86
Butanol	1.59	2.54	24.93	969.94
Acetone	0.85	0.30*	23.35*	62.42
Butanone	1.35	0.37*	23.97	130.88
Propyl acetate	3.23	0.54	24.30	274.47

*Calculated property values using group contribution methods (Conte et al., 2008; Martin & Young, 2001).