THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

Integrated Product and Process Design for Mass Customization:

A Road Towards Patient Access to Individualized Pharmaceutical Therapy

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I, Rydvikha Govender, hereby certify that this thesis is my original work and, to the best of my knowledge, does not contain any material previously published or written by another person, except where due reference or acknowledgement is made.

Cover:
The cover depicts the concept of reconfigurable assembly in modular pharmaceutical products to achieve enhanced product variety from a limited number of standardized module variants. This cover was created by Rydvikha Govender and featured as the cover story of MDPI's *Pharmaceutics*, Vol. 12, Issue 8, 2020.

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Abstract

Individualized pharmaceutical therapy strives to attain optimal health outcomes *a priori* in all patients treated with pharmaceutical products by tailoring these products to each patient's holistic needs. However, existing mass-produced pharmaceutical products are not available in sufficient variety to enable adequate tailoring to the diverse needs of individuals. Consequently, this thesis has, firstly, recognized a potential alternative production approach designed for the provision of affordable variety, namely, mass customization. Thereafter, key product and process design requirements for establishing mass customization opportunities in the pharmaceutical value chain were identified and demonstrated. The foundation and key contribution of this thesis is a proposed patient-centric framework of design requirements for individualization of each oral dosage form feature. Additionally, an overarching product requirement for multifunctional individualization was determined, i.e., the simultaneous, independent individualization of multiple product features, which had not been addressed prior to this thesis. With a primary focus on product modularization, this thesis demonstrates that multifunctional individualization and the enhanced product variety crucial for affordable individualization may be achieved through reconfigurable modularization. Hot melt extrusion and fused deposition modelling were collectively deemed high-potential technologies for the fabrication of individualized products. However, this thesis reveals key material and manufacturing trade-offs between material diversity, dispensing precision, and geometric design flexibility, arising due to strict product and process requirements, which remain unsolved. Throughout, a systems approach is demonstrated to tackle existing interdependencies and, in future, navigate change on the road towards realization of accessible individualized therapy.

Keywords: *individualized therapy, mass customization, modularization, integration, patient-centric product design, reconfiguration, pharmaceutical manufacturing, hot melt extrusion, fused deposition modelling, polymeric solid dispersion*

Abbreviations

API	active pharmaceutical ingredient
HME	hot melt extrusion
FDM	fused deposition modelling
FEL	felodipine
EC	ethyl cellulose
MS	metoprolol succinate
PEG 1500	polyethylene glycol 1500
VA64	polyvinylpyrrolidone-vinyl acetate (Kollidon VA64)
NAP	naproxen
PLA	polylactic acid
PVA	polyvinyl acetate
IM	injection moulding
CAD	computer aided design
RSD	relative standard deviation
DSC	differential scanning calorimetry
SDS	sodium dodecyl sulphate
HCl	hydrochloric acid

List of Articles

This thesis is based on the work contained in the following articles:

Article I. Therapy for the Individual: Towards Patient Integration into the Manufacturing and Provision of Pharmaceuticals. Rydvikha Govender, Susanna Abrahmsén-Alami, Anette Larsson, Staffan Folestad, *European Journal of Pharmaceutics and Biopharmaceutics* **2020**, *149*, 58-76. doi:10.1016/j.ejpb.2020.01.001.

Article II. High Content Solid Dispersions for Dose Window Extension: A Basis for Design Flexibility in Fused Deposition Modelling. Rydvikha Govender, Susanna Abrahmsén-Alami, Staffan Folestad, Anette Larsson, *Pharmaceutical Research* **2020**, *37*(9), 1-10. doi:10.1007/s11095-019-2720-6.

Article III. Independent Tailoring of Dose and Drug Release via a Modularized Product Design Concept for Mass Customization. Rydvikha Govender, Susanna Abrahmsén-Alami, Anette Larsson, Anders Borde, Alexander Liljeblad, Staffan Folestad, *Pharmaceutics* **2020**, 12(8), 771. doi:10.3390/pharmaceutics12080771.

Article IV. Individualized Multidrug Therapy with Modular Dosage Forms: Expanding the Design Window for Poorly Water-Soluble Drugs. Rydvikha Govender, Susanna Abrahmsén-Alami, Staffan Folestad, Martina Olsson, Anette Larsson, *Submitted* **2021**.

Contribution Report

My authorship contributions are described according to Contributor Roles Taxonomy (CRediT). The Consortia Advancing Standards in Research Administration (CASRAI) and National Information Standards Organization (NISO) are responsible for refining these standards on a continuous basis. Current definitions of the terms are tabulated in the Appendix following the thesis summary.

Article I. Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Writing-Original Draft, Writing-Review and Editing, Visualization, Project Administration

Article II. Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Writing-Original Draft, Writing-Review and Editing, Visualization, Project Administration

Article III. Conceptualization, Methodology, Validation, Formal Analysis, Investigation*, Writing-Original Draft, Writing-Review and Editing, Visualization, Project Administration
*excluding performance and data collection of UPLC-UV and X-ray micro-computed tomography

Article IV. Conceptualization, Methodology, Validation, Formal Analysis*, Investigation*, Writing-Original Draft, Writing-Review and Editing, Visualization, Project Administration, Funding Acquisition for wide-angle X-ray scattering
*excluding performance, data collection, and analysis of wide-angle X-ray scattering experiments

Contents

1

Introduction

In 1946, the Constitution of the World Health Organization formally declared that "the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition" [1]. Improvements in health status, to fulfil this right and promote wellbeing, constitute the primary aim of healthcare systems and the treatments they provide [2]. Furthermore, the impact of medicines has been recognized to extend beyond clinical benefits for specific patients to offset direct and indirect costs to society associated with disease [3, 4]. Figure 1 depicts selected examples of medicines providing value to patients and society through increased life expectancy, improved quality of life, disease prevention, reduced healthcare costs, and improved productivity [3, 5-12].

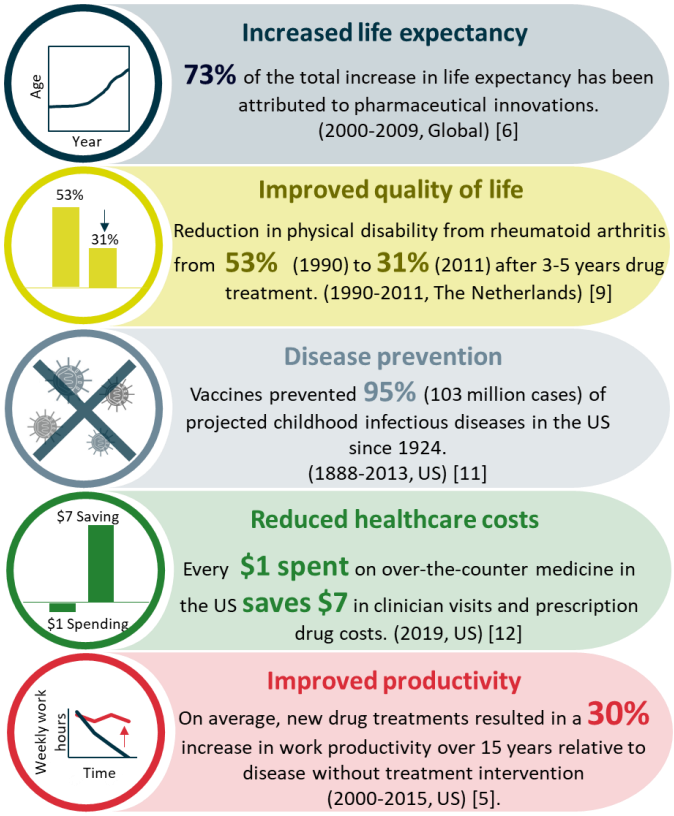


Fig. 1. Examples of the patient and societal value provided by medicines. The years and countries in which each study was conducted are included in parentheses, with the study reference in square brackets.

However, there is considerable heterogeneity in the magnitude of these contributions across different types of medicines, pathologies, healthcare delivery systems, socioeconomic regions, and patient groups [13-17]. Consequently, despite substantial progress in medicine and healthcare, unmet medical needs persist. Although this is a worldwide, multifaceted public health concern involving, *inter alia*, disease burden, healthcare system costs, lack of resources for timeous access to interventions, scientific roadblocks, and prevalent diseases without existing treatment, unmet medical needs also exist despite treatment with pharmaceutical products.

The global patient population contains an extensive array of heterogeneous medicine-related needs, which originate from unique biological, behavioural, and environmental characteristics as well as patient preferences [18-25]. Collectively, these influence therapeutic outcomes when a patient is treated with a pharmaceutical product [23, 26-38]. Suboptimal therapeutic outcomes at the patient-product interface may therefore be attributed to inadequate tailoring of treatment to meet this heterogeneous needs-base. Consequently, individualized therapy strives to optimize therapeutic responses *a priori* in all patients who are treated. It is based upon the premise that intra- and inter-individual variability in response to treatment occurs, not merely due to the heterogeneity that characterizes patients and their medicine-related needs but, more specifically, because existing pharmaceutical products are not available in sufficient variety to enable adequate tailoring to the diverse needs of individuals (Figure 2) [39]. The success of individualized pharmaceutical therapy therefore relies upon the provision of sufficient product variety to support selection of a specific treatment that satisfies an individual patient's holistic needs.

Currently, pharmaceutical products are produced by mass production, which is characterized by high production volumes and low product variety in order to drive productivity and cost effectiveness *via* economies of scale. During individualization, patients are stratified into progressively smaller segments of the population, each with unique needs from the pharmaceutical product. This requires not only progressively enhanced product variety but also progressively smaller production volumes for each product variant [39-42]. Eventually, this is expected to surpass what is technically and/or

economically feasible with any technology in a mass production context, rendering individualized products either inaccessible or unaffordable. There is therefore a need for alternative production approaches, which can concurrently promote variety provision for individualized therapy and harness the cost effectiveness of mass production. This thesis proposes mass customization as such an alternative, owing to its potential for cost-effective variety provision for individualized therapy.

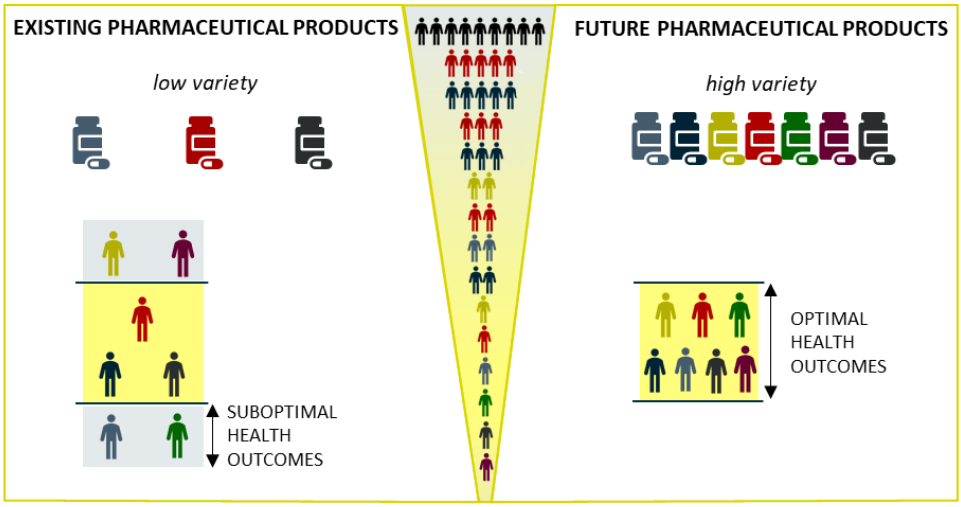


Fig. 2. Existing vs. future pharmaceutical products showing that differences in variety in the product offering may contribute to differences in health outcomes in diverse patient populations.

Generating a product offering characterized by enhanced variety requires first establishing the manner in which products should vary to promote individualization. This specifically pertains to identifying the product attributes which require individualization and exploring how they could be designed to enable individualization. Explicit and holistic requirements on the design of pharmaceutical products for individualized therapy, which systematically integrate patient needs and preferences, had not yet been established prior to the commencement of this thesis. Furthermore, although several current and emerging manufacturing technologies claim suitability for individualized therapy [43-50], they have not yet been designed in the context of a holistic patient needs-driven framework for individualization and/or in the context of an economically feasible production approach to drive accessibility to individualized medicines [51]. Therefore, in addition to alternative production approaches for promoting the provision of affordable variety, product design concepts and associated manufacturing concepts are required, which can both facilitate patient-centric individualization and support consistent, reliable access to individualized medicines.

1.1. Purpose, Overarching Aim, and Key Research Questions

The purpose of this thesis is to promote the development of individualized pharmaceutical products that are both functional and accessible so that it may steer individualized therapy closer to realizing the ambition of safety, effectiveness, and acceptability for all patients who are treated with pharmaceutical products.

The overarching aim is to identify and demonstrate key design requirements for establishing mass customization opportunities in the pharmaceutical value chain during individualized single-drug and multidrug therapy. To fulfil this aim, this thesis is constructed around several key research questions:

i. What are the pharmaceutical product design requirements for patient-centric individualization?

ii. Which production approaches and principles could support affordable access to individualized pharmaceutical products by diverse patients?

iii. What are the manufacturing process requirements for fabrication of individualized pharmaceutical products with acceptable performance?

iv. What are the implications of implementing alternative production principles for the design and manufacture of individualized pharmaceutical products?

1.2. Thesis Structure, Scope, and Research Strategy

This thesis comprises four appended articles, which are preceded by a composite summary. Beyond this introduction (Chapter 1), this summary consists of a series of additional chapters (Chapters 2-7) dedicated to key elements of the unified product–process–production approach to individualized therapy. Included within these chapters are their theoretical considerations in brief, followed by the principal contributions of this thesis. These contributions, which respond to specific gaps identified in current research and/or practice, are introduced using italicized phrases within each chapter. Key findings from each of the appended articles and insights from the confluence of all

the articles are summarized within each chapter. The aforementioned research questions are collectively answered through analysis and/or demonstration in each of the appended articles that comprise this thesis. In the thesis summary, research questions *i* and *ii* are primarily addressed in Chapters 3 and 4, research question *iii* is addressed in Chapters 5 and 6, and research question *iv* is addressed in Chapter 7. The specific article(s) on which each chapter is based can be found described within the chapters themselves. These chapters are followed by brief concluding remarks in Chapter 8. Since the integrated design and development of products and processes into a pharmaceutical mass customization context is still in its infancy, Chapter 8 also provides and an outlook on future research directions. This outlook will highlight important required contributors to the eventual realization of patient-centric individualized therapy.

Determinants of health and contributors to health outcomes upon intervention are multifaceted, however this thesis focuses solely on health outcomes associated with pharmaceutical therapy at the patient–product interface. Although several dosage form types exist, which can be delivered *via* several administration routes, this thesis is limited in scope to oral dosage forms containing small molecule active pharmaceutical ingredients (APIs). Henceforth in this thesis, the word "product" refers to the dosage form and excludes its packaging. For the fabrication of the solid oral dosage form components in this thesis, melt-based processing, primarily by hot melt extrusion (HME) and fused deposition modelling (FDM), are in focus. Consequently, the solid dispersion material systems in this thesis correspond solely to melt-extruded drug–polymer solid dispersions. These include felodipine (FEL) in ethyl cellulose (EC) in *Article II*, metoprolol succinate (MS) in polyethylene glycol 1500 (PEG 1500) and polyvinylpyrrolidone-vinyl acetate (VA64) in *Article III*, and both FEL in VA64 and naproxen (NAP) in VA64 in *Article IV*. These material systems are summarized in Table 1, together with the articles in which they are fabricated and investigated. The rationale for the selection of each manufacturing process and each material system, in accordance with individual study aims, can be found in the appended articles and in Chapters 5 and 6 of the thesis summary, respectively. Beyond the manufacturing process, an extension to manufacturing networks and the associated requirements for scale-up and stability

testing under conditions applicable to product storage and transport are beyond the scope of this thesis.

Table 1. Drug–polymer solid dispersions studied in this thesis. Drugs include felodipine (FEL), metoprolol succinate (MS), and naproxen (NAP). Polymers include ethyl cellulose (EC) and polyvinylpyrrolidone-vinyl acetate (VA64).

Drug	Polymer(s)	Article
FEL	EC	II
MS	PEG 1500 and VA64	III
NAP	VA64	IV
FEL	VA64	IV

The specific product design features that were in scope for each article in this thesis are depicted in Figure 3. *Article I* proposed the patient-centric framework of product design requirements for individualized therapy, upon which the subsequent articles were based. From *Article II* to *Article IV* a progressively increased product design complexity was targeted towards the holistic, integrated individualization of the entire product.

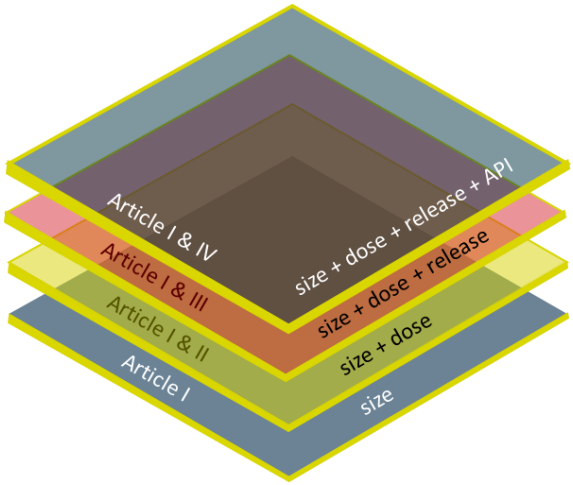
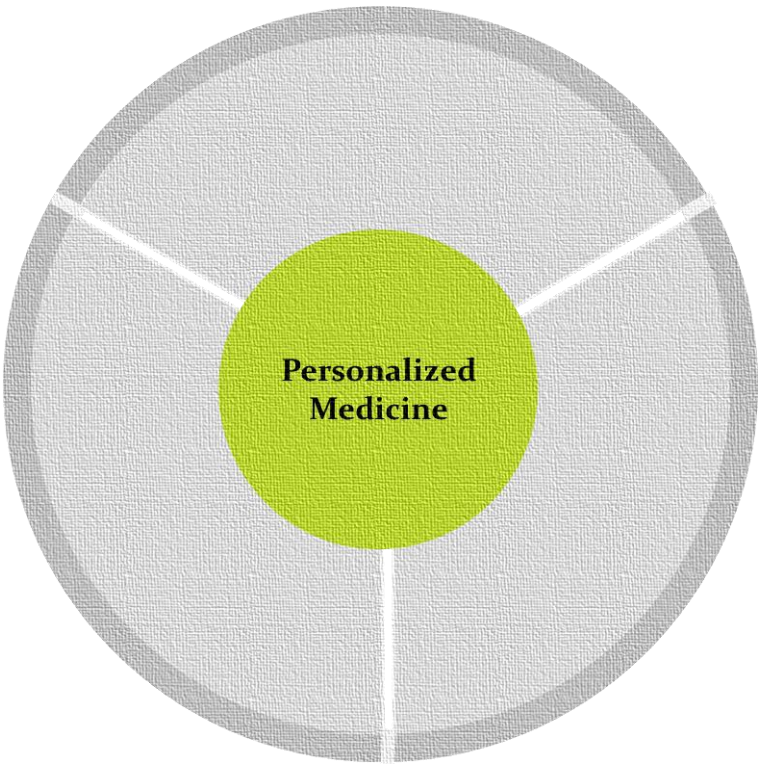


Fig. 3. Scope of product design features for each article in the context of the overarching research strategy employed in this thesis.

Furthermore, the articles also mark a progression from single-drug therapy towards multidrug therapy considerations for individualization. At each stage, key opportunities, requirements, and challenges for mass customization of pharmaceuticals are probed in order to eventually broaden applicability to fully multifunctional products for individualized therapy.

1.3. Thesis Statement

Global provision of and access to patient-centric individualized pharmaceutical therapy relies upon a shift from the currently dominant pharmaceutical mass production paradigm towards mass customization strategies, which are integrated into both the design of individualized products and their associated manufacturing technologies, in response to holistic, individual patient needs.


Personalized
Medicine

2

Personalized Medicine

Personalized medicine is characterized by the practice of tailoring therapies to individual patient needs and arose in response to inter- and intra-patient variability in drug response. Observations of extensive variability in drug response date back to at least the 1950's [52-54], during which time they were primarily attributed to genetic diversity amongst patients. With its origins in pharmacogenetics and subsequently pharmacogenomics, it is unsurprising that the mapping of the human genome in the early 2000's coincides with an acceleration in research and development in the field of personalized medicine [52, 55, 56]. Figure 4 shows the results of a Scopus database document search conducted in December 2020 for the number of publications containing personalized medicine and related terms in the title, abstract, or keywords. This search was conducted in an identical manner to the search for trends in personalized medicine reported in *Article I*. Details on the search method and conditions may be found in *Article I*.

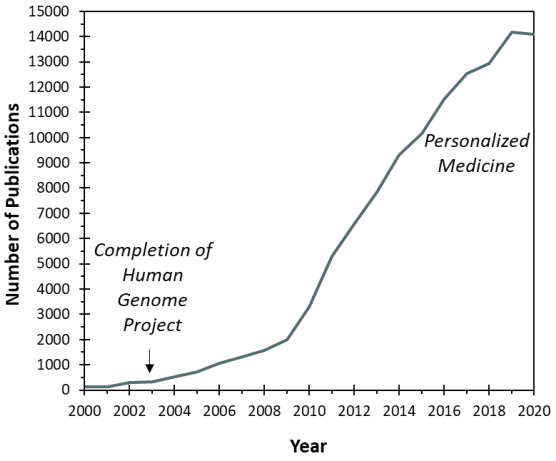


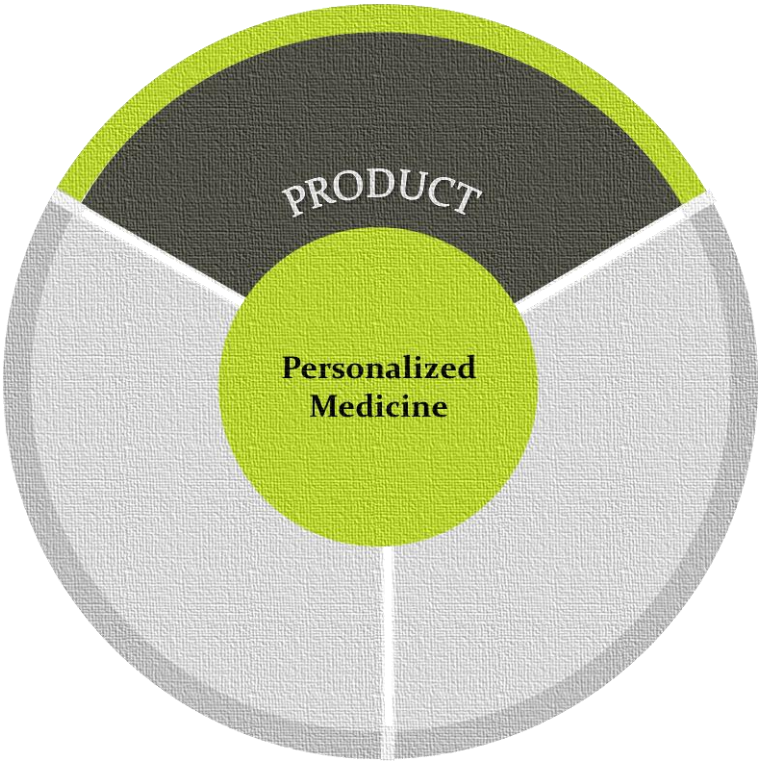
Fig. 4. Trends in the field of personalized medicine from 2000-2020. The data for 2020 does not include publications yet to be indexed by the database.

Although it may be argued that the practice of personalized medicine long precedes its establishment as a dedicated field of research, it was not until the developments of the 20th century that a greater extent of personalization has been triggered than was previously deemed necessary to implement or possible to achieve [52, 55, 57-62]. Whilst these

developments include field-specific advances in genetics, molecular, cellular, and structural biology, biochemistry, diagnostics, and digitalization to name a few, it is the confluence of these and other advancements that have propelled the field of personalized medicine into popularity in the 21st century.

One contribution of this thesis is founded on the observation that this popularization is not merely an acceleration but also an evolution in the concept of personalized medicine. Despite the initially reductionist association between personalized medicine and genetic variability, there has been growing evidence of the contribution of non-genetic factors to variability in drug response, some of which are significant enough to potentially mask the contribution of genetic variability to therapeutic response [54]. This growing multidimensionality of personalized medicine has given rise to a multitude of alternative terminologies, which are defined and addressed in *Article I* [59, 63-76]. A significant implication is that consensus definitions for personalized medicine have proven challenging to adopt. In this thesis, personalized medicine is primarily referred to as individualized therapy, a generic description that strives to avoid exclusive connotations with the strictly genetic aspects long associated with personalized medicines. With this view, any reference to either individualization or personalization in this thesis describe the act of tailoring therapy without intended distinction between the terms nor restriction to the various terms and definitions existing in current literature.

This thesis explores the expansion of the concept of personalized medicine to encompass all known aspects of patient variability (beyond only the genetic) and the implications this holistic view has on the design of individualized pharmaceutical products (beyond only the API and its dose).


PRODUCT
Personalized
Medicine

3

Product Design for Individualized Pharmaceutical Therapy

3.1. Patient-Centric Pharmaceutical Drug Product Design

Patient-centric pharmaceutical drug product design has been defined as "the process of identifying the comprehensive needs of individuals or the target patient population and utilizing the identified needs to design pharmaceutical products that provide the best benefit to risk profile for that target patient population over the intended duration of treatment" [72]. As such, it is a key enabler of individualized therapy. Scrutinizing the comprehensive needs of individuals reveals a broad range of patient characteristics, which either individually or collectively, determine a patient's response to treatment [23-38, 77]. Such characteristics could be genetic, physiological, psychological, lifestyle-related, and so forth. Not only do these characteristics vary between individuals but many vary within the same individual over time. This diversity in individual patient characteristics is often accompanied by an unpredictable, often undesirable, diversity in drug product usability and/or *in vivo* performance and therapeutic response. Therefore, patient-centricity, in an effort to mitigate this, inevitably implies and demands individualization.

Current knowledge on inter- and intra-patient variability in therapeutic response is vast, as are associations between patient characteristics and specific product design features, which determine therapeutic response [21, 55, 78-94]. Some product design features are universally patient-centric due to a shared requirement amongst all individuals throughout the population (*Article I*). Such requirements include, for example, portability and product stability throughout usage. Within the same product, other design features require tailoring to the needs of the individual (*Article I*). These include, amongst others, the API, dose strength, drug release functionality, composition, sensory attributes, and dosage form appearance. In these cases, associations between patient characteristics and specific product design features influencing therapeutic response

encompass, for example, the need to tailor the dose to account for drug–drug interactions with other medications in the therapeutic regimen or to account for the influence of genetic polymorphisms in drug metabolizing enzymes on the required dose [79, 80, 86, 88, 94]. They also include the need to tailor the type or size of a dosage form to aid swallowability [91, 95-101], the flavour of a formulation to improve palatability [38, 93, 100, 102-104], and so forth. For a comprehensive discussion of further key drivers for individualization of each product feature and for the entire dosage form, with supporting literature, the reader is referred to *Article I* and the references contained therein. Figure 5 depicts an overview of individual patient characteristics requiring translation into design requirements for specific pharmaceutical product features, based on the analysis of patient needs performed in *Article I*. Although associations between patient characteristics and specific product features influencing therapeutic response may be vast, their translation and collation into a framework of explicit, holistic, patient-centric drug product design requirements for individualized therapy was lacking by comparison.

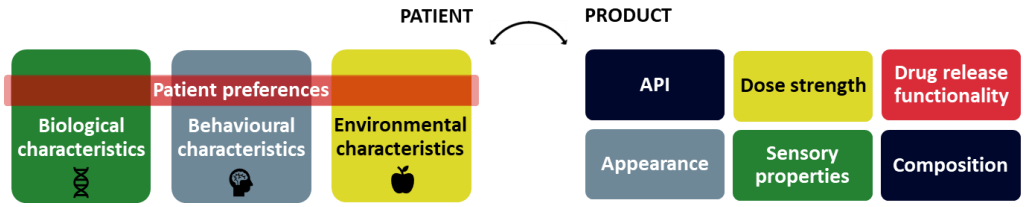


Fig. 5. An overview of individual patient characteristics requiring translation into design requirements for specific pharmaceutical product features. Further details of the patient characteristics and product features at play at the patient–product interface may be found in *Article I*, with selected highlights in section 3.2. of the thesis summary.

Furthermore, during patient-centric drug product design, associations between patient characteristics and drug product features relevant to individualization are frequently made in relation to special population subgroups, for example, paediatrics or geriatrics [22, 25, 38, 81, 84, 87, 105-113]. These subgroups arise upon stratification of the patient population on the basis of one or more differentiating patient characteristics. Whilst stratification provides a firm basis for individualization and reveals special subgroup specific considerations, caution should be exercised regarding the number and variety of patient characteristics that were used to differentiate one subgroup from another and the extent of stratification (i.e. how broadly or narrowly the subgroups are defined). Insufficient

stratification could run the risk that an individual subgroup is not sufficiently homogeneous in the characteristics influencing therapeutic response, which is expected to have direct implications on the success of individualized therapy.

In this thesis, product design for individualized therapy is extended across all patient characteristics, which include but are not limited to those of specific population subgroups. As such, in the context of pharmaceutical product design for individualized therapy, the contribution of this thesis is a proposed framework of patient-centric product design requirements for individualization, accompanied by a demonstration of how under-explored product design opportunities may be leveraged to meet these requirements and drive patient access to individualized therapies (research question i.).

3.2. Pharmaceutical Product Design Requirements for Patient-Centric Individualization

To generate a patient-centric framework of design requirements for pharmaceutical products for individualization, primary sources of scientific information were collected on resulting health outcomes after treatment with mass-produced oral pharmaceutical products in a wide range of therapeutic areas. The relationship between patient characteristics and specific product design features, which influence health outcomes at the patient–product interface, were subsequently translated into a set of specific product design requirements for individualized therapy. Examples spanning therapeutic areas and types of oral dosage forms provided a means to qualitatively validate the generic pharmaceutical product design requirements that were developed. Figure 6 summarizes patient-centric requirements on each pharmaceutical product feature for the provision of individualized therapy. Together, Figures 5 and 6 serve as a summary of the patient-centric framework of product design requirements proposed in *Article I*. For specific examples of the translation of patient needs into pharmaceutical product design requirements, along with key drivers and references, the reader is referred to A*rticle I*.

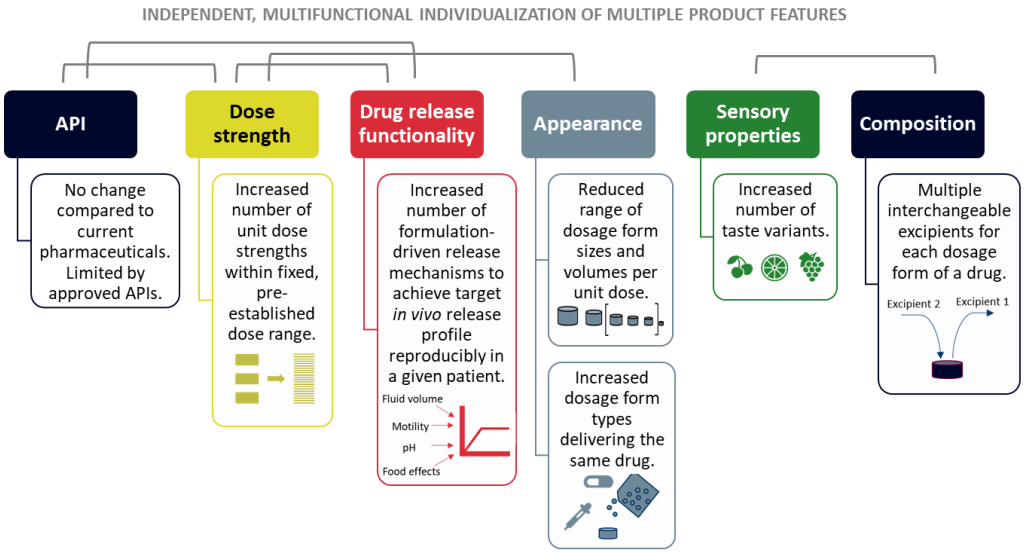


Fig. 6. A summary of pharmaceutical product design requirements for oral dosage form individualization. For specific examples of the translation of patient needs into pharmaceutical product design requirements, along with key drivers and references, the reader is referred to A*rticle I*. The connector lines above selected product features exemplify interdependencies.

3.2.1. Single-Drug Therapy

API and Composition

During single-drug therapy, API individualization entails selection of a discrete dosage form containing the API of choice. Since this thesis is limited in scope to drug product individualization and not drug substance discovery, design, or synthesis, the capacity for API individualization is limited to approved products containing the desired API. Under the paradigm of mass production, the development of dosage forms of a given API with a variety of alternative excipients, based on individual patient requirements, or the change of excipients in approved dosage forms, although permitted within certain conditions [114, 115], are not common practice for the purpose of individualization. However, in the case of excipient-related allergies or intolerances, interchangeability of excipients may be a desirable design feature for individualized therapy.

Dose Strength

The dose strength is one of the product features that leads to considerable manipulation by patients, caregivers, or healthcare providers to compensate for the lack of dose strength variety provided by mass production in achieving a desirable administered dose. In the case of solid oral dosage forms, this is exemplified by the splitting or

crushing of dosage forms or administration of multiple dosage units, sometimes of different dose strengths, all leading to increased regimen complexity [38, 116]. In turn, this may result in decreased adherence or dosing inaccuracies in some cases, which may be detrimental to health outcomes. Consequently, the provision of individualized therapy demands an availability of more dose strengths within a fixed, pre-established dose range. This can facilitate accurate dosing *via* administration of a single dosage form (as a target best case scenario) that delivers a safe and effective dose for the individual patient, circumventing challenges with handling and adherence. For further details on the design of flexible-dose products and the implications they have for required drug contents and product performance at a fixed dosage form size, the reader is referred to *Article II*.

Drug Release Functionality

Drug release, absorption, and resulting bioavailability, are influenced by several gastrointestinal parameters encountered after oral administration. These include pH, transit time, motility, fluid volume, fluid composition, gut microbiota, enzymes, mucous layer thickness and composition, food effects, and pre-systemic metabolism in the intestinal epithelium [82, 117]. These gastrointestinal variables are subject to large intra- and inter-individual variability [29, 92, 118]. In particular, depending on the release mechanism of the formulation, drug release and transit time may be differently susceptible to variations *in vivo*. Individualized therapies therefore require the dosage form to have formulation-driven release trigger mechanisms that not only facilitate variety provision for individualization but that also keep the target *in vivo* release profile as desired between individual patients and within one individual on different occasions. In doing so, *in vivo* release and uptake are both individualized and robust against variable gastrointestinal conditions. For a demonstration of how product design may be utilized to obtain a variety of dosage form release profiles for individualization, independent of the dose and size of the dosage form, the reader is referred to *Article III*.

Appearance and Sensory Properties

In addition to visual attributes, the appearance of a dosage form includes the size of solid oral dosage forms, the volume of liquid oral dosage forms, and the type of dosage

form. The latter refers to monolithic solids, multiparticulates, liquids, and so forth. Unlike other dosage form attributes, which demand an increased variety, the size of solid oral dosage forms or volume of liquid oral dosage forms need to be optimized for both swallowing and handling and are therefore limited to an acceptable range [87]. These product attributes signify constraints on the design of pharmaceutical dosage forms for individualization. The dosage form sensory attributes refer specifically to the organoleptic properties of taste, texture, and smell. Both appearance and sensory properties are subjective, preference-driven characteristics, which are often unpredictable. Consequently, studies on patient preferences indicate that availability of each drug in a range of dosage form types, where possible, could be beneficial to facilitate individualization [87, 89, 91]. For example, increasing the number of flavour variants that can be incorporated into dosage forms, at the request of the specific patient, or employing taste masking, may assist in improving the acceptability of oral formulations and, in doing so, potentially improve adherence.

3.2.2. Multidrug Therapy

The requirements stipulated in Figure 6 and section 3.2.1. remain true for single-drug and multidrug therapy alike, however, multidrug therapy demands further product design requirements for individualization. An ideal case for individualized multidrug therapy is the concurrent administration of multiple APIs in a single dosage form, which is designed to reduce polypharmacy and facilitate adherence. In this case, a change in API to suit the needs of an individual patient, for example due to differences in genes encoding drug-metabolising enzymes, or drug interactions, will require interchangeability of APIs within a combination product and the manufacture of a greater number of combinations based on available APIs. Currently, a change of API within a mass-produced combination product, with limited or no variants, reverts to separate administrations of each drug or necessitates re-development. Furthermore, for typical regimens containing multiple medications, a patient is often required to administer these medications on several occasions during a day. When moving towards individualization, manufacturing each drug with tailored drug release functionalities to achieve their target *in vivo* release profiles, whilst allowing the patient to reduce the total number of daily administrations, or at least administer their drugs at the same

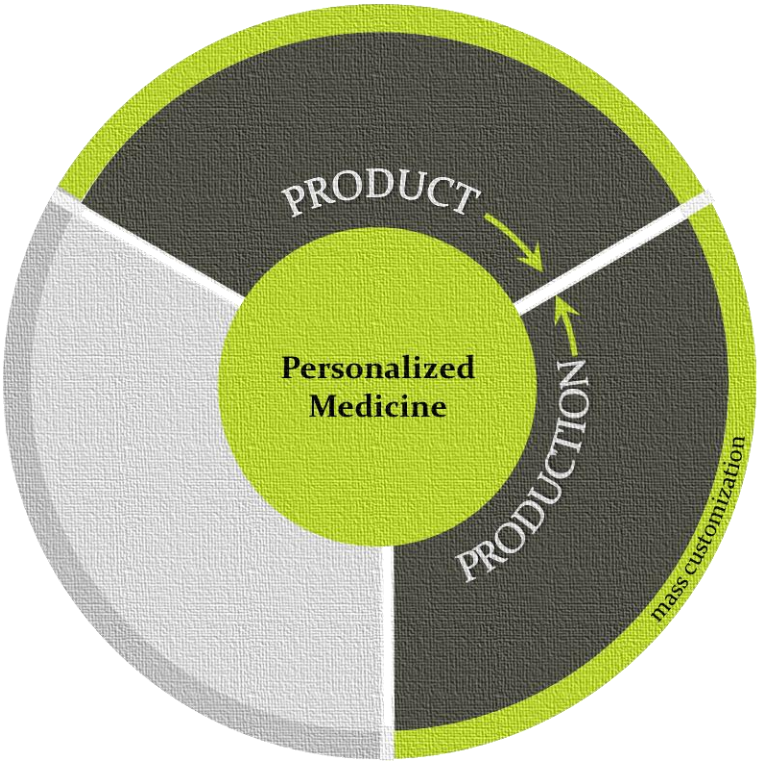
time, is required. The goal in this case should be synchronized administration of multiple drugs with independently controlled release of each drug [119]. Ideally, this should be achieved in a single combination product or, at least, as discrete dosage forms with synchronized administration. Each API in multidrug therapy will still need to satisfy requirements for dose individualization and release individualization. Within combination products, this will require interchangeability of not just the API but each API's dose and release as required by an individual patient. This makes enhanced flexibility in combination dosage forms a key factor in the provision of individualized multidrug therapy. For a comprehensive introduction to and discussion of design considerations for individualized multidrug therapy and how to expand the design window for APIs of varying characteristics, the reader is referred to *Article IV*.

3.2.3. Holistic, Integrated Individualization During Single-Drug and Multidrug Therapy

Product features for individualization co-exist within the same dosage form. Consequently, beyond attribute-specific design requirements for individualized therapy, consideration of the interplay between product features is crucial to enabling holistic individualization of the entire dosage form . One commonly encountered interdependency involves the relationship between the dose and size of dosage forms (*Article II*). Increasing or decreasing the dose strength of a dosage form is often met with a corresponding increase or decrease, respectively, in the size of a dosage form. This perceived dose flexibility might intend to promote optimal health outcomes through individualized dosing. However, without considering the size constraints of dosage forms to facilitate handling or swallowability, this approach may ultimately hinder treatment outcomes *via* reduced acceptability. Consequently, the constraint of a fixed dosage form size is applied to all dosage form concepts investigated and demonstrated in *Articles II*, *II*, and *IV* in this thesis. Other interdependencies include the relationship between the dose strength and drug release kinetics at a fixed dosage form size (*Article III*) or the relationship between the API and the drug release performance (*Article IV*). Product design for individualized therapy therefore demands individualization of a given product feature according to the design requirements stated in sections 3.2.1 and 3.2.2. without hindering individualization of other product features in a dosage form. This corresponds to an overarching product design requirement for

individualized therapy being simultaneous, independent individualization of each product feature (multifunctional individualization), i.e., the ability to individualize each product attribute as required without adversely impacting the ability to individualize other attributes. As described in section 1.2 and depicted in Figure 3, *Articles II*, *III*, and *IV* were each based on distinct requirements for different product features from the framework of design requirements proposed in *Article I*. However, they were all in the context of multifunctional individualization with a progression towards higher product complexity and full multifunctionality from *Article II* to *IV*. To enable the provision of individualized products to patients, this overarching product design requirement on an individual product level is embedded into the requirement for enhanced product variety in the total product offering.

During individualization, each subgroup of the patient population, and upon further stratification, potentially each individual, will possess a distinct set of needs to be met by the product. Effectively targeting these needs will require provision of a diverse product offering (i.e. increased product variety) at smaller production volumes, consistent with the specific subgroup or specific individual instead of the population average [40, 41, 116]. This requirement for enhanced variety provision is at the heart of access to individualized therapy, where the production platform is expected to play a pivotal role.


PRODUCT
PRODUCTION
Personalized Medicine
mass customization

4

Production Platforms for Individualized Pharmaceutical Therapy

4.1. Mass Production

Mass production is defined as "the production of large quantities of the same kind of product for a sustained or prolonged period of time" [120]. It has existed for over a century, since 1913 [121-123], reaching its peak in 1955 [122, 123]. Initially, mass production arose in response to an expanding global population and improved standards of living, which led to a large, predictable, continuous demand of commodities from the end-user and a need for enhanced productivity [120, 123].

As a production approach characterized by economies of scale, i.e., the cost-effective provision of large volumes of standardized products, mass production creates value for the end-user by promoting affordability and timely, reliable access to high quality standardized products. Economies of scale are also well-suited to assuring productivity and cost feasibility for the manufacturer. These attributes are satisfied *via* several means: fixed and specialized production lines designed to suit standardized processes and materials, specialized machining equipment primarily arranged sequentially to promote rapid, large volume production of the same product within tight tolerances for variations between identical products, well-defined operations, high quality standards, and high inventories due to a made-to-stock approach [124]. Interchangeable part production and moving assembly lines are key enablers of mass production [120, 121, 125].

The efficiency and economies of scale of mass production explain its place as the currently dominant production paradigm in the pharmaceutical industry, where its success is rooted in driving population-wide patient access to pharmaceutical products. Amidst a growing need for individualized pharmaceutical products, key attributes of mass production, i.e., the requirement for high quality, affordable products delivered in a timely manner, persist. However, the demand originating from predefined patient populations is required to be sufficiently large and represent sufficiently homogeneous

needs over time for mass production to be suitable. This is not the case during individualization. Increased overall product variety at smaller production volumes for stratified patient groups is a critical challenge for production approaches intending to support provision of individualized therapy [39, 40, 42]. The current paradigm of mass production employed in the pharmaceutical industry is characterized by the opposite, i.e., high production volumes and low product variety, to drive productivity [121]. Whilst efficiency and cost-effectiveness are indeed desirable attributes during individualization, as is the fact that they are employed to drive patient access, mass production currently offers inadequate flexibility and product variety [39, 126] to meet the requirements of individualization.

Consequently, this thesis explores the necessary shift towards alternative production approaches that may support the provision of individualized products whilst maintaining the benefits of mass production. This is accompanied by the implications such a shift might have for product design and manufacturing (research questions ii and iv).

4.2. Mass Customization

Mass customization is defined as a "paradigm for developing, producing, marketing and delivering affordable goods responding to the needs and demands from the individual customer" [121, 127-129]. Mass customization emerged in the late 1980's due to a demand for higher variety [121, 126, 129]. The term was coined by Davis [130, 131] but later popularized by Pine [129], with automotive and electronics manufacturers being early adopters [132]. Unlike mass production, mass customization is driven by a heterogeneous and volatile demand [123, 133] and need for high variety. Mass customization is therefore characterized by economies of scope, with its primary value proposition for the end-user being access to affordable, personalized products [123, 130, 133, 134]. Table 2 summarizes and contrasts mass production and mass customization on the basis of their fundamental drivers, overarching principles, characteristic traits, and the evolving role of the end-user.

The contribution of this thesis in the context of pharmaceutical production is, firstly, to suggest mass customization as an alternative to mass production on the basis of its potential suitability for the provision of individualized therapy and subsequently,

demonstrate how mass customization principles may be translated into the pharmaceutical value chain (research question ii).

Table 2. Summary and comparison of key differentiators between mass production and mass customization.

Key Differentiators	Mass Production	Mass Customization
Drivers	Predictable, consistent demand Need for productivity	Heterogeneous, volatile demand Need for variety
Overarching principle	Economies of scale	Economies of scope
Characteristic traits	Standardization (of products and processes) Made-to-stock (using high inventories)	Combined standardization and differentiation (of products and processes) Made-to-order (using delayed differentiation)
End-user role	Recipient of products	Selector of products

Although mass customization is a well-established production concept in other manufacturing industries, attempts at translation to the pharmaceutical value chain are minimal [42, 135], leading to an underexplored opportunity for making individualized products a reality. Figure 7 emphasizes the contrast between the number of publications in the field of personalized medicine (total of 115768 hits), as reported in Figure 4, compared to publications mentioning "mass customization", "mass personalization", or "mass individualization" within this search (total of 15 hits).

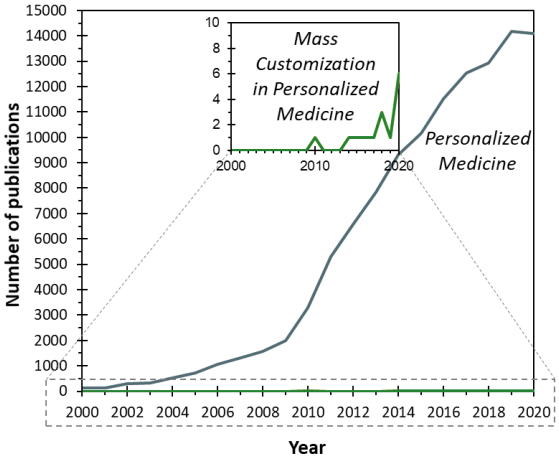


Fig. 7. Contrast between the overall research activity in the field of personalized medicine with that of mass customization in personalized medicine.

The first article by Pallari *et al* in 2010 [136] involved mass customization of foot orthoses using selective laser sintering. Note that articles referring to these terms only within their reference lists were excluded. Furthermore, this search contains the indexed articles appended in this thesis as well as articles that transiently mention mass customization within a single introductory or concluding sentence without an evaluation or demonstration of mass customization for individualized pharmaceutical therapy. The 15 articles mentioning mass customization in personalized medicine are therefore an overestimate of actual activity in this field. This confirms a considerable gap despite the potential of mass customization for individualized therapy, which this thesis aims at beginning to fill.

The heterogeneous customer base that drives the need for mass customization outside of the pharmaceutical industry parallels the heterogeneity in patient populations, whereby the satisfaction of individual patient needs depends on the alignment of product attributes with these individual needs [137]. This is consistent with the patient needs-driven product design described in the previous chapter, rendering mass customization a promising production paradigm for the provision of individualized pharmaceutical products. During individualization, patients are stratified into progressively smaller segments, each with unique needs from the pharmaceutical product. Figure 8 depicts the increasing heterogeneity of the customer base in each production scenario during stratification, which is accompanied by a need for progressively increased product variety at progressively smaller production volumes, corresponding to subsets of the patient population. This highlights the required progression from mass production towards mass customization and potentially to individuals under a full customization paradigm. This progression is met by the evolving role of the typical end-user (Table 2).

Unlike traditional mass production where the end-user is a recipient of a product, mass customization considers the end-user integrated into the design and development process through active involvement [123, 138]. This facilitates selection of the product most suited to their needs and preferences.

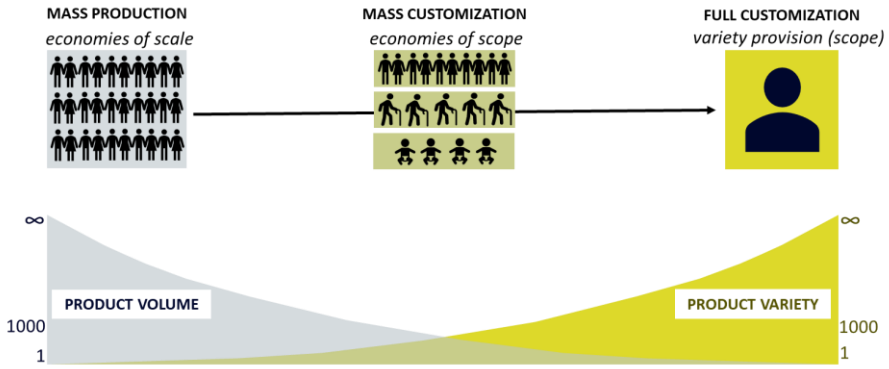


Fig. 8. Progression of production paradigms required to support the provision of increased product variety at decreasing production volumes.

Personalized production has occasionally been described as a successor to mass customization, where it is primarily differentiated from mass customization by the extent of customer involvement, where the customer chooses the product during mass customization but designs the product during personalization [122, 125, 126]. In other literature, "personalization" has been distinguished from mass customization, mass personalization, and mass individualization by its association with increasing costs [139]. Neither mass customization nor personalized production are represented in the mainstream pharmaceutical production landscape. It therefore becomes imperative to consider whether the aforementioned distinctions applied in other industries are translatable to a pharmaceutical production context.

Pharmaceutical end-users are patients who, unlike the end-users in nonpharmaceutical branches of industry, arrive at an individualized treatment scenario in consultation with healthcare providers. Patients and healthcare providers alike represent crucial resources during the integration of individual needs and preferences into the design of products for individualized therapy. Currently, neither of their roles involve the autonomous design or selection of the pharmaceutical treatment. Furthermore, the pharmaceutical product also differs from typical personalized consumer goods in that its function is not only driven by the specifications of the customer but relies upon the competencies and design inputs of several stakeholders in the healthcare system for its successful use. Consequently, in this thesis, mass customization refers to a strategic research direction encompassing the entire mass customization system, which collectively includes *mass* customization and/or *mass* individualization and/or *mass* personalization. All are

geared towards affordable variety provision. To avoid confusion, the descriptors *full* customization or *fully* personalized production are used to describe the provision of high product variety at high cost, similar to the craft production of the pre-mass production era.

In order to prevent the typically high costs associated with variety provision, mass customization intends to harness the flexibility and variety of full customization whilst retaining the efficiency and economies of scale of mass production. Facilitating access of individualized pharmaceuticals to patients through the provision of affordable variety may be achieved through mass customization's key principles of modularization of the product and process, process flexibility, postponement (a delayed point of product differentiation in the supply chain), and supply chain integration [123, 126, 132, 135, 137, 140-148]. The articles comprising this thesis primarily explore product modularization.

Modularization has been defined as "the extent to which the components of a product can be separated and recombined in order to make variants of the same product" [149]. As per this definition, in the context of pharmaceutical products for individualization, product features (including the API, dose strength, drug release functionality, appearance, etc.) can be considered discrete functional modules, existing as module variants, which can be combined in varying configurations to achieve overall product design modularity and variety. In order for modularization to be harnessed for mass customization, it is important to distinguish product modularization for mass customization from product modularization for mass production or full customization. Modular products are ubiquitous on the market and in pharmaceutical academic research as granules, pellets, layered dosage forms, and compartmentalized structures [39, 102, 119, 150-165]. However, they typically lack reconfiguration either due to fixed assembly of module variants to generate a final dosage form or due to the existence of identical modules comprising a dosage form. Consequently, without reconfigurability, they are not designed for the provision of affordable variety characteristic of mass customization. For further details on theoretical considerations for pharmaceutical product modularization and the design and performance demonstration of a modular product based on reconfigurable assembly, the reader is referred to *Article III*.

4.2.1. Mass Customization Opportunities for Enabling Access to Individualized Therapies

Product modularization is used in this thesis to not only promote the provision of affordable variety but also to meet specific patient-centric product design requirements for individualization such as the overarching product design requirement for multifunctional individualization. The modular dosage form concepts described in this thesis contain unique functional modules which may, in turn, consist of smaller building blocks, called components, from which each module is constructed. This results in a hierarchy of length scales in order of decreasing size from dosage forms > modules > components.

Article III demonstrates how reconfigurable modularization can enable multifunctional individualization, enhance product variety, and potentially facilitate both process flexibility and postponement. For details on the design of the product concept and its fabrication, the reader is referred to the appended *Article III*. This work was based upon a modular dosage form comprising any combination of two module variants from three available module variant designs. These module variants contain smaller components called the core, cup, and lid. Figure 9 shows the drug release kinetics of each module variant.

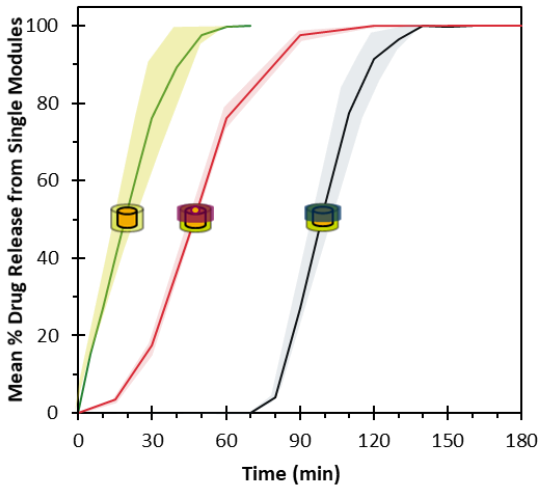


Fig. 9. Mean % drug release vs. time from single modules of three variants (green, red, and blue solid lines). Faded areas indicate the range in % drug release from duplicate experiments. Adapted with permission from https://doi.org/10.3390/pharmaceutics12080771 (*Article III*), © 2020 Govender *et al.* licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/legalcode).

All three module variants depicted in Figure 9 had identical drug-containing, rapidly erodible cores with an identical dose fraction of MS (40% w/w MS: 20% w/w PEG 1500: 40% w/w VA64). The reader is referred to Table 1 in Section 1.2. of this thesis summary for a reminder of the material systems used in this thesis and their abbreviations. All three module variants also had identical water-insoluble polylactic acid (PLA) cups enclosing the bottom and sides of the core, allowing the surface area available for drug release to be controlled by the top surface of each core. The presence and/or type of lid provided each module variant with its unique drug release kinetics and was the only component that was not standardized between modules. The module variant without a lid (green line) provided rapid drug release. The module variant with a water-soluble polyvinyl acetate (PVA) lid (blue line) provided an initial lag period corresponding to the lid dissolution time, followed by rapid drug release from the core. The module variant with a water-insoluble PLA lid with central orifice provided a reduced surface area for initial hydration of the core and consequently, initially slower drug release kinetics. These three single modules release kinetics were sufficiently distinct such that they could be reconfigured into a final dosage form, which comprised two module variants in this study.

Figure 10 shows the resulting dosage form release kinetics, upon combining two identical or two unique modules to represent a dosage form. Regardless of whether identical modules (Figures 10A, 10B, and 10C) or unique modules (Figures 10D, 10E, and 10F) are combined, the composite dosage form release kinetics was a predictable net effect of that of its constituent modules. In modular dosage forms that only contain identical modules and therefore do not enable reconfiguration, only three dosage from release profiles would result from three module variants (Figures 10A, 10B, and 10C). Therefore, combining unique modules together to enable reconfiguration is crucial to obtain enhanced product variety. In this case, enhanced variety in dosage form release kinetics was obtained independent of the dose and size of the dose form, with six dosage form release profiles obtained from only three module variants. This is one of the main design considerations that differentiates this modular product design approach from conventional modular product archetypes typically encountered on the market, for example, granules, pellets, or minitablets.

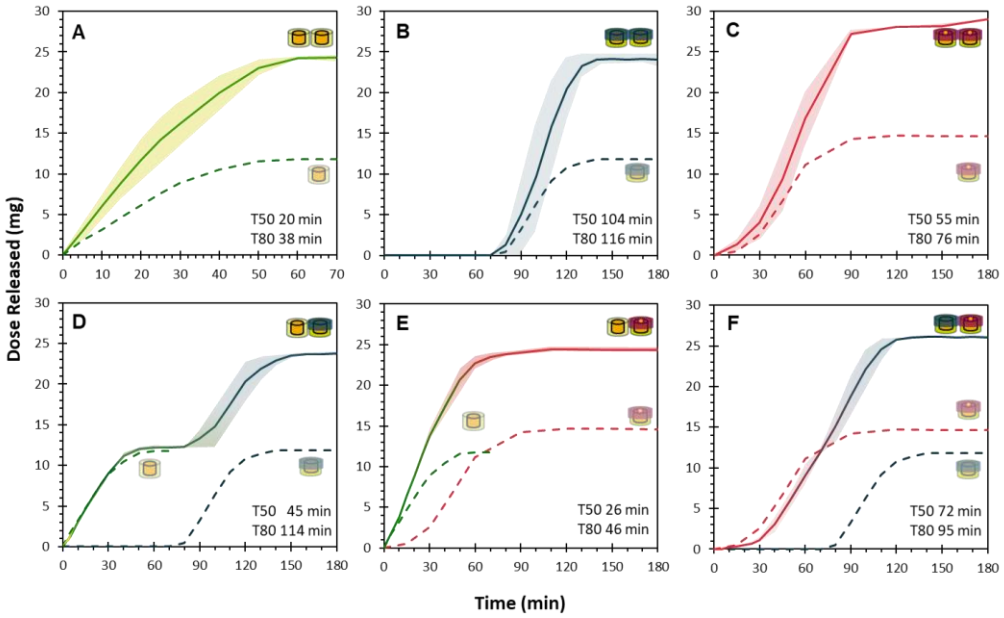


Fig. 10. Mean dose released vs. time from dosage form variants combining either two identical modules (10A, 10B, and 10C) or two distinct modules (10D, 10E, and 10F). Faded areas indicate the range in the dose released at each time point from duplicate experiments. Mean dose released vs. time from single modules used to construct the dosage form are indicated with a dashed line in each frame. Adapted with permission from https://doi.org/10.3390/pharmaceutics12080771 (*Article III*), © 2020 Govender *et al.* licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/legalcode).

Articles II and *IV* complement this demonstration in *Article III* by exemplifying how the core of such a construct could also be modularized to facilitate reconfiguration and enhanced variety in the dose alongside the drug release. Whilst *Article III* has demonstrated enhanced variety from a conceptual level, *Articles II* and *IV* explore key technical challenges encountered when extending modular product concepts towards extremes, with the aim of individualizing the dose (*Article II*), the release (*Article III*) and the API (*Article IV*) simultaneously and independently of each other using reconfigurable modularization. Furthermore, having distinct module variants in a dosage form does not inherently allow reconfiguration unless the product design allows for varying combinations of modules during assembly. Consequently, this proposed modular product design is also differentiated from modular combination products that are based on fixed assembly, which are not designed for reconfigurability.

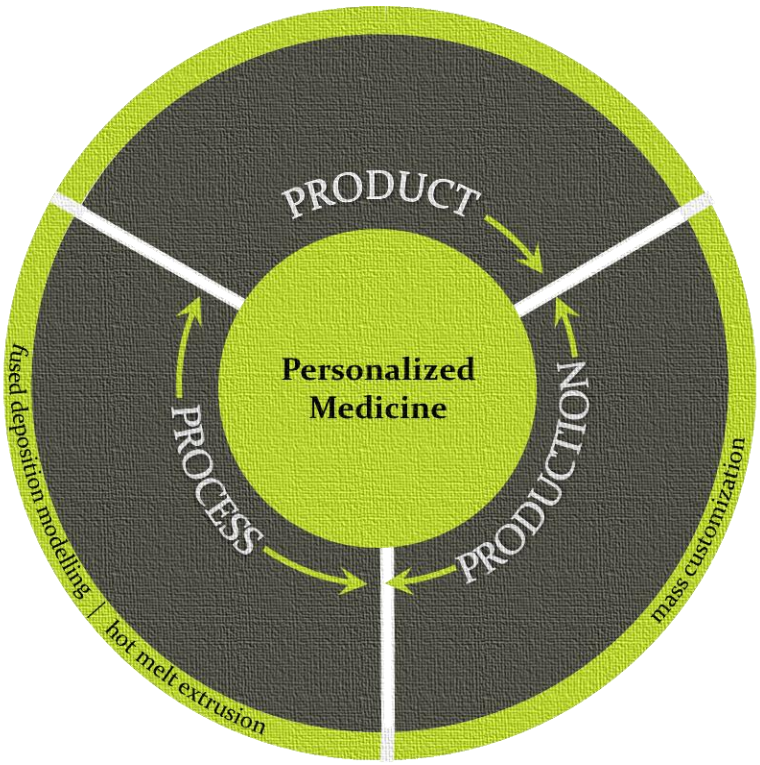
The ability of modularity to promote the provision of affordable variety, as required for individualized therapy, depends on at least two characteristics, namely, a correlation

between the physical and functional architecture of the product and the minimization of interactions amongst the physical components of a modular product [144]. Interestingly, these are the same characteristics that allow reconfigurable modularization to meet the overarching patient-centric product design requirement for individualized therapy, namely, simultaneous and independent individualization of multiple product features in a controlled and predictable manner. In addition to the promotion of product variety, these characteristics may lead to a number of additional benefits associated with reconfigurable modularization. These include, amongst others, economies of scale at the component level, ease of product change, and flexibility in use [144]. In this thesis, these theoretical opportunities have been demonstrated *via* several design choices that were integrated into a single modular product concept for reconfiguration in *Article III*, some of which are listed below.

- **Economies of scale at the component level** was achieved by a balance between standardization and differentiation in components. Most components were standardized (core and cup) with only one unique component (lid). Furthermore, the number of module variants will play a key role in achieving economies of scale and was limited to three variants in *Articles II* and *III*. In addition to economies of scale at the component level, modularization also enables process- and quality-control at the component level.
- **Enhanced product variety** was achieved through a lack of interactions between modules, allowing various combinations of module variants to be assembled into a final dosage form. *Article IV* builds upon enhanced variety by exploring a higher degree of product modularity than *Article III* and a widened applicability of the concept to APIs of varying characteristics.
- **Flexibility in use**, i.e., multifunctional individualization, was achieved by spatial separation of the dose-controlling and release-controlling functionalities, each of which were denoted by a specific dose-controlling or release-controlling structural component.
- **Potential for process flexibility** was enabled by a design that facilitates independent fabrication of each component prior to assembly, allowing parallel component manufacturing to occur, if desired.

- **Potential for postponement**, was enabled by allowing the unique component (the lid) to be the last component to be assembled.

Product design strategies may be used to harness and integrate a wide assortment of mass customization opportunities to meet the requirements of individualized therapy. In addition to harnessing these mass customization opportunities, key mass customization challenges will also be encountered, of which the co-development of product, process and production [123] is the major challenge addressed in Chapter 7 of this thesis. To this end, Chapters 3 and 4 have together explored integrated development of the product design and production approach. The next chapter will introduce and evaluate the process considerations that are critical to the realization of individualized therapy.


PRODUCT
PROCESS
PRODUCTION
Personalized Medicine
fused deposition modelling
hot melt extrusion
mass customization

5

Manufacturing Technologies for Individualized Pharmaceutical Therapy

Modern manufacturing networks comprise the manufacturing plants, suppliers, and dealers responsible for producing and delivering final products to the market [166]. Manufacturing networks are beyond the scope of this thesis. However, specific manufacturing technologies have a pivotal role to play during individualized therapy. Generating the intended product design for individualization is only one contribution of the manufacturing technology. To drive patient access to individualized therapies, the manufacturing technology also needs to abide by and/or enact the principles of the production approach. In this dual role, the manufacturing technologies act as the bridge between product and production. Manufacturing technologies based on continuous manufacturing [167-172] and additive manufacturing [49, 173-186] principles have gained attention in recent years. Current literature reveals that several technologies incorporating either or both principles are associated with potential for individualization (*Article I*).

The contribution of this thesis, beyond elucidating the dual role of the manufacturing process in enabling individualized therapy, includes providing a generic list of manufacturing process requirements for individualized pharmaceutical products, evaluating current and emerging manufacturing technologies for their existing suitability for individualization, and elucidating key material and manufacturing trade-offs encountered, which form the basis for suggested future developments in this space (research question iii).

5.1. Manufacturing Process Requirements for Individualization

Once design requirements for various pharmaceutical product features were established based on key patient-centric drivers (*Article I* and Chapter 3 of this thesis summary), various manufacturing technologies were then evaluated for their ability to deliver individualization according to the requirements stipulated in Chapter 3 of this thesis.

Manufacturing technologies associated with the field of personalized medicine were identified using the Scopus scientific database search described in *Article I*. The choice of database was determined by the need for a comprehensive, multidisciplinary collection of literature spanning all scientific disciplines relevant to this thesis e.g. medicine, pharmaceutical sciences, materials science, and engineering. The selection of manufacturing technologies for evaluation was based upon their relative prevalence in the database search results and the fact that they represent a broad design space in terms of varying degrees of use in pharmaceutical applications, varying manufacturing and material principles, and applicability to different product concepts. Shortlisted technologies included HME [171, 187-194], injection moulding (IM) [171, 194-199], FDM [48, 176, 178, 196, 197, 200-207], drop-on-demand additive manufacturing technologies [44, 45, 208-211], and particle replication in non-wetting templates [151, 212-216]. For a description of each technology and their implementation in pharmaceutical applications, the reader is referred to *Article I*.

Regardless of the processes eventually selected for demonstrating product concepts for individualized therapy in this thesis, certain manufacturing process requirements for individualization of each product feature need to be satisfied, which are collated in Table 3. Some manufacturing process requirements are of specific importance for the tailoring of a certain product feature, for example, payload flexibility for dose tailoring, however, Table 3 reveals that many process requirements are common for individualization of several product features. In fact, since these product features co-exist within the same product, all manufacturing process requirements for individualization need to be satisfied for holistic, integrated individualization of the entire dosage form and to promote independent, multifunctional individualization. To assess suitability for individualization, processes in solid oral dosage form mass production were used as references in a delta analysis of each selected technology, since they are the current state of the art in pharmaceutical production. This suitability analysis revealed that, whilst these technologies did improve flexibility of many of these features, no single technology could inherently satisfy all requirements concurrently. This indicates that, in future, adapted, hybrid or new technological development will be crucial for achieving individualized therapy.

Table 3. Manufacturing process requirements for individualized pharmaceutical products.

Product Feature	Manufacturing Process Requirements for Individualization
API and composition	*Material diversity* Equivalent capability to process various APIs and excipients with a wide range of properties.
Dose strength	*Payload flexibility* Feedstock drug content homogeneity across a wide drug loading range. *Precision dispensing* Large volume and small volume precision dispensing is required, the latter of which is crucial to create small feature size geometries and fine tune the dose.
Drug release functionality	*Material diversity* Equivalent capability to process various API and excipient combinations with a wide range of properties. *External design flexibility* Ability to generate different geometries before or during final dosage form assembly. *Internal design flexibility* Ability to fabricate internal compartments at different length scales e.g. an ability to incorporate channels within an oral dosage form or an ability to control porosity through structural design. *Precision dispensing* A co-requirement that accompanies material diversity and external and internal design flexibility for precise control of release through material selection and/or geometry.
Appearance	*Material diversity* Equivalent capability to process materials with a wide range of properties to generate a variety of dosage form types. *External design flexibility* Ability to generate different geometries that dictate final dosage form shape and size. *Precision dispensing* Small volume precision dispensing is required for small feature size geometries and optimal surface finish in final dosage forms.
Sensory properties	*Material Diversity* Equivalent capability to process materials with a wide range of properties. *External Design Flexibility* Coating capability for taste masking.

Nevertheless, of the manufacturing process requirements listed in Table 3, FDM and IM offered unique capabilities of compartmentalizing and coating, with FDM's freeform fabrication indicating particular benefits for both interior and exterior design flexibility with high geometric complexity [119, 154, 160, 178, 185, 205, 217, 218]. Without this capability, complete requirements for appearance, sensory properties, and especially the drug release functionality, would not be achievable. Therefore, FDM was selected as one process warranting further investigation in this thesis. However, conventional FDM typically requires upstream processing by HME for its operation. Incidentally, per the suitability analysis, maintaining a homogeneous melt during deposition from the FDM nozzle is dependent on the generation of homogeneous melts by HME, particularly at small length scales relevant for fine tuning product features such as the dose. HME was also expected to allow greater API payloads to be incorporated into its filament extrudates. Together, FDM and HME may be viewed as complementary with respect to the product features they are suited to individualize. This contributed to their rational selection as the focal process technologies in this thesis.

5.1.1. Additive Manufacturing of Pharmaceuticals (Technology in Focus: FDM)

Additive manufacturing is characterized by layer-by-layer deposition of materials to generate a three-dimensional object, based on a virtual computer aided design (CAD) model or a scan [186, 219, 220]. Several additive manufacturing process categories have been described by ISO/ASTM 52900, which defines a common set of standards on additive manufacturing [221]. These process categories include material extrusion, material jetting, binder jetting, powder bed fusion, VAT polymerization, directed energy deposition, and sheet lamination [182, 222], of which only the first five in this list have applications in the pharmaceutical research setting thus far. The earliest additive manufacturing technologies date back to the 1980's and were introduced as a means to achieve rapid prototyping. Since then, applications of additive manufacturing have been extended to include rapid tooling and rapid manufacturing of components of products or entire products [222]. Although additive manufacturing has been employed in several engineering and biomedical applications, as well as in a few clinical pharmaceutical applications, it is not yet a routine manufacturing technology across the entire pharmaceutical industry [186]. Nevertheless, growing research activity in additive

manufacturing of pharmaceuticals is often attributed to advantages such as process flexibility, reduced material waste, the generation of complex parts, and the ability to introduce product variety through altered CAD models [220, 223]. Such advantages make additive manufacturing approaches promising for the manufacturing of dosage forms tailored to individual patient needs [173, 186]. As described above, of the additive manufacturing process categories, this thesis focuses on the material extrusion-based additive manufacturing process, FDM.

FDM is currently the most widely investigated additive manufacturing technology for pharmaceuticals in the research setting and the most dominant additive manufacturing technology for oral formulations [48, 177, 178, 196, 201-207, 224]. For specific remarks on current and ongoing research on FDM in pharmaceutical applications, the reader is referred to the appended *Articles I, II, and III,* and the references contained therein. In addition to the affordability and availability of FDM printers for lab-scale use, its benefits are analogous to those of additive manufacturing technologies in general, and therefore largely attributed to complex product design capability and process flexibility. Like additive manufacturing technologies in general, FDM is based on digitally controlled deposition of successive layers of material to generate a three-dimensional object from a digital model. Specifically, FDM conventionally involves the feeding of a thermoplastic polymeric filament into a heated chamber leading into a heated nozzle through which the molten or softened polymer is extruded and deposited onto a platform, where it solidifies (Figure 11) [178]. FDM is preceded by HME in order to generate the filament feedstock required for subsequent printing.

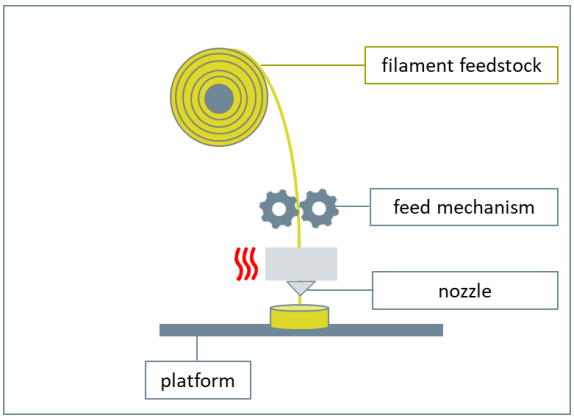


Fig. 11. FDM process from filament feedstock input to solid three-dimensional object output.

5.1.2. Hot Melt Extrusion

HME generally involves feeding of thermoplastic material *via* a hopper into a heated barrel containing either a single screw or two co-rotating or counter-rotating screws (Figure 12). Upon feeding, exposure to heat from the barrel and shear stress from rotating screws subject the material to melting, conveying, mixing, and ejection through a die [48, 187, 190, 191]. HME, when applied to pharmaceutical materials, involves the use of an API in a polymeric carrier in a minimum of a binary system. HME occurs upstream of the FDM process when applied to the generation of filaments for FDM, with both processes typically operating as discrete unit processes instead of in continuous mode. Unlike FDM, which currently lacks widespread industrial-scale applications for pharmaceutical solid oral dosage forms, HME is, in fact, one of the most utilized industrial-scale solid dispersion manufacturing processes [187, 225-228]. The following section summarizes the suitability of HME and FDM with regards to each of the manufacturing process requirements for individualization.

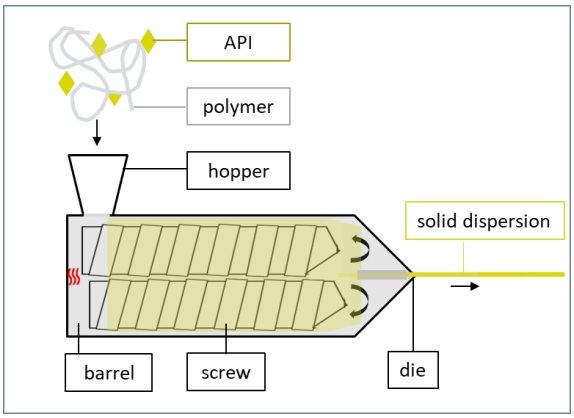


Fig. 12. HME process from raw material (API and thermoplastic polymer) input to solid dispersion output.

5.2. Suitability of Hot Melt Extrusion and Fused Deposition Modelling for Meeting Manufacturing Process Requirements for Individualization

5.2.1. Material Diversity

The range of processible APIs and excipients by HME and FDM are comparable and currently narrower than the total range of approved APIs and excipients, therefore absolute multifunctionality is not yet possible with either technology. The range of APIs are limited to those that are not thermosensitive [225] and excipients used are restricted

to thermoplastics. Regardless, unlike direct compression and wet granulation commonly employed in solid oral dosage form mass production, HME and FDM may remain advantageous for oxygen-sensitive, moisture-sensitive, and poorly water-soluble APIs [191]. Furthermore, their modular designs, with separate hoppers, barrels, and exit die configurations for HME and multiple nozzles for FDM, may allow interchangeability of excipients and APIs and simultaneous processing of multiple APIs.

5.2.2. Payload Flexibility

Due to its ability to achieve dispersive and distributive mixing, HME can potentially incorporate APIs across a wide drug loading range, whilst maintaining homogeneity of the drug in the polymer(s). Material compatibility plays a key role in payload flexibility regarding solubility or miscibility of the API in the selected polymer(s) and potential API–polymer interactions. The incorporation of high drug loads is of critical importance since restriction to filaments with low drug loads could result in unacceptably large dosage forms or an unacceptably high pill burden, depending on the required dose. Since HME provides mixing and the resulting feedstock for downstream processing by FDM, FDM payload flexibility is primarily derived from that of HME.

5.2.3. Precision Dispensing

The ability to accurately and precisely dispense both small and large volumes through nozzles and dies, which requires appropriate material rheological properties [211, 229], is critical to fine tuning product features such as the dose. Precision dispensing from the HME die is largely dependent upon which downstream processes are available for sectioning of the extrudate. Varying shapes and diameters of the extruder dies may allow the thickness or diameter of the extrudates to be adjusted. When higher drug loads are incorporated into the resulting extrudate during HME, in the case of drugs remaining in crystalline form, there may be a hindrance to ejection through the FDM nozzle. FDM processing temperatures can typically reach higher values than required for melting pharmaceutical materials, therefore, this depends largely on the window between the melting temperature and degradation temperature of the API. Small volume dispensing precision depends on printer resolution [230] and the ability to eject materials, which have different viscosities, through the nozzle [231]. Nevertheless, complex

layered or compartmentalized structures have been demonstrated previously with FDM, allowing the API layer or compartment to contain a polymer with lower viscosity upon melting surrounded by a structurally supportive polymer [218, 232, 233].

5.2.4. External and Internal Design Flexibility

External and internal design flexibility are required primarily for the dosage form appearance and for the tailoring of drug release, where both materials and geometry play a key role [163, 234, 235]. In this thesis, compartmentalizing capabilities are favoured for independent control of different product features through their spatial separation (*Article III*). Despite an ability to produce a variety of shapes through varying exit die configurations, for example, granules or pellets, HME lacks compartmentalizing capabilities [190, 236]. Furthermore, there is a reliance on downstream processing to generate the final dosage form. FDM, which represents a potential downstream process, is capable of freeform fabrication of a wide variety of sizes and shapes with varying geometric complexities. FDM is particularly advantageous for the simultaneous processing of several materials into the final product or module geometry, allowing coated, multi-layered, or compartmentalized dosage forms to be generated. However, the lower limit for printing smaller sizes is subject to the same considerations described in Section 5.2.3.

Interestingly, the process requirements for individualization are also the key manufacturing process challenges for individualization as technologies are applied to a wider spectrum of materials. This indicates that process requirements are not only intrinsic to the process capabilities but often depend on the materials that are being processed. The next section highlights some of these material and manufacturing trade-offs encountered in this thesis.

5.3. Material and Manufacturing Trade-Offs

Despite the apparent suitability for HME and FDM in meeting the aforementioned manufacturing process requirements for individualization, this thesis unveiled key material and manufacturing trade-offs, which need to be addressed in order to enhance the full technology potential for individualization. This section focuses on FEL in EC

(*Article II*), PLA (*Article III*), and PVA (*Article III*), at the material–manufacturing technology interface.

5.3.1. Dispensing Precision and Material Diversity During FDM

Figure 13, which presents the percentage relative standard deviations (% RSD) in mass during FDM dispensing of various materials at comparable print volumes, shows that FDM dispensing precision is not an intrinsic technological capability but rather shows a strong dependence on the specific material being processed.

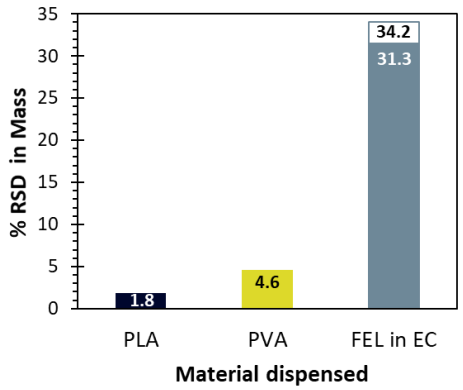


Fig. 13. % RSD in mass during FDM dispensing of various materials at comparable volumes including PLA, 25 mm^3, n=20; PVA, 32 mm^3, n=20; and FEL in EC, 25 mm^3 (hollow bar) and 39 mm^3,(solid grey bar), n=29.

Figure 13 shows that the drug-containing filament has a considerably lower dispensing precision than pre-manufactured PLA and PVA filaments at the volumes dispensed from the FDM nozzle. Despite an acceptable precision in dispensing both PLA and PVA within 5% RSD in mass, PVA showed a lower dispensing precision (4.6% RSD) than PLA (1.8% RSD) at similar printing volumes. Two considerations are important for dispensing precision at the material–technology interface. Firstly, material compatibility with the feeding system and secondly, deposition from the nozzle. The typical FDM feeding system, as shown in Figure 11, consists of a feed mechanism comprising two drive gears whose rotation drives the filament downwards towards the heated nozzle. The filament feedstock acts as the piston, which pushes the molten or softened material out of the heated nozzle onto the platform. Filament mechanical properties are therefore crucial for feeding through the drive gears [237]. The FEL in EC system forms a highly brittle feedstock with insufficient flexibility to withstand compression by the drive gears. The imprecision shown for the FEL in EC system reflects

a reliance on manual feeding in this study (*Article II*) to circumvent the lack of feedability through the drive gears. For such systems, inclusion of plasticizers or polymer blends may improve mechanical properties to facilitate consistent, automated feeding [201], however, this may involve further trade-offs with final product performance or stability. Suboptimal feeding of drug-containing filaments can indeed reduce the overall material diversity of FDM. Notably, the pace of technological evolution in this area has, since the process design suggestions put forth in *Article I* and since the execution of these studies in this thesis, resulted in modified feeding mechanisms to those of typical FDM that can avoid the need for filament feedstocks altogether [238-240]. The FEL in EC bar in Figure 13 represents the average dispensing precision for three drug loads, namely, 5% w/w FEL in EC, 30% w/w FEL in EC, and 50% w/w FEL in EC. Although different material viscosities for each of these compositions were expected to influence dispensing precision from the nozzle, no correlation was noted between the dispensing precision and the drug load in the filament. In this case, the reliance on manual feeding had a more prominent influence on dispensing precision, which could have masked any imprecision arising from material viscosity differences at the nozzle end.

In comparison, PLA and PVA exhibited considerably improved dispensing precision. They were both commercially available, prefabricated filament feedstocks amenable to consistent, automated feeding through the FDM drive gears. Here, material viscosity differences at the nozzle end are expected to contribute more to dispensing precision. Provided the temperature processing windows are wide enough, nozzle temperature can be adjusted to allow extrusion through the nozzle without degradation and without deformation of the filament between feeding gears. Although temperature adjustments are expected to contribute significantly to the materials' melt viscosities and feedability, the feasibility of using fine adjustments in temperature to modulate viscosity effects at the nozzle end requires consideration of the heat distribution in the filament over the short residence times at the nozzle. Feedability can also be related to other material properties, like hygroscopicity in stored filaments. Taken together, this trade-off reveals a multidimensional material influence on dispensing precision, potentially exacerbated at low printing volumes.

5.3.2. Dispensing Precision and Internal/External Design Flexibility

Figure 14, from right to left, shows a gradual increase in % RSD in mass with a decreasing print volume (corresponding to a decline in dispensing precision with decreasing print volumes), eventually reaching a sharp increase in % RSD in mass beyond a certain low-volume threshold with the FEL–EC system investigated in *Article II*.

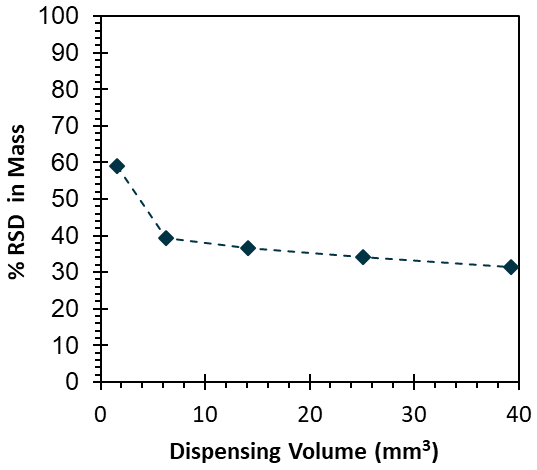


Fig. 14. % RSD in mass during FDM dispensing of FEL in EC filaments at progressively smaller print volumes, n≥27. Adapted with permission from https://doi.org/10.1007/s11095-019-2720-6 (*Article II*), © 2019 Govender *et al.* licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/legalcode).

These measurements are in agreement with an observed over-deposition of residual molten or softened material from the nozzle end at the end of the print. Even with materials that feed consistently and automatically, like PLA and PVA, this over-deposition at the end of the print may still occur, contributing to potential dispensing imprecision at small feature sizes. Figure 15 shows X-ray micro-computed tomography images, highlighting the over-deposition occurring for both PVA and PLA to varying extents (*Article III*). These may not be significant at large print volumes, corresponding to final dosage form sizes, but become critical at the small volumes associated with modular products and small feature size geometries. Due to the patient-centric size constraint on solid oral dosage forms to be swallowed intact, modularization inevitably demands small volume dispensing precision. Small feature sizes are also found in geometrically complex, non-modular dosage form designs and are important for achieving optimal surface finish. This trade-off is therefore not exclusive to modular product designs, although they are the focus of this thesis.

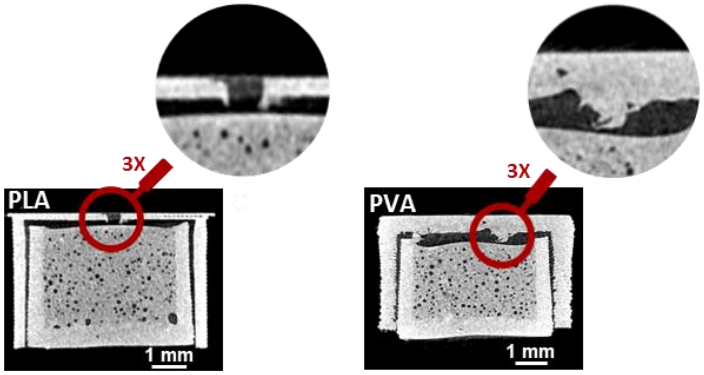
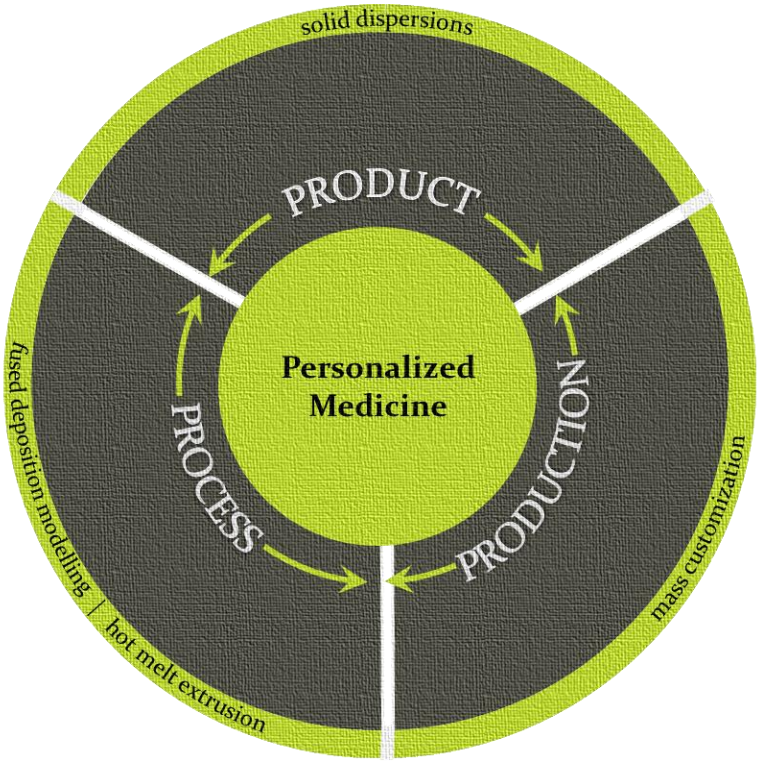


Fig. 15. X-ray micro-computed tomography images showing over-deposition from the FDM nozzle in printing PLA and PVA. Adapted with permission from https://doi.org/10.3390/pharmaceutics12080771 (*Article III*), © 2020 Govender *et al.* licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/legalcode).

Importantly, these trade-offs occur as a consequence of the process technologies' current abilities to individualize products according to the patient-centric product design requirements for individualized therapy. They are neither introduced by mass customization nor modularization as a product design strategy to meet these requirements. As indicated previously, several of the apparent benefits of the process technologies for individualization are not merely intrinsic to the technology and largely depend on the material system being processed. This emphasizes the need for an integrated co-evolution of product–process–production approaches for individualized therapy, which will be discussed further in Chapter 7. Even when these trade-offs are appropriately managed, in order to bring promising manufacturing technologies closer to industrial realization of individualized pharmaceutical therapy, in addition to optimized process capabilities that respond to established patient needs, a systems perspective is required to consider factors such as cost, speed, reliability, and quality of produced parts [222, 223, 241]. So far, the discussions in this thesis have progressed from the product to the production approach to the process. In light of the material and manufacturing technology trade-offs highlighted in this section, the following chapter comes full circle and returns to the product dimension to explore the material systems in focus in this thesis.


solid dispersions
PRODUCT
Personalized
Medicine
PROCESS
PRODUCTION
fused deposition modelling
hot melt extrusion
mass customization

6

Melt-Extruded Polymeric Solid Dispersions in Individualized Pharmaceutical Therapy

The phrase "solid dispersions" has been used to broadly describe formulations of a drug finely dispersed in a carrier [242-245]. In this thesis, these carriers are also solids. Solid dispersions may be classified as crystalline or amorphous solid dispersions depending on the solid-state form of the drug and carrier (Figure 16).

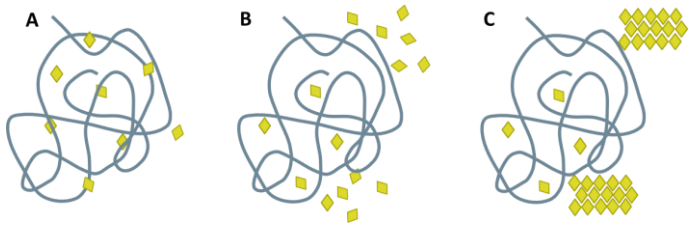


Fig. 16. Solid dispersions of drug molecules (green) in polymeric carrier (grey). Solid solution of molecularly dispersed drug in polymer (A); solid dispersion with amorphous drug aggregates (B); solid dispersion with crystalline drug aggregates (C).

Figure 16A depicts that solid solutions are a category of solid dispersion whereby the drug and carrier exist as a molecularly homogeneous single-phase system [246, 247]. Solid dispersions are not a specific requirement for individualized therapy *per se*. However, since individualized therapy demands applicability to a broad range of APIs, these include currently challenging API categories such as those with poor aqueous solubility. Poor aqueous solubility of a large proportion of new drug candidates remains one of the major challenges encountered during oral dosage form development since it often results in poor oral bioavailability and consequently, poor therapeutic effect. This has popularized solid dispersions, particularly solid solutions and solid dispersions with the drug in amorphous form, which provide a means to capitalize on the increased apparent solubility of the amorphous form, improving the dissolution rate and bioavailability of poorly water-soluble drugs [242, 245-257]. This is achieved either by dissolving the drug on a molecular level (Figure 16A) or maintaining the drug in amorphous form (Figure 16B), which reduces the energy barrier for dissolution when compared to drugs in crystalline

form (Figure 16C) [245, 254]. Not only can this approach improve bioavailability but improving the apparent aqueous solubility in this way could, in turn, allow reduced dosage form sizes, which incorporate an effective dose. Consequently, the eventual success of individualized therapy relies on surmounting major pharmaceutical hurdles in developing products which can elicit optimal health outcomes.

Incidentally, HME lends itself to the formation of solid dispersions and is in fact, one of the major processes employed for the manufacture of amorphous solid dispersions of APIs with poor aqueous solubility [226, 227, 244, 258, 259]. In order to exploit solid dispersions for their advantages in individualized therapy, the APIs and polymers contained therein are required to possess suitable material characteristics such as appropriate API–polymer miscibility, glass transition temperatures, and degradation temperatures [236, 252, 258, 260-266]. The physicochemical and thermal characteristics dictate stability against recrystallization during storage and *in vivo*, ability to obtain the target exposure, processability, and applicability to a wide range of APIs with varying thermosensitivities, which are all critical to the development of an individualized pharmaceutical product.

Whilst the entire solid dispersion research space is not within scope of this thesis, there are some benefits that are common to the field of individualized therapy and key findings with direct implications for individualized therapy. There are two major benefits of melt-extruded solid dispersions during individualization, namely, achieving a homogeneous distribution of the drug in the carrier at low and high payloads and achieving a process-induced change in the solid-state form of the API from crystalline to amorphous. The latter is only strictly required for APIs with poor aqueous solubility. Of all the product features for individualization, the benefit of amorphization pertains specifically to the release performance of the product or module. The following subsections highlight findings and considerations related to these benefits for the material systems studied in this thesis, namely, FEL in EC (*Article II*), MS in PEG 1500 and VA64 (*Article III*), FEL in VA64 (*Article IV*), and NAP in VA64 (*Article IV*).

6.1. FEL in EC

Typically, the aggregation tendency of drugs increases with their concentration in the polymer [248]. This could impact both drug content homogeneity and stability against recrystallization. *Article II* demonstrates that this is crucial since, within the scope of solid dispersions, the use of APIs at high drug loads, is a prerequisite for achieving pharmaceutically relevant dose flexibility for APIs with intermediate to high doses. Payload flexibility is a key requirement that was achieved with regards to drug content homogeneity with the FEL in EC solid dispersions studied in *Article II*. Figure 17 shows that not only was drug content uniformity maintained between 10% w/w and 50% w/w API, but it was achieved at module sizes ranging from 1.6 to 39.3 mm^3. Note that Figure 14 in Chapter 5 displayed % RSD in mass, not drug content. Since FEL in EC solid dispersions showed high variability in FDM dispensing precision, the results presented in Figure 17 reflect drug content normalized to the mass of each printed disc.

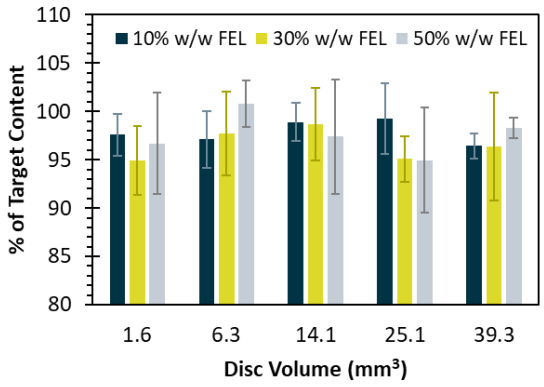


Fig. 17. Mean FEL content as a % of target FEL content in FDM discs at each composition and disc size (normalized to disc mass). Error bars indicate standard deviations of n=4 discs. Adapted with permission from https://doi.org/10.1007/s11095-019-2720-6 (*Article II*), © 2019 Govender *et al.* licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/legalcode).

This drug content uniformity reflects homogeneity in the feedstock at an equivalent or smaller length scale than the desired module size. In this regard, usually, the higher drug loads at which a solid solution can be achieved, the better for homogeneity. Figure 17 shows drug content uniformity within 10% RSD regardless of module size or drug load. The lower drug loads are necessary for fine tuning the dose, with the lowest dose indicating the smallest increment that can technically be fine-tuned. In this study that increment was demonstrated at approximately 50 µg based on the mean disc mass and

mean drug content in the smallest disc at the lowest drug load. This could be decreased further towards the inclusion of placebo modules. The highest required payload is determined by the upper dosing limit in the clinical range and the size constraint of the dosage form, regardless of whether or not modular product designs for reconfiguration are used. However, employing a modular design for reconfiguration imposes stricter requirements on the extent of homogeneity required at each payload in lieu of the fact that homogeneity should be assured on the length scale of a single module to harness the full potential of reconfigurability. As a hypothetical example, for a standard tablet containing 50 mg of API, this 50 mg can be distributed homogeneously on the length scale of a whole tablet without a strict requirement for each quarter of the tablet to contain 12.5 mg API each. However, designing for reconfigurable modularization demands that each module at a given payload contains an identical dose fraction of the drug.

This strict requirement on homogeneity is based upon patient-centric requirements for individualized dose and release at an appropriate dosage form size. Although it is not introduced by modular design strategies for reconfiguration, such strategies nonetheless need to surmount this challenge *en route* to individualizing therapy. Notably, conventional non-modular solid oral dosage forms, or even modular dosage forms comprising identical modules, may have a less strict requirement for homogeneity, as described in the hypothetical example above. However, such products are neither designed for multifunctional individualization nor for the provision of affordable variety as required for individualized therapy. Moreover, they are not entirely exempt from the homogeneity requirements posed by the need for payload flexibility. This is because many of these current pharmaceuticals are often treated as "modular" by patients or healthcare providers resulting in splitting or crushing of dosage forms to administer a portion of the dose, despite uncertainties regarding the length scales of homogeneity in such products [86, 88, 267-269].

Drug release was beyond the scope of this early investigation in *Article II*, however, both differential scanning calorimetry (DSC) and Raman spectroscopy on HME filaments revealed that FEL was converted to the amorphous form after HME and remained

amorphous for at least 2 weeks at ambient conditions. Figure 18 shows an absence of melting endotherms in melt extruded filaments at 10-50% w/w FEL in EC during the first heat cycle of DSC, indicating the formation of amorphous solid dispersions at each drug load by HME processing.

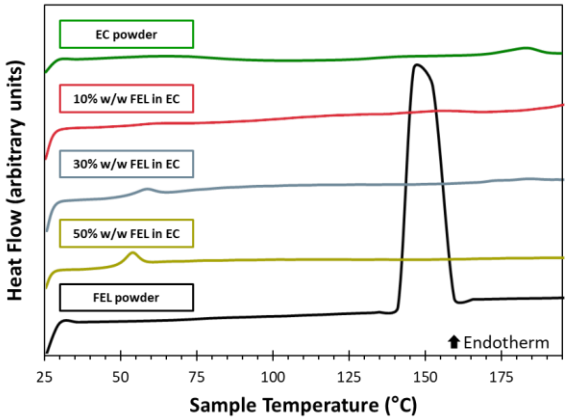


Fig. 18. DSC traces (endotherm up) of raw materials and extruded filaments at varying FEL drug loads during the first heat cycle. Adapted with permission from https://doi.org/10.1007/s11095-019-2720-6 (*Article II*), © 2019 Govender *et al.* licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/legalcode).

Figure 19 shows the Raman spectra of raw materials and the same melt extruded filaments subjected to the DSC analysis shown. Once the presence of FEL in each filament was confirmed at expected drug loads, the lattice mode region of their Raman spectra was used to distinguish between the solid-state forms of FEL.

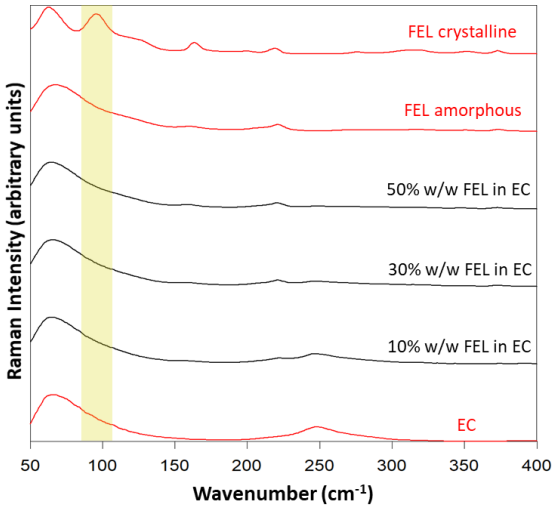


Fig. 19. Raman spectra of crystalline FEL powder, amorphous FEL, EC powder, and melt-extruded filaments at 10-50% w/w FEL in EC in the lattice mode region. Adapted with permission from https://doi.org/10.1007/s11095-019-2720-6 (*Article II*), © 2019 Govender *et al.* licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/legalcode).

In agreement with DSC, the Raman spectra confirmed a process-induced change in FEL from crystalline to amorphous during HME and a lack of FEL crystallinity maintained in the melt-extruded filaments for 2 weeks after HME when the Raman spectra were collected. This is shown by the absence of the characteristic sharp FEL band at 96 cm^{-1} [270] in amorphous FEL or in melt-extruded filaments at each composition. Methodological details for both the DSC and Raman analysis can be found in the appended *Article II*.

6.2. MS in PEG 1500 and VA64

Since MS has a high aqueous solubility, it was not a requirement to induce a change from crystalline to amorphous form during HME. Instead the melt-extruded solid dispersion was intended to ensure sufficient homogeneity for reproducible drug-containing components to be generated. To encourage homogeneity and reduce the likelihood of phase separation at length scales that would compromise homogeneity, materials with comparable solubility parameters were chosen. The system was also processed below the melting point of the drug to form a stable crystalline solid dispersion with the MS that is not solubilized by the carriers. In *Article III*, MS content in the cores of the fabricated modules was targeted at 40% w/w. Measured MS content along the length of the melt extruded filament was 39.4% ± 1.3% w/w, indicating high accuracy and precision at an approximately 6-fold smaller length scale (approximately 5 mg) than that required for the drug-containing core components of the resulting dosage form (approximately 30 mg). As the DSC trace in Figure 20 shows, crystallinity indeed remains in this filament despite some solubilization that occurs in the carriers.

For drugs with a high aqueous solubility, further additions of drug towards even higher payloads are acceptable even if they remain in crystalline form. However, the higher the drug load, the more crystalline or amorphous aggregates could contribute to a loss of homogeneity at smaller length scales. Although processing above the melting temperature can be used to solubilize MS at higher drug loads, the size and distribution of aggregates (crystalline or amorphous) relative to the desired size of the module will remain a key contributor to homogeneity of modular dosage forms for reconfiguration.

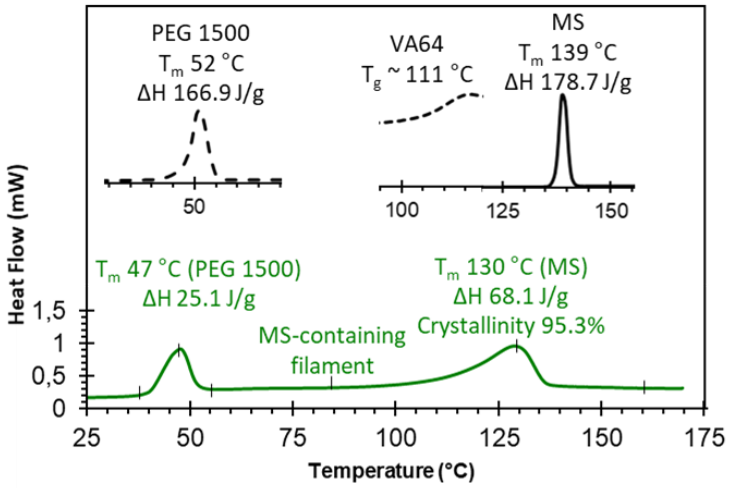


Fig. 20. DSC traces (endotherm up) of MS-containing filament for heat cycle 1 (green) with reference traces (black) for PEG 1500, VA64, and MS powder shown above. Adapted with permission from https://doi.org/10.3390/pharmaceutics12080771 (*Article III*), © 2020 Govender *et al.* licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/legalcode).

6.3. FEL in VA64 and NAP in VA64

Article IV extends the modular product concept for reconfiguration in at least two manners compared to *Articles II* and *III*. Firstly, it extends the concept to include the release performance of poorly water-soluble APIs, in addition to the dose, on a single module level. Secondly, it extends the concept towards multidrug therapy. During multidrug therapy, the administration of separate dosage forms corresponds to a higher pill burden than the comparable dose of single-drug therapy. When administered as combined dosage forms with modular architecture, i.e., polypills, for improved patient acceptability, a lower product volume is available per API to administer the same clinical dose as the single-drug therapy equivalent. This requires higher payloads to be incorporated into each API module, which may or may not be feasible for all types of API. With a focus on poorly water-soluble APIs, the dose and release performance of NAP and FEL were compared, with NAP having a higher inherent recrystallization tendency from amorphous form than FEL. This was anticipated to contribute to greater variability in drug release kinetics at a single module level, especially at high drug loads. Reproducibility in dose and release performance at a single module level is crucial to achieving the overarching product design requirement for individualization of simultaneous, independent individualization of multiple product features in a controlled and predictable manner.

For FEL in VA64 and NAP in VA64 at 50% w/w API, precise module fabrication (3.60 mg ± 0.05 mg in mass) and drug content homogeneity (within 1.5% RSD for FEL content and 5.0% RSD for NAP content) was achieved. Furthermore, both NAP and FEL were amorphous in the solid state. Under sink conditions with respect to crystalline solubility, with 50 mM sodium dodecyl sulphate (SDS) added to 0.1 M hydrochloric acid (HCl) at 37 °C, this precision fabrication and drug content homogeneity translated to reproducible dose fractions and drug release kinetics from both 50% w/w FEL and 50% w/w NAP modules, regardless of the recrystallization tendency of each API. Figure 21 shows that FEL and NAP exhibited comparable variability in the amount of drug released at T10 and T40 for 50% w/w drug load. Complete drug release was used to quantify the dose fraction in the module.

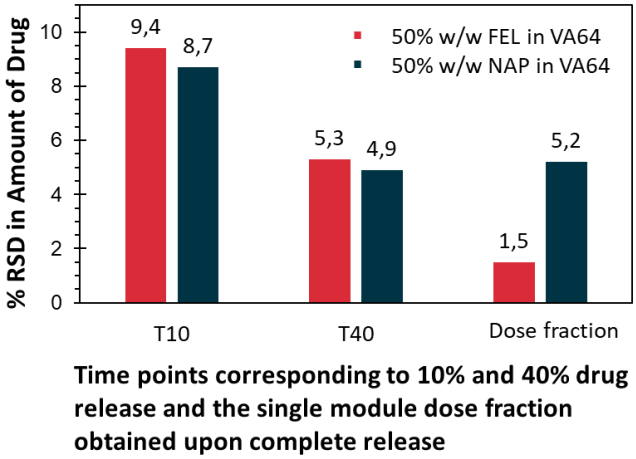
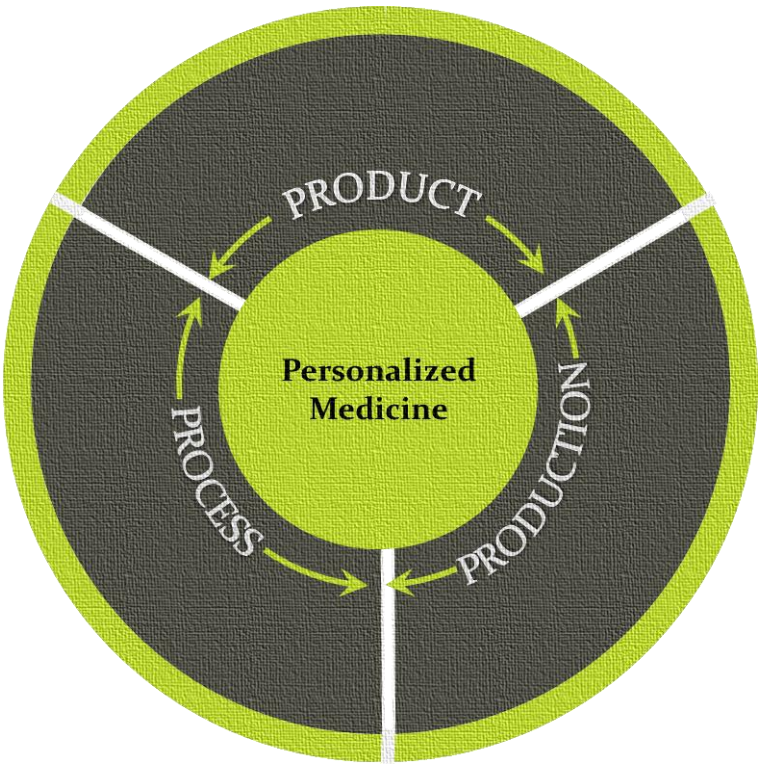


Fig. 21. % RSD in the amount of drug released from FEL and NAP 3.6 mg modules containing 50% w/w API (n=5) at T10 and T40 and % RSD in the dose fraction (quantified after complete release). The release medium is 0.1M HCl with 50 mM SDS at 37 °C.

Despite the low variability in release performance, the high drug load led to recrystallization at the surface of the module upon hydration for both FEL and NAP, which inhibited drug release under non-sink conditions with respect to the crystalline solubility of each API. Crystallization on the module surface upon hydration did not occur at 5% w/w of either API. The reader is referred to *Article IV* for drug release profiles of 5% w/w and 50% w/w compositions under varying tests conditions. With regards to higher payloads, without optimal polymer selection to inhibit this crystallization in the solid state and throughout dissolution, when non-sink conditions are encountered, lower drug loads may be needed for robust dose and release performance, which may

hinder applicability to individualized multidrug therapy. Importantly, payload flexibility encompasses both dose and release performance but has different implications depending on the properties of the API. For highly water-soluble APIs, payload flexibility requires precision fabrication and drug content homogeneity in single modules at a wide drug loading range regardless of the solid-state form. Robust release performance for poorly water-soluble APIs additionally requires the drug to be maintained in amorphous form both in the solid state and throughout dissolution. Recrystallization of poorly water-soluble APIs at higher payloads reveals a potential trade-off between payload flexibility and material diversity, which was due to the material system in this study and therefore differs from the material and manufacturing trade-offs presented in Chapter 5. Importantly, amorphization was achieved in the solid state using HME at 5% w/w and 50% w/w FEL or NAP in VA64, with sufficiently precise sectioning of the filaments to generate each module.

Payload flexibility is a critical challenge that needs to be addressed in order to meet individual patient needs for dose and drug release at an acceptable dosage form size, both for single-drug therapy and especially, for multidrug therapy *via* combination products. Whilst solid dispersions do exhibit key benefits for individualized therapy, fully exploiting these benefits require dedicated research efforts to incorporate varying drug loads with robust, reproducible performance. This challenge is faced by reconfigurable modular dosage forms for individualization and by conventional mass produced pharmaceutical solid oral dosage forms alike. It is therefore evident that whilst modularization does not introduce these challenges into product development, as a design approach for individualized therapy, it is obliged to fulfil stricter requirements to elicit predictable, desired performance.


PRODUCT
Personalized
Medicine
PROCESS
PRODUCTION

7

Integrated Product and Process Design for Mass Customization

This section holistically summarizes the previous chapters of this thesis to affirm the need for an integrated approach in the realization of individualized therapy and the existing drawbacks or risks associated with inadequate integration (research question iv).

In the context of eventual realization of individualized therapy, Figure 22 depicts the major challenge faced in delivering high product variety at low production volumes relevant for individualization.

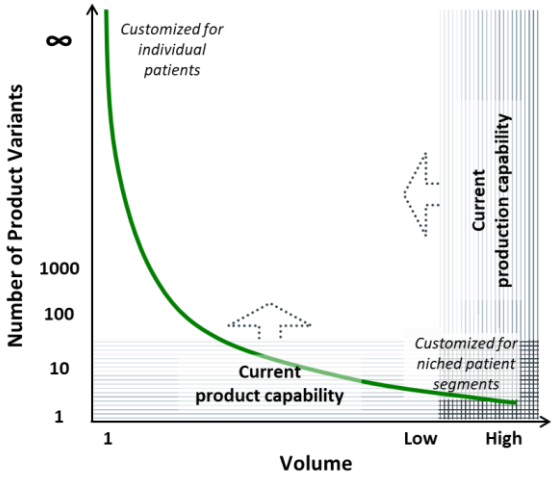


Fig. 22. The individualized therapy challenge faced at progressively lower production volumes and progressively higher number of product variants. Adapted with permission from https://doi.org/10.1016/j.ejpb.2020.01.001 (*Article I*), © 2020 Elsevier B.V.

The green curve illustrates that the progressively reduced production volume during individualization, for niched patient segments and, eventually, for individuals in an extreme "market-of-one" scenario, is accompanied by a considerable increase in the number of required product variants. The shaded areas correspond to current product and production capability, with patient needs being met at the intersection between the two, i.e., the cross-hatched region in Figure 22. Whilst some product variety is indeed provided currently, to take advantage of economies of scale, this provision of variety is restricted to higher production volumes and larger patient segments.

Providing enhanced variety for individualization requires both product and production capabilities to traverse the white area in Figure 22, which is not yet achieved. This could be due to a lack of technical capabilities and/or feasibility and/or that the requirements for closing this gap are not yet fully understood. Importantly, only pushing the capabilities of the pharmaceutical product towards an increased number of variants without also pushing production capabilities towards lower production volumes, will not achieve an overlap between product and production capabilities in the white area (cross-hatching) and therefore still restrict applicability to larger patient segments only. This means that, in a mass production context, even when a large number of product variants can technically be designed and developed for individualization, this is not sufficient if the production system cannot deliver affordability and efficiency at small production volumes. Co-development of both product and production in an integrated manner is therefore essential to successful individualization. This was one of the major insights from *Article I*, which reflects learnings in non-pharmaceutical branches of industry where mass customization has been explored or established [271]. Yet, the lack of pharmaceutical mass customization systems examples was recognized in *Article I*. In response to this gap, articulating the need for and demonstrating an integrated approach to realizing individualized therapy was identified as an important research and development direction in this thesis and onwards.

In this thesis, integration describes the combination of elements in a system to form a unified whole. The system elements addressed in this thesis are depicted in Figure 23 as patient, process, product, and production. These individual system elements are systems themselves. For example, the patient system element comprises the biological, behavioural, and environmental dimensions as well as patient preferences. Analogous to how these dimensions co-exist and interact within each patient, the system elements (patient, process, product, and production) also co-exist and interact. In fact, successful integration relies upon managing the interdependencies at the interfaces between these system elements [143]. For a system which delivers individualized pharmaceutical therapy, integration of the patient into the product–process–production system is a crucial first step. Patient integration relies upon scrutinizing individual patient needs and preferences and their link to therapeutic outcomes.

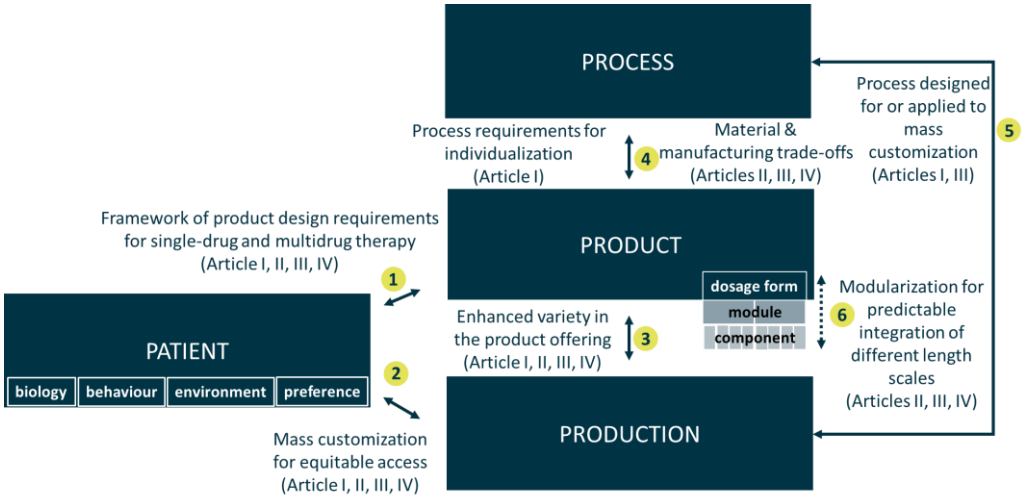


Fig. 23. System elements at play during integrated product and process design for mass customization based on individualized patient needs. Interdependencies are highlighted with arrows between system elements and key thesis contributions are indicated in the text fields.

At the patient–product interface (Figure 23, arrow 1), integration of the comprehensive needs and preferences of diverse individuals led to the patient-centric framework of product design requirements for single-drug and multidrug therapy. This is a major contribution and foundation of this thesis. This framework, as presented in Chapter 3 of this thesis summary, was proposed in *Article I* and technically verified and demonstrated in *Articles II*, *III*, and *IV*. Specifically, an overarching requirement for multifunctional individualization in pharmaceutical products arose, i.e., simultaneous, independent individualization of multiple product features in a controlled and predictable manner. At this patient–product interface, suboptimal integration of individual patient needs into the design and development of pharmaceutical products is a known contributor to suboptimal therapeutic outcomes in a proportion of the patient population during treatment with existing pharmaceutical products [23, 26-38]. Even during existing product design for individualization, fundamental examples of dose adjustments by adjusting the size of the dosage form, without consideration of patient limitations in handling and swallowability, reflect insufficient integration of patient needs into product design. Appropriately capturing patient needs in pharmaceutical products for individualized therapy is therefore one crucial aspect to contribute to overcoming the challenge of unmet medical needs.

Article I also addresses that, despite individualization being central to value-based and patient-centric care, the wider integration of the patient into the manufacturing and provision of pharmaceuticals had been little addressed prior to this work. Concurrent integration of the patient system element into both the product and production system elements highlights the need for a production approach that supports equitable access to individualized therapies (Figure 23, arrow 2). As Chapter 4 describes, both mass production and mass customization are designed for affordable access to pharmaceutical products. However, scrutinizing the product–production interface (Figure 23, arrow 3) reveals that the production approach utilized for individualized therapy must also support the provision of enhanced variety in the product offering. Therefore, mass customization, designed for both affordable, equitable access and high variety, was identified as the production context into which all other system elements would be integrated in this thesis.

The need for high variety in the product offering arises at the interface between product and production and is therefore not a direct patient requirement. The individual patient requirement is only that a specific product suited to their needs is available and accessible. The need for high variety at low production volumes for segments of the patient population, or individuals, is a means to cater to the heterogeneity in the patient population and is what enables a patient to obtain the product variant best suited to their individual needs. Without multidimensional integration of patient–product–production, full customization may emerge as attractive to meet patient needs at the patient–product interface and mass production may emerge to meet patient needs at the patient–production interface. An integrated approach is therefore essential to capture direct and indirect patient needs. Insufficient integration may explain why design for full customization or design for mass production approaches are still favoured in the research setting for individualized pharmaceutical therapy. Together, the first three arrows in Figure 23 already highlight the importance of an integrated approach to appropriately characterize the required system capabilities. Importantly, patient and societal benefits from individualized therapies can only be derived if their associated pharmaceutical products are designed, manufactured, and made accessible to patients and healthcare providers (*Article I*). This was addressed in Chapter 4 of this

thesis summary and *Article I*, with product modularization for mass customization forming the primary context of technical product design explorations and in *Articles II*, *III*, and *IV*.

The analysis of patients' medicine-related needs did not reveal any specific requirements that patients have of the manufacturing process. Instead, the process is required to meet patient needs indirectly *via* the ability to fabricate individualized products with high quality and performance (Figure 23, arrow 4) and *via* process design for a mass customization context (Figure 23, arrow 5). The latter is expected to involve integration of the entire manufacturing network into the supply of individualized products, which is beyond the scope of this thesis. Nevertheless, process design is expected to play a key role in achieving modularization, process flexibility, and postponement for mass customization. As such, a demonstration of reconfigurable modularization, as a product design approach in *Article III*, highlighted how product design can in turn enable process design for mass customization. For example, postponement may be facilitated through a product design that allows the module that provides differentiation to be assembled last and a process design that allows this to occur. In addition, a product design that enables the manufacturing of parts in parallel, instead of in a sequence of unit operations, was also discussed in *Article III*. Chapter 5 and *Articles II* and *III* revealed key material and manufacturing trade-offs at the product–process interface regarding material diversity, precision dispensing, and geometric flexibility. These trade-offs arise from required individualization of the product, with inherently stricter requirements to be met at the module level in modular dosage forms for reconfiguration compared to at the dosage form level for non-modular products or products comprising identical modules. The implication of integrating the process into the rest of the system depicted in Figure 23, is that regardless of what manufacturing type is used, e.g. continuous and/or additive manufacturing, its benefits for individualized therapy cannot be realized until it is designed for a production approach that can drive affordable access to a high variety of individualized products.

The combination of elements in a system to form a unified whole is equally applicable between system elements, as described above, and within each system element. Within

the product element (Figure 23, arrow 6), the integration of different length scales from component to module to dosage form, exhibits a strong likeness to the concept of modularization [272] to obtain dosage forms of predictable and predefined individualized performance. In this thesis, product modularization is not only a potential enabler of mass customization but also an example of integration between different length scales in the product system element. During integration between and within system elements, knowledge of the length scale at which integration is performed could provide essential guidance to the expected interdependencies at play.

As long as interdependencies exist in complex systems, co-development of system elements will remain crucial to the success of the overall system. Furthermore, the impact of specific interventions on the success of individualization can only be accurately determined once the effect of the intervention on interacting system elements are also known. Integration is also an approach to manage change in systems with interdependent elements. For example, despite the fact that the system elements depicted in Figure 23 are equally relevant for a mass production or mass customization production paradigm, a shift towards mass customization will demand managing changes within and across system elements. In this chapter and throughout the thesis, integration was largely addressed conceptually, with a few technical demonstrations in *Articles II*, *III*, and *IV*, of how successful integration may be achieved. Notably, successful integration is not achieved yet and will require that strategic/conceptual integration is accompanied by operational integration to industrialize and realize individualized therapy. In addition, further integration of the system elements depicted in Figure 23 with system elements belonging to the greater healthcare context will also require addressing in future [273-275].

A few key contributions of this thesis are described at each arrow in Figure 23, showing that most are not constrained within each system element but rather arise at the interface between interdependent system elements. Without sufficient integration, there exists a risk of having a fragmented and uncoordinated approach to individualized therapy. In the best case, this may delay realization of individualized therapy, with more frequent corrective adjustments needed along the way, or, in the worst case, this may

prevent realization of individualized therapy entirely. Altogether, this chapter emphasizes that, in order to realize individualized therapy and therefore maximize the value medicines bring to patients and society, an integrated approach is not only beneficial, but essential.

8

Concluding Remarks and Outlook

Individualized pharmaceutical therapy strives to optimize therapeutic responses *a priori* in all patients who are treated. Through combatting currently unmet medical needs, it has the potential to enhance the value of medicines for individuals and, by extension, society. This value reaches beyond improvements in health status to include wider social and economic benefits. However, it is crucial that the potential added value of individualized therapies is equitably distributed in society. Universal access is a major strategic priority in healthcare. It is here where pharmaceutical mass customization plays a pivotal role in ensuring equitable access to individualized therapies. Consequently, this thesis has provided the scientific and strategic foundation for elevating the prominence of pharmaceutical mass customization in upcoming research agendas. Emerging digital technologies, biotechnologies, advanced materials, and so forth, have the potential to solve several global challenges, of which unmet medical needs due to insufficient individualization is just one challenge. In order to leverage advancing science and technology for its potential benefits in individualized therapy, integration into the overall patient–product–process–production system and greater healthcare context is necessary to realize the ambition of individualized therapy without creating or widening inequalities in access to such therapies and to healthcare in general.

The patient-centric framework of product design requirements for individualization developed in this thesis, although based on oral dosage forms, provides a generic, systematic approach, which can be extended to various alternative product concepts as a means to translate patient needs into specific product design requirements in the context of mass customization. This framework is not intended to be a static collection of requirements but instead provides a foundation to be built upon and evolve as further insights into the patient experience and contributors to variability in health outcomes are gathered. A key gap area encountered in this thesis is the medical knowledge gap

regarding what constitutes individualized drug release, particularly for single-drug therapy where the need for concurrent administration of multiple medications is not a factor.

An overarching patient-centric requirement for multifunctional individualization was addressed and demonstrated, which applies regardless of the type of product the framework of design requirements is adapted to. Based on fulfilling a dual need for multifunctional individualization on a per product basis and the provision of affordable variety in the total product offering, a design concept based on reconfigurable modularization was demonstrated. Using this concept revealed how a wide assortment of mass customization opportunities may be harnessed and integrated to meet the requirements of individualized therapy. These opportunities include enhanced product variety, flexibility in use, economies of scale on the component level, and potential for process flexibility and postponement. Adaptation from a generalized concept to a specific product can therefore be facilitated by adopting similar design strategies to translate key mass customization principles, such as modularization, to the pharmaceutical value chain for the realization of individualized therapy. To this end, alternative dosage form types and routes of administration need to be evaluated to establish how far these generic design principles and benefits of reconfigurable modularization may be extended.

Key generalized manufacturing process requirements for individualized therapy were assembled. Despite the existence of high-potential technologies for individualization, a single manufacturing technology which exhibits all process requirements for individualization has not been encountered yet. An adaptation from concept to realization will further rely on addressing the key materials and manufacturing trade-offs highlighted in this thesis. In a rapidly evolving technological landscape, characterizing the extent of these challenges in patient-centric individualization of pharmaceutical products, provides a first step in directing design and engineering solutions that may enable individualization. In order to harness the full potential of these and other processes for individualized therapy, further research efforts dedicated to managing or diminishing these trade-offs will be essential. In addition, product and

process optimization for scale-up and automation as well as translation to clinical applicability *via* biopharmaceutical considerations for individual patients, are intuitive next steps.

Regardless of the processes eventually employed, a fundamental overarching consideration is that patient integration into the design of individualized pharmaceutical products requires a systems approach, involving concurrent development of product, process, and production platforms, which can drive access of individualized pharmaceutical therapies to patients. In this regard, this thesis served to lay the foundation for future design efforts towards the realization of accessible, affordable, individualized therapy.

Regardless of the choice of product design, process, or production approach, products for individualized therapy are subject to the same high quality and safety standards that apply to current pharmaceutical products. This thesis acknowledges but does not analyse the impact that mass customization may have on how quality is evaluated for products for individualized therapy. In this regard, progressing modular product design approaches will require quality requirements to be defined, at a minimum, for the dosage form, the modules, and the sub-modular components as well as appropriate methods to reliably evaluate these quality requirements.

In addition to satisfying process requirements for individualized product design, the manufacturing system, in its entirety, is also required to support mass customization in order to drive patient access to individualized therapies. An evaluation of the existing manufacturing and supply network to establish either suitability, future adaptations, or redesign for mass customization will be necessary to support the provision of and access to individualized pharmaceutical therapy. Mass customization as a strategic direction towards individualized therapy was selected to favour cost-effectiveness during variety provision. However, a cost analysis and health economics assessment were beyond the scope of this thesis. Nevertheless, they are expected to be crucial elements driving accessibility to patients when concepts for individualized therapy are closer to realization.

Finally, individualized pharmaceutical therapy is based in a health systems context and, as such, will inevitably rely upon a multi-stakeholder undertaking for its realization. This will include governments and policy makers, health insurance payers, regulatory bodies, scientific researchers, technical specialists in varying disciplines, healthcare providers, and of course, patients from all walks of life. A re-evaluation of the traditional roles of individual stakeholders throughout the pharmaceutical value chain and in society at large, together with increasing knowledge exchange to encourage development and cross-fertilization of competencies, can be anticipated on the road towards realization of accessible, affordable individualized therapy.

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"When you're writing a book, it's rather like going on a very long walk, across valleys and mountains and things, and you get the first view of what you see and you write it down. Then you walk a bit further, maybe up onto the top of a hill, and you see something else. Then you write that and you go on like that, day after day, getting different views of the same landscape really. The highest mountain on the walk is obviously the end of the book, because it's got to be the best view of all, when everything comes together and you can look back and see that everything you've done all ties up. But it's a very, very long, slow process."

— Roald Dahl

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Appendix

Table A1. Definition of contributor roles obtained verbatim from the Consortia Advancing Standards in Research Administration Information (https://casrai.org/credit/) as at January 2021.

Contributor Role	Definition
Conceptualization	Ideas; formulation or evolution of overarching research goals and aims.
Data curation	Management activities to annotate (produce metadata), scrub data and maintain research data (including software code, where it is necessary for interpreting the data itself) for initial use and later re-use.
Formal analysis	Application of statistical, mathematical, computational, or other formal techniques to analyse or synthesize study data.
Funding acquisition	Acquisition of the financial support for the project leading to this publication.
Investigation	Conducting a research and investigation process, specifically performing the experiments, or data/evidence collection.
Methodology	Development or design of methodology; creation of models.
Project administration	Management and coordination responsibility for the research activity planning and execution.
Resources	Provision of study materials, reagents, materials, patients, laboratory samples, animals, instrumentation, computing resources, or other analysis tools.
Software	Programming, software development; designing computer programs; implementation of the computer code and supporting algorithms; testing of existing code components.
Supervision	Oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team.
Validation	Verification, whether as a part of the activity or separate, of the overall replication/reproducibility of results/experiments and other research outputs.
Visualization	Preparation, creation and/or presentation of the published work, specifically visualization/data presentation.
Writing – original draft	Preparation, creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation).
Writing – review & editing	Preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision – including pre- or post-publication stages.