Harnessing the personalized tailored medicines to digital-based data enriched edible pharmaceuticals

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Teaser: *Digital-based data enriched edible pharmaceuticalsmarked as new and personalized drug delivery systems that cater the need of all age group of patients.*

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Abstract

Tailoring drug products to personalized medicines posses challenges for conventional dosage forms. The prominent reason is the restricted availability of flexible dosage strengths in the market. Inappropriate dosage strengths last with adverse drug reactions or compromised therapeutic effects. The situation gets worsens when the drug has a narrow therapeutic window. To overcome these challenges, data-enriched edible pharmaceuticals (DEEP) are novel concepts for designing the solid oral products. The DEEP contains individualized dose and information embedded in quick response (QR) code form. When data is presented in QR code, the information is printed with edible ink that contains the drug in tailored doses required for the patients.

Keywords: Quick response, personalized medicine, paediatric, digital dosage, drug delivery

Introduction

Initially, the pharmaceutical sector is expanding at an exponential rate, and recent advancements have undoubtedly assisted the creation of novel dosage formulations for targeted therapy. Nonetheless, industrial production of these pharmaceutical dosage forms is currently limited and continues to rely mostly on modified tablets and traditional drug delivery systems. The introduction of 3D printing (3DP) technology has expanded the study and development of novel dosage forms, particularly personalised and modified tablets. Traditional dosage form manufacturing is intended for mass production, but it has a number of drawbacks, including expensive capital expenditures for obtaining the key equipment, the need for a big operational space, a well-trained and skilled crew, and a lack of dose adjustment flexibility. Additionally, it lacks the flexibility to make personalised medicine a reality due to its lack of flexibility and complex processes.

William Osler, a distinguished Canadian physician, stated more than a century ago, “Were it not for the vast variety among people, medicine would be a science, not an art” [1].

The growing awareness of individual differences in drug response has prompted a re-evaluation of the pharmaceutical industry's "one-size-fits-all" approach and a shift toward the development and production of personalised medicines[2,3]. A broad definition of personalised medicine is "providing the right treatment to the right patient at the right dose and time." In this work, personalised medicines are discussed in terms of patient-tailored dose, dosage form and its design, and drug release kinetics in terms of what would be most beneficial and available on-demand for an individual, taking into account all pertinent patient characteristics (weight, age, sex, medicines intake, co-morbidities, physiology, metabolism, genetics, lifestyle, preferences and routines, etc.).

Although the feasibility of personalising medicines on an individual level could be questioned, the production of personalised medicines is already widespread. Compounding, also known as the preparation of magistral or extemporaneous medications, has long been a vital part of the pharmacist's work in the pharmacy setting; however, this position has diminished significantly due to the rise in pharmaceutical industry manufacturing. Today, compounding in pharmacies is primarily considered a small-scale procedure, reserved for instances in which individual patients require an unregistered, unavailable, or specially modified medication to satisfy their specific needs. The advent of the concept of individualised treatment, however, casts small-scale compounding in a new light.

At the beginning of the twenty-first century, we have also witnessed the rise of digitalization. Modern civilization is dependent on the virtual world and vast amounts of data, as well as increasingly digital. In the healthcare industry, digitalisation will improve treatment by storage of digital available records like medication ingestion by patients and monitoring parameters, such as blood pressure, heart rate, oxygen saturation, simultaneously [4]. Thus, it can aid healthcare providers in making sound decisions regarding following treatment alternatives that results in improved outcomes in terms of therapeutics and patient management. Additionally, the traceability component of digitalized medications will contribute to a more prominent pharmaceutical supply chain (PSC), that enables new techniques for decreasing medicinal waste, producing more sustainable goods, and attaining circular economy aspects for PSC (**see Figure 1**) [5]. Additionally, these digitalized pharmaceuticals should be intended to be useful, as well as accessible and inexpensive, so that they may be utilised in low- and middle-income nations [6].The digitalization process in healthcare settings has covered the wearable devices/ personal monitoring devices that revolutionised the healthcare process [7]. Apart from this digital pharmaceutical governs the track and trace concept of formulated medicines to minimise their counterfeiting or theft. The daily lives of patients are accelerating the healthcare industry's due to digital transformation. Past decade has reported about the wearable sensors and personal mobile that detect a person's functioning, breathing, perspiration biomarkers, and emotional state [8].

The pharmaceutical product is the weakest link in this digital revolution. This is due to the limited alternatives available for its traceability, on-dose verification, and interaction with current digital health platforms. To enable and provide fully individualized care, the healthcare industry must undergo a comprehensive transformation. The system should pay heed to develop and build Personalized Drug Delivery Systems (PDDS). The existing mass manufacturing paradigm for pharmaceuticals does not provide customisation [9]. However mass customization principles are required for product modification depending on a patient's genetic, metabolic, and activity level. For PDDS, many concepts have been emphasised. From all the concepts 2D or 3D pharmacoprinting is in place.

2D or 3D printing, often known as pharmacoprinting, is a potential method for achieving more individualised medication therapy. The technology suggests that finished drug products such as capsules, tablets, oral films are printed in a layer-by-layer, step-by-step in a digitally controlled manner in the desired amount of an active pharmaceutical ingredient (API) that released at desired rate from the drug product. Consequently, pharmacoprinting enables the

incorporation of many APIs into a single unit to produce a polypill intended for safe administration form and colour for both personalised dosages and individualised controlled release systems[10,11]. Pharmacoprinting can enhance the efficacy of a medical therapy, decrease side effects, and enhance adherence. The Food and Drug Administration (FDA) has authorised the first pharmacoprinted pill, making it a technical reality in the business today. Pharmacoprinting is in a process for that can be manufactured at medical profession, community pharmacies and patients' homes. With public access to printers, patients may print their drugs at home (in later stages). For this, the printers could be managed either remotely by healthcare experts or patients themselves. Such concerns can be mitigated by a variety of methods, such as having health care experts check the settings of home printers. Additionally, preloaded API-containing cartridges and fitted with anti-counterfeiting measures can be made accessible in advance, in local pharmacies. The dose forms can then be printed, for instance, as quick response (QR) codes and validated using barcode scanning with smartphone applications (**see Figure 2**). However, numerous political, ethical, safety, and technological factors must be considered for the successful application of pharmacoprinting in society[12].

The majority of the literature in the field of pharmacoprinting focuses on the technical elements of the manufacturing process, such as the selection of suitable materials and printing equipment with process parameters optimization etc. The number of studies addressed the anticipated consequences of pharmacoprinting on patients. In short, pharmacoprinting reduces medical burden, a reduction in adverse effects, increased medical adherence, an increase in the efficacy of drugs, eliminates the use of split tablets, and the creation of new types of therapeutic combinations. Thus, pharmacoprinting as a novel technology has opportunities, but it may also provide difficulties for patients, since reaching anticipated advantages may out to be a complicated procedure. It was once assumed that the advent of "automated dose-dispensing" in pharmaceutical technology would help patients become more aware and compliant. However, it resulted in uncertainty and suboptimal compliance among many patients.

This review article focuses mostly on the latter part of personalised medicine, termed "Personalized Drug Delivery Systems" (PDDS) in the form of digitally-based, data-enhanced edible medicines (DEEP). This article will discuss some of the unexpected repercussions of personalised on-demand pharmacoprinting for patients in relation to the future scenarios of mostly community pharmacies and the pharmaceutical business.

Current challenges in the pharmaceutical field

The efficacy and safety of contemporary treatments depend greatly on the quality of pharmaceutical items. However, inferior and counterfeit pharmaceuticals raise the morbidity of illnesses, kill people, and erode confidence in health care institutions. However, the counterfeiting of pharmaceuticals is a global issue. Multiple deaths have been attributed to the use of counterfeit medications in underdeveloped nations, where the problem has reached a crisis level. In 1995, over 2500 infants in Nigeria died after receiving a bogus meningitis vaccination[13]. Almost 100 patients perished in Panama because of a cough medication containing counterfeit glycerine. Glycerine was substituted with less costly diethylene glycol (being a chemically and industrial solvent similar to glycerine). In 2008, a further 80 infants perished in Nigeria after ingesting a counterfeit paracetamol syrup containing diethylene glycol. According to the World Health Organization (WHO), more than 120000 people each year die in Africa due to counterfeit antimalarial medications, either because the pills are inferior or contain no active components. But particularly in developed nations counterfeiting is observed in weight-loss pharmaceuticals, dietary supplements tainted with addiction drugs, drug ingredients, potency boosting drugs (such as Viagra® (registered trademark of Pfizer Inc.). In 2008, for instance, 150 persons in Singapore were hospitalised after using glyburide-tainted sexual enhancement medications, and four of them died. As per the WHO verdicts, the counterfeiting and illegal business of pharmaceuticals are enormous. Hundreds of billions of dollars are generated in global sales of counterfeit pharmaceuticals sold in retail and online pharmacies. The World Health Organization estimates that more than 10% of the worldwide pharmaceutical industry is comprised of counterfeits and this number is increasing as time passes. In industrialised nations, counterfeit medications contribute for close to 1 percent of the market value. In several Eastern European nations, the rate of counterfeit pharmaceuticals appears to exceed 20%. In underdeveloped nations of Africa, Latin America, and Asia, however, the prevalence of counterfeit pharmaceuticals ranges from 10% to 30%, and even reaches 70% in Nigeria [14,15].

Other than this present arrangement, conventional pharmaceutical manufacture is centred on the mass production of chosen dosage strengths. This presents particular issues for the management of chronic illnesses such as type 2 diabetes, cardiovascular diseases, and brain disorders. Depending on the lifestyle changes, severity of the condition, co-administration of other medications, and withdrawal from medicine, many disease treatments require repeated doses to be administered to the patient. Different patients group, such as children and the

elderly, require appropriate dosages. Nanotechnology assisted medicines have emerged as a good alternative to conventional delivery systems because to their numerous benefits, such as better drug delivery efficacy and targeted drug delivery. Nevertheless, nanoparticulate systems must be described in terms of their safety and toxicity. In a number of studies, nanoparticles caused reticuloendothelial system uptake and inflammation of the liver, lung, and brain due to oxidative stress induced by nanoparticles. In brain diseases, the capacity of nanocarriers to traverse the blood–brain barrier is advantageous; yet, it produces neurotoxicity when the brain is not the intended site of action. In rare instances, nanoparticles also induce immunomodulatory effects [16].

Challenges faced by paediatric group

An specialist in paediatrics notes that optimal drug delivery to paediatric patients can only be achieved by overcoming the fundamental disparities between children and adults[17].The preferred route of administration, oral dosage forms, may not always be appealing or available in appropriate dosages for youngsters.Consequently, dosage forms like as pills and tablets are frequently altered in ways that are not optimal for delivering safe, effective, and consistent amounts[18]. Health professionals and pharmacists who compound medications can be of assistance, but their methods may vary, thus results are not always replicable. In addition, these services may not always be accessible, particularly in underdeveloped regions of the world[19]. Patients frequently provide medications in quantities that have not been appropriately evaluated, such as by dividing doses, crushing and dissolving them in liquids (water, juices, etc.) and administering them in untested quantities. The author of the paediatric pharmacotherapy newsletter states that oral medication delivery optimization has been one of the greatest hurdles in paediatric pharmacology. Swallowing solid dose forms can be taught to the majority of children over the age of six, although many children remain uncomfortable with it until puberty. In one research of children, 54 percent of those aged 6 to 11 reported difficulty swallowing tablets. Children cannot be compared to small adults and require paediatric studies to verify the appropriate dose, safety, and efficacy of a drug in this population. However, the conduct and design of these paediatric trials have lately improved as a result of the growing participation of paediatric experts[20].

Challenges faced by geriatric patients

It is impossible to establish age groups for the creation of medications for elderly people. In response to paediatric patients, the needs of the elderly are primarily decided by the patient's ability, which is largely influenced by his or her condition of health. Numerous elderly

patients are multidrug-treated for multiple disorders. Some patients are dependent on alcohol, cigarettes, and prescription drugs. A drug's pharmacokinetic characteristics may be drastically altered by diminished kidney and liver function, as well as dehydration. It is necessary to anticipate and account for the limited ergonomic and audiovisual capacities of elderly patients during drug development. Unfortunately, the domestic environment of certain elderly patients is likely to be unhygienic, which influence the choice of drug formulation. Therefore, it has been proposed to derive a "biological" or "functional" age. This is however difficult to define and establish [21,22].

Drug edible films and digital edible films

As the Human Genome Project (HGP) is completed in 2003, personalised medicine has received more attention than before. In 2018, 42% of FDA-approved novel molecular entities fell under the category of "personalised medicine." This shows that current research is pushing more towards patient-specific therapy as opposed to the decades-old paradigm of "one size fits all." In addition to the targeted design of pharmacological molecules based on pharmacogenomics, personalised medicine involves the customization of a drug product's dose, dosage form, and drug release kinetics, as well as its physical look and usefulness[23]. Patients can collaborate on the design of their medication in terms of colour, pattern, and more, as a result of the adaptable options for altering the drug's physical look. This, in turn, can be utilised to promote drug adherence by fulfilling the preferences and demands of patients (e.g., polypharmacy patients).

Additive manufacturing (AM), which includes 2-dimensional and 3-dimensional printing, is a viable approach to achieving individualised medicine (3DP). AM is computer-controlled and provides manufacturing on demand. This means that the production process may be digitally well-controlled, and that exact, patient-specific doses can be easily obtained. Additionally, it can be generated in a variety of settings, including hospitals, pharmacies, and other facilities. Currently, the US Food and Medicine Administration has only approved one 3D-printed drug product, Spritam®, which was produced by Aprecia (FDA) (**see Table 1**) It was licenced in 2015 and is commercially available in fixed dosages manufactured in huge quantities by the pharmaceutical industry [24,25]. GMI Research says that the global market for printed drugs in 2017 was worth USD 214.3 million. North America had the biggest share of the global market with4.2% compound annual growth rate and expected until 2025 up to USD 295.5 million. These printing methods are traditional and digital methods. The traditional method includes all kinds of printing that don't use electronic devices, like flat and relief printing. The

second category, on the other hand, refers to printing materials onto substrates based on information stored on a computer, like inkjet, 3D printing, electrophotography. This below section talks about the current state of the art of inkjet (IJ) printing. It also talks about important things that need to be done to optimise, scale up, and mass produce this technology so that it can be used to make custom dosage forms for the pharmaceutical industry.

IJ printing is one of the digital printing methods that can be used to make different drug delivery systems. This method is a non-contact method that works by putting 1–100 pL droplets of ink on a certain part of a 3D or 2D substrate or structure[26]. To make a pharmaceutical ink solution or dispersion, the drug or material of interest is dissolved or spread out in a liquid. For IJ printing ink must exhibit excellent flow properties[27]. IJ printing possesses different printing speeds, little human involvement, low processing costs, little waste, the ability to process different types of substances with little contamination, and the ability to make customised dosage forms for each patient's illness. But the main problems with IJ printing are that the nozzle gets clogged when particles in the ink stick together or settle out during the printing process, and that the process of wetting and drying the ink to make uniformly printed systems is very complicated. IJ printing comes in two forms: drop-on-demand (DoD) and continuous IJ (CIJ)[28]. CIJ printing was invented in the 1960s. This makes droplets that are evenly spaced, but the size of the droplets may lower the printing resolution. During the printing process, droplets are separated from the steady flow by giving them an electric charge as they pass through an electrostatic field[29,30]. DoD printing, on the other hand, was created in the 1970s. It works by forcing droplets out of the nozzles with a pressure pulse. These droplets are smaller than those used in CIJ printing, ranging in size from 10 to 50 m and having a final volume of 1 to 70 pL. This gives DoD printing a higher printing resolution and, therefore, more accuracy. DoD printing can also be broken down by how the pressure pulse is made, which can be piezoelectric, thermal, acoustic, electrostatic[30]. Thermal DoD printing, or bubble jet printing, works by locally heating the ink to form a bubble that pushes some of the ink droplets via multiple nozzles. And, the main ejection happens when the bubble bursts, which creates a pressure wave and pushes ink droplets from nozzles. Electrostatic DoD printing works by the electrostatic force appliedto the nozzles. This may cause the ink to stick to the surface of the nozzle and break up into small droplets. In acoustic-driven DoD printing, droplets are made by using an acoustic lens to focus an ultrasound beam on the surface of the ink. As the fluidity, viscosity, and surface

tension of the ink have a lot to do with how the drug dissolves, how droplets form, and how quickly they dry after IJ printing[31,32].

Many dosage forms have been created and manufactured using 2D and 3D IJ printing, giving highly repeatable products with accurate dosing to deliver the desired medicine. Polymeric thin films are one of the most researched printing substrates for 2D IJ printing. This type of dosage form is characterized by a thin, flat, and flexible polymer substrate that may contain a plasticizer. Thin films are easily manufactured and can be tailored to the desired rate of drug release. Thereby, enhancing the drug's efficacy, and can target sensitive sites, superior to tablets, which results in less bulk dosage form, which increases patient compliance. Additionally, films can be constructed with mucoadhesive polymers to improve retention within a biological site of delivery, such as the oral mucosal barrier.

Using the IJ printing technology, a uniform coating and highly reproducible process was established, resulting in the availability of an efficient way for optimising the creation of drug-eluting medical devices. In recent innovations involving IJ printing, data-enriched edible pharmaceutical (DEEP) dosage forms have been manufactured[33]. The required medicine is produced in the form of ink and surface printing onto the surface of an edible substrate in the form of a quick response (QR) pattern. QR code is designed to encode any pertinent information regarding the drug, dose, and patient, and may be accessed using smartphones. Edinger et al. have produced intelligent flexible, porous, stable orodispersible utilising solubilized antipsychotic haloperidol as a paradigm (**see Figure 3 and 4**)[34]. The drug-filled ink was fed into a PixDro LP50, piezoelectric IJ printer, and the printed QR pattern was successfully scanned using a smartphone to get to the samples' encoded information. In addition, the drug content was deposited precisely and properly, and the dosage forms printed have not compromised qualities when compared to non-printed substrates. Using a piezoelectric IJ printer, Oblom et al. successfully printed two weakly water-soluble cannabidiol, cannabinoids,9-tetrahydrocannabinol, in a QR pattern on the edible surface (Epson XP8500). In addition, when the number of printing cycles grew (up to 10), a highly accurate drug content was acquired, eliciting a linear correlation, preserving QR design readability, and therefore allowing access to the encoded information[33,35]. As a result, IJ printing can be used to produce smart DEEPs that have enormous potential for the development of individualized dosage forms. In addition, 2D IJ printing is combined with other methods to create various dosage forms. Palo et al. have combinedinkjet printing (PixDro LP50) with electrospinning to generate a piroxicam-cross-linked gelatinnovel

oromucosal solid dosage form for loading lidocaine intended for dual administration. Thus, electrospinning and IJ may be a viable combination to produce dosage forms for dual drug delivery. Consequently, IJ printing can efficiently limit the quantity of deposited polymer by managing the volume and number of droplets, to produce the primary matrix and subsequent drug loading process, resulting in a faster dissolution rate and oral dosage form with a solvent-free formulation[36]. Consequently, 2D IJ printing is a highly adaptable and reproducible technology for accurately loading pharmaceuticals onto the surface of flat dosage forms, such as porous substrates, polymeric thin films, non-flat platforms, such as drug-eluting medical devices and transdermal microneedles. Moreover, smart and individualized dosage forms can be customizedutilizing 2D IJ printing by encoding all pertinent information, such as QR patterned-DEEPs, within the same dosage form[37]. Using 2D IJ printing, a combination of several processes, such as electrospinning and supercritical carbon dioxide impregnation, can be utilised to generate the required drug-loaded dosage form. Additionally, 3D dosage forms can be manufactured via IJ printing. This technology creates and renders a designed product using a single manufacturing process. After proper drying, the ink itself acts as the substrate or matrixfor the final fabrication of a solid dosage form when a 3D IJ printer is utilised for this purpose[38]. Resins, thermoplastic materials, or other desired molten polymers are used to create the ink, which is then deposited layer-by-layer onto a flat platform before undergoing solidification to generate the final solid dosage form. Depending on the drying and wetting of the surface, the droplet's impact during its flight along with deposition pattern, several geometries are possible with this 3D IJ printing technique.

Taking everything into consideration, 2D IJ printing can be used to load various types of medications onto the surface of a variety of non-flat and flat dosage forms, including microneedles, films, DEEPs, medical devices. In addition, 3D IJ printing can be used to create solid dosage forms by employing the same ink as a substrate for solid dosage formulations. Despite the 2D or 3D approach, IJ printing of pharmaceuticals is a promising way for developing customizable solid dosage forms, which is essential for achieving a more individualised therapy with less time-consuming processes, low cost, high reproducibility, dose accuracy.

Data enriched edible pharmaceuticals (DEEP)

Data-enriched edible pharmaceuticals (DEEPs) are proposed as new solid dosage forms created by AM, in which an ink formulation containing an API is imprinted on edible

orodispersible 'paper' in the pattern of Quick Response (QR) codes (substrate). The QR encoded pattern carrying the tailored dose can be created on demand, and the QR code pattern contains unique patient information that can be utilised for traceability and rapid on-dose verification of a single dosage form. The latter phrase refers to a procedure that may authenticate an individual dosage form as an authentic drug product, even when the secondary and/or primary packaging has been removed. As per WHO, more than 10% of the worldwide medicine market comprises of counterfeit and falsified medicine, and 20% to 30% of the medicine market in Asia, Africa, and the Middle East.

DEEP in the shape of a QR code on edible orodispersible "paper" using 2D printing was reported. The unique thing about this method is that, in addition to the information that is wrapped up, the QR code pattern also contains the exact and personalised dose of the API(s)[39,40].DiHeSys, German company has put money into developing similar type of technologies. The drug is printed in the form of a QR code on the edible carrier[41].But the current DEEP technology based on 2D printing can only make potent low-dose APIs. However, single step 3D enabled technology 3D printer that has a direct printing nozzle[42,43].Colorcon was one of the first companies to put unique physical identifiers (called "taggants") into a single dosage unit and follow the PCID (Physical-Chemical Identifiers) guideline. In this they incorporate smart tracers to its Opadryfilm-basedcoating technology for tablets and capsules. Colorcon and Applied DNA Sciences Inc. (APDN) worked together in 2019 to add DNA taggants to the coating. This made it possible to identify a single dosage form, for example, a portable DNA reader. Apart from this Colorcon jointly work with TruTag Technologies, Inc. to come up with a coated dosage form. The coating has edible silica microtags with a unique optical signature that can be read by an app on a smartphone[44].Freund-Vector was the first company to use "on-dose" QR codes digitally in the pharmaceutical industry. It did this with its TABREX Rev., a machine for printing QR codes on tablets in 2017[9]. InfraTrac came up with the "formulation-as" tag to get around the need for very special taggants. This is predicated on the notion that each composition of a pharmacological product has a unique spectral fingerprint. It is very hard to make a fake drug that has the same properties as the real one, like the same NIR spectrum[45].But the fact that it needs an internal spectral library of the real dosage forms for each instrument limits how often it can be used[46]. Zhang et al. (2020) provide an overview of the physical possibilities of "in-drug labelling" of oral tablets and capsules in order to reduce the number of fake medicines that get into circulation[47].

Utilizing novel dosage forms with digital features, such as DEEPs, may be one method for combating counterfeit medicines. In addition, people with swallowing difficulties, such as many children and the elderly, can benefit from DEEPs since they scatter in the mouth without the need to swallow a huge object. This sort of solid dosage form containing digital features is also strongly associated with digital healthcare and self-monitoring, in which patients can monitor important health metrics longitudinally and discretely using, for instance, wearable digital devices and a smartphone. For instance, a smartphone can be used as a "sensor for medication adherence" because it can serve as a reminder or engagement service to prevent missing or double-dosing. It might also analyse and show parameters obtained from wearable devices, such as pulse metres and/or oxygen saturation monitors. This information can be shared digitally with healthcare practitioners for follow-up and drug consumption monitoring. A DEEP with an integrated QR code can contain useful patient-tailored and patient-collected information that is digitally and in real-time available to both patients and healthcare providers, on their demand, and in their preferred format (e.g., language, specific information). In addition, a daily medicine update can be tracked and recorded by scanning the DEEP with a smartphone and transmitting this data on an online site. This available and processed information could assist healthcare practitioners in gaining a better treatment perspective and making well-informed judgements regarding subsequent therapy alternatives, ultimately leading to improved therapeutic outcomes.

Digital healthcare offers the ability to address nonadherence difficulties. A barrier for digital healthcare is that its effectiveness depends on the participation of healthcare professionals and patients. Patients' readiness to self-monitor and adopt digital healthcare is significantly affected by their age and digital literacy. Digital literacy is defined by UNESCO as "a collection of basic abilities including the usage and production of digital media, information processing and retrieval, involvement in social networks for the creation and sharing of knowledge, and a vast array of professional computing skills." Due to their limited digital literacy, geriatric individuals are thought to be the group most prone to doubt digital healthcare and self-monitoring. To completely accomplish patient adherence to and satisfaction with novel dose forms and the potential usage of digital healthcare, it is essential to understand patients' wants and concerns.

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The idea of cryptopharmaceuticals, which is based on blockchain technology, was introduced along with a smartphone app to show that it would be possible to track each DEEP from the site of manufacturing to the patient[48–50]. Also, DEEP makes it possible to track the origin of all ingredients to make sure that the end user gets a high-quality product with as little variation as possible[51]. As an example, the effects of cannabinoids on the body are different depending on the strain. This means that a drug product must contain the right strain. Also, being able to track the drug down to the dose level can help find drug abuse early and stop it quickly, which could save money. The European Medicines Agency (EMA) and other regulatory bodies support and encourage the use of mobile technologies and 2D barcodes to give patients more information. Scanning QR codes could make it possible to get customised information about a medicine instantly on the screen of a smartphone in the language and font of your choice [52].

Even though DEEP has clear benefits, the fact that visible QR code patterns are easy to copy makes it less useful for stopping fake drugs. To solve this problem, QR-based three-dimensional (3D) codes with multiple layers printed that can't be seen were made [39,40,53]. In addition to the 2D barcodes, digital "on-dose" physical unclonable functions (PUFs) based on different mixes of digestible and edible fluorescent and silk proteins were suggested to protect against copying and forging as much as possible [5]. This asymmetric technology makes it possible to create cryptographic keys (the response) that are very hard to copy [54].

Apart from this some patients does not want their regular monitoring by some other sources [55]. Also, sensitive information that is encoded in QR codes should be kept safe in any way possible to protect patients' privacy and safety, even if cyberattacks happen. Also, the inks should have dyes and pigments that are non-toxic and edible in the amounts shown in the 2D barcode pattern [56]. It is suggested that patterns of barcodes with a higher level of error correction be used to make printed 2D barcodes more reliable [57]. Still, these and many other things about people may make it harder for people to accept these new technologies and solutions.

IoT could also be used to help people remember to take their medications, especially older people who sometimes forget [58]. There are mostly lab-based prototypes of wearables that can sense movements like twisting the cap, putting your hand to your mouth, pouring a pill into your hand, and swallowing the pill or swallowing itself [16,59].

IoT-based technologies have a wider range of uses. They can track behaviours and individual states related to taking medications as prescribed or related to the therapeutic effect (e.g., relief of pain) of medications [60]. These IoT based technologies can be very customised, like wearables that are made for a specific person[61]. Personalization could mean anything from simple fixed-time reminders to managing a complex medication schedule (including rescheduling if a dose is missed) to context-aware systems, just-in-time[62].

Using mobile and personal devices, like smartphones, has shown to have a lot of potential to improve healthcare, including the treatment and prevention of diseases. Over the past 10 years, 85% of mobile phone users in the US and Europe had a smartphone [63]. The smartphone become a "sensor for medication adherence" by acting as an engagement or reminder service for the medicine or pronounced as to avoid double dosing, or by using smartphone sensors to measure human behaviours and states related to adherence or track symptoms (or the lack of symptoms) in the person's daily life environment [64].

It is also used as a displaying and processing tool that can be shared to keep track of how much of a drug is taken, decide on a treatment plan, possibly change how a medicine is given, and/or customise the dose for ingestible electronics sensors (IESs), also called “smart pills” [65,66]. IESs like Atmo Gas and Abilify MyCitecapsule have been made to make monitoring easier and improve medication adherence. This is because sensors that are not eaten do not guarantee that the medicine is taken. Also, a smartphone can track how well a person takes their medication by using radio-frequency identification (RFID) or near-field communication (NFC) to pick up the bottle and remove the dosage form (**see Figure 5**). In addition, the smartphone may be used as an analytical instrument to identify and validate the medication product and/or dose form by reading the built-in smart tracers, such as 2D barcodes[67].They initiate use of digital therapeutics, but they probably also have other diseases that need drugs to treat or control[68].In this case, PDDS would be important to give each patient the exact doses and release profiles they need[69].

FDA consider digital therapeutics as part of Mobile Medical Applications (MMA). They have become very popular in the last ten years, especially at the start-up level[70,71]. They are using algorithms that range from simple rule-based to machine learning (ML) and artificial intelligence (AI).

The Digital Healthcare Act (DVG) made it legal for doctors in Germany to give their patients insured health apps for the first time in October 2020. At the moment, ten apps have been approved[72][73].

For better patient outcomes, more technologies could be used. For example, adding smart tracers, such as a 2D barcode, to the PDDS at the dosage unit level could help people (patients, healthcare professionals, caregivers) find and track medication and verify each medicine and adherence all in the same app. Thus, the data from the dosage forms combined with the results of digital therapeutics on the same platform. This could help decide what the next dose should be (s). Also, digital therapeutics could be used to measure how well a drug treatment is working, especially when a change in how the drug is taken is needed. During clinical studies, they could also be used to see how patients react to the investigational drug products. There is a lot of potential for improving society by combining PDDS with digital health.

Current trends in pharmaceutical acceptance for DEEP

Human factors for acceptance of PDDS

The PDDS could help patients better (self-)manage their treatment plans, which could improve their health outcomes. But PDDS need to be improved to take into account the different ways that patients and their formal and informal caregivers use them as people[55].

In one of the surveys done by German Federal Ministry of Education and Research (BMBF) in six countries i.e., Germany, Italy, France, USA, Japan, UK on the perception of personalized based medicines in patients and physicians.This survey is focused on Personalized Medicine awareness, cost-saving perception from public and the responsibility of cost covering. Kichko and coworkers done a survey on perception of personalized medicines in two states of USA (Bavaria and Pennsylvania) both in patients and physicians. The workers suggested in Pennsylvania physicians suggest personalized medicines are more effective with more safety profile. The physicians are interested to pay for training how to handle the personalized medicines. Apart from this, physicians wants to standardize the procedure for the personalized medicines. The patients wants that some reimbursement must be provided for the use of personalized medicine and in case of complete failure total insurance coverage under certain policy. However, same observation was not reported when studied in Bavaria. In another study done by Chao and coworkers where they selected 13 participants to understand the perception of patients about DEEP. In this the shape, type of pattern, size and color is of patient’s choice. The interesting part of the study is that patients

express thorough interest in the DEEP based personalized medicine over the conventional medicine. Apart from this app based data monitoring was also done.

We talk about the human factors considering recent research on how chronically ill people use (or don't use) technology (N = 200). About 20% of patients will not be willing to use any personal technology, including PDDS, no matter how small or personalised it is or how many other advanced features it has. These patients are not adopters, so they need to be kept track of. Another 20% will be sceptical about using technology, and a programme to teach them or a peer support service may help them change their minds.As for the patients who might agree to use PDDS, the following human factors will affect how the system is used and the quality of the data it collects[74]. Political problems also concern whether printing in pharmacies should be required or voluntary. For homeprinting, one may imagine several harmful scenarios if patients mistakenly print medications improperly or if they print too many drugs with the goal to sell them[75,76].

Ethical, privacy and security challenges

In particular, there are still a lot of ethical questions about the use of personalized based treatment or diagnostic products that haven't been answered. This area is made even more confusing by the use of both PM products and new technologies that neither consumers nor clinicians have seen on the market before. As rolling out of basic and early-stage research and make more PM products, people will be more interested in discussing and finding solutions to these ethical issues.

First, the service's terms and conditions must be clear and easy to understand by the user. All international and national rules must be followed by the terms and conditions. For PDDS with encapsulated information, figuring out and prescribing the patient-tailored dose would require collecting, managing, and storing a huge amount of personal health information[77,78]. The use of supercomputers and computer clusters to protect data would be a key part of putting personalized medicines into place. So far, only authorised parties, like patients and healthcare professionals (like nurses, doctors, pharmacists), can see private information about patients. Who will decide on the personalised dose and how will it be decided? This needs to be done in a way that meets privacy and security rules like the European General Data Protection Regulation (GDPR)[79,80].One could say that it would be easy to make a fake dose form shown in this study, i.e., QR code printing on a regular office printer that doesn't have any API in its ink. So, more improvements are needed of the QR idea should be done, for instance by adding features like holograms that make it hard to copy

something which could keep fake QR-coded dosage forms from being brought to the market.Another way could be to make apps for mobile devices, phone apps to keep track of medications, QR encoded dosage forms. For instance, the app that the patient used could give the patient only the information that was important to him or her. Make sure the right treatment is given, while the manufacturer's app would give the necessary details about the supply chain and raw materials as well as the tools used to make the product. Also, the use of certain apps on mobile phones could be used as a way to prove that the patient took the medicine. Getting patients to stick with their treatment plans. There are even more possibilities for making smart QR codes with inkjet printing encoded dosage forms. For example, instead of having information on it.

The QR code could tell you a lot about the dosage form shown in this study. Encode the URL of a web page with any amount of information (Number of letters) that isn't limited by how many letters a QR code can hold. This time around, individual can get around the rules about how big a QR code must be for smart devices to be able to read it. In addition, bydata redundancy, putting less information in the QR code, can be made bigger. This will make it harder for mistakes to happen in the QR code introduced with mechanical damage or flaws from the printing process. Thus, it is possible for safe medicine that would give patients all the information they need about the dosage form.

Regulatory consideration and consent for DEEP

The pharmaceutical industry and its mass production method could not keep up with slow pace in this field and the calls to switch to personalised medicine. The growth of different kinds of 3D printing and the proof that it can make drugs in small batches with customised doses and release profiles have made this technology a possible future solution for personalised medicine.As a result of their belief in the importance of personalised medicines for more effective and safe treatment, there is a high level of interest among practising pharmacists to implement this technology as a method of drug dispensing, and may alter the traditional workstream in clinical practise.

Despite this backing and the high theoretical prospects for this technology, there is still a long way to go until the technological and regulatory obstacles preventing its actual application in the healthcare system are addressed[81]. There is no regulatory guidance for the production of pharmaceuticals with this advanced technology is the greatest hindrance to the implementation of this technology. The FDA rule governing the use of 3D printing in the medical industry focuses on the use of this technology for prosthetics and medical devices but

excludes the creation of drugs. If drug manufacture utilising 3D or 2D printing is considered a manufacturing process, typical laws that apply to conventional pharmaceutical items cannot be applied to personalised medicine that is produced on demand[82]. The FDA's Emerging Technology Team (EET) has already begun working on this matter. The primary objective of EET is to motivate technical innovation in production and design, such as DEEP in pharmaceutical research [83]. For instance, crystallisation might cause physical instability difficulties during storage of some medications. To best utilise the technology of personalizedpharmacoprinting, independent of the future context, patients may need to regularly monitor their health and prescription decisions must be made. For example, the number of daily pharmacoprinted medications, as well as the quantity of APIs they should include and shape and colour considerations. This allows patients to become more active in their own medical decision-making. There are general challenges that limit the application of printing in pharmaceuticals which are covered in concluding section. Even with automated methods including such 3D printing, numerous unanticipated variances might result from the exact same 3D computer- aided design model, depending on factors like the quality or age of ink supplies and altered slicer program- based printer settings.The best 3D printer for a pharmacy should be easy to use, require little setup and training, and save time compared to traditional printing methods. Since all the printing material used for pharmaceutical materials is edible that might generate microbial contamination. Most of the polymers that are currently used to make pharmaceuticals don't print well, so non-pharmaceutical grade polymers are used.When choosing a 3D printer to print medications, it's important to think about the concentration and size of drug products you want to print. Various printer models have different tolerance ranges, which can affect how well the drug product is printed. IJP can also be used to print different kinds of ink to make different drugs colours in a single QR-coded dosage form. Because of this, the visual recognition of these drugs is possible, and if they are printed in even avoid drug-drug interactions and non-adjacent dots. Also, the strength of colour could change depending on how much was printed, for example, it could be brighter colour to make it stronger. All of these options mean that a full and simultaneous optimization is needed of all the parts, including the way the ink is made, the formulation, printer, substrate, printer head, and smartphone app is needed.

But putting the idea of QR codes into practise would be difficult. There are some things you can't do with dosage forms. The fact that there are smart devices is important for these kinds of pills. If there are any problems with how it should be expected that patients will use

electronic devices. Among other things, what if the smart device's battery is dead, it's lost or forgotten, or the network isn't working accessible, especially if the URL and all other needed information are encoded in the QR code. Also, the QR code can be hard to read if it is not encoded correctly. During transport, dosage forms would get creased or crushed storage. QR codes can also lose their colour or move from one place to another place while being stored. So, they are resistant to light, humidity, and heat, but dyes or pigments that can be eaten should also be used correct package for the printed forms of the doses. Even with the problems, if digital printing is improved and used more, it could be used for making new drug products to help patients take their medicines.

Conclusion and future perspectives

Pharmacoprintingis personalised medicines on demand with the chance to make individualised dosage forms. People are asking for patient-tailored therapy more and more to improve the overall outcome of health carebetter cost-effectiveness all around. Personalized drug delivery systems (PDDS) are a new, digitally-designed way to get drugs to where they need to go. Overcome the problems with the drugs that are currently on the market, especially: (1) giving a personalised and accurate dose on demand,release kinetics and dosage form, (2) improve adherence to medication and give a better picture of the treatment, (3) provide the individual dosage units should have unique identifiers, like 2D barcodes, so that the drug can be tracked and its authenticity can be checked. Individual dosage units should also make it easy to get specific information about the drug. Also, PDDS can build a bridge between the pharmaceutical world and the digital world. This is important because the healthcare industry is becoming more digitalized, and a new type of therapy, called digital therapeutics, is one example. But for the PDDS concept as a whole to work and be sustainable, related technological, economic, data privacy and security, and human factors problems need to be solved and taken into account. Also, the rules and guidelines for the flexible on-demand dose need to be clear.

Conflict of Interest

The authors declare no conflict of interest among themselves.

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