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Research
Smart Process Manufacturing—Perspective

Smart process manufacturing for formulated products

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ABSTRACT

We outline the smart manufacturing challenges for formulated products, which are typically multicomponent, structured, and multiphase. These challenges predominate in the food, pharmaceuticals, agricultural and specialty chemicals, energy storage and energetic materials, and consumer goods industries, and are driven by fast-changing customer demand and, in some cases, a tight regulatory framework. This paper discusses progress in smart manufacturing—namely, digitalization and the use of large datasets with predictive models and solution-finding algorithms—in these industries. While some progress has been achieved, there is a strong need for more demonstration of model-based tools on realistic problems in order to demonstrate their benefits and highlight any systemic weaknesses.

1. Introduction

1.1. Characteristics of this industry and its products

Formulated products such as food, pharmaceuticals, agricultural and specialty chemicals, energy storage and energetic materials, and consumer goods are among the largest and most dynamic businesses in the UK manufacturing sector, bringing sales and exports in excess of 168 billion GBP to the UK economy each year. The UK food industry sector alone employs over 3.8 million people [1], and the UK pharmaceutical industry also has a large share in the UK manufacturing sector and employs a workforce of approximately 73,000 [2]. Within Europe, of the 507 billion EUR trade in chemicals (excluding pharmaceuticals), 13.6% (68 billion EUR) is in consumer chemicals [3]. A further 258 billion EUR is in pharmaceuticals [4], so the chemical and pharmaceutical industries make up a major sector of the UK and EU economies. This industrial makeup is characteristic of advanced economies, and we can expect the manufacture of these products to grow in developing economies in order to cope with increasing demand.

In contrast to bulk chemicals, formulated products are often multicomponent. These are structured, multiphase products (i.e., granules, tablets, emulsions, and suspensions) whose performance characteristics—critical quality attributes (CQAs)—are just as dependent on the product structure as they are on the chemical composition. Such products have a complex performance designed in, for example, the controlled-released profile of a pharmaceutical tablet. The structure of the products allows for apparently incompatible CQAs to be achieved, such as a water-dispersible herbicide granule that is strong enough to resist attrition and dust formation during handling, but disperses "instantaneously" to a stable dispersion when mixed with water on the farm. This tension between physical and chemical stability during handling, transportation, and storage, with "instability" (i.e., dispersion, dissolution, reaction, etc.) on delivery, is a common characteristic of formulated products. To meet increasingly demanding performance criteria, products are becoming more complex in nature and are often designed and marketed in conjunction with the delivery device, such as a coffee pod and espresso machine (see Fig. 1) [5].

Formulated product manufacture can also be compared with the industrial engineering of more traditionally made products. An aircraft wing made from composite materials is highly complex, with important structures on many length scales. A manufacturing plant may produce dozens of aircraft wings each year, and their lifetime is decades. A detergent granule is also a complex structure. A manufacturing plant makes billions of granules each day, and their lifetime in use is seconds to minutes. Thus, formulated products need to combine the most sophisticated tools of *process engineering* and *product engineering* in their design and manufacture (see Fig. 2).

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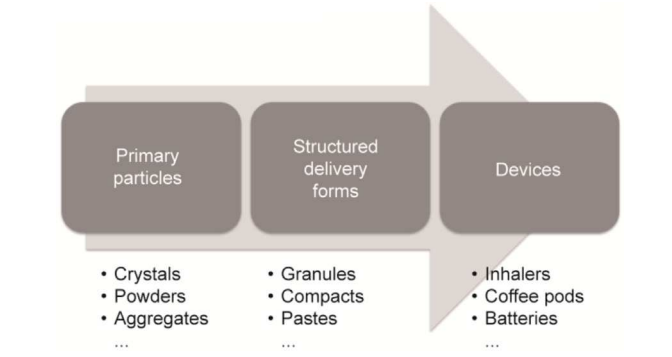

Fig. 1. Increasing sophistication of formulated products.

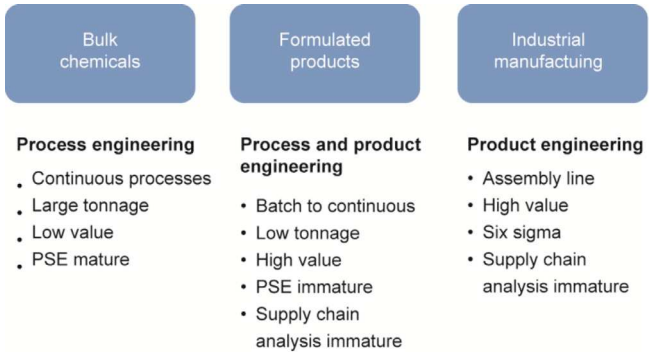

Fig. 2. Manufacturing formulated products—the nexus between process and product engineering. PSE: process system engineering.

1.2. Smart process manufacturing

Smart manufacturing refers to the goal of using data, models, algorithms, and computer control to optimize the whole supply chain in the production of manufactured products. Smart manufacturing is a stated priority of most major economies, including the US, China, and the EU. Smart process manufacturing is the application of this approach to process manufacturing [6,7]. It is also often referred to as Industry 4.0. Timely data and massively connected systems are important, but to make the most use of data, it is necessary to have models and algorithms.

The smart manufacturing revolution is said to have three phases: ① Factory and enterprise integration and plant-wide optimization, ② the exploitation of manufacturing intelligence, and ③ the creation of disruptive business models.

The challenges for smart process manufacturing have been set out by Bogle [6]. In particular, these have been framed in terms of the need for ① flexibility and uncertainty; ② responsiveness and agility; ③ robustness and security; ④ selling molecules, structured products, or function; and ⑤ modeling and mathematics.

Smart manufacturing capability is particularly needed in a number of process sectors that produce formulated products. Consumer goods need to be very responsive to customer demand (in the same way as the food industry), so their manufacture must be quickly adjusted to product and volume changes, which are very dependent on changing consumer demand. The pharmaceutical industry has historically had to be less responsive as healthcare requirements are more regular, but there are many pressures on healthcare providers, with drug-purchasing budgets—often by national agencies—requiring greater efficiency and less inventory. In the future, as the promise of personalized medicine becomes more realistic, there will be a need for much more responsive manufacturing for specific patients or patient groups, which will often be small groups. The pharmaceutical industry is also expecting to bring new products faster to market in order to give them a competitive edge and to have very rapid response in producing vaccines for epidemics/pandemics. There may also be a more changeable regulatory environment and faster response to changing product quality requirement, as well as possibly greater regulation of manufacturing operations.

This paper addresses the challenges for the smart process manufacturing of formulated products, focusing on the five challenge areas listed above in turn. First, however, we outline the current situation and some new developments arising from the research community.

2. Current situation

A great deal of factory and enterprise integration and plant-wide optimization has taken place in the chemical and oil industries, but for formulated products, this trend seems to be less well advanced. The need for faster response has driven technical strategy towards better supply chain optimization. However, plant control and optimization are more challenging due to the more complex products—often in the solid phase—and the use of unit operations that are less well characterized for the wide range of products being manufactured [8].

The process industry is undergoing a major change to embrace manufacturing intelligence, driven by the need for more tightly integrated supply chains on the basis of consumer demand. This is particularly true for formulated products.

Maier [9] reported to the UK Government in 2017 with "a set of proposals that will equip the UK with the means to fully embrace the next industrial revolution." In particular, he proposed "adoption of state-of-the-art digital simulation tools," "a product paradigm away from the 'make and test' to a more predictive digital framework," and the need for new infrastructure and skills to achieve these goals. He highlighted the need for integrated manufacturing capability for efficiency and responsiveness.

Maier highlights a number of barriers to the introduction of digitalization in the pharmaceutical industry, namely:

- Regulatory environment;
- Lack of skills in digital design and mathematical process models;
- Lack of skills in digital technologies;
- Capital, development, and regulatory costs to make the change.

Introducing disruptive technologies such as integrated continuous end-to-end manufacturing with the aid of high-quality models can allow the on-shoring of pharmaceutical manufacturing [10]. Digital technology in new and existing production facilities improves manufacturing productivity by 30%–35%. Smart packaging, which allows the adoption of an adaptive supply chain model, can reduce lead times by 45%–55%.

Opportunities for digitalization involving the application of model-based methodologies and tools of process systems engineering (PSE) to the pharmaceutical industry include:

- Accelerated scale-up, design, and modeling of new manufacturing processes;
- Boosting manufacturing productivity through automation and predictive process control;
- Smart packaging and optimized supply chains;
- Novel diagnostics, patient monitoring, and modeling.

For new medicines, flexible production facilities that can manufacture both clinical and commercial supply are needed (i.e., scale-up and -down production rates in the same facility).

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The Industry 4.0 and smart manufacturing paradigms embrace the use of artificial intelligence, machine learning, and big data approaches, although research in these fields is relatively new. Ning and You [11] recently presented a new approach for data-driven stochastic robust optimization using machine learning. A number of works have been published presenting data-driven approaches to the optimization of process systems [12–15]. Jordan and Mitchell [16] present more general trends and prospects for machine learning.

The final element of smart manufacturing is the development of disruptive business models. From a historical standpoint, the pharmaceutical industry has moved from discovery-driven companies to manufacturers of generics and consumer goods, as companies and manufacturers struggle to find new blockbuster drugs. The advent of personalized medicine challenges many things about both the business model and the regulatory model, with the advent of smaller batches for small groups of patients where there will not be large groups for safety and efficacy testing.

Many of these barriers and opportunities are also relevant to the broader range of formulated products. For example, the agrochemicals industry is also changing, with tighter environmental and safety constraints, and with better biological understanding resulting in more targeted product dosage and delivery. This shift could result in a need for small local manufacturing close to demand. The developing world has different needs: The biological requirements are different, the environmental challenges are severe, and the economic pressures make it necessary to cut costs and waste.

In the following sections, we consider each of the five aspects of smart process manufacturing outlined by Bogle [6]. We discuss drivers for change for the formulated product industries, examine progress using PSE techniques and others, and highlight potential challenges and opportunities.

3. "Who knows?: Flexibility and uncertainty

3.1. Drivers for change

While the chemical industry mostly produces chemical feedstocks—which are the building blocks for other manufactured products in the construction, transport, aerospace, energy, and other key industries—many formulated products are produced for almost immediate use, notably in consumer goods and pharmaceuticals. Customer demand must drive the manufacture of consumer products. The pharmaceutical industry is currently less driven by immediate demand, but personalized medicine may change that in the future.

Global markets are more closely linked than ever before; yet regulations vary between jurisdictions. This requires manufacturers either to ensure that their products satisfy the regulations in all the markets they serve, or to be able to adjust their manufacturing processes to manufacture to the appropriate standard. Of course, this also means that if any regulatory changes are made, it is important for manufacturers to respond quickly. Similarly, it is increasingly important to be able to respond quickly and efficiently to quality concerns and changes demanded by the consumer.

In pharmaceutical dosage form manufacturing, very small amounts of material are needed for phase I, II, and III clinical trials during the development and registration of a new drug and formulation. This formulation then needs to be scaled up to the development and then manufacturing scales, and must often be transferred and validated in different manufacturing sites around the world. It is a real challenge to maintain the product CQAs during this process. While chemistry is relatively easy to scale, *structure* (on length scales from nanometers to millimeters) does not scale well using traditional chemical engineering approaches. Being able to scale up and scale down during the development process is critical.

Speed to market is also critical for new pharmaceutical products, whose value reduces dramatically once they come off patent. A delay of six months due to issues in the development and scaling of the manufacturing process could result in lost revenue of millions of GBP [9].

To extend the patent life of pharmaceutical products, new dosage forms (immediate release, controlled release, etc.) may be introduced. Flexibility in manufacturing facilities to allow different dosage forms—or dosage forms with different performance characteristics—is very necessary.

A significant future requirement is the promise of personalized medicines. The explosion in genetic and metabolic information about individuals and small groups of patients with specific conditions is leading to the possibility of medicines being tailored for small groups of patients or even for individuals. Clearly, there are very significant challenges in this endeavor. The manufacturing expense is one small part; more significant is the expense of ensuring the safety and efficacy of a drug that has not had extensive trials. This will be a significant challenge to the regulatory framework for new medicines, although the technical capability is being developed. The capability to manufacture and deliver in a timely way also needs to be developed.

3.2. Smart manufacturing progress and challenges

The pharmaceutical industry has particularly tight constraints to innovation in product and process design [17]. Regulatory restrictions have made flexible manufacturing constrained, except within tightly constrained operating windows. Efforts have been made to define these windows and to expand them while still retaining regulatory permission [18]. To obtain more generalizable and robust operating conditions, there have been developments in the more comprehensive design of experiments to determine the most appropriate set of operating conditions [19]. Reconfigurable manufacturing capability has provided scope for more flexible manufacturing, although much of it is limited by the extent of the manual operational change that is required. Finally, there has been a move from batch operations to continuous operations in the specialties areas, which has provided some efficiencies and a degree of flexibility, albeit with the limitations of changeover periods.

Uncertainty also poses considerable challenges, with changes in demand, raw material supply, and regulatory conditions all resulting in uncertainty in manufacturing schedules. Systems engineering approaches for this problem have been well studied. Some recent contributions showing the power and scope of these methods can be found in Refs. [15,20–22].

In pharmaceutical products for oral dosage forms, there is a major move toward continuous manufacturing. In many cases, this allows scale-out in time—rather than scale-up in volume—to overcome the scale-up issues described above. Development batches can be produced while running a facility for a few minutes to a few hours. Full-scale manufacturing may be achieved using identical equipment that is run continuously for tens to hundreds of hours. This approach is possible because of the small production capacities required, which are typically in the tens to hundreds of kilograms. This luxury is not available to other formulated product industry sectors, where production rates of hundreds of kilograms to tonnes per day are required at full-scale production [23,24].

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4. "I want it now!: Responsiveness and agility

4.1. Drivers for change

Aligned to the uncertainty of predicting future markets is the need to respond quickly to changes once they are known. Consumer goods requirements can change very quickly, as they are driven by quality, fashion, and—of course—price. The food industry works by tracking customer preferences to help predict regular customer expectations and changes in demand as they occur. In particular, supermarket chains retain big datasets of customer information that they can mine to detect changes and speed of change, so that they can change purchasing and distribution to respond to demand. Consumer goods must also be responsive to customer demand and can do so without major regulatory restrictions. Wealthier countries are already becoming more demanding and as the economies of developing countries strengthen, we can expect even greater demands.

4.2. Smart manufacturing progress and challenges

One way this situation has been addressed in the past is to develop worldwide supply chains with alternative suppliers of parts of the product in order to ensure that the product can be made regardless of local conditions. The limiting extension is to outsource all aspects of manufacturing for risk management, although this means complete reliance on third parties.

Many industries have moved to just-in-time manufacturing. This type of manufacturing is common in the parts manufacturing industry (e.g., computers and automobiles). Some formulated products are just mixtures, where this method might be applicable; however, where there are sophisticated manufacturing requirements, just-in-time manufacturing would be difficult.

A great deal of research has been done on developing supply chain optimization methodologies for high-value low-volume product industries [25–28] and for the manufacturing of consumer-centric products [29]. These techniques have great potential for improving the responsiveness of the supply chain. Maier [9] outlined some of the enabling technologies that are required: smart plant equipment, sensor networks, high-throughput testing, virtual reality simulation and modeling tools, wireless connectivity, artificial intelligence, and so forth. Some of these technologies are mature, while others require more development and testing. However, integration of the tools for product delivery requires considerably more development through simulation and pilot-scale testing before the tools will be ready for implementation and their full benefits delivered.

5. "Can you guarantee it?: Robustness and security

5.1. Drivers for change

Quality—and its reliable delivery—is a major driver for change. Pharmaceutical and food products must be physically, chemically, and biologically stable during handling and storage. Stability and shelf life are critical attributes. Failure in this regard can be catastrophic, with potential for the injury or death of customers/patients in worst-case scenarios. The recall of products due to stability failure is extremely damaging to any company. Although the consequences of failure are less catastrophic, many consumer goods rely on robust stability and long-term shelf life. For example, the caking of powdered products and the separation of emulsified liquid products can render those products valueless.

Breakdown of product stability occurs over long timescales—from days to months to years—and is often related to the tails of the distribution of the properties of the material; that is, the single largest flaw may lead to the brittle failure of a compact, or a single nucleation site may lead to unwanted crystallization of an amorphous drug product. These effects make stability very difficult to predict from simple measurements made during manufacturing and product release. Increasing the fidelity of predictive models for product quality and stability will lead to their use in the integrated monitoring and control of whole supply chains.

It is still common to predict the point or mean values of product quality. Measurements and models really must be able to cater to variable distributions in order to ensure consistent quality within individual units, as well as in batches or continuous lines of product. Modeling methods have long been able to cater to product distributions using population balance methods. Nevertheless, they require more sophisticated solution techniques when integrated with large-scale models, and will require more data to ensure accuracy. We will then be in a position to use these models for predictive dynamic performance and to include them in the optimization of whole supply chains in order to ensure reliable delivery of high-quality products following disturbances.

The need for such responsiveness is growing. Consumers expect timely delivery of high-quality products even during major health scares and consumer goods shortages, which can be affected by outsourced manufacturing and transportation through international trouble spots.

5.2. Smart manufacturing progress and challenges

Advanced control and robust scheduling are both now commonplace in these industries (e.g. see Ref. [30]). However, there is rarely any automated communication between these two layers. Links are often close in the consumer products industry, where regulation is less tight. Van Vactor [31] discusses healthcare system response to crises, which is of increasing concern (see also Refs. [32,33]). Supply chain optimization could provide real benefits.

In the pharmaceutical industry, product testing before release is an essential regulatory requirement. It is traditionally performed on a batch-by-batch basis, where a few tablets are tested to represent a full batch. Modern continuous processing is moving toward real-time release, based on in-line process analytical technologies (PAT) measurements. This improves robustness, as often a much larger sample—or even all the tablets—are measured. For real-time release, high-quality in-line measurement techniques, robust measurement, and product models are all required [8].

6. "What do you want?: Selling molecules, structured products, or function

6.1. Drivers for change

While the chemical industry—and, to a larger extent, the pharmaceutical industry—are selling molecules, an important characteristic of the consumer products industry is that the functional requirements required of the products are fuzzy and depend on the customer. Some of these requirements, such as feel, taste, and shelf life, can be linked directly or indirectly to specific measurable properties such as solubility, density, vapor pressure, and opacity. But many either cannot be measured, or are dictated by combinations of measurable and unmeasurable properties; or, in some cases, are subjective and reliant on consumer choice and perception. As societies become more affluent, they become more demanding.

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6.2. Smart manufacturing progress and challenges

The ability to relate function to product structure and chemistry requires *product models* as well as *process models* (Fig. 3). While the development of process models for manufacturing remains a strong area of research and development, product models are much less studied. In some cases, these models can be quantitative and based on a strong understanding of the physics of the formulated product, such as models for attrition and breakage, dispersion and dissolution, or stability of a colloidal suspension [5]. In other cases, the models must by fuzzy or qualitative, especially those built around consumer responses or demand.

Ideally, a reverse-engineering approach is required, starting with a clear specification of the required functionality (performance characteristics, CQAs) and working backward to product structure, process, and formulation choice. Often, a clear statement of the required functionality is difficult, particularly when it is related to consumer perception.

Just-in-time manufacturing of consumer products will require not just product, process, and supply chain models, but also models for customer demand. Economics and psychology will dictate these models, and will require much closer integration to produce the benefits from smart manufacturing.

7. "Please help!: The enablers—modeling and mathematics

Developing process design and product design models for formulated products is more challenging than doing so for bulk chemicals. In the latter case, molecular modeling can often be used to predict with confidence bulk thermodynamic properties (solubility), and kinetic properties (viscosity) that can be used in well-established process design models. In formulated products, the functionality (performance characteristics) depend on the structure at many intermediate length scales, from the nanoscale roughness on individual particles, to micron- and millimeter-scale properties (e.g., dispersed phase size distribution and shape distribution, pore size and shape distribution and connectivity), with component distributions overlaid at all these scales. For this reason, fully *a priori* design models for formulated products are rare.

Other challenges for process and product models include:

(1) The models need to model the full distribution of product attributes, as product failure is often associated with the tails of the distributions, not the point value (mean)—for example, the single largest flaw leading to brittle failure of a compact, a single nucleation site leading to unwanted crystallization of an amorphous product, or just one tablet being present whose active ingredient dosage is too high.

(2) Flow and handling of formulated processes is difficult; there is a need to model and treat materials transfers as unit operations in and of themselves, and segregation is common while mixing is difficult. Spatial variations in composition, stresses, and temperature are less likely to be ignorable. Lumped parameter models are rarely sufficient.

(3) Product turnover is high. New products and process designs must often be done with a very small amount of material to test, but design is very dependent on formulation material properties. We are often data poor during process development—the opposite of the big data challenge.

Kayrak-Talay and Litster [34] proposed three levels of modeling of macroscopic process models for formulated products (Fig. 4). The first level, when there is little or no mechanistic information, requires statistical experiment designs with experiments across all scales. Where there is some quantitative understanding of the controlling mechanisms, models are built based on fewer experiments and scale-up is performed using dimensionless groups. Eventually, it would be desirable to have fully predictive mathematical models covering all physical phenomena, such that the number of experiments required to validate the model and estimate parameters is small and usually well characterized.

Predictive models need to be able to track the evolution of property distributions. Where the product is discrete, therefore, they are commonly presented in a population balance model framework, although other approaches such as Monte Carlo simulations are also used. These models may be coupled to continuum models

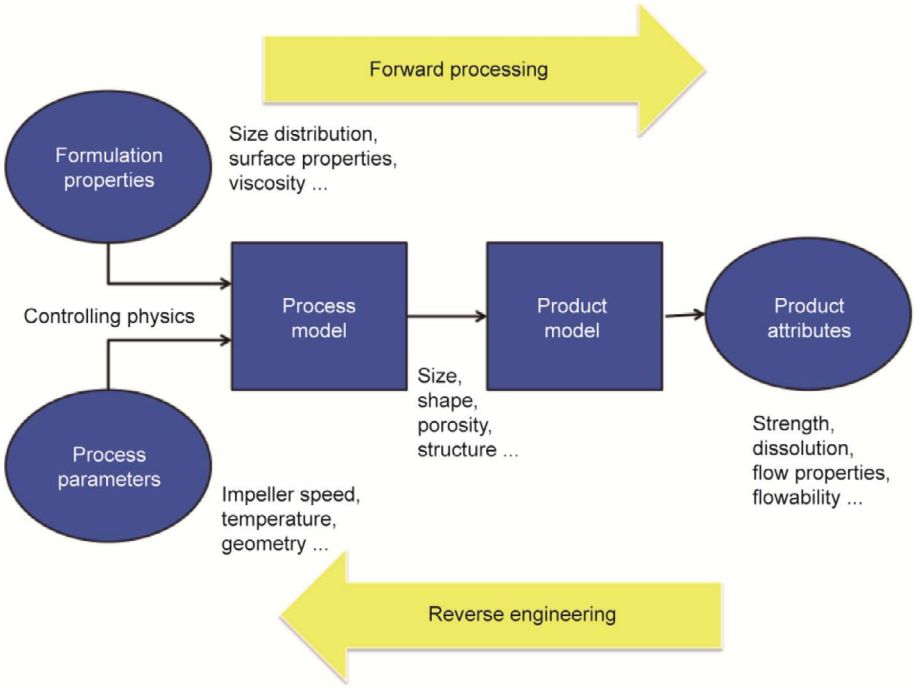

Fig. 3. Reverse engineering of formulated products; both the process model and the product model are important.

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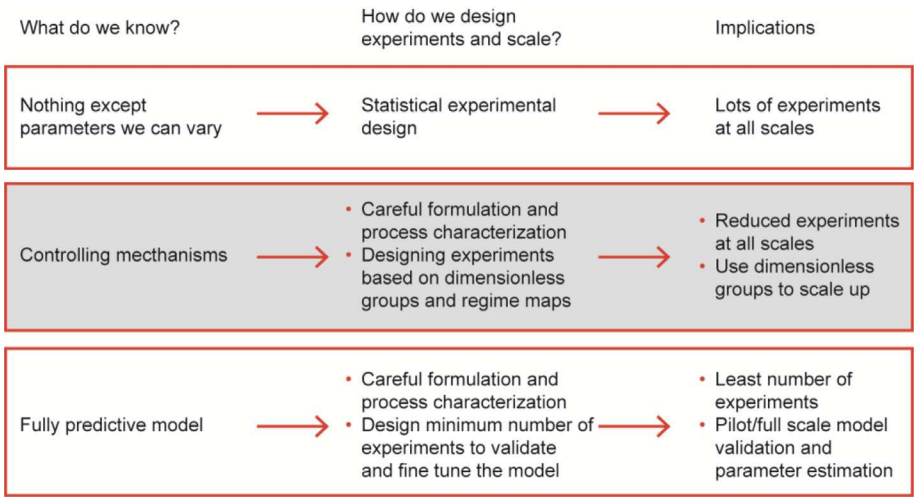

Fig. 4. Levels of sophistication for the design and scaling of formulated product processes.

for continuous phase (finite element models (FEM) and computational fluid dynamics (CFD)) or particle-scale simulations.

Where the process involves handling and delivering single-particle processes (e.g., crystallization, grinding), predictive models are well established. For processes that build structured products (e.g., granulation, compaction), level 2 models have been used over the last 15 years. However, robust predictive models are now being reported (e.g., Refs. [35,36]). There are no processes for which we can now say "we know nothing but we can vary the parameters." Nevertheless, much industrial practice relies on data-driven (level 1) models based on statistical experimental design.

These model frameworks and predictive models are now available in robust, commercial software packages such as gFormulate (Process Systems Enterprise Ltd., UK) and ASPEN (Aspen Technology, Inc., USA). The time is ripe to transition from the statistical design of experiments to model-driven design of formulated products and processes (MoDD FoPP) [37,38]. In this paradigm, experiments done during development are designed to provide necessary inputs for the design model and to provide model validation. As the process is scaled up, the model is used to establish the design and operating space, and target experiments are used for process and model validation. In MoDD FoPP, the model drives the experimental design, rather than vice versa.

In general, the models are not *a priori* fully predictive. The workflow for obtaining key parameters and validating the model is key. It is important to know which parameters to ① measure independently, ② take from the literature, ③ estimate from particle- or molecular-scale simulation, ④ guess (estimate), or ⑤ back fit from process experiments. At present, these decisions are often heuristics and rely heavily on the expert modeler/practitioner, in the same way that the operation of these processes in industry used to rely heavily on the brain of the expert operator. Robust general frameworks for MoDD FoPP workflows are still required.

Models for operation to support model predictive control and the real-time optimization of whole plants will be simpler, and should ideally be reduced from design models that capture key physics. Many of the design models are highly nonlinear, and the risk of exceptional events is much higher than for fluid processing. While approaches developed by the PSE community for bulk chemical processing (oil and gas) may be transferrable, very few true attempts have been made to test and validate these approaches on real processing plants [39]. New approaches to model-based control strategies and risk analysis may be required [8].

Models to support adaptive supply chains are also a major challenge, as they must balance the need for appropriate accuracy to reflect robust operation for quality and safety with the complexity of the dynamics of the supply chain in order to result in a computationally tractable problem. Supply chain models have traditionally been based on very gross assumptions about scale and performance, often only on fixed timespans of batch operations. Flexibility for quality measures will require models to accommodate adaptive timings as well as operating conditions. It will also require the comprehensive incorporation of dynamic models into supply chain models, with appropriate solution techniques (for a review, see Ref. [40]).

8. Conclusions

Much research progress has been achieved in the concepts, methods, and tools for smart process manufacturing for formulated products, building on progress in the oil and chemical sectors. However, the formulated products sector is different in that the products are more complex; the supply chains need to be more responsive, as they are closer to the consumer; and the product volumes tend to be smaller, creating larger unit costs. We consider there to be a real need for greater use of mature model-based tools to demonstrate proof of concept before a significant degree of take-up can be expected.

For this to occur, there must still be progress on product models, better models for consumer demand, and greater integration of all of these with model-based design, control, and optimization in order to drive a culture change in industry. Manufacturers of formulated products are very consumer-focused, and thus are acutely aware of the need for optimized supply chains; however, at this stage, they are skeptical of the ability of smart manufacturing to deliver these. Of course, there are differences between the pharmaceutical, vaccine, soap, and fertilizer industries and their customers; nevertheless, all will benefit from integrated digitalization to enable them to be more responsive to their customers in order to produce timely products with reliable high quality.

9. Compliance with ethics guidelines

James Litster and Ian David L Bogle declare that they have no conflict of interest or financial conflicts to disclose. Funding was not received for this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eng.2019.02.014.

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