Editorial

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Modified-release 3D printed tablets: challenges and opportunities based on geometry and materials

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The oral administration of drugs is the most common route of delivery due to the preference of patients. There are numerous solid dosage forms (SDFs) that allow a medication to be administered by swallowing, with tablets and capsules the most commonly used. From the technological point of view and focusing on production at medium and large scale, tablets have many advantages over capsules because they can be produced at a lower cost in less time.

The tablets are solid dosage unit dosage forms, obtained by mechanical compression of granules or mixtures of powders with one or more active pharmaceutical ingredients (APIs), with addition, in most cases, of various excipients. The shape, size and weight of tablets may vary, but with restrictions derived from the use of punches and matrices. For this reason, this type of dosage form does not allow for considerable changes in the geometry of the tablet, let alone achieving individual dose adjustments for patients.

Based on the aforementioned issues, there are two little explored aspects of pharmaceutical technology. On the one hand, the use of geometric strategies can be used to modify the release of APIs or to achieve mechanical effects after administration, such as modifying the buoyancy of the tablet in the stomach. On the other hand, it is very difficult to achieve SDFs with individual doses adjusted for each patient, taking into account current trends referring to customized or personalized medicine. These two aspects can be overcome using additive manufacturing or 3D printing. An increase in the use of this technology is foreseen in the coming years.

3D printers allow for to making objects from a digital model, mostly through additive manufacturing processes, where the material is added layer by layer to form the final piece, which can have an unlimited variety of geometries [1]. The production of drugs by 3D printing has the potential to respond to the issues described above, as it will be possible to individualize, from pill to pill, the dosage, geometry and even release properties. The possibility of printing SDFs with multiple active ingredients, tailored to the patient, would decrease the number of unique doses that the patient should take, thus improving compliance. In addition, this method allows for personalized manufacturing in various geographical locations, such as pharmacies, expanding access and creating new business models [2]. In addition, this technology will make it possible to, in real time, modify the geometry of SDFs and explore alternatives related to the release of the API (kinetic aspects) as well as the spatial location of the device in the body (for example, retention in the stomach or another portion of the gastrointestinal tract). In this commentary, we will analyze these challenges.

Although drugs are produced on a large scale, patients do not respond in an equivalent way. Therefore, it is increasingly necessary to move towards personalized medication systems. Naturally, when we think of personalized medicine and therapies of the future, we focus on the enormous genetic variability identified in the human population, which can affect the response of patients to treatments. However, the term personalized medicine

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should also be extended to specific groups of patients, such as older adults and children, who have different characteristics than the average adult. Currently, we have a lack of availability of drugs in doses and formulations suitable for the pediatric population. Additionally, ageing is related to physiological changes; when older adults consume multiple medications simultaneously, the risks related to medication use increase [3].

The need to move towards personalized medicines will require changing manufacturing processes towards approaches that allow more flexible designs [4]. With great advantages with respect to traditional technologies, 3D printing (3DP) can be quickly converted into a very simple process and therefore is likely to be accepted to achieve customized pharmacotherapy. With respect to the design of drug release systems, 3DP applied to pharmaceutical technology has a promising future and a solid present.

Many research groups are trying to adapt to different methods of additive manufacturing to obtain SDFs with the required properties like immediate/sustained release, multiactive content or precise dose control. Kyobula *et al.* described fenofibrate inkjet printing. In this technique, the material is disposed using multiple nozzles and small volumes that allow for high resolution control (about 50 m). This method requires appropriate temperature control in order to maintain a molten dispersion of the drug in the carrier from the chamber to the nozzle [5]. Zhang *et al.* printed acetaminophen tablets by a fused deposition modeling technique from a solid dispersion drug filament obtained by hot melt extrusion. In this work, the filament properties of the printer were studied and optimized, with the extruder at 200°C. The printed tablets showed better extended drug release rates than directly compressed tablets [6]. Goyanes *et al.* obtained a budesonide-loaded filament by hot-melt extrusion (HME) and developed 3D printed tablets coated with an enteric polymer; the final product had a better release profile than the commercial preparation. This work demonstrated the feasibility of combining 3D printers with pharmaceutical processes to obtain better results [7]. Khaled *et al.* used an extrusion technique, without heating, to prevent the degradation of thermally sensitive drugs. Because the solids were mixed with acetone, dimethylsulphoxide (DMSO) and water to obtain a homogeneous printing paste, the tablets needed 24 h of vacuum drying. The result was a polypill with five compartmentalized drugs and two independent release profiles, in other words, immediate and sustained [8].

In our group, we have developed 3D printing based on the principle of fusion-solidification, adapting it to Generally Reconized As Safe and economic excipients such as lipids (Gelucire®, Gattefossé, France). These have the advantage of melting at a low temperature and forming dispersions with the drug that are loaded into 'cartridges' that isolate it from the medium. Additionally, the release profile can be modified according to the hydrophilic–lipophilic balance (HLB) of the carrier and due to its low density, gastroretentive SDFs can be printed.

In addition to everything described above, an interesting use for I3D is the use of geometric variations and the combination of specific materials to achieve buoyancy in the stomach.

While some drugs have ideal absorption characteristics through the gastrointestinal tract, others present difficulties. A system of modified release of drugs, called gastroretentive, provides an important focus on the residence time in the stomach for drugs that have: local activity in the stomach (misoprostol, antacids); an absorption window in the stomach or in upper portions of the small intestine (L-Dopa, furosemide); intestinal or colonic instability (captopril); or low solubility at high pH values (diazepam).

Numerous strategies have been investigated to increase the residence time in the stomach, such as:

- Bioadhesive systems, which adhere to the superficial mucosa [9].
- Expandable systems, which upon contact with gastric fluids rapidly increase their size and delay passage through the pylorus [10].
- Systems controlled by density or buoyancy [11].

In the latter system, density is an important factor that influences the duration of gastric residence. High density systems use their weight as a retention mechanism, and when it reaches the stomach, it lodges at the bottom of the stomach and remains there below the pylorus. On the contrary, low density systems are characterized by their floating properties. Low density is achieved by air entrapment or by adding low density materials. Different designs have been developed for these matrices. One of the most innovative systems involves multilayer matrices, which do not float immediately, but generate carbon dioxide via the reaction of an organic acid with the water that enters it, generating an air chamber *in situ* that promotes the flotation of the system. Clearly, manufacturing by addition allows for the design of tablets with materials of low density that also present complex geometries with one or more watertight compartments that permit long periods of buoyancy.

Undoubtedly, 3D printing provides a large number of options related to the oral administration of APIs. In this brief synthesis, we have focused on analyzing how the type of strategy (geometry, flotation and dose adjustment) can contribute to improving pharmacotherapy, but clearly we must move forward with the design of more reproducible processes and improve our knowledge of the properties of each material involved.

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