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Siiskonen, M., Folestad, S., Malmqvist, J. (2018). Applying Function-Means Tree Modelling to Personalized Medicines. Proceedings of NordDesign: Design in the Era of Digitalization, NordDesign 2018

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Applying Function-Means Tree Modelling to Personalized Medicines

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Abstract

Recent breakthroughs in diagnostics, genotyping and so forth, has created opportunities to satisfy the individual therapeutic needs of each patient, i.e. treatment can be tailored according to the patient's biological attributes as well as according to behavioural and environmental factors. Medicines, when tailored to the individual needs are often referred to as personalized medicines. So far, pharmaceutical production platforms are dominated by mass production in a batch manner with limited possibilities to fully satisfy the emerging customization needs of pharmaceutical products. To face the challenge of customization in an economically feasible manner, re-engineering of the product and production concept is inevitable. The aim of the present work is to introduce a novel approach to customize treatments by structural parameterization of the medicinal product concept. The primary adaption is here evaluated for solid oral dosage forms (SODFs), e.g. tablets. The tablet concept is re-designed to embrace a modular architecture. A platform approach, more specifically the Configurable Component (CC) method (Claesson, 2006), is used for efficient configuration of product families. To support the design work, computer-aided design tools are used. The Configurable Component modeller (CCM) (Claesson, op. cit.) is used for the function-means tree modelling of the tablet concept and from this product variants are automatically generated. The properties of the generated product families are then evaluated with regards to following criteria; product variety and manufacturing complexity to identify critical trade-offs.

Keywords: *Product Design, Digital Design, Product Platforms, Platform-based Design, Personalized Medicines, Mass Customization*

1 Introduction

In recent years breakthroughs have been made in diagnostics, genotyping and so forth, which has created opportunities to satisfy the individual therapeutic needs of each patient (Crommelin et al., 2011). This means, that a patient can be offered an optimal treatment according to the

patient's biological attributes such as for example genetics, age, and weight, according to behavioral factors such as for example administration difficulties, as well as environmental factors such as UV exposure, food and alcohol habits, as well as severity of dehydration. The factors mentioned above can be compared to *functional requirements* and *constraints* and can be connected to *design parameters* (Tjalve, 1979; Suh, 1990) such as the active pharmaceutical ingredient (API), the dose of the API, and the composition of the dosage form. Medicines, when tailored to the individual needs and designed according to these design parameters are often referred to as personalized medicines (Govender et al., 2017).

So far, pharmaceutical production platforms are dominated by mass production in a batch manner due to a highly regulated production environment (Plumb, 2005; Lee et al., 2015). A prevailing batch production paradigm is limiting the possibilities to fully satisfy the emerging customization needs of pharmaceutical products.

Approaches to customization of medicines are emerging in literature and mainly presented from two separate ends. The first end focuses on empirical attempts to customization of the product concept and the second end is focusing on an efficient production and a flexible handling of the increasing amount of product variants in the supply chain, which is a consequence from customization.

A direct consequence of moving from mass production to mass customization is not only the decreasing production volumes per product variant but also the increasing requirement on the flexibility of production, stemming from the increasing number of product variants. To approach these challenges continuous production processes for primary active ingredient processing as well as secondary formulation processing is widely researched (Lee et al., 2015). Additionally, reconfiguration of the supply chain of medicine production by adopting continuous processing technologies and integrating these with downstream processes such as product packing and distribution as an ambition to support management of increasing number of product variants has been evaluated (Srai et al., 2015).

However, we have not been able to find any reports regarding the integration of the product concept for customization with the production concept in the literature. To fulfil this gap, inspiration from the manufacturing industry could be taken. Thus, the present work suggests a novel approach to customize treatments, specifically solid oral dosage forms (SODF) of treatments, e.g. tablets, by adapting methodologies from manufacturing industry and applying these to enable mass customization of medicines. More specifically the Configurable Component (CC) method (Claesson, 2006), which is an expanded function-means tree modelling approach, has been used as an approach to establish a SODF product platform and to support efficient configuration of product families. A product family, in this study, is aligned with the definition by (Meyer & Lehnerd, 1997) and characterized by sets of product variants that share the same components as configurational means. Empirical attempts to customization of medicines have been reported in the literature but we have not found any reports regarding structural parameterization of the product concept. The focus of this study will thus be aimed at the product concept design but evaluations of the design implication on the manufacturing complexity will also be performed. However, the production concept of these customized medicines is out of the scope of this study. A discussion is conducted regarding the product design implications on the level of customization as well as the manufacturing complexity and, the sufficiency of the model to evaluate manufacturing complexity is assessed.

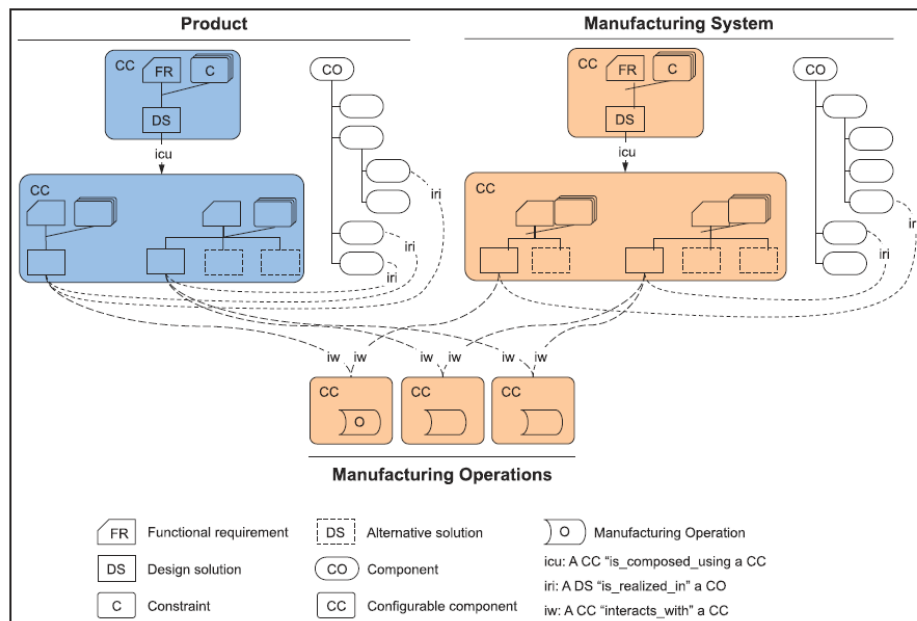


Figure 1. An overview of the integrated product and manufacturing platform (Levandowski et al. 2014).

Manufacturing industries, especially industries for discrete part production, such as for example the automotive industry, have realized the value of mass customization, i.e. producing streams of product variants, product families, to fulfill the needs of stratified customer groups, increasing the attractiveness of products, and thus, improve sales (Ho & Tang, 1998; Wortmann et al., 1997). Therefore, manufacturing industries have worked towards adopting methodologies to enable mass customization in an economically feasible manner. Product platforms are an example of such methodology and can be described as a technology, founded in a common structure, i.e. product architecture, and sets of subsystems and interfaces, that supports an efficient development and configuration of sets of product variants, called product families (Meyer & Lehnerd, 1997). According to Ulrich and Eppinger (2012), a product architecture is a basis for enabling configurations of product variants. Two approaches to this were presented by Du et al. (2012), a *modular* product architecture approach or a *scalar* architecture approach.

Levandowski et al. (2014) developed an integrated product and manufacturing platform model and applied for a case study in the aerospace industry, see figure 1 for an overview of the model. In this platform approach, the modelling is performed by the CC method which is an approach to function-means tree modelling and a tool for a joint modular and scalar product architecture approach to enable product variety (Claesson, 2006). The CC method provides a system structure, product architecture, that consists of several configurable subsystems, configurable components, operating independently but providing functions to the overall performance of the system. These independent subsystems provide the system with a modular structure. The modelling of functions and the design solutions of the functions of each configurable component, subsystem, is realized through function-means tree modelling. This allows for design bandwidths of each function and its design solution, and hence a scalable design of the subsystems is achieved (Claesson, op. cit.).

The remainder of the paper is organized as follows; section 2 describes the method used in this study, the modelling approach, as well as the experimental set-up and clarifies assumptions made. Section 3 presents and discusses the results of the modelling as well as from the experimental work and section 4 concludes the work and discusses opportunities for future work.

2 Method

This section provides a short description of the system modelling approach, the experimental work carried out, and assumptions made during modelling.

2.1 System model and experimental set-up

To conceptually structure a solid oral dosage form (SODF), more specifically in this study a tablet, into its functions, the CC method is used. In this study, the tablet is embracing a modular architecture and thus, the subsystems of the product architecture are physically realized by standardized modules. These modules are the building blocks of the tablet and embed one or a few functions of the tablet. More specifically, this study focuses on the functions *treat disease* and *provide a suitable size* of the SODF and thus, the standardized modules used for product configurations are modules containing an active pharmaceutical ingredient (API module) and modules for filling purposes (filling module). A system configuration, a product variant, is realized as an assembled entity.

To identify opportunities with a modularized tablet concept, system model evaluations needs to be performed and for this purpose, the cases presented in table 1 are simulated. The different cases, use different sizes and combinations of standardized API modules as building blocks to configure a product variant.

Module sizes that the different cases use for product configuration are marked *x* in table 1. For example, case A uses API module of a single size, 1, and case D uses a combination of two sizes of API modules, sizes 1 and 5, and so forth for configuring product variants. The API module sizes are given in mass units since this is the commonly used unit for dosages of medications, usually given in mg, but to keep it general the expression *mass units* is used.

The drug loading of the API modules is set to 80% (80% of the module consists of the API and the remaining consists of another material, for example, material for binding purposes) and the proportionality constant for converting mass units into volume units is set to 1 for the API modules. The order of magnitude of these modules are in mm³, but to keep it general the expression *volume units* is used. The API modules are embracing a cubic shape. Additionally, each case has access to filling modules of one standardized size, 1 mass unit, for system filling purposes. The proportionality constant for converting mass units into volume units is set to 1. The filling modules are embracing a cubic shape.

Table 1. Cases for system model simulations. Module sizes that the different cases use for product configuration are denoted *x* in the table.

		API modules			Filling modules
		1 mass unit	5 mass units	10 mass units	1 mass unit
Cases	A	x			x
	B		x		x
	C			x	x
	D	x	x		x
	E	x		x	x
	F		x	x	x
	G	x	x	x	x

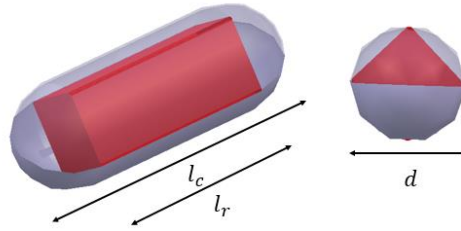


Figure 2. A capsule enclosing a cuboid seen from two perspectives and including the dimensions for calculations of the maximum volume of the system.

2.1.1 System size and shape

The minimum size of the system is set as 4 volume units embracing a cuboid shape and dimensions of $2 \times 2 \times 1$. This follows results from a study performed on children's, aged 0.5-5 years, preferred medication, concluding that mini-tablets of a cylindrical geometry with a diameter of 2 mm was the preferred choice (the height not stated) (Klingmann et al., 2013).

The Food and Drug Administration (FDA) (2015) provided recommendations regarding largest tablet and capsule sizes to ensure convenient administration. These provided measurements such as the largest dimension of a tablet should not exceed 22 mm and the capsule size should not exceed the standardized capsule size 00. A capsule size 00 has slightly different size properties depending on the manufacturer and in this study, the size properties are chosen according to capsules produced by Medisca (n.d.). The overall closed length of a 00 size capsule is 23.3 ± 0.3 mm, dimension l_c in figure 2, the external diameter of the body part is given as 8.18 ± 0.06 mm, dimension d in figure 2. The cap part has a slightly larger diameter, 8.53 ± 0.06 mm, but as a measurement, the body diameter is used.

To comply with the FDA recommendations regarding tablet and capsule sizes, but simultaneously simplify the calculations, it is assumed that a capsule of size 00 is enclosing a rectangular cuboid where the smallest face embraces a square geometry. The diagonal of the smallest face, denoted d in figure 2, is equal to the largest diameter of the capsule, stated as 8.18 mm above. The capsule is assumed to embrace the form of a cylinder with full half spheres attached at the respective end and thus, the length of the rectangular cuboid, denoted l_r in figure 2, has the same length as the cylindrical part of the capsule. The volume of the cuboid is then 506 volume units and this value is used in the simulations as the maximum system volume. Additionally, it is assumed that if the total volume of the modules in the system is less or equal to the maximum volume depicted here, they still assemble to a conveniently sized tablet. The order of assembly of the modules and thus, the resulting geometry of the assembly is out of the scope of this study.

2.2 System simulation and data analysis

The system response is evaluated for two scenarios:

- 5 dose levels; [20:20:100]
- 100 dose levels; [1:1:100]

The smallest dose, the step length in between the dose levels and the largest dose are stated inside the brackets.

A combinatorial problem is solved to calculate the number of product variants, system configurations, that each case presented in table 1 can generate for each dose level. All the product variants for each case represents a product family. The combinatorial problem is solved

in the CCM software (Claesson, 2006), which compiles a list of all product configurations. This list is then exported to MATLAB to filter the data as well as to calculate the number of product variants.

The manufacturing complexity, as an indication of the assembly cost, of a product variant is evaluated by applying the complexity factor, introduced by Pugh (1990). According to Pugh the complexity factor, C_f , can be defined as follows if the number of functions are equal for each product variant;

$$C_f \propto \sqrt[3]{N_p N_t N_i} \quad (1)$$

Where N_p is the number of parts, N_t is the number of types of parts and N_i is the number of interconnections and interfaces in between the parts in an assembly.

To calculate the number of interfaces, N_i , in between each module in a product configuration, the order of assembly needs to be known. As assembling of the modules is outside the scope of this study, the following is assumed; each face of a module is interconnecting to exactly one other module (as if each module would be of the same size). The form of the total assembly is maximized as a cube and the leftover modules are assembled as additional rows in one dimension. The calculations are performed in MATLAB. Since each case can generate a family of product variants solely at one dose level, to simplify analysis the mean number of the complexity factor on each dose level is calculated for each product family.

3 Results and discussion

This section presents the resulting system model of the tablet, as well as, the results from the system simulations and trade-off curves of compiled results. Discussions of the results are provided.

3.1 Adaption of function-means tree modelling to medicinal product design

Figure 3 presents a suggested architecture of a solid oral dosage form (SODF) structured conceptually into its functions and encapsulated as independent subsystems with the aid of the CC method. This architecture is describing a tablet containing an active pharmaceutical ingredient (API) and filling material.

Each autonomous CC object in figure 3 embeds an enhanced function-means tree that describes the design rationale (DR) of that subsystem and thus, consists of the functional requirements (FR), design solutions (DS) and constraints (C) of the subsystems. In the architecture of a SODF, the primary function is to provide treatment, hence the FR of the CC object is *Provide treatment*. This FR is realized through the DS *tablet*. The tablet is constrained with regards to size, a minimum volume of 4 volume units and a maximum volume of 506 volume units. Even though, the FR *provide treatment* is realized by the DS *tablet* it is not restricted to one DS but could as well be realized by several DSs, such as for example capsule filled with pellets. But, as the first attempt to functional modelling of a tablet the focus is rather on evaluating if functional modelling of a tablet can be made using the CC method, and thus, only a few functions of a tablet has been included in the model.

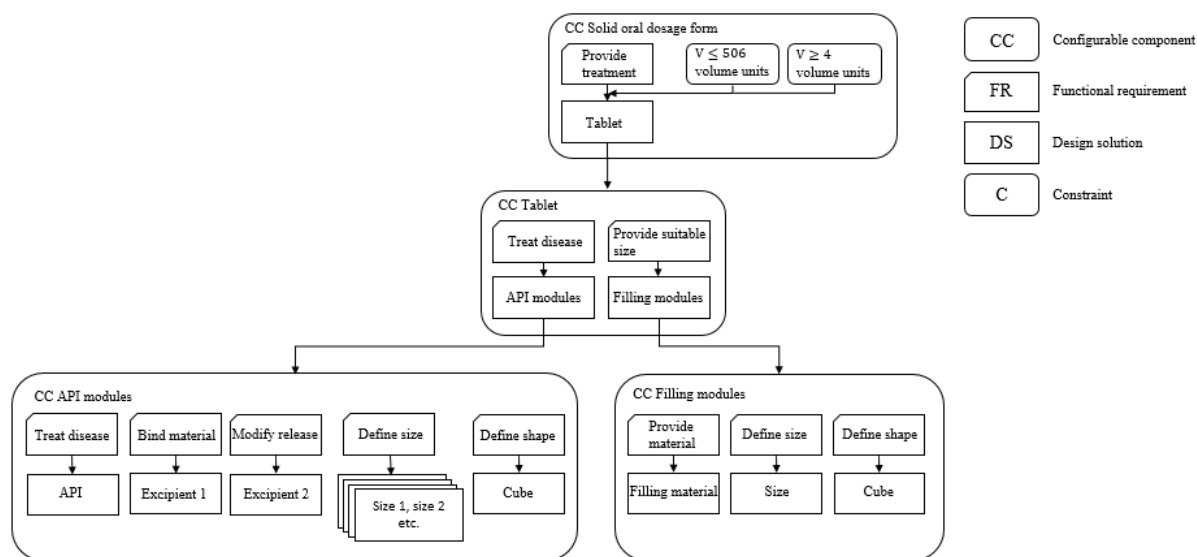


Figure 3. The architecture of SODF modelled by using the Configurable Component method.

The DS *tablet* is structured into sub-functional requirements (sub-FRs) such as *Treat disease* and *Provide suitable size*. These sub-FRs are realized by the DS *API modules* and DS *Filling modules* respectively. Each sub-FR interacts with one another to form a system, the tablet, and thus this is encapsulated as a CC object. Likewise, the DSs to the FRs of the CC object *Tablet* are realized through independent subsystems and thus, are encapsulated into autonomous CC objects.

The design solutions *API modules* and *Filling modules* are further structured into sub-FRs, such as *Treat disease*, *Bind material*, *Modify release*, *Define size*, *Define shape* and *Provide material* for the DS *API modules* and *Filling material*, *Define size* and *Define shape* for the DS *Filling modules*. These sub-FRs are realized by respective design solution and thus, composes autonomous CC objects. Note, that the FR *Define size* of the CC object *API modules* is realized through several design solutions and thus, provides a set of alternative solutions to that function, hence, platform approach.

The CC objects *API modules* and *Filling modules* are modelled as one CC object respectively but the physical realization of the CC object consists of several modules. For example, a product variant is not configured from solely one API module providing a dose of 20 units, but rather 20 modules providing a dose of 1 unit each and as a system constitutes the whole dose of 20 units. This is possible to model due to the scalability properties of the CC method and thus, a modelling decision was made to scale the number of modules used to generate product variants of the CC object, simply, to increase the flexibility of configuring product variants and thus, increase the opportunities of product customization. Not only, by varying the number of API modules, can systems of different doses be configured, but also, by varying the number of filling modules, variety regarding size and shape of the systems can be facilitated, and thus, this could aid treatment of children and elderly as it has been reported that these groups pose administration difficulties (Breitkreutz & Boos, 2007). This, however, differs from the modelling approach in the manufacturing industries where the scalability property is generally used to, for example, tamper with the size of one object and not to tamper with the number of standardized objects.

Modularizing the tablet concept is not restricted to the increased level of customization of one treatment solely but, provides an opportunity for combination therapeutics. Combining several

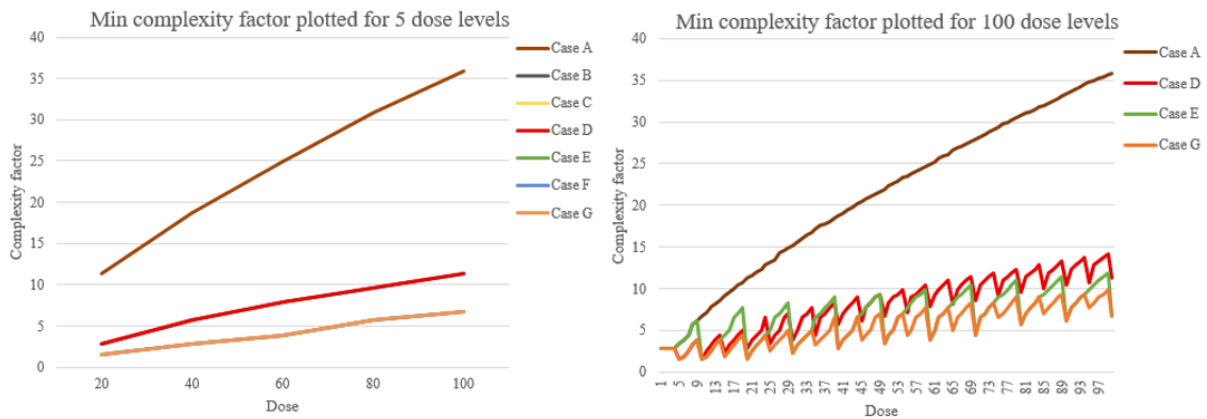


Figure 4. The lowest assembly cost indicated by complexity factor of product variants for each dose level of each product family, at 5 and 100 dose levels.

API into one tablet could especially aid an ageing population who generally are under several treatments. At the extreme, each module in the system, the tablet, could be a unique active pharmaceutical ingredient (API). However, restrictions arise from the resulting sizes of the tablets to still prevail a convenient administration. A large dose indicates increasing number of modules and thus, the size of the system can rapidly increase. Material properties is another restriction to freely modularize, assemble and combine. Material suitability is essential, especially highly potent active pharmaceutical ingredients might restrain opportunities.

3.2 Design and the implications for system response

Figures 4 and 5 present results from system simulations, of system configurations, consisting of one API, for product families of five and 100 dose levels. Note that the simulations for 100 dose levels, do not present cases B, C and F. That is since the sizes of the modules are inconvenient and thus, cannot provide a product variant of each dose level simulated.

Figure 4 presents the lowest resulting assembly cost, indicated by the complexity factor, of each case at each dose level. For 5 dose levels a minimized assembly cost is provided by product variants of product families for cases C, E, F and G and for 100 dose levels a minimized assembly cost is provided by a product variant of the product family for case G. A minimized assembly cost requires increased sizes of standardized modules, but on the contrary, an increased module size might not be able to provide product variants for each dose desired. A product family consisting of several standardized modules of different sizes can result in low complexity factor by configuring a product variant from the module combinations giving the lowest complexity factor but simultaneously generate product variants for each dose level desired.

The lowest assembly cost can give an indication of the best system design only if the dose of the system is considered and thus, the product variant of a product family minimizing the assembly cost is considered as the suitable system design. However, a product family can provide several product variants, equal with regards to the system dose, but unique regarding the combinations of modules used as building blocks for product variant configuration. Thus, these product variants differ from each other with regards to size and shape, which can be varied with the aid of filling materials as well as with the aid of different module types, which in this study are differing in size. Considering that the size and the shape of a tablet are proven to have an impact on the release of the API in the body, the order of assembly of the modules is important (Goyanes, 2015; Siepmann & Siepmann, 2012). This facilitates opportunities to

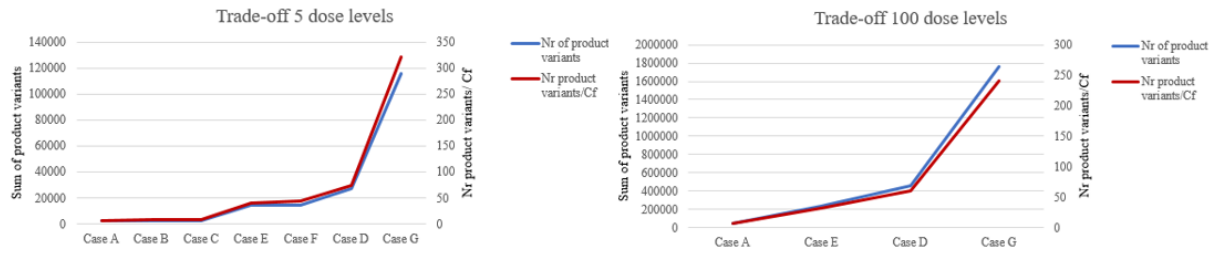


Figure 5. Trade-offs between the sum of the product variants at each dose level, for 5 and 100 dose levels and the ratio of the number of product variants and the complexity factor.

manipulate the release rate of a system solely by introducing different assembly sequences. Product families can construct several unique product variants at one dose level and thus, increase the level of customization. Even though assembling of the modules is out of the scope of this study and thus, the resulting shape of the assembled product variants will not be discussed in more detail, it is important to point out that the increasing number of product variants provides opportunities for customization in various ways and thus, solely choosing the complexity factor as an indicator for best design is not sufficient.

Trade-offs between the *number of product variants* and the ratio of the *number of product variants* and the *complexity factor* for product families are presented in figure 5 to emphasize an increased customer value (associated with an increased level of customization) and thus, judged to provide a better foundation for design decision making. On the horizontal axis, the resulting product families are ordered in an increasing order with regards to the number of product variants. The *number of product variants* is plotted on the primary axis, to the left, and given as a sum of every product variant of each product family at all dose levels simulated, solely considering the unique combinations the modules can generate. The ratio of the *number of product variants* and the *complexity factor* is plotted on the secondary axis, to the right. The ratio, in this case, is given as a mean number of every product variant of each product family on all dose levels.

An evident result, as seen in figure 5, is that the *number of product variants* can be rapidly increased by introducing few standardized modules as building blocks for constructing a product family. Additionally, the ratio of the *number of product variants* and the *complexity factor* is showing the same behaviour and thus, this means that the complexity factor, for product families embedding modules of several sizes, is not increasing as fast as the number of product variants for these families. Thus, a product family consisting of several standardized modules would be a suitable design choice for the SODF.

The validity of using the complexity factor as an implication of manufacturing complexity needs further investigation, though. In this study, the number of dimensions of a product configuration was complicating the usage of the complexity factor. For example, a product family could at one dose level consist of several identical product variants regarding the dose of the system but different from the size, shape and consequently the release behaviour point of view. But, to conduct simple analysis a mean value for each product family was calculated on each dose level. The complexity factor seems to be a more suitable approach in the manufacturing industry, where the product families are smaller and a complexity factor of each configuration can be calculated and analyzed.

4 Conclusions and future work

Function-means tree modelling, more specifically the CC method in this study, can be used as an approach to modelling a product platform for SODF in ambition to re-design the product concept to increase the level of customization. As this was the first attempt at functional modelling of SODF only a few vital functions were included in the model. In the future, the model should be expanded to include other functional requirements arising from customer needs. It should be emphasized that, even though a SODF was used as a means of modelling, this model is transferable and generalizable to other concepts of medicinal products beyond the SODFs, for example products for parenteral and inhaled administrations including also combinations of medical devices and various dosage forms.

Standardized components on a subsystem level provide substantial flexibility on a system level. By configuring product variants, from smaller standardized modules, a significant increase in the level of customization can be made. Not only can products for a range of different doses be provided but as well, by considering assembly sequences, combinations of different sized modules and the amount of filling modules, product variants of different sizes and shapes as well as products embedding different release behaviour can be generated. However, the increasing level of customization has consequences on the manufacturing complexity which leads to a conclusion that product design cannot be discussed independently of the manufacturing consequences and thus, future studies need to be conducted on expanding the model to integrate the production platform as well. Additionally, the model should be expanded with some additional cost and value drivers apart from the complexity factor and the number of product variants to make a more solid foundation for design decisions.

The validity of using complexity factor as an indication of the assembly cost cannot be confirmed and thus, the model needs to be expanded to suit modelling of pharmaceutical products better.

Acknowledgement

This work has been carried out with funding from Chalmers University of Technology Foundation. This support is gratefully acknowledged. The support received from my colleagues Jonas Landahl and Jakob Müller at Chalmers University of Technology when getting started with the CCM software is greatly acknowledged.

References

- Breitkreutz, J., & Boos, J. (2007). Paediatric and geriatric drug delivery. *Expert Opinion on Drug Delivery*, 4(1), 37-45. doi:10.1517/17425247.4.1.37
- Claesson, A. (2006). *A Configurable Component Framework Supporting Platform-Based Product Development*. Doctoral Thesis, Department of Product and Production Development, Chalmers University of Technology. Gothenburg.
- Crommelin, D. J. A., Storm, G., & Luijten, P. (2011). 'Personalised medicine' through 'personalised medicine': Time to integrate advanced, non-invasive imaging approaches and smart drug delivery systems. *International Journal of Pharmaceutics*, 415(1), 5-8. 10.1016/j.ijpharm.2011.02.010
- Du, G., Jiao, R. J., & Chen, M. (2014). Joint optimization of product family configuration and scaling design by Stackelberg game. *European Journal of Operational Research*, 232(2), 330-341. 10.1016/j.ejor.2013.07.021
- Food and Drug Administration. (2015). Physical Attributes of Generic Tablets and Capsules. Guidance for Industry. U.S. Department of Health and Human Services. Center for Drug Evaluation and Research.

- Govender, R., Larsson, A., Abrahmsén-Alami, S., & Folestad, S. (2017). 'Manufacturing Platforms for Access to Precision Pharmaceuticals'. Paper P-C-011, Pharmaceutical Sciences World Congress (PSWC) 2017, Stockholm, Sweden, 21-24 May.
- Goyanes, A., Martinez, P., Buanz, A., Basit, A., & Gaisford, S. (2015). Effect of geometry on drug release from 3D printed tablets. *International Journal of Pharmaceutics*, 494(2), 657-663. 10.1016/j.ijpharm.2015.04.069
- Ho, T., & Tang, C. S. (1998). *Product variety management: Research Advances*. Boston: Kluwer Academic.
- Klingmann, V., Spomer, N., Lerch, C., Stoltenberg, I., Fromke, C., Bosse, H., Breitreutz, J., & Meissner, T. (2013). Favorable acceptance of mini-tablets compared with syrup: A Randomized controlled trials in infants and preschool children. *Journal of Pediatrics*, 163(6). 1728-U283. 10.1016/j.jpeds.2013.07.014
- Lee, S. L., O'Connor, T. F., Yang, X., Cruz, C. N., Chatterjee, S., Madurawe, R. D., Moore, C. M. V., Yu, L. X., & Woodcock, J. (2015). Modernizing pharmaceutical manufacturing: From batch to continuous production. *Journal of Pharmaceutical Innovation*, 10(3), 191-199. 10.1007/s12247-015-9215-8
- Levandowski, C., Michaelis, M. T., & Johanneson, H. (2014). Set-based development using an integrated product and manufacturing system platform. *Concurrent Engineering*, 22(3), 234-252. 10.1177/1063293X14537654
- Medisca. (n.d.) Capsule Sizes Chart. Retrieved from <https://www.medisca.com/Files/ReferenceCharts/Capsule%20Size%20Reference%20Chart%20-%20MUS%20&%20MCA.pdf>
- Meyer, M. H., & Lehnerd, A. P. (1997). *The power of product platforms - Building value and cost leadership*. New York: Free Press.
- Plumb, K. (2005). Continuous processing in the pharmaceutical industry: Changing the mind set. *Chemical Engineering Research and Design*, 83(6A), 730-738.10.1205/cherd.04359
- Pugh, S. (1990). *Total design: Integrated methods for successful product engineering*. Wokingham: Addison-Wesley.
- Siepmann, J., & Siepmann, F. (2012). Modeling of diffusion controlled drug delivery. *Journal of Controlled Release*, 161(2), 351-372. 10.1016/j.jconrel.2011.10.006
- Srai, J., Harrington, T., Alinaghian, L., & Phillips, M. (2015). Evaluating the potential for the continuous processing of pharmaceutical products-a supply network perspective. *Chemical Engineering and Processing*, 97, 248-258. 10.1016/j.cep.2015.07.018
- Suh, N. P. (1990). *The principles of design*. New York: Oxford University Press.
- Tjalve, E. (1979). *A short course in industrial design*. London; Boston: Newnes-Butterworths.
- Ulrich, K. T., & Eppinger, S. D. (2012). *Product design and development*. New York: McGraw-Hill.
- Wortmann, J. C., Muntslag, D. R., & Timmermans, P. J. M. (1997). *Customer-driven manufacturing*. London: Chapman & Hall.