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INTEGRATION OF PERSONALIZED DRUG DELIVERY SYSTEMS INTO DIGITAL HEALTH- A REVIEW

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ABSTRACT

Personalized drug delivery systems (PDDS), implying the patient-tailored dose, dosage form, frequency of administration and drug release kinetics, and digital health platforms for diagnosis and treatment monitoring, patient adherence, and traceability of drug products, are emerging scientific areas. Both fields are advancing at a fast pace. However, despite the strong complementary nature of these disciplines, there are only a few successful examples of merging these areas. Therefore, it is important and timely to combine PDDS with an increasing number of high-end digital health solutions to create an interactive feedback loop between the actual needs of each patient and the drug products. This review provides an overview of advanced design solutions for new products such as interactive personalized treatment that would interconnect the pharmaceutical and digital worlds. Furthermore, we discuss the recent advancements in the pharmaceutical supply chain (PSC) management and related limitations of the current mass production model. We summarize the current state of the art and envision future directions and potential development areas.

KEYWORDS: PDDS, PSC.

INTRODUCTION

More than 100 years ago, a renowned Canadian physician, William Osler, quoted that, ‘‘If it were not for the great variability among individuals, medicine might as well be a science, not an art.” Over the past century, most therapeutic strategies were developed based on randomized clinical trials and applied or a ‘‘statistically average patient”. Although medicine may continue to remain an art, the 21st century brings a new hope with success of, for example, the ‘‘human genome” project to take consideration of genetic variability and deliver personalized therapy solutions.[1] Recent advancements in the field of pharmacogenomics have made it possible to start implementing tailor- made and increasingly personalized therapies. One such example is the marketed anticancer drug product Herceptin, which has been successfully used as targeted monoclonal antibody therapy for 25–30% of breast cancer patients, where HER-2 protein is over-expressed.[2] One aspect of personalized medicine is designing molecules based on pharmacogenomics and targeting specific patient sub-group, as mentioned above. The other aspect of personalized medicine is tailoring the dose, the dosage form and drug release kinetics to fit the needs of the individual person, as well as severity and stage of the disease.[3] In this review article, we are mainly focusing on this latter aspect of personalized medicine, which is hereafter phrased as ‘‘Personalized Drug Delivery Systems” – PDDS. Another revolution we have witnessed in the early 21st century is an advent of digitalization. The modern society is becoming increasingly digitized and dependent on the virtual world and enormous amount of data. This is changing how we design products and deliver them to customers – an example of this is the recent revolution in value creation and customer demand due to the COVID-19 pandemic that has spiked the whole e-business industry. This development is partially dependent on the efficient use of online services and traceability of products. Recently, distribution of pharmaceutical products has been one of the key challenges and, among others, the established ‘‘Pharmaceutical strategy for Europe” from 2020 is aiming to ‘‘make sure that patients across Europe have new medicines and therapies in their countries quickly and under all circumstances and that there are fewer shortages of medicines”.[4] This should be ensured while at the same time (1) delivering solutions allowing for personalized medicine, (2) combating falsified and counterfeit products, and (3) reducing the environmental footprint of related manufacturing. One solution for this challenge is integration of data elements into drug products. This would allow for simultaneously (a) secured distribution, (b) more precise and timely dosing of an active compound, and (c) tracking of each consumed dose by involved actors (i.e., healthcare professionals, patients, caregivers) and in this way, transforming the regular drug products into digitalized drug products. Similar approach has revolutionized the

monetary transactions with the introduction of digital currencies. In the healthcare sector, this would provide healthcare professionals with better treatment overview by keeping the digitally retrievable records of medicine intake by patients with simultaneous monitoring of their surrogate markers[5], such as heart rate, blood pressure and oxygen saturation. In turn, this can help healthcare professionals making the informed decision for subsequent treatment options, ultimately resulting in better therapeutic outcome. In addition, traceability aspect of digitalized medicines will aid towards more efficient pharmaceutical supply chain (PSC), facilitating new strategies for reducing the medicinal waste, designing more sustainable products, and finally, achieving the PSC with elements of circular economy (cf. Section 4.1).[6] Furthermore, these digitalized drug products should be designed to be functional, and at the same time accessible and affordable to be also used in low and middle-income countries. Digitalization of the healthcare sector is proceeding fast by a gradual integration of diagnostic point-of- care sensors and connected computation platforms into patients' everyday routine.[7] Nowadays personal mobile and wearable sensors, so called Internet of Things (IoT), can measure, amongst others, functioning, respiration, biomarkers from sweat and even assess the emotional state of the individual.[8,9] The transmitted signals from IoT can be received, quantified and visualized with a help of, for example, a standard smartphone. These digital possibilities enable a completely new type of a human–machine interface in the healthcare sector.[10] There is already an increasing number of digital solutions providing virtual visits with medical doctors based on an app-based communication between the patient and the medical doctor.[11–13] Even the clinical trials are becoming more and more virtual.[14,15] In this digital revolution, the weakest link in a chain is the drug product. This is because the options for its traceability, on-dose verification and its integration into the existing digital health platforms are limited. To be able to deliver a truly personalized care, a holistic change in the healthcare sector is needed – and a key element in this change will be the way we design and manufacture PDDS. The current mass production model of drug products does not allow personalization[16], while modification of the product based on the individual patient's genomic, metabolic and activity level needs implementation of mass customization principles.[17–21] In this review, we report the rationale for PDDS in the current pharmaceutical sector. Furthermore, we provide an overview of advanced approaches for manufacturing personalized medicines and more specifically, how to bridge pharmaceutical and digital worlds with the appearance of new products such as digital drug products and digital therapeutics.

Patient Needs for Personalized Medicines

The current set-up of conventional pharmaceutical manufacturing is based on mass production of selected dosage strengths. This creates challenges especially for treatment of chronic diseases including cardiovascular diseases, type 2 diabetes as well as brain disorders. Many of the disease treatments require multiple doses to be delivered to the patient based on severity of the disease, lifestyle changes, co- administration of other medication, as well as going off medication.[22,23,24] Furthermore, different subgroups of patients such as, pediatrics and geriatrics, would require age-appropriate doses. In this context, there are three major challenges with currently marketed oral drug delivery systems:

(1) the absence of on-demand personalized and precision dosing (especially for pediatric population),
(2) non-adherence and lack of treatment overview due to the use of multiple drugs, so called polypharmacy (especially for geriatric population), and,
(3) the deficiency of easily reachabletai-lored information regarding the drug products.

- ✓ Personalized & precision dosing – significance in pediatric delivery

Most of the pediatric medicines are liquid formulations provided with measurement cups or as measurement of tea-spoonful or table-spoonful. In case of solid dosage forms, available doses are divided by e.g., crushing or splitting into halves or smaller, and then consumed as such or by dispersing in oral liquids.[25] These are not very accurate measurement systems and are quite susceptible to human errors.[26] Furthermore, the age, weight and metabolic capacity of children can be crucial factors in determining the correct dose.[27–29] The significance of the right dose for pediatric use has quite often reflected in market recalls related to dosing precision needs.[30,31] Such recalls are cumbersome and costly, and could cause the loss of the trust in the recalling company. Recently, the dosage forms that have captured attention for pediatric medicines are minitablets and granules.[32] Minitablets are miniaturized tablets, which could be counted to get the required dose. They are suitable even for new-born infants.[32,33] However, there is a need to use a separate device that would allow the precise counting of minitablets, such as a specially designed pen. This adds to the cost of the drug product. Further-more, although production of minitablets is well-established, the same involves various technical challenges including content uniformity as well as maintenance and mechanical stability of multitap punches. Also, due to their small sizes, minitablets are not easier to handle independently, which may impart additional challenges for patients with impairment of motor functions and geriatric patients.[34] The granules in hard capsules or sachets for pediatric use have also been designed to improve administration of the required dose. The desired number of granules is supposed to be dispersed by parents or caregivers in semi-solid food, like apple pudding, yogurt or fruit juice, to make children eat the medicine unnoticed and by that minimize spillage, spitting out and refusal to take the medicine.[35,36] However, such an approach might incur additional challenges with insufficient drug intake due to

e.g., child's unwillingness to intake the entire food portion as well as additional stability requirements of active pharmaceutical ingredients (APIs) and other ingredients in the presence of food. The other innovative way for overcoming administration challenges with granules have been inserting granules in a straw.[37] To add, even though minitablets and granules are currently mass produced; on-demand manufacturing of the same does not exist yet.

✓ Significance in value-added geriatric medicines

Polypharmacy, patient morbidity and poor adherence are the major factors contributing to sub-optimal outcome of drug delivery systems in the elderly. Poor adherence to medicine is caused, among the others, by patients' inability to recognize their medicine due to similar appearance, oblivion or misunderstanding of the administration regimen, unwillingness to follow the complex dosing regimen and/or swallowing difficulties.[38] A key challenge in developing appropriate geriatric drug delivery systems is to provide the innovation that best meets the specific physiological, psychological and multiple drug requirements of individual elderly patients.[39] Although digital literacy might be a challenge for elderly patients, care-takers at nursing homes may be well-trained to use the digital media. Additionally, the people, who is in their 50 s and 60 s and advancing in their age, is already well-versed with the digital world.

✓ Accessible information

Due to the digital revolution, patients are more informed than previously. According to a 2019 report, there are over 1-billion health related searches on google everyday.[40] Various studies have shown specifically that more and more people search for their medications and related information online.[41–43] Furthermore, people find it useful to check the origin of raw materials and their logistics, especially if patients have allergies or trust concerns. This aspect would be increasingly important when pharmaceutical products and PSC are being modified towards more sustainable solutions with circular economy elements. For example, a pharmacist can receive unused traceable drug products without the original package from patients. The embedded information at a dosage unit level in these traceable drug products can help pharmacist sorting out them based on the API, dose, expiry date etc., whether to reuse or recycle.

Additive Manufacturing (AM) As A Digital Technology for Personalized Drug Delivery Systems (PDDS)

To overcome the challenges of the currently marketed drug products, innovative solutions with improved functionalities are needed. One such innovation is personalized drug delivery systems (PDDS) defined in this review as solid dosage forms, containing the patient-tailored precise dose of a single or multiple APIs and possessing customized appearance that can aid in drug identification, swallowability, release and monitoring of the treatment. Additive manufacturing (AM), based on different two-dimensional (2D) and three dimensional (3D) printing techniques, has recently emerged as a new technology for PDDS due to its versatile possibilities of producing on-demand flexible doses.[44–47] It is not the purpose of this review to cover the technical details of all these methods, but rather focus on the integration of PDDS manufactured using AM into the digital health environment. By using AM, the dose can be adjusted digitally, by a quick manipulation in the computer-aided design (CAD) of the dosage form to be printed. For example, by changing the physical dimensions of the dosage form, print density (resolution), internal geometry and the number of printed layers, the dose and the release profile can be customized.[48] Interestingly, the use of AM offers the possibility for producing a 'polypill', where multiple APIs with a desired dose and pre-programmed release profiles for each API can be incorporated into a single dosage unit.[23,49] Reduction in the number of dosage forms to be consumed per day could significantly improve patients' adherence to medicine and provide cost savings to the healthcare sector.[50,51]

The first and so far, the only 3D printed drug product developed by Aprecia - Spritam (generic drug product of Keppra), containing anti-epilepsy drug levetiracetam, has been approved by the US Food and Drug Administration (FDA) in 2015 and is available on the market.[52] It has an advantage of or dispersible formulation in terms of easy swallowing, combined with the potential for digital dose adjustments on- demand. In February 2021, FDA gave the Investigational New Drug (IND) approval for 3D printed drug product T19 by Triastek.[53] The company expects to file a New Drug Application (NDA) for T19 in 2023. Recently, 3D printed chewable PDDS have been tested in pediatric population with a rare metabolic disease in a hospital setting.[54] The physical appearance in terms of size (different doses) and colour together with the taste of the dosage form were manipulated as an attempt to improve the treatment outcome. The implementation of additive manufacturing as a better alternative to the compounding practice with regards to cost and safety and overall benefits to the patients, has been demonstrated in clinical settings.[55] In another study, comparison of the dosage forms prepared by 2D printing, 3D printing and conventional compounding in the hospital setting has been reported.[56] The production of PDDS by printing appeared to be more precise, though the overall production speed by printing (preparation of feedstock, printing, cleaning) could be slower than the conventional compounding by mechanically altering the dose of already marketed drug products (e.g., grinding, mixing, weighing, cleaning).[56] Merck Group has invested into 3D printing process with the ''One Zero-Med" business concept to allow cheaper drug development by cost savings during clinical studies, where small batches with escalating doses are needed. In turn, this will potentially allow bringing urgently needed

medicine, such as orphan and oncology medicine, faster to the patients.[57] In line, the Netherlands Organization for Applied Scientific Research (TNO) has recently started 3D printing of pediatric dosage forms for treatment of heart diseases in the hospital settings.[58] Overall, 2D and 3D printing techniques were positioned as an automated approach with a high digital flexibility and precision dosing that have a small footprint with a possibility of the remote control, consumption of less materials and possibility of mass customization of PDDS.

With a current demand of the society for PDDS to offer a better treatment for patients[45], these recent advancement in manufacturing could allow the production of the medicine upon patient request at industry setting, pharmacy setting, both compounding and community, and even at patient's home.[48] These possibilities would challenge the conventional pharmaceutical supply chain (PSC) and rearrangement of the same with new solutions would be needed.

Challenges For Implementation Of PDDS

PDDS is a new way of manufacturing and distributing medicines. There are multiple challenges to be solved before PDDS can be implemented in the real-life treatment scenarios.

- ✓ Influence of human factors on the acceptance of PDDS

The PDDS have the potential to enable better (self-) management of treatment regimen and can lead to improved patients' health outcome. However, PDDS must be further refined to address different human aspects of their use by the patients and their informal and formal caregivers. We discuss the human factors, in light of recent research results on technology (non)use by the chronically ill patients (N = 200).[61] Namely, around 20% of the patient population will not be willing to use any personal technologies, including PDDS ones, despite their miniaturization or personalization or other advanced features. These patients are non-adopters and shall be accounted for. Additional 20% will be sceptic towards the use of technologies, and an educational program, or a peer support service may help to gain their acceptance. As for the patients, who may accept the use of PDDS, there are following human factors that will influence the system use and its collected data quality. First, the interface design and especially the system notifications, should be user-friendly and allow for personalization. Patients are unlikely to accept a solution that is designed poorly, and that make them feel that they do not have a control over it. It became clear that the patients would rather abandon the system use, than let it to rule and interrupt their daily activities. Further, the aspect of the battery efficiency of the system is crucial. If the battery lifetime of the system is too short and the system requires extended charging – for example every day, that is likely to interrupt the flow of daily activities of the patient, and the patient is likely to forget it. Not only such a situation risks data loss, but, if unattended, it may influence the patients' medication adherence and hence his/her health outcomes. The overall psychological concept is related to the fact that the patients are optimizing their daily life for improved quality of life, and their actions are driven by their perception of self-efficacy; and they do not want to be reminded by a PDDS or any other system that they are sick and incapable of taking care of themselves.[59,61,63–64] The second critical human factor, influencing the PDDS acceptance, relates to the system/service performance experienced by the patients. Namely, if the system is not accurate (e.g., launches wrong notifications) or is not timely enough (e.g., notifications are late, out of date), the users will lose trust in it and stop using it as well.[61,65,66] The third aspect relates to the potential costs of using the PDDS that may influence its usage and the collected data quality. The examples of cost influencing the medication intake include a potential patient's belief that a given costly medical treatment can be taken more sparsely with the same therapeutic effect, while incurring less costs.[61,67–69]

Overall, there are many human factors that relate to the design and use of the PDDS and that may influence the patients' health outcomes. To maximize the patients' acceptance, any PDDS design choices must be easy to personalize to match closely the existing patient's routine and lifestyle choices. For example, for the medications taken upon waking up or at the meal times, the interactive design (i.e., number of interactive steps to activate the system or size of the system to be accommodated at the patients' cabinet or breakfast table) of a PDDS must match the patient's morning routine or around the meal routine. Overall, the previous research results show that the design elements and personalization choices of system like PDDS must be operationalized such that they make the users feel good about themselves; enable them to become empowered and motivated for self-care.[61] Any design elements that may feel for the patient too complex to understand, or perceived as stigmatizing, will lower the system acceptance, and may result in the failure of the medication adherence service provision, in turn, possibility having implications on the patients' health outcomes.

The overall recommendation would be a design of the PDDS solution that makes it easy and enjoyable for the patient to adhere to.

- ✓ Ethical, privacy and security challenges

In the context of the medical adherence solutions, there are several aspects to be considered, because the data collected via a solution and interactivity features (e.g., digital reminders) may directly impact the behaviour and the state of the health of its user. First of all, the terms and conditions of the service must be clear and understandable for the user, who, can only use the service, if accepts them. The terms and conditions must respect all relevant international and national

regulations.[62]

Defining and prescribing the patient-tailored dose for PDDS with encapsulated information would require collection, management and storage of enormous amounts of personal health related data. There have been evidence of data leakage and systematic misuse of personal data with social media such as Facebook and Cambridge Analytica.[60] This underlines the significance of a thorough design of big data platforms to avoid the misuse of sensitive information. Data cyber security with the use of the computer clusters and supercomputers would be a key factor for implementation of PDDS. So far, only authorized parties, e.g., patients, healthcare professionals (e.g., doctors, nurses, pharmacists) have access to the patients' private data, whereas pharmaceutical industries do not. The question is who will define the personalized dose and how will it be defined and at the same time to comply with data privacy and security regulations such as European General Data Protection Regulation (GDPR).

CONCLUSIONS

There is an increasing demand of the society for the patient-tailored therapy to improve the overall healthcare outcome with better overall cost-efficiency. Personalized drug delivery systems (PDDS) offer an innovative digitally designed solution that can overcome the challenges of the currently marketed drug products, especially, (1) provide personalized and precise on-demand dose, dosage form and release kinetics, (2) improve medication adherence and give a better overview of the treatment, (3) provide the possibility of track and trace and verification of the genuineness of the drug product by inclusion of unique identifiers, e.g., 2D barcodes, at the individual dosage unit, and (4) offer an easy access to tailored information regarding the drug product. Furthermore, PDDS can establish a bridge between pharmaceutical and digital world as the healthcare sector is becoming increasingly digitalized with an invention of a completely new type of therapies, such as digital therapeutics. However, to make the overall PDDS concept operational and sustainable, related technological, economical and data privacy and security challenges should be solved, and related human factors should be taken into consideration. Furthermore, the regulatory framework for the flexible on-demand dose also needs to be well-defined.

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