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INTEGRATED DESIGN METHODOLOGY: A PROPOSAL FOR A SCIENTIFIC RESEARCH-BASED DESIGN PROCESS FOR STIMULI-RESPONSIVE PRODUCTS

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ABSTRACT

Complex global problems, such as sustainable crop production, where conventional products do not fully solve the problem due to their low efficacy and negative environmental impact, require rationally designed products. Generally, these products are based on efficient technologies and stimuli-responsive and high-performance materials. Considering the product design approach with a science-based approach such as drug development through QbD. We propose to merge the most relevant elements of these approaches in an integrated design methodology. Regarding the conceptual analysis, we propose two phases: initially, an early phase with conceptual solutions, followed by an advanced phase based on QbD elements to define the research hypothesis. Hence, optimal product conditions defined in the design space must comply with the required performance of the stimuli-responsive product. So, with this proposed integration we pretend to potentialize and strengthen the established tools for product design, achieving an advanced and robust design methodology.

Keywords: Quality by Design - QbD, Intelligent materials, Research methodologies and methods, Conceptual design, science-based design process

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1 INTRODUCTION

Throughout human history, advancements in materials have been instrumental in improving the quality of life. Today, we are in a new era of smart or stimuli-responsive materials, which have the potential to revolutionize conventional products. However, the design methodologies developed so far can be leveraged for products that emerge as customized solutions with high added value. By integrating science, promoting research, and encouraging the application of stimuli-responsive materials, we can design and create products that offer precise solutions to highly complex global problems.

An illustration of such a situation is the urgent concern about increasing food demand, population growth, and fertilizer shortages that affect sustainable crop production. Historically, agricultural problems have been addressed through crop management practices. But the products used, such as limes for soil acidity correction and fertilizers for plant nutrition, have shown low efficiency and high product losses, leading to significant soil problems. In addition, limes and fertilizers must be applied separately in the soil due to their antagonistic interactions decreasing the product's effectiveness. Considering that, precision agriculture came out in recent years, requiring innovative solutions that meet soil constraints and specific plant needs to overcome ecological problems. Specialized products are necessary to enhance and optimize their performance, as conventional and simple products are unable to meet these conditions.

In recent years, there has been a growing interest in stimuli-responsive controlled-release systems (CRS) that can protect, transport, and deliver active compounds with a quantifiable, predictable, and controllable delivery profile in a specific medium (Vega-Vásquez, Mosier and Irudayaraj, 2020). Initially, CRSs were developed for drug delivery and their use has been extended to pharmaceutical products, food applications, and soil fertilization (Cao *et al.*, 2014; Eghbal and Choudhary, 2018; Sikder *et al.*, 2021). Research on CRSs as pharmaceutical products have been growing significantly, although their application in agriculture is still incipient. Although slow- and controlled-delivery fertilizers similar to drug-release systems are commercially available, products related to liming practices have not been studied sufficiently to improve their efficiency for soil acidity correction.

Despite the interest in precision agriculture, as far as it is known, no solutions meet at least two distinct functions (liming and fertilization) with antagonistic active compounds applied to the soil from a single product with dual action. These solutions require accurate design due to their complexity, structure, specific function, and expected performance (Cross, 2021). New design methodologies are necessary especially for products that show unique features and functions such as smart products related to the 4.0 Industry such as those utilizing artificial intelligence, the internet of things, nanotechnology, and others (Anderl, Picard and Albrecht, 2013). These stimuli-responsive products have several user benefits, such as easy interaction, accessibility, and customization. As a result, their attributes can be tailored, considering the user's needs (Pereira Pessôa and Jauregui Becker, 2020). For that reason, stimuli-responsive products could be complex and technologically unfeasible and thus require advanced design methodologies that incorporate enabled and advanced technologies (Qutb, 2020). A well-designed product is necessary to meet user requirements and achieve the benefits of stimuli-responsive products. (Pereira Pessôa and Jauregui Becker, 2020). Therefore, design significantly influences the development of smart products.

Scientific research and product design share the goal of achieving a product with specific technical characteristics that support its functionality. Based on this premise, scientific research products are susceptible to being designed from the basic principles of product design methodology. Nevertheless, some authors state that design methodology strongly differs from scientific methodology due to rigorous and abstract explanations of sound science (Cross, Naughton and Walker, 1981; Rodgers and Milton, 2013). Hence, it is necessary to consider that scientific research are embedded in the product in many ways. During the scientific research process, the researcher's common trend is to evaluate a previously conceived hypothesis about the research product, but the pathway or the methodology to obtain that initial idea is often not reported. Therefore, the absence of a systematic way in which the researcher approaches to that initial hypothesis is considered a research gap. Based on these concerns, we identified two approaches that could be related to CRS design: the product design methodology as a design approach; and the Quality by Design (QbD) from pharmacological product development as a scientific approach.

From the design approach, the product design methodology combines technical knowledge and creativity to satisfy user needs through proposing solutions (Ulrich, 2003; Boeijen *et al.*, 2013; Ulrich, Eppinger and Yang, 2019). The design process, based on the user-centered aspect, should have structured stages, explore innovative solutions and be applicable for a wide range of products. However, the product design process may be fragile if the design methodology does not consider the analysis of higher-level requirements for the product context and scientific experimentation. Therefore, using established product design tools, potentialized from a scientific approach, can result in a robust methodology for developing smart agricultural solutions.

From the scientific approach, QbD concepts are included in the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use considerations, guideline ICH Q8, and are established by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) as statements for the quality assessment of new pharmacological products (FDA Services U.S. Department of Health and Human, 2009; European Medicines Agency, 2014). The QbD approach emphasizes the importance of designing pharmacological product quality from the beginning stages of development and involves understanding the product profile, critical attributes, and processing parameters based on scientific knowledge.

QbD states that pharmacological product quality must be created from the design stage. QbD concepts are included in the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use considerations, guideline ICH Q8, and are established by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) as statements for the quality assessment of new pharmacological products (FDA Services U.S. Department of Health and Human, 2009; European Medicines Agency, 2014). The QbD approach encourages knowing the product profile, critical attributes, and processing parameters based on scientific knowledge.

While the ICH guidelines do not provide a specific design methodology for pharmacological or CRS products, they outline the key aspects that researchers should consider for developing such products. QbD concepts are essential in defining the quality profile, critical material attributes, and process attributes for the drug dosage form, covering all technical characteristics that a product must have based on scientific knowledge (FDA Services U.S. Department of Health and Human, 2009; European Medicines Agency, 2014; Li, Qiao and Wu, 2017). The QbD approach also encourages the use of Design of Experiments as a tool to analyze effects and interactions between the main factors described in the overall profile for the pharmacological product, identifying the optimal conditions and boundaries for the Design Space, an operational region for product quality assurance. Although QbD concepts have been implemented in food and pharmacological products such as tablets (Su *et al.*, 2019), vaccines (Haas *et al.*, 2014), ocular drugs (Rathod, Shah and Dave, 2020), nasal sprays (Pallagi *et al.*, 2015), among other drug delivery systems, there is little evidence of QbD implementation in agricultural products. While many studies have applied the QbD approach to previously created and evaluated products to achieve the design space, few have reached implementation levels up to large-scale production phases.

We consider that scientific research, predefined objectives, and QbD concepts design space features offer key benefits that have the potential to be implemented in general product development, despite QbD not being a design methodology but rather an FDA application form. However, the question remains: how can researchers arrive at a solution concept? Is it possible to apply a design methodology for an accurate solution? This prompts the question of whether it is feasible to develop an integrated product design methodology that incorporates QbD concepts. So far, there have been no reports of an integral design methodology or any other application of a design methodology in science-based product research. Furthermore, QbD concepts have not yet been integrated into the design methodology for the pharmaceutical or agricultural products.

This study aims to integrate features from both approaches -design methodology and QbD- to propose a new Integrated design methodology, called **Integrated Design Methodology**, that can lead to precise solutions and innovative products by following systematic steps based on design, scientific knowledge, and experimental development. Also, this Integrated Design Methodology could be applied not only in CRSs but could be extended to design other product types as smart and precise solutions in food engineering, agriculture, and many other fields.

2 INTEGRATED DESIGN METHODOLOGY

The Pahl & Beitz design methodology has been well accepted and used in some reports as a basis for extending new product design (Borges and Rodrigues, 2010; Weiss and Hari, 2015). Our proposed Integrated Design Methodology builds on the Pahl & Beitz framework, with a focus on the need to integrate design methodology with QbD concepts. These concepts are guided by research and scientific knowledge including biology, pharmacology, medicine, materials, and manufacturing processes. Our Integrated Design Methodology proposal aims to facilitate and make the design process visible in scientific research to obtain an accurate solution or product. The methodology, its stages, and related activities are presented in Figure 1, in which, the new proposed elements and stages are highlighted.

2.1 Problem delimitation

The initial stage of the proposed design methodology involves compiling context and background information related to the identified need, idea, or problem. To capture the need effectively, it is crucial to establish the main requirements, demands, and desirable attributes from the user's perspective. Our proposed design methodology involves a change in the way of analysing the user, as outlined in user- or human-centred design methodologies (Cooley, 2000). For example, in the case of agricultural solutions, the user would not be the farmer who applies the product to the soil, but the plant-soil system as the delivery media for the active compound. This change in the user framework reflects the product-user interaction, problem specificity, and advanced technical needs that increase the scientific level of product development, since it will have a strong interaction with the soil-plant system rather than with the farmer. Thus, the farmer's needs will be accomplished indirectly if the product fulfils the technical requirements of the plant-soil system. Defining the user is a critical element to consider at the start of this methodology. Furthermore, this will expand the solution possibilities to other paths by applying the top-down strategy, which includes a wide solution range of solutions to screen conceptual solutions against the selection criteria.

The problem delimitation stage is crucial in establishing a theoretical basis for the problem context and background. Although user surveys and designer experience are typically used in this stage of the design methodology, it can lead to a subjective process. However, understanding the problem context through a scientific approach is essential because the plant-soil system cannot communicate its needs. Therefore, it is highly recommended to search for scientific knowledge and theory about the problem to obtain a well-defined problem statement and context.

2.2 Overall specifications

The general problem statement specifications can be broad and unspecific. Therefore, breaking down the problem into subproblems can make the process clearer and more manageable. The starting point is to reveal each user requirement and analyse all product considerations. The product design specification (PDS) matrix becomes a helpful tool to examine and translate the initial description of user needs into technical requirements. Each element could be considered from Pugh's list which includes size, processes, environment, disposal, quantity, and more product specifications (Ulrich, 2003). We recommend including microbiological, biological, physicochemical, and other aspects concerning the specific application, such as whether the product will affect the microbiota surrounding the plant roots and whether it will cause phytotoxicity to the plant. These are fundamental aspects that must be considered.

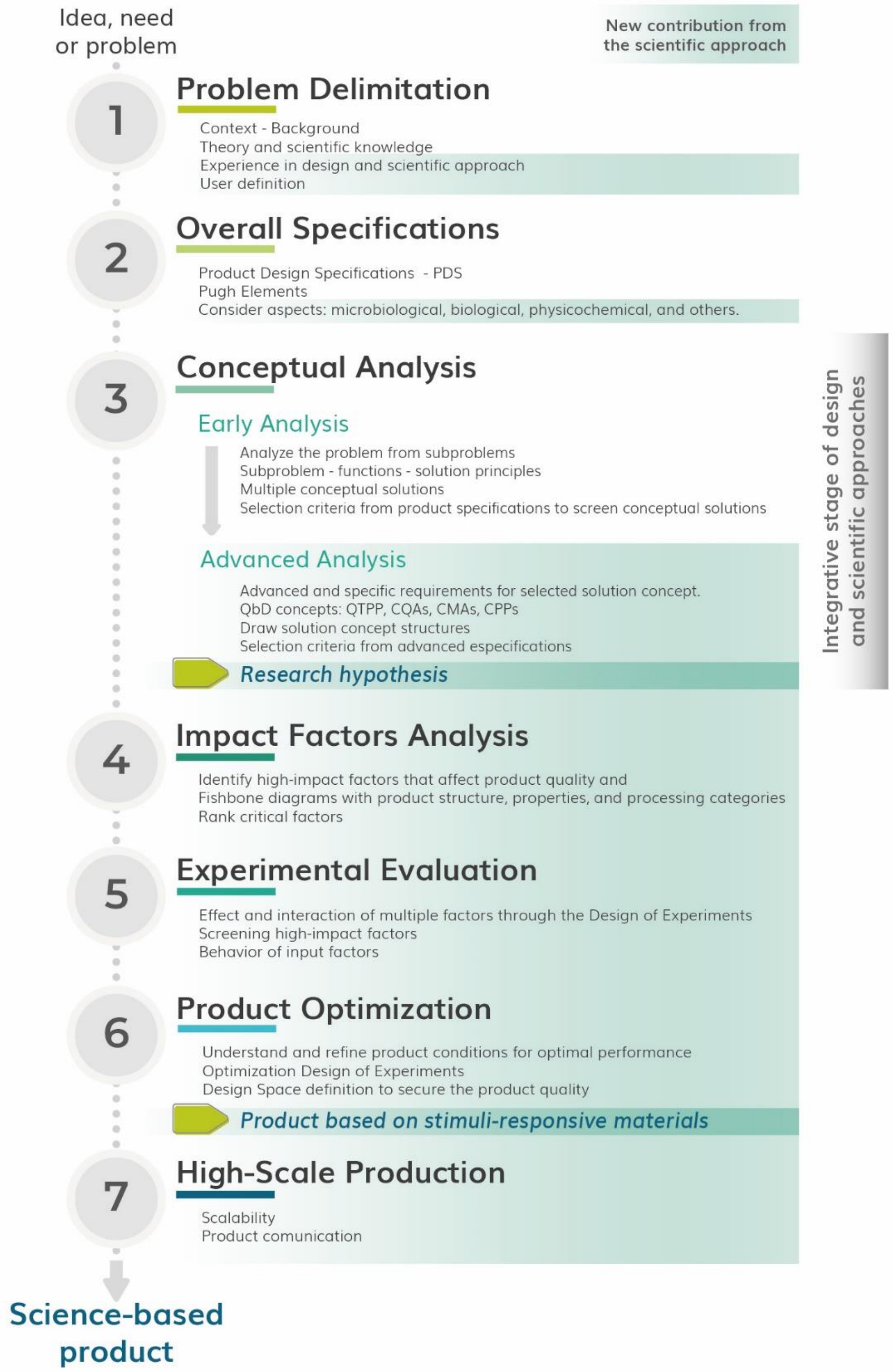

Figure 1. Structure, stages, and activities of the proposed integrated design methodology.

At this stage, it is crucial to interpret technical specifications, background, and data to define the product's technical limits. For example, if the product's requirement is to have a higher nutrient delivery efficiency, it means that the product should have a high absorption efficiency in the plant-soil system. The specification limits should be determined against the conventional products efficiency, which have a current absorption efficiency between 30% and 50% (López-Valdez and Fernández-Luqueño, 2014; FAO, 2019; Lawrencia *et al.*, 2021). A thorough understanding of the context and well-translated user needs into input specifications are essential for the design process and product performance.

2.3 Conceptual analysis

The Integrated Design Methodology proposes two broad phases: early and advanced analysis, due to the highly conceptual solution´s complexity and specificity. The schematic representation of this stage is observed in Figure 2.

2.3.1 *Early conceptual analysis*

The proposed early phase aims to screen all possible solution concepts. Each subproblem must fulfill not only one but two or more functions the product must meet. At this divergent stage, the product design methodology suggests that each problem should correspond to several solution principles (Boeijen et al., 2013), but in addition, these solutions should be supported by specialized literature. The connection between identified problems, expected functions, and well-defined solution principles will be crucial to obtain a wide solution concept variety, by combining solution principles. Figure 2 shows this early conceptual analysis like a funnel, in which the definition and analysis of subproblems, functions, and solution principles, will sort the solution concepts represented here in a spherical form. All these possible solution concepts must be analysed and sifted out through the perspective of the product requirements and constraints, which are transformed here in the product strategy selection criteria like the narrowest part of the funnel. The selected solution concept Figure 2. Schematic representation of the conceptual analysis stage divided into two phases early and advanced conceptual analysis.in this stage is still broad and requires more specificity.

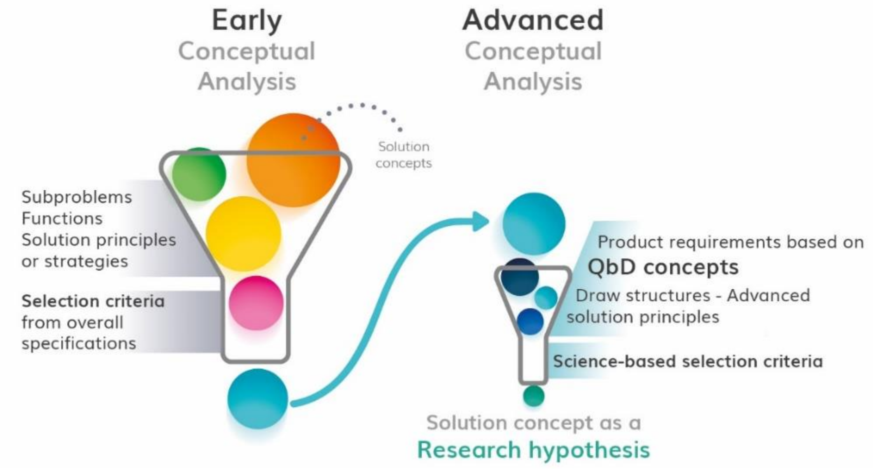

Figure 2. Schematic representation of the conceptual analysis stage divided into two phases early and advanced conceptual analysis.

2.3.2 *Advanced conceptual analysis*

The Advanced phase delves into the details of the product characteristics by using a scientific approach to consider the selected solution concept. To illustrate this, imagine selecting the colour orange as the only option to paint a sunset, which is the broad solution concept. However, there are numerous hues and shades related to a sunset, and similarly, there are many ways to evaluate a CRS solution concept based on various factors like materials, structure, release profile, and other attributes that vary according to the intended application. Figure 2 shows how these two phases can be envisioned as sequential funnels, with the advanced analysis phase being reliant on the initial phase to filter the solution concept. Consequently, the conceptual analysis helps to narrow down the concept and gain a thorough understanding of all product details.

The Advanced Analysis records all additional and specific requirements of the selected solution concept identified in the Early Analysis stage, but now considers the main QbD concepts to go deep and detail the solution concept based on scientific knowledge. The Advanced Analysis phase integrates the following QbD concepts (Yu, 2008; Zhang and Mao, 2017):

- **Quality Target Product Profile** (QTPP) refers to ideal technical characteristics a product must achieve, according to the active compound delivery form, such as delivery system type and attributes, physicochemical factors affecting compound delivery, dissolution profile, distribution method, and specific function, and more (Rathore and Kapoor, 2016; Zhang and Mao, 2017).

- **Critical Quality Attributes** (CQAs) are the fundamental product characteristics derived from QTPP that must be established within a suitable range to assure product quality (FDA Services U.S. Department of Health and Human, 2009; European Medicines Agency, 2014). CQA examples are particle size distribution, polydispersity, solubility, stability, crystalline structure, and more.
- **Critical Material Attributes** (CMAs) refer to the raw material characteristics to ensure the desired quality of the final product, including include biodegradability, viscosity, density, and more (Pallagi *et al.*, 2015).
- **Critical Process Parameters** (CPPs) refer to parameters that must be validated or adjusted during the manufacturing process and that influence the product quality, purity, and yield. Stirring speed, process temperature, voltage, and environmental conditions are some of these CPPs.

The QbD concepts should be analysed in parallel to the ideation and drawing of the possible solution concept structures based on the new QbD technical specifications. In this case, the solution structures will be considered by the specific function and delivery form for the active compound e.g., core-shell, emulsions, lipid-derived particles, liposomes, and fibres, among other structures. The selection criteria for the specific solution concept will also change to science-based criteria, including delivery mechanisms, reported scientific literature, and process and material availability. It is important to highlight that process selection depends on various factors as the product type, size, scalability, specificity, structure, and material attributes.

The Advanced Analysis output is the research hypothesis, which consists of an outlined structure with defined materials attributes, process parameters, and a specific functional profile. Therefore, the Advanced Conceptual Analysis is not optional but mandatory for the product's success. From this point of view, the proposed conceptual analysis stage is the fundamental key to integrating the design and scientific approach in a single product.

2.4 Impact factors analysis

n the impact factor analysis stage, the aim is to identify the potential factors that significantly affect product quality and performance, based on the risk assessment QbD concept. Commonly used risk assessment tools such as Ishikawa or fishbone diagrams are employed to manage quality in categories such as materials, methods, man, machines, environment, and measurement (Liliana, 2016). However, considering the paradigm in materials science (Askeland and Wright, 2018), we propose to analyse potential factors in categories such as structure, properties, and processing as presented in Figure 3.

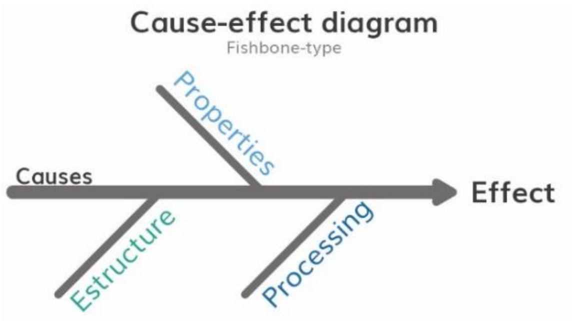

Figure 3. Cause-effect fishbone-type diagram with the proposed categories. Adapted from (European Medicines Agency, 2014).

For example, when electrospinning is utilized to produce particle-decorated nanofibers, it would be relevant to identify which parameters heavily affect that fibre morphology, such as polymer, processing and environmental conditions (Sahay, Thavasi and Ramakrishna, 2011). Thus, high-impact factors must be selected from prior scientific knowledge to effectively rank the critical factors depending on their effect on product performance. Those factors are then studied in the subsequent experimental stages.

2.5 Experimental evaluation

The selected factors will be evaluated using Design of Experiments (DoE) to understand their effects and interactions. This experimental evaluation is a crucial step in understanding the most influential factors in product performance. This stage is not commonly specified in design methodologies (Ulrich, 2003; Weiss and Hari, 2015; Cross, 2021), as it is a research-oriented activity supported by the Quality by Design (QbD) approach. However, in product design methodology, prototyping can serve a similar purpose to understand the assembly of parts and the product as a set (Cross, 2021).

The experimental evaluation stage typically employs screening Designs of Experiments, such as full factorial, fractionated factorial, and Placket-Burman. These designs are cost-effective ways to explore the behaviour of input factors, allowing for the study of multiple variables, their effects, and interactions with the lowest possible number of runs (Fukuda *et al.*, 2018). The statistical model describing the results obtained will be the basis for identifying the factors with the most significant effects.

2.6 Product optimization

Product optimization involves refining the conditions that result in optimal product performance based on all product specifications. It begins with experimental optimization of critical parameters identified in the screening Design of Experiments. Full-factorial, central composite, and Box-Behnken designs are often used to obtain an accurate response surface from evaluated factors. The statistical optimization process enables finding the maximum or minimum trend and obtaining optimal conditions from the mathematical model. The optimal conditions must be validated experimentally to verify the model's accuracy.

The product optimization stage ends with optimal conditions validation that results in a specific product profile. However, just a factor combination for the optimal product response is not practical, so QbD does not request a single optimal condition, but a **Design Space** acquired from the optimization design. This design space describes the combination and interaction between factors that result in optimal performance, and within the Design Space boundaries, the product quality is guaranteed.

Sometimes in optimization designs, it is necessary to identify the data trend for the optimized response. If there is a maximum or minimum response failure, the next step will involve an iterative process to find other accurate values in the trend direction. In this way, experimental screening and optimization designs can be iterated until optimal product performance is achieved. Generally, most QbD research studies only report the implementation progress up to obtaining the Design Space, but they do not report the QbD Control strategy and Process validation concepts (Xu, Khan and Burgess, 2011, 2012; Pallagi *et al.*, 2015; Garg *et al.*, 2017). It is important to highlight the achievements of this Integrated Design Methodology in creating a **product based on stimuli-responsive materials.**

2.7 High-scale production

The design space must have sufficient operational flexibility so that the product can be manufactured at any scale. Although large-scale production during research is not typically reported, it is crucial to perform scalability analyses for the optimized product and to plan product communication activities (Roozenburg and Eekels, 1995; Cross, 2021). Packaging must communicate basic information, instructions for use, and warnings, such as external use, allergies, and flammability, among other attributes, given the product's nature. This stage is primarily concerned with developing an action plan for large-scale production.

3 DISCUSSION

The Integrated Design Methodology merge the main aspects of scientific research and design methodologies for stimuli-based products. Particular emphasis is placed on the development of the initial stages as these fields of knowledge do not usually overlap. The conceptual analysis, proposed as two phases: early and advanced, is particularly important. At this stage, there is a strong coupling between the design approach and the scientific approach, as conceptual solutions are screened by advanced scientific criteria. This allows for the refinement and concretisation of the research hypothesis.

Due to the nature of this new proposed methodology, a case study is required to verify its successful implementation. The case study will involve the sequential application of the methodology in different product developments utilizing stimulus-based materials. Although, this proposed Integrated Design Methodology is initially part of a research project focused on the design and fabrication of controlled-release systems for potential use in agriculture, which will serve as a case study, the wider aim is to extend the methodology to various product types requiring both design and research.

4 CONCLUSIONS

In conclusion, the proposed Integrated Design Methodology represents a significant advancement in product design methodology by integrating QbD elements for products design based on stimuli-responsive materials. This combination implies a strong coupling between two approaches, which are usually considered separate fields. This proposal starts by defining the problem and identifying the overall product specifications based on user needs. The next stage involves conceptual analysis, where advanced specifications are incorporated using QbD elements to arrive at a solution considered as the hypothesis research, which is decomposed into main factors to analyse the effects on the product. Selected factors are then evaluated experimentally, and optimal product conditions are defined for the final science-based product. This methodology allows for a more rational design of innovative and smart products with high specificity and complexity that require both design and research.

The scope of this methodology is not limited to controlled-release systems but can be extended to other scientific products based on stimuli-responsive materials. From this, future work will extend the use of the proposed methodology to science-based products such as CRSs for dual active compound delivery in agriculture. A case study will be conducted to verify the successful implementation of the methodology, with a focus on examining the plant-soil system as the user in the early and advanced conceptual analysis stages, where both design and scientific methodology approaches are incorporated into a research hypothesis. Therefore, the proposed Integrated Design Methodology can be considered as a design methodology for scientific research in smart and precise solutions, providing a more efficient and effective way to design products based on stimuli-responsive materials.

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