3D printing: potential clinical applications for personalised solid dose medications

Three-dimensional printing or additive manufacturing has the potential to transform personalised medicine

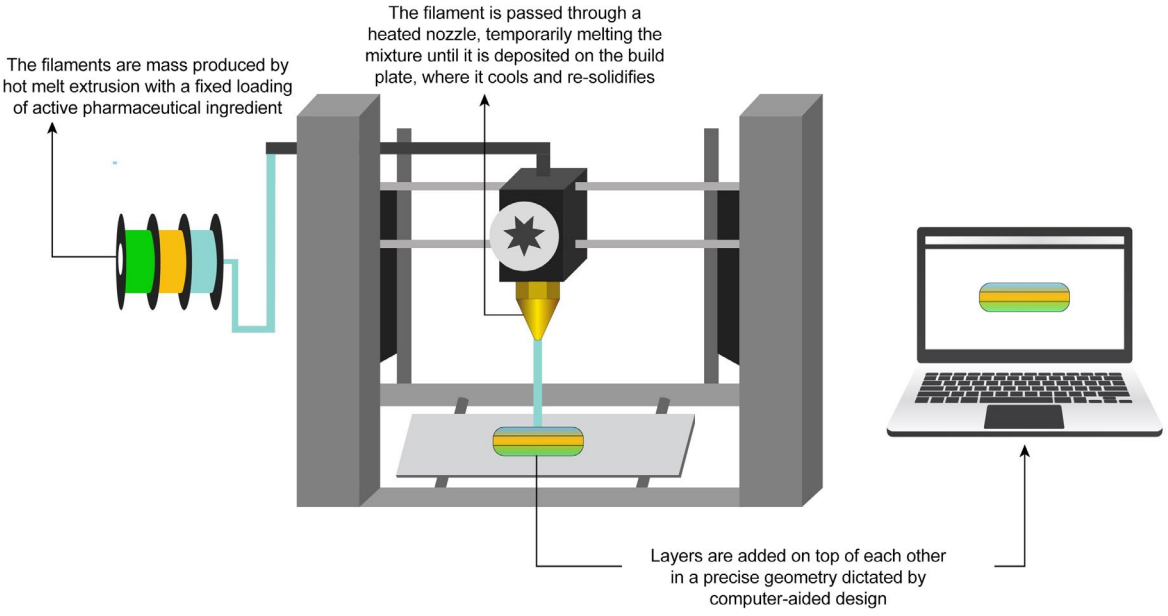
Personalised medicine aims to move gold-standard care away from empiric prescribing for a typical patient towards tailored treatment for the patient as an individual.[1] It is well known that the effect of a medicine on an individual can vary based on factors including sex, genetics and even hormones. Currently, the personalisation of medicines to adjust for factors such as these is limited by the doses and combinations that are commercially available. This inflexibility makes it difficult for clinicians to tailor the medication for individual needs. One technology that could revolutionise personalised medicine is a process called additive manufacturing. In this process, a three-dimensional (3D) object is produced by fusing thin layers of materials on top of each other until the complete object is formed. This 3D printing method could be applied to medicines to include several drugs in a single tablet at entirely customisable doses set by the clinician, such as the proof of concept five-in-one polypill developed in 2015.[2]

What are 3D-printed medicines?

The field of 3D-printed medicines is rapidly emerging. Spritam (Aprecia Pharmaceuticals) is an orodispersible levetiracetam tablet that completely dissolves in the mouth within 10 seconds; and in 2015, it became the first 3D-printed medicine to be approved by the Food and Drug Administration.[3] Since then, there have been several studies that have confirmed the safety, efficacy and feasibility of 3D-printed medicines against their traditionally manufactured counterparts.[4] With the right techniques, 3D-printed medicines can be made to mimic the immediate or sustained release profiles of conventional tablets or even accommodate several medicines with different release profiles in the same tablet.[2,5] These dosage forms are of a high quality and accuracy, and they can mimic all the characteristics of conventionally made dosage forms but with the ability to adjust and fine-tune the dose of each medicine in the tablet.[5]

3D-printed tablets can be produced using common fused deposition modelling 3D printers, which are portable, easy to use, and cost-effective. Fused deposition modelling printers melt a filament through a heated nozzle to draw a two-dimensional cross-section on the build plate, then the third dimension is constructed by depositing layers of material on top of one another consecutively until a complete object is formed (Box 1).[3,5] The materials used in fused deposition modelling 3D printers are commonly thermoplastic polymers — materials that soften upon heating but return to their previous solid state when cooled. For pharmaceutical 3D printing, a variety of biodegradable and biocompatible polymers such as hypromellose, povidone and polyvinyl alcohol can

1 Schematic representation of a fused deposition modelling three-dimensional (3D) printer consecutively layering several active ingredients into a single tablet



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be used, all of which are already used in traditionally manufactured medicines.[6,7]

What will this look like in practice?

3D-printed dosage forms have the potential to address many of the problems encountered with conventional dosage forms, including customisable dose titration, reducing pill burden, removing barriers to medicine adherence, modifiable excipients, and improving accessibility in times of disaster (Box 2).

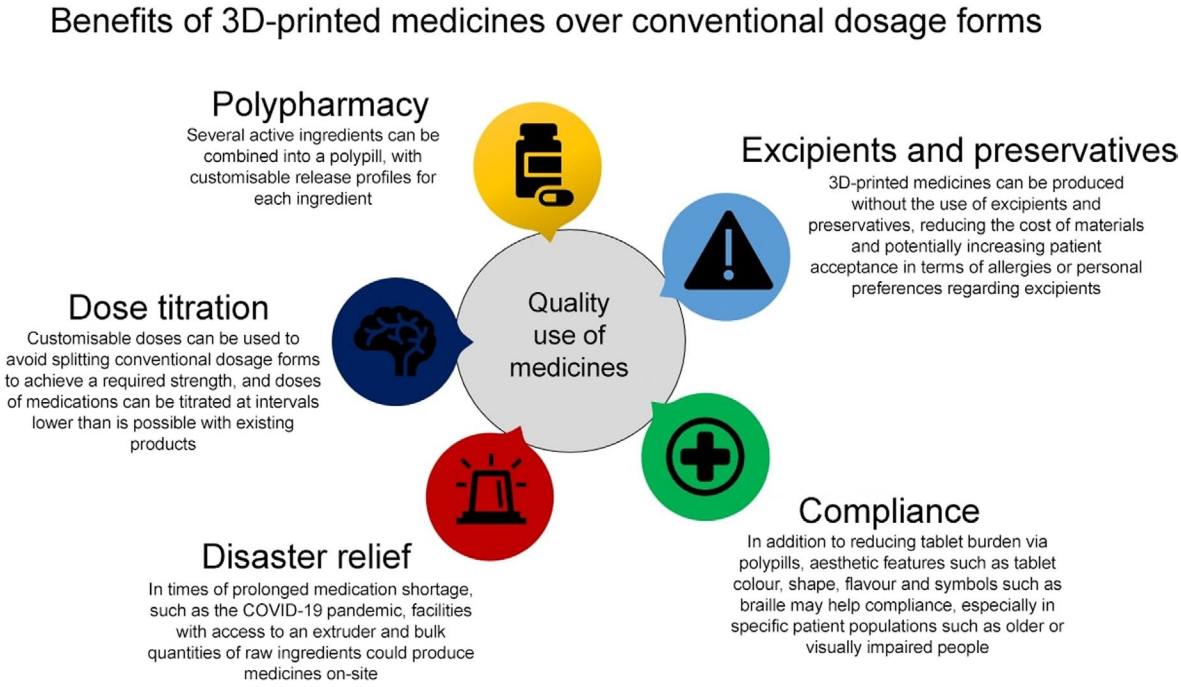
The ability to titrate doses of medicines slowly is a particular benefit of 3D-printed dosage forms. This is especially applicable to medicines prone to adverse events on initiation and dose increases, including serotonergic effects on initiation of antidepressants such as serotonin and noradrenaline reuptake inhibitors or dizziness associated with antihypertensive drugs such as angiotensin receptor blockers.[8,9] Initiation doses could be started lower than currently marketed strengths and could be increased at increments smaller than is possible with existing dosage forms.

Perhaps the most exciting opportunity is the potential to reduce the tablet burden of our ageing population, with an example being the five-in-one polypill.[2] In practice, a combination of several drugs is often used to achieve optimal patient outcomes for many conditions, such as in heart failure and secondary prevention of cardiovascular disease. In these complicated treatments, an advanced 3D-printed medication regime could simultaneously help the patient take the right medicines at the right doses at the right time, while also reducing the number of pills the patient must swallow. Certain patient populations, especially older people, can be increasingly non-adherent to medication regimens due to reasons such as forgetfulness, difficulty managing medicines, and the cost of medicines.[10] If multiple medicines in individualised doses could be combined into one single tablet or capsule, it could ease this difficulty in managing medicines and even reduce the cost of medicines.

3D printing would also allow for advancements in the aesthetics of tablet design. Braille or visual descriptors, such as a heart symbol for cardiovascular medicines, could be used to assist the visually impaired. Flavoured or coloured shells could be implemented with the intention to improve adherence in children. It has been shown that pharmaceutical 3D printing processes are possible without excipients,[11] not only reducing the cost of consumables but also allowing smaller tablets to be produced. Patients and their carers often resort to splitting or crushing tablets and opening capsules in order to reduce the size and allow incorporation with food and drinks to facilitate swallowing.[12] Combining smaller tablet sizes with an individual's preferred shape and flavour characteristics could improve swallowability and, consequently, adherence.

The ability to 3D-print tablets with fewer components[11] also potentially provides a solution for medicine supply shortages in times of disaster. During the coronavirus disease 2019 (COVID-19) pandemic, many patients have been unable to obtain adequate supply of several commonly used medicines. In Australia, this may be worsened by long supply chains, where medications are made and processed overseas before being freighted to Australia.[13] For example, the blood thinner combination dipyridamole–aspirin was

2 Three-dimensional (3D)-printed tablets as a solution to help overcome challenges faced with traditionally manufactured products



COVID-19 = coronavirus disease 2019. ◆

unavailable in any brand for almost an entire year, forcing doctors and pharmacists to find alternate solutions.[14] A compounding pharmacy or hospital with access to extruders, 3D printers and bulk quantities of raw medicine and polymer base could manufacture replacements on site to ensure adequate supply of regular medications during unexpected shortages.

Challenges

The goal of 3D-printed personalised medicine is an admirable target, but the logistics of this type of manufacturing must be considered. For example, the current state of the technology has limited throughput, requiring significant time to produce a single dose. This raises issues of scalability, requiring multiple 3D printers to quickly produce enough doses for a patient or to provide personalised medicines for multiple patients. In addition, although the materials used for 3D printing are relatively inexpensive, the printers themselves range from a few hundred dollars to tens of thousands of dollars, contributing significantly to the cost of this type of operation. As the technology continues to develop, however, it is likely that production speed will improve while costs will fall. When 3D-printed pharmaceuticals are integrated into practice, health professionals administering the service will require training. Initially, this training may be as specific additional qualifications, but as it enters mainstream use, we may see incorporation into university degree programs for relevant health professions.

Although the active ingredients themselves remain the same as in our current medications, the formulation, including excipients; the number of active ingredients; and their doses will be new. There are many factors to consider when designing each new dose form, not least the potential for interactions between medications and interactions between a medication and an excipient. Compatibility testing could be supported through the development of software and machine-learning tools to develop formulae for consistent and compatible filaments that relate to different combinations of drugs and release profiles. These tools could be used to optimise the material and process variables, which in this application could be the quantity of filament, nozzle temperature, and printing speed calculated from the intrinsic properties of the filament.[15] A concern about this rapid development is that regulatory requirements lag behind. Quality control may become a topic of debate, as each batch of products made via mass manufacturing can be tested, but this is unlikely to be possible for custom 3D-printed tablets produced in small quantities for an individual patient. This will require the development of regulations and standards of practice by the Therapeutic Goods Administration with input from prescribers, producers and users of 3D-printed dosage forms.

Conclusion

3D printing has the potential to be a disruptive technology by revolutionising the status quo of oral dosage form design, but many barriers exist to its broader acceptance in practice.[16] The Food and Drug Administration approval of Spritam is a promising sign for 3D-printed medicines, but there is a still a long way to go. Spritam is not available in truly personalised doses, but in fixed strengths just like the traditionally manufactured counterpart. This highlights the fact that pharmaceutical companies stand to gain little from the integration of 3D-printed medicines into the current health care environment. Rather, the true potential for 3D-printed medicines is for prescribers and their patients through fully customisable doses, unique medication combinations, and with design considerations to improve patient adherence. Although the patient and practitioner benefits are apparent, without regulatory approval or further interest of pharmaceutical companies in 3D printing, seeing the technology in practice may not be a reality over the next 5–10 years. Hopefully, personalised medicine will become available, all in a dosage form 3D-printed at a local hospital or pharmacy at the click of a button.

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