Towards printing of medicine in 2D and 3D

Maren Preis - Pharmaceutical Sciences Laboratory, Åbo Akademi University, Artillerigatan 6A, 20520 Turku, Finland – mpreis@abo.fi

Abstract

The pharmaceutical industry showed an increasing interest for printing technologies during the recent years. Besides diagnostic aspects, printing techniques are nowadays used for the fabrication of actual dosage forms or to enable the drug loading of pre-manufactured devices and dosage forms. The present work intends to give an overview of the opportunities given by inkjet printing and extrusion-based printing systems for the manufacturing of medicine.

Inkjet printers have been widely used in the pharmaceutical field for depositing small amounts of drug-loaded liquids onto suitable substrates, such as orally disintegrating polymer films [1]. The precise printing process and a layer-by-layer printing approach enables flexibility in dosing. In particular with regard to special patient groups who need individualized doses and drug combinations, respectively, a fast and flexible printing process combining several active components can be considered a promising solution for on-demand patient supply.

Extrusion-based printing, for example using semi-solid materials, or more common using polymer melts in a fused-deposition modeling approach, can moreover be described as a three-dimensional printing technique. The required dosage form in terms of size, shape, surface area, and total weight, can be designed with computer-aided design softwares. The most challenging part of the 3D manufacturing process is, however, identifying the right polymers and excipients for the formulation to match with the requirements for drug release and overall disintegration of the dosage form once it has been administered to a patient [2,3].

The current developments show that more printers will enter the market, including hybrid systems combining inkjet and extrusion-based systems specifically for pharmaceutical purposes.

Figure 1. Different patients with individual needs.

Introduction

Printing technologies enable a flexible production of a variety of different products. Therefore, it was just a matter of time until printing would enter the pharmaceutical field as an alternative manufacturing technique for medicine and other drug products.

The world is changing fast and 'one-size-fits-all' approaches appear obsolete, in particular, when it comes to health care and patient treatments. The growing awareness that different patient populations, different age groups, and multimorbidity require individual therapies, lead to an increasing interest in innovative solutions for the design of drug delivery systems (Fig. 1).

Printing of dosage forms will presumably not replace conventional pharmaceutical manufacturing processes in general, but the new approach opens up new markets for niche products and personalized medicine. Standard medications and over-the-counter medicinal products will most likely be produced by the established procedures resulting in the regular compressed tablets, capsules (soft and hard), solutions, and suspensions, when for example talking about oral dosage forms.

Oral administration appears as the most convenient options for most patients, since it is non-invasive and usually no healthcare professional is required to assist (in contrast to most invasive administrations).

Table 1: Examples of printing technologies used for pharmaceutical purposes

Technology	Potential application
Inkjet	Printing of drug-loaded inks on dosage forms/substrates
Screen printing	
Fused-deposition Modeling (FDM)	Printing of dosage forms, implants, prototypes, …
Stereolithography (SLA)	
Selective Laser Sintering (SLS)	Implants (stents), organ replacement, other dosage forms
Stereolithography (SLA)	

Fabrication of drug delivery systems by means of printing

The scientific work in the field of drug product printing gained more and more interest in the recent years. Concepts and prototype studies have been performed and published [4]. Ink-based printing is often referred to as two-dimensional (2D) printing, whereby any

additive manufacturing processes usually have been described as three-dimensional (3D) printing (Table 1). However, there is a rather seamless transition between the two categories, since it highly depends on the ink, printed material and the printed design.

Inkjet-printed dosage forms

The advantage of inkjet-based printing is the high precision of the printheads enabling the deposition of small amounts on a defined surface. The precision enabled by this printing technology is in particular interesting for low dose drugs.

The most popular application of inkjet printing for pharmaceutical use is the printing onto pharmaceutically relevant substrates [4]. Orally disintegration, or also called orodispersible films (ODFs) are one example for a convenient oral drug delivery system. ODFs are in most cases thin soluble hydrophilic polymer sheets, which can be placed on the tongue where they disperse rapidly upon contact with the saliva. Therefore, they do not require water for the intake and are thus highly convenient dosage forms suitable for every age group, even for patient populations with swallowing issues.

The flexibility of inkjet printing with drug-loaded inks opens up multiple opportunities for dose adjustments, drug combinations, and can also be combined with identification prints for safety and anticounterfeit purposes (Fig. 2).

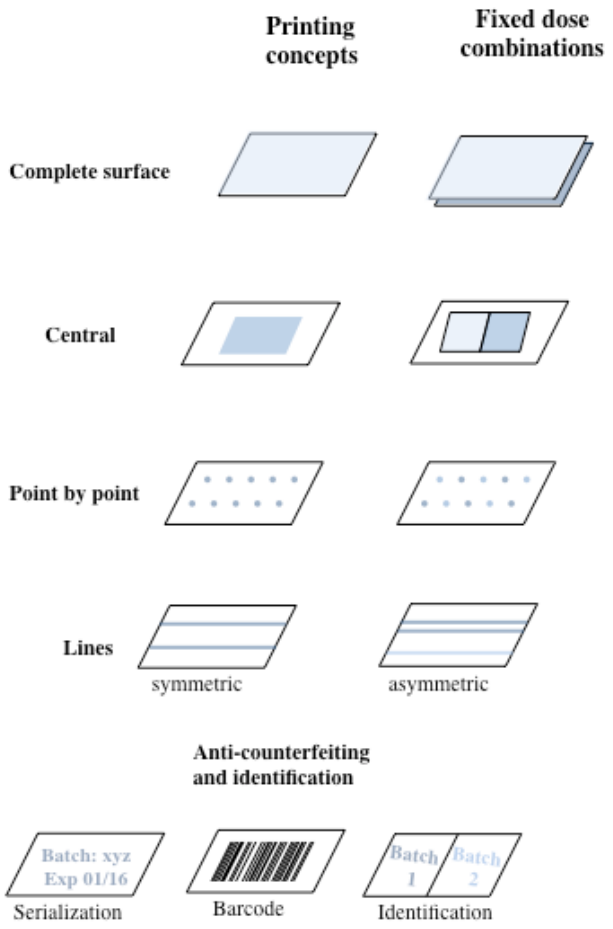

Figure 2. Printing on edible substrates – proposed concepts (4).

Flexibility in dosing can be achieved by adjustments of printing pattern, droplet spacing and number of layers printed on top of each other [5]. Using two or more drugs either in the same ink or in separate inks can create multi-drug-systems. By using separate inks, potential incompatibility issues between the combined drugs can be avoided. When using a thin polymer sheet as substrate, which can be cut into smaller doses after printing, the single doses will depend on the cutting and printing pattern, enabling even higher flexibility for the final doses.

Printed doses of water-soluble active pharmaceutical ingredients have shown almost immediate drug release in dissolution experiments (Fig. 3).

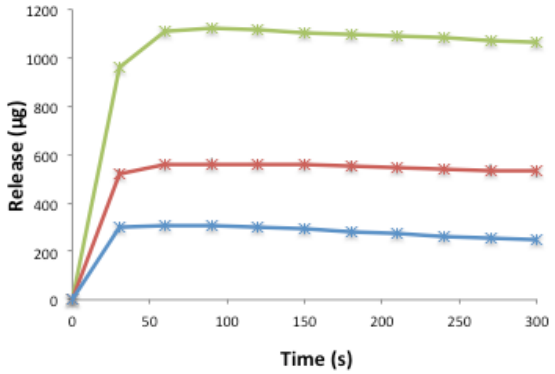

Figure 3. Drug release from orodispersible dosage forms – drug-loaded ink has been printed in 3 (blue), 5 (red) and 10 (layers) onto a polymer-based film substrate.

3D Printing

The use of the abovementioned inkjet printed dosage forms have mostly been described as 2D printing. Nevertheless, even an inkjet process, depending on the number of printed layers and ink material used may result in a 3D product.

In 2015, the United States Food and Drug Administration (FDA) approved the first 3D-printed tablet (Spritam®, Aprecia Pharmaceuticals). The company uses their proprietary ZipDose® Technology, a drug-formulation platform, to manufacture tablets in a layer-by-layer powder printing approach, where a binder solution is deposited between every powder layer. The resulting tablet is highly porous and thereby fast disintegrating.

However, when talking about 3D printing for pharmaceutical purposes, one of the most common techniques is fused deposition modeling (FDM).

Hot-melt extrusion (HME) is a widely used process in the pharmaceutical area. Extrudates are usually processed in subsequent manufacturing steps to obtain granules or pellets, which are pressed into tablets or filled in capsules. Therefore, HME-based 3D-printers appeared to be the tool of choice in recent years, since they can be operated with drug-loaded polymer filaments as feedstock material [6, 7].

Nevertheless, underlying processes are already well known, but the regulatory aspects are still a work in progress. The FDA published guidance and points to consider when printing drug products [8]. Multiple aspects have to be taken into account when printing pharmaceutical products. At a later stage it can even be discussed where the printed medicine will be produced, which

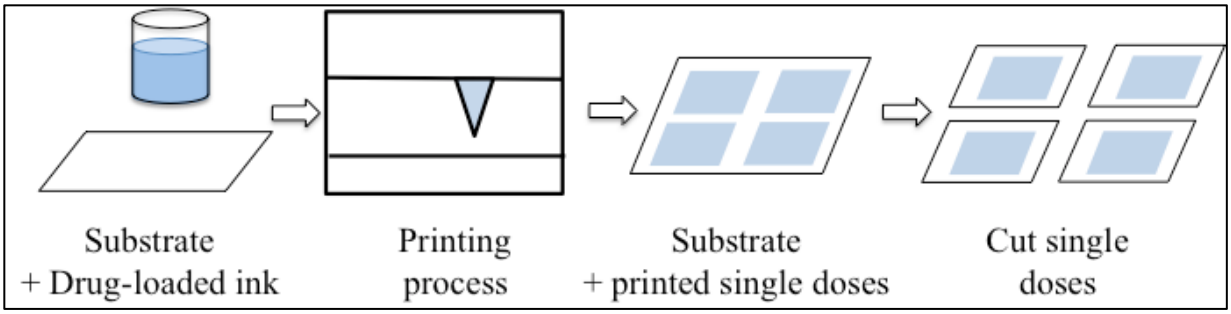

Figure 4. Printing and subsequent cutting into single doses.

could be in an industrial setup, but also in a compounding pharmacy. Future scenarios could involve new business models, such as pharmaceutical companies, which are specialized in producing on-demand printed medicine for local hospitals and pharmacies (Fig. 5). In any case, pharmacist should be involved in the design process of the printed dosage forms. Shape, materials, surface area and other components influence the final properties of the dosage form, and have to be carefully evaluated before the medication is given to the patient. A print-at-home approach has often been discussed in public media, but safety aspects of medicine and its distribution appear to be reasonable arguments against this model [2].

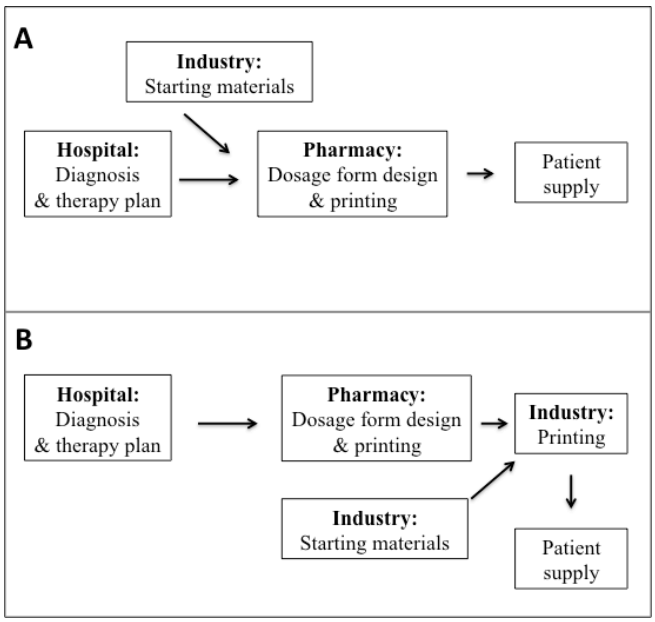

Figure 5. Possible scenarios for work distribution for the production and provision of printed medicine.

Hot-melt extrusion based 3D printing

Current research involves the analysis of the double-extrusion process on active pharmaceutical ingredients. At this point, filament production and 3D printing are two separate processes.

Thus, the impact of two heating procedures on drug stability and drug release properties is worthwhile to investigate (Fig. 6).

Using polymers of different molecular weights and solubility properties enables the modification of drug release patterns. Therefore, the opportunities to achieve drug-eluting products for immediate release, sustained release, or even a combination of these properties become feasible.

The most important advantages of 3D-printed medicine are the flexibility of the printing process, the opportunity to design tailored dosage forms for the individual needs of patients, and being able to serve niches and thereby also opening up an option to provide orphan drug products that would otherwise never be produced.

However, printed medicinal products will most likely never replace conventional pharmaceutical manufacturing processes in total, but they are a valuable addition by enabling more flexible, individual, and on-demand production of medication.

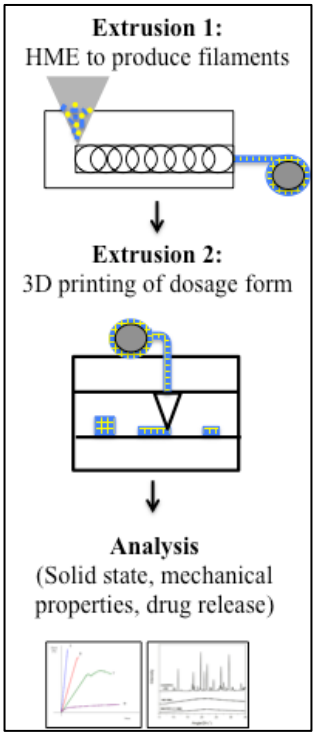

Figure 6. Production of hot-melt extruded filaments for subsequent 3D printing and analysis

Conclusion

The opportunities to fabricate dosage forms by means of different printing technologies are great. Nevertheless, formulation development is key and finding the right composition to achieve the desired properties of the therapeutic system while keeping the active pharmaceutical ingredients stable throughout the manufacturing process. It is expected that the printing and pharmaceutical industry will work closer together in the future to be able to provide high quality printed pharmaceuticals.

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Author Biography

Maren Katherina Preis studied pharmacy at the University of Düsseldorf in Germany, where she also received her pharmacist license in 2010. She received her PhD (Dr.rer.nat.) from the Faculty of Natural Sciences at the University of Düsseldorf (2014). Her work mainly focuses on oral drug delivery systems and the application of printing technologies for pharmaceutical purposes. Since 2015, she is a senior researcher at the Åbo Akademi University, Finland.