Innovations in Chewable Formulations and 3D Printing

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Since their introduction, chewable dosage forms have gained traction due to their ability to facilitate swallowing, especially in paediatric, geriatric and dysphagia patients. Their benefits stretch beyond human use to also include veterinary applications, improving administration and palatability in different animal species. Despite their advantages, current chewable formulations do not account for individualised dosing and palatability preferences. In light of this, three-dimensional (3D) printing, and in particular the semi-solid extrusion technology, has been suggested as a novel manufacturing method for producing customised chewable dosage forms. This advanced approach offers flexibility for selecting patient-specific doses, excipients, and organoleptic properties, which are critical for ensuring efficacy, safety and adherence to the treatment.

3D printed medicines and pharmaceuticals | orally disintegrating formulations | human and veterinary medicine | precision medicine | taste masking

1. Introduction

The oral route is the most common route for administrating medicines as it is the most convenient and is easy to handle, making it the first choice for clinicians and most patients [1]. In general, oral formulations are considered to be cheaper than formulations designed for other routes [2]. Moreover, many drugs are well suited to be administered orally using different types of dosage forms, including liquids, capsules, tablets or chewable formulations.

Despite their advantages, conventional solid (e.g., tablets and capsules) and liquid (e.g., solutions and suspensions) dosage forms still have some limitations [3][4][5]. One of the main disadvantages associated with the solid forms is the swallowing difficulties encountered by some patient populations (e.g., paediatrics and geriatrics) [4][6]. Although liquid dosage forms are easy to swallow, they suffer from stability issues and dosing errors [3]. Chewable formulations—e.g., chewable tablets, gummies, gums and lozenges—on the other hand, are gaining attention due to their ease of administration, safety and lack of stability challenges. These formulations can be produced using different pharmaceutical methods, depending on the type of dosage form being made. However, most of these processes are complex, involving multiple unit operations.

Three-dimensional (3D) printing is an additive manufacturing tool that offers a sophisticated way of creating personalised chewable formulations [7]. The technology has been widely investigated to fabricate various types of

3D printed dosage forms, termed Printlets™, in different sizes, shapes, flavours and drug doses [8][9][10][11]. Moreover, it offers the possibility of engineering multi-drug dosage forms, known as PolyPrintlets, which could benefit patients on a polypharmacy and simplify their dosing regimen [12][13][14]. This is achieved through the development of patient-friendly formulations that are tailored to each patient's needs and preferences, improving medication adherence [15][16]. The benefits are particularly significant in the case of drugs with narrow therapeutic indices, where a small variation in the drug dose can cause severe side effects.

2. 3D Printing of Chewable Tablets: An Innovative Approach

Typically, medicines are manufactured in large batches with fixed doses through multi-step processes that are performed in centralised locations. Recently, with the introduction of new production technologies, the pharmaceutical industry has experienced a paradigm shift, causing treatments to move away from "one-size-fits-all" approaches and advance towards "precision medicine". Precision or personalised medicine focuses on addressing the specific needs of patients and their medical condition, taking into account their genetic makeup and the inherent properties of the pharmaceutical product [17]. Thus, the overall goal is to improve the efficacy of the treatment whilst ensuring unwanted side effects are reduced.

In this new healthcare model, the end user's needs and preferences are considered from the beginning of the formulation design stage to the point of administering the final product [18][19]. Personalised therapy has long been a remarkable goal in therapeutics but has not been adopted yet, mainly because of the lack of necessary tools and incentives, economic barriers as well as insufficient medical and pharmaceutical professionals willing [18]. As current production methods are wholly unsuitable for personalisation, this calls for the need for new manufacturing methods that are both simple and flexible, permitting the on-demand fabrication of medicines.

The 3D printing technology has been identified as a disruptive force in other fields, making it well suited for this application [10][20][21][22]. It is an additive manufacturing technology that enables the layer-by-layer fabrication of 3D objects based on digital 3D designs, created using a computer-aided design (CAD) software or obtained via 3D imaging techniques [7]. Although 3D printing is well-known in the automobile, aerospace and engineering fields, its use within the pharmaceutical space is somewhat new [23]. In fact, attention was drawn to it in 2015, following the FDA approval of the first 3D printed medicine (Spritam, levetiracetam) [24]. Since then, abundant research has been done on 3D-printed medicines and medical devices [20][25][26][27], with several attempts being made to launch 3D-printed drug products on the market. The main motivation behind the interest in this technology is its versatility and ability to customise doses, sizes, shapes and drug release profiles of small batches of medicines in a short time frame [28][29][30]. Thus far, its applications have extended to include personalised medicines, tissue engineering [31], controlled-release systems, as well as customised food products for specific needs [32][33][34]. Therefore, with this in mind and with the presence of suitable materials, 3D printing can be regarded as an ideal alternative method for producing personalised chewable tablets.

According to the American Society for Testing and Materials (ASTM) International, there are seven major 3D printing categories: binder jetting, vat polymerisation, powder bed fusion, material extrusion, material jetting,

directed energy deposition, and sheet lamination [35]. Of these, material extrusion is the most widely used one and includes the fused deposition modelling (FDM) and semi-solid extrusion (SSE) technologies. In general, the material extrusion process involves selectively dispensing a material through an orifice with the aid of heat [35]. In FDM, filaments are melted through a heated nozzle at a specific temperature, after which the material is deposited on the build plate to form the layers [36][37][38]. While SSE operates in a similar fashion, syringes containing gels, pastes or waxes are used instead of filaments [39][40][41].

SSE is an affordable 3D printing technology that can offer many advantages in this field [39]. As an example, the preparation of its ink is generally considered easy and requires a few excipients. Due to the nature of the starting materials, SSE can employ lower printing temperatures compared to FDM, making it suitable for use with thermolabile drugs [42]. Additionally, the use of disposable and pre-filled syringes provides benefits for meeting the critical quality attributes demanded by regulatory agencies [39][43]. In particular, this enables the syringes to be prepared and filled as per GMP requirements at normal pharmaceutical production facilities. Furthermore, cross-contamination between different drugs or formulations can be avoided without the need for additional decontamination steps.

To date, the SSE technology has been successfully used for the preparation of a wide range of chewable formulations in different shapes, colours and textures [44][45][46][47][48][49][50][51][52][53][54]. The most notable example is its use for the fabrication of isoleucine Printlets for children suffering from Maple Syrup Urine Disease, a rare metabolic disease characterised by the deficiency of the enzyme complex branched-chain alpha-keto acid dehydrogenase [53]. A clinical study involving the use of these Printlets has shown their ability to provide tighter control over the blood levels of isoleucine compared to treatment provided using conventional capsules. Furthermore, children receiving the treatment and their caregivers have shown positive responses indicating their acceptability to the flavoured Printlets, with some flavours (e.g., orange) being more preferred over the other flavours. These findings have shed light on the potential of the SSE technology as a novel pharmaceutical production method for manufacturing personalised oral dosage forms.

A following study involved comparing children's perceptions of Printlets made using different 3D printing technologies (i.e., FDM, digital light processing (DLP), selective laser sintering (SLS) and SSE) [55]. Despite the DLP Printlets being initially the preferred choice of the participants (aged 4–11 years), after being informed that SSE Printlets are chewable, the participants changed their minds, and 79% of them were in favour of the chewable Printlets. In another acceptability study, it was shown that the shape, size and colour of Printlets could influence patients' willingness to take them [56], thus highlighting the importance of selecting a dosage form that meets a patient's particular preference to ensure his/her adherence to treatment.

The versatility of the 3D printing technology could be exploited to create multi-drug formulations termed PolyPrintlets. An example of such is the Lego-like chewable dosage forms fabricated using SSE [48]. The gelatine-based formulations contained a combination of paracetamol and ibuprofen and are aimed at simplifying administration by being dispensed as a single dosage form that provides a synergistic therapeutic effect. In another approach, it has been shown that it is also possible to fabricate chocolate-based dosage forms for paediatric

applications [52]. The formulations were loaded with either paracetamol or ibuprofen, wherein the inherent drug properties governed its release behaviour. More recently, cereal-based 3D printed dosage forms have been suggested for paediatric use [57]. The concept involved concealing the drugs, namely ibuprofen and paracetamol, in a common breakfast ingredient, cereals. Herein, the crushed cereal was used as the ink for SSE 3D printing of oral formulations in different shapes (e.g., various letters, star, heart, torus and flower shapes). These formulations are aimed at improving adherence to treatment in paediatric patients during their hospital stay.

Owing to the digitised nature of the technology, it is forecast that in the future, 3D printing could be seamlessly integrated with other digital technologies, including artificial intelligence [58][59][60], biosensors [61][62] and robots [63][64], streamlining a new era of digital healthcare [65][66]. With the aid of these technologies, the personalisation of medicines can be facilitated by expediting the process and enabling execution in remote locations, including patients' homes. In fact, research in this area has already begun with the introduction of smartphone-enabled 3D printing [67]. This recently developed technology involves the use of a smartphone's screen to initiate the 3D printing of medicines inside a compact, portable 3D printing system. Whilst the concept is still in its infancy, more advancements are expected in the near future, fast-forwarding the implementation of 3D printing in clinical practice.

3. Veterinary Applications

Veterinary pharmaceuticals play an important role in the preservation and restoration of animal health [68]. In the veterinary field, animal-appropriate medicines, which are available in a wide range of dosages, are also required to meet animals' needs. Species differences affecting the design and performance of veterinary dosage forms include pharmacokinetic differences, feeding habits, environmental factors, age and management practices [69]. Generally, the medicine's dose is adjusted based on the weight of the animal [68]. Therefore, it is common for a drug to be marketed with several strengths. This is best exemplified with fluralaner, clindamycin hydrochloride and mavacoxib. Alternatively, it is ordinary practice for vets and pet owners to split marketed tablets into two or four pieces to meet an animal's requirements (e.g., dose or swallowing abilities). Like humans, animals have preferences that affect their compliance and willingness to take a medicine [69]. Thus, when a veterinary medicine is developed, animals' preferences are an important aspect to consider. For instance, dogs prefer animal-based proteins (e.g., chicken, pork and beef), whilst horses like fruit flavours (e.g., apple). As such, the Simparica Trio product contains pork liver powder, hydrolysed vegetable protein, sugars, and gelatine to address dog-specific sensory requirements.

Historically, oral dosage forms and parenteral formulations have been the primary dosage forms used for animal care [69]. Nowadays, with the advancement in pharmaceutical production, several more convenient oral dosage forms (e.g., palatable tablets) have been launched [69]. Indeed, chewable tablets have found applications in veterinary medicine for administration to domestic animals, especially cats [70] and dogs [71]. In fact, chewable tablets play a more essential role in veterinary pharmaceuticals than human ones. As a matter of fact, the number of commercialised chewable formulations for veterinary use exceeds those for humans. A reason for this may be their easier administration due to the animal's willingness to ingest the medicine.

The benefits of 3D-printed medicines are not only limited to humans but can also extend to include veterinary applications. In this regard, 3D printing has been used for the production of animal prosthetics and implants [72][73][74] as well as veterinary dosage forms. Representative examples include orodispersible films containing prednisolone for the treatment of inflammatory diseases in cats and dogs [75], chewable tablets (or ChewTs) containing theophylline for the treatment of asthma [76] or gabapentin for the treatment of neuropathic pain or prevention of seizures [77], both for use in cats and dogs. Dosage forms with precise doses and palatability could be 3D printed, especially using SSE technology, in the veterinary clinic or at the owner's home to ensure their suitability for the pet [7][75]. Further examples on 3D printing for animal use can be found in previous research [78][79].

4. Conclusions

Chewable tablets are dosage forms suitable for use in certain patient populations, especially paediatrics, geriatrics and those who suffer from dysphagia, complying with their individual requirements. Despite the advantages that chewable formulations offer, the current methods used for their production are inherently time-consuming and inflexible, making it difficult to optimise the dosage form characteristics based on the individual needs and preferences of patients, both of which affect their adherence to the therapeutic plan. In addition, it can be noted that chewable dosage forms are widely used in routine clinical practice, both for humans and animals. However, there is still a need for new approaches capable of addressing the limitations of conventional manufacturing methods.

Recently, 3D printing, in particular the SSE technology, has gained attention as a novel fabrication method for the production of chewable medicines. The implementation of this disrupting approach is set to revolutionise the way dosage forms are fabricated in the near future. This technology can create palatable dosage forms with personalised doses, shapes, colours and textures in a simple and fast process, using the same excipients as conventional chewable tablets and, therefore, making it superior to manufacturing methods currently in use. This statement is reflected in many of the aforementioned examples, in which the SSE technology was successfully used to prepare bespoke chewable formulations.

Indeed, this innovative concept has already been tested in a clinical trial performed in a hospital setting with children, wherein the positive findings are a testament to SSE technology's great potential. More recently, further studies were carried out in patients, wherein the application of chewable formulations can be further understood; one such included an acceptability study related to children's perceptions of Printlets (3D printed oral dosage forms) made using different 3D printing technologies. Although SSE Printlets were not originally the participants' top choice, after being informed that SSE Printlets were chewable, the majority of participants shifted their preference in favour of the chewable Printlets. The benefits of 3D printing are not only limited to human healthcare but also extend to veterinary medicine, where both vets and pet owners could exploit it to create customisable formulations in a fast and simple manner, avoiding dosing errors or the animals' rejection of unpalatable medicines.

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