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3D printing of pharmaceutical dosage forms: Recent advances and applications☆

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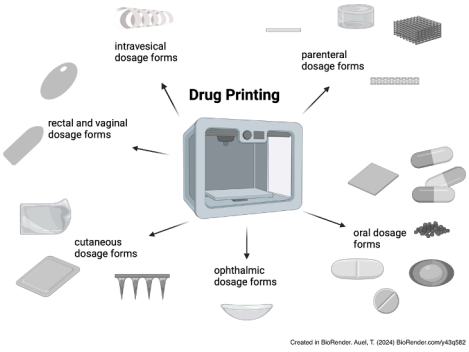
HIGHLIGHTS

- 3D printing offers unique possibilities in dosage form design.
- Reports on peroral, parenteral, cutaneous, and other solid dosage forms.
- Extrusion-based techniques dominate the manufacturing of 3D printed dosage forms.
- Unique control of drug release and shape of dosage form.
- Might be the key technique for individualized dosage forms.

GRAPHICAL ABSTRACT



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ABSTRACT

Three-dimensional (3D) printing, also referred to as additive manufacturing, is considered to be a game-changing technology in many industries and is also considered to have potential use cases in pharmaceutical manufacturing, especially if individualization is desired. In this review article the authors systematically researched literature published during the last 5 years (2019 – spring 2024) on the topic of 3D printed dosage forms. Besides all kinds of oral dosage forms ranging from tablets and capsules to films, pellets, etc., numerous reports were also identified on parenteral and cutaneous dosage forms and also rectal, vaginal, dental, intravesical, and ophthalmic preparations. In total, more than 500 publications were identified and grouped according to the site of administration, and an overview of the manuscripts is presented here. Furthermore, selected publications are described and discussed in more detail. The review highlights the very different approaches that are currently used in order to develop 3D printed dosage forms but also addresses remaining challenges.

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1. Introduction

The interest in three-dimensional (3D) printing has greatly increased during the last decades. The techniques that are summarized under this term are sometimes referred to as an industrial revolution [1] and may have the potential to disrupt even developed markets [2]. When the first 3D printed medicinal product Spritam® received approval by the United States of America Food and Drug Administration (FDA) in 2015, many people assumed that this revolution would also spread quickly in the pharmaceutical sector. However, to date, no further 3D printed medicinal products have been approved by the FDA or by the European Commission (following a recommendation by the European Medicines Agency (EMA)), in spite of an immense increase in the number of research articles published on the topic. However, several companies are working on 3D printed products. Triastek, for example, has reported to have received investigational new drug (IND) clearance to allow for shipping across state lines within the United States of America for at least four different 3D printed products under development [3]. These products are based on an extrusion technique, which is quite different from the ZipDose® technique used for Spritam® - nevertheless, both methods belong to 3D printing technologies.

3D printing technologies have in common that during the production process, data sets are used, which describe the position of every element in the created object using three coordinates. Typically, computer-aided design (CAD) is employed to devise a digital plan of the product, and then the goods are produced using the digital information in an additive, often layer-wise manner. This leads to a very precise control of the arrangement of materials, which is not common in other manufacturing techniques in which often homogenous arrangements of all components throughout the dosage form are essential to assure the correct dosing. 3D printing, therefore, offers the possibility to produce unconventional new shapes and also material arrangements which may be used, for example, to control release behaviors or to accommodate separated compartments within one dosage form. As the processes are either free-forming processes or within a material bed/bath of which only certain parts are solidified, the volume and/or outer dimensions of the dosage form can be varied easily, allowing for an adaptation of the dose without the need to change tooling, etc. Also, inner structures can be controlled with some techniques via the infill. These and other potential benefits of 3D printing of dosage forms have already been compiled in 2017 in a review concluding that the FDA encourages the development of such approaches [4]. However, to date, the 3D printing techniques also have limitations concerning dosage from production. One of the main challenges seems to be the comparably long production times which make the process currently economically rather inefficient. Nevertheless, when, for example, personalization is desired, and only small batches are needed, these techniques may offer economical and standardized alternatives to traditional compounding techniques. It is expected that these markets will grow as more knowledge, for example, on pharmacogenomics becomes available and screening tools as well as algorithms to support prescribers become available [5–7]. However, personalized dosage forms pose further challenges, e.g. regarding regulatory approaches to approval and batch release. In this context, the FDA published a discussion paper in 2021 on 3D printing of medical devices at the point of care, which shows that the agency is willing to discuss these issues [8]. In addition to finished product production, 3D printing techniques may be beneficial in rapid prototyping of dosage forms even if the final products might be manufactured using a different approach, e.g. to provide dosage forms for early phase clinical studies in which a great dosing or release profile flexibility may be desirable.

Many different techniques and names are used for 3D printing processes. It may be assumed that not all techniques are equally suitable to produce all types of dosage forms and that the size of the dosage forms as well as the materials that may have beneficial properties for the site of application and, last but not least, the processing conditions will play a major role in choosing the most suitable method for a certain drug product. For the purpose of this review article, the authors decided to use a terminology to differentiate between the 3D printing methods based on the guidelines by the International Organization for Standardization (ISO) in cooperation with the American Society for Testing and Materials (ASTM) on additive manufacturing [9]. Therefore, the following terms and abbreviations will be used to describe the different processes where possible. Firstly, the techniques were divided into the following main categories: material extrusion (MEX), material jetting (MJT), binder jetting (BJT), powder bed fusion (PBF), and vat photopolymerization (VPP).

MEX describes processes where the deposition of the material is performed by extruding it through an orifice or nozzle. As there is a wide variability between the different methods used in MEX-based techniques, these were further categorized for this review as filament extrusion (FE), syringe extrusion (SE) and screw extrusion (SCE).

In FE, a filament is used as an intermediate product, which is typically produced by hot-melt extrusion (HME). During the printing process, the filament is softened again in the nozzle area, while the extrusion is driven by the mechanical feed of the downstream filament. The terms fused deposition modeling (FDM) and fused filament fabrication (FFF) are often used synonymously for this type of process. Several reviews on the various methods of drug incorporation, the materials used, the process parameters, typical challenges, and other topics have already been published [10–12].

Syringe extrusion (SE) describes processes where the typically semi-sold material (a semi-solid state often caused by the addition of solvent/dispersant or application of heat or a combination) is extruded from a syringe or similar container. Extrusion through the nozzle is usually achieved by pressurized air or mechanically. In some cases, especially when using solvents, post-treatment of the printed objects, e.g. drying, might be necessary. Other names and acronyms are also commonly used for this printing method and its different variants, such as semi-solid extrusion (SSE), pressure-assisted microsyringe (PAM) printing, pneumatic extrusion, direct ink writing (DIW), paste or gel extrusion. Reviews have been published on common materials, areas of application, and process parameters, including post-treatment [13,14].

The term screw extrusion (SCE) defines extrusion methods where a solid material is pushed through the nozzle by a screw-driven process, such as in many dry powder extrusion (DPE) setups. Powders and granules can serve as raw materials. The extrusion setup can consist of one or more screws. The recently published review by Aguilar–de–Leyva et al. describes the different setups, formulation and printing parameters, and applications of SCE [15].

MJT describes processes in which the object is built up by selectively jetted droplets of material. Examples of printable materials include molten substances, photopolymer resins, or solvent-based inks, which may need to be processed further (e.g., by drying or UV-curing) during or after the printing process. Processes or terms that belong to material jetting include inkjet printing, drop–on–demand (DoD) and electrohydrodynamic printing (EHD). For further information on the principles, process details, and materials of material jetting in the pharmaceutical context, the reader is referred to more specific reviews on this topic [16–18].

While in MJT, the object is built up from the jetted material alone, BJT processes utilize the presence of a powder bed. The powder is bound together by jetting it with liquid. The bond between the powder particles can be strengthened by adding a binding agent, which can be present in both the powder bed and the jetting liquid. Other commonly used names for binder jetting are drop-on-powder (DoP) or powder bed inkjet. An overview of the most important aspects of the BJT for drug printing has been given by Wang et al. [19].

A powder bed is also used in the PBF. Instead of inducing bonds via a jetting liquid, they are created here by fusing the particles together through the input of thermal energy. Lasers are often used for the targeted application of the required energy; examples of such processes are selective laser sintering (SLS) and selective laser melting (SLM). In their

review, Awad et al. analyzed the applications of PBF in healthcare, including pharmaceutical dosage forms and medical devices. They also evaluated technical considerations and challenges [20].

Another 3D printing method known as VPP also utilizes light or lasers. However, here, the light induces local photopolymerization reactions within the liquid resin, which then leads to solidification and bonding of the irradiated region. The technologies of digital light processing (DLP), stereolithography (SL or SLA), and two-photon polymerization describe VPP processes. An overview of VPP techniques, their applications in the manufacture of dosage forms and medical devices, examples of materials, advantages and challenges can be found in a review by Xu et al. [21].

The ISO/ASTM guideline on additive manufacturing also describes other manufacturing principles but to the authors' knowledge these have not yet had any considerable influence on the manufacturing of pharmaceutical dosage forms. For a review of different 3D printing techniques and materials and the advantages and disadvantages of pharmaceutical manufacturing in general, the reader is referred to other review articles, such as [22–25].

Lately, authors have also been referring to 4D printing. The "fourth dimension" in these products is typically time as these products change their shape over time (e.g. due to shape memory effects) [26]. As mentioned above, very different materials are also used in the different 3D printing technologies. For 3D printing of medicinal products and medical devices, the suitability of the materials has to be ensured. While for some techniques traditional pharmaceutical excipients can be used of which pharmaceutical grades are available, and safety has been shown. This is problematic for other processes using materials that have not been used for this type of application before. Some of the challenges associated with new excipients in pharmaceutical dosage forms, in general, are reviewed by Elder et al. [27]. Another important topic is the equipment used for the manufacturing process. However, this problem seems solvable, as there are reports on an FDA-approved printer for medical devices as well as a GMP-ready pharmaceutical printer [28,29]. Nevertheless, the quality strategy, including equipment, digital design, raw and intermediate materials, as well as manufacturing and controls, have to be carefully considered in order to ensure that the high pharmaceutical standards are met and to allow for regulatory approval. Further insight into this topic was provided by Khairuzzaman [30].

There are a couple of other reviews dealing with 3D printed dosage forms. However, their scope differs from that of this review. Some reviews focus either on a few chosen dosage forms [31,32] or on single printing techniques [13]. Other reviews, like the one from dos Santos et al., examine publications from an earlier period of time than the ones studied here and focus on specific materials [33]. The purpose of this review is to provide the reader with an overview of recent developments regarding 3D printed pharmaceutical dosage forms. In the scope of this review article, the authors cover pharmaceutical dosage forms that have been manufactured using a 3D printing formulation strategy to define the shape and/or composition of the dosage form. Aspects such as drug design (3D printing to synthesize molecules, etc.) are not included here. As the arrangement of the different components or the shape of the dosage forms are in the focus, typically solid dosage forms are produced, even though for some applications also semi-solids such as hydrogels have been described, that however do not change their shape during the administration (except for 4D printed objects, as defined above).

In order to prepare this review and to exclude bias due to the selection of literature and/or authors already known by the authors of this review, a systematic literature research based on the database PubMed® (https://pubmed.ncbi.nlm.nih.gov) was performed using the search terms "3D printing drug" on March 26^{th,} 2024. The search was constricted to the years 2019 – 2024 (until the above-mentioned date) and yielded 3828 results. All abstracts available from these 3828 manuscripts were screened by at least one of the authors. Manuscripts were excluded from the further review process in which no pharmaceutical dosage form was produced (e.g. with a focus on material development but without a specific use case) or no 3D printing technique was used, research that did not include a drug or model drug or in which the drug was not included in the printing process (e.g. by spray- or dip-coated printed dosage forms or 3D printing of molds for injection molding), manuscripts in which the main focus was on bioprinting or tissue engineering, manuscripts that were entirely off topic (printing of organ models, printing of analytical tools, printing for cell culture) and review articles, editorials, opinions, etc.. Some of the excluded topics are addressed in other articles of this special issue. After the initial abstract screening, the remaining full manuscripts were re-considered and evaluated using the same criteria. After this process, 538 manuscripts published from 2019 until March 26th 2024 remained that were included. These were roughly grouped into the following categories: oral dosage forms, parenteral and associated dosage forms and other dosage forms: cutaneous, ophthalmic, vaginal, intravesical and rectal. The categories were further subdivided, as will be addressed in the individual chapters of this review. Fig. 1 shows the distribution of the identified manuscripts among the categories. In rare cases, manuscripts were assigned to more than one subcategory, such as orodispersible minitablets (ODMT) which were assigned to orodispersible tablets as well as pellets and minitablets.

Among these papers, MEX-based techniques were by far the most frequently used methods with more than 75 % of the manuscripts, nevertheless some trends for certain dosage forms were also observed and will be discussed in the following chapters. An overview of the distribution of printing methods is given in Fig. 2. A small difference in the total number of methods used to the number of publications identified results from the fact that in a few manuscripts, more than one technique was explored. In spite of the immense effort and care that was put into literature screening, the authors wish to point out that this review cannot provide an overview of all reported data and manuscripts may have been falsely excluded or were not identified as the search terms may not have been suitable, even though these were on purpose chosen to be very general as the authors assumed that they would thereby cover a large range of manuscripts. However, manuscripts not listed in the PubMed® database are also not included. As the authors also perform their own experimental research work on the topic of 3D printing of dosage forms, also additional literature known to the authors from the respective period of time may have been included. The complete tabular overview of all the literature included from 2019 until March 26th 2024, sorted by categories, including the citations is given in the supplementary material to this review (see supplementary material).

2. Oral dosage forms

Oral dosage forms belong to the most common dosage forms and include dosage forms that are swallowed and dosage forms that are placed in the oral cavity. Spritam®, the first and so far only FDA-approved 3D printed dosage form belongs to this group.

Solid oral dosage forms for human use listed in the European Pharmacopoeia (Ph. Eur.) include powders, granules (which include pellets by the Ph. Eur. definition), capsules, tablets, medicated chewing gums and oromucosal preparations such as films and lozenges.

In this review, the authors grouped the oral dosage forms identified from the literature in tablets, pellets and minitablets, capsules, and films. Furthermore, dosage forms with a specific feature are described separately such as gastro-retentive dosage forms (GRDF), chewable dosage forms and other very specialized dosage forms including dental devices. The discussions concerning the individual dosage forms are given in the individual chapters. In general, for oral dosage forms, 3D printing is mainly applied in order to individualize the dose(s) of drugs, to influence the drug release behavior, or, in some cases, to promote patient adherence. The 3D printing techniques used for this purpose showed high variability. However, some trends were detectable, such as the use of solvent-free techniques for orodispersible forms and MEX methods for extended-release peroral tablets. The excipients used for

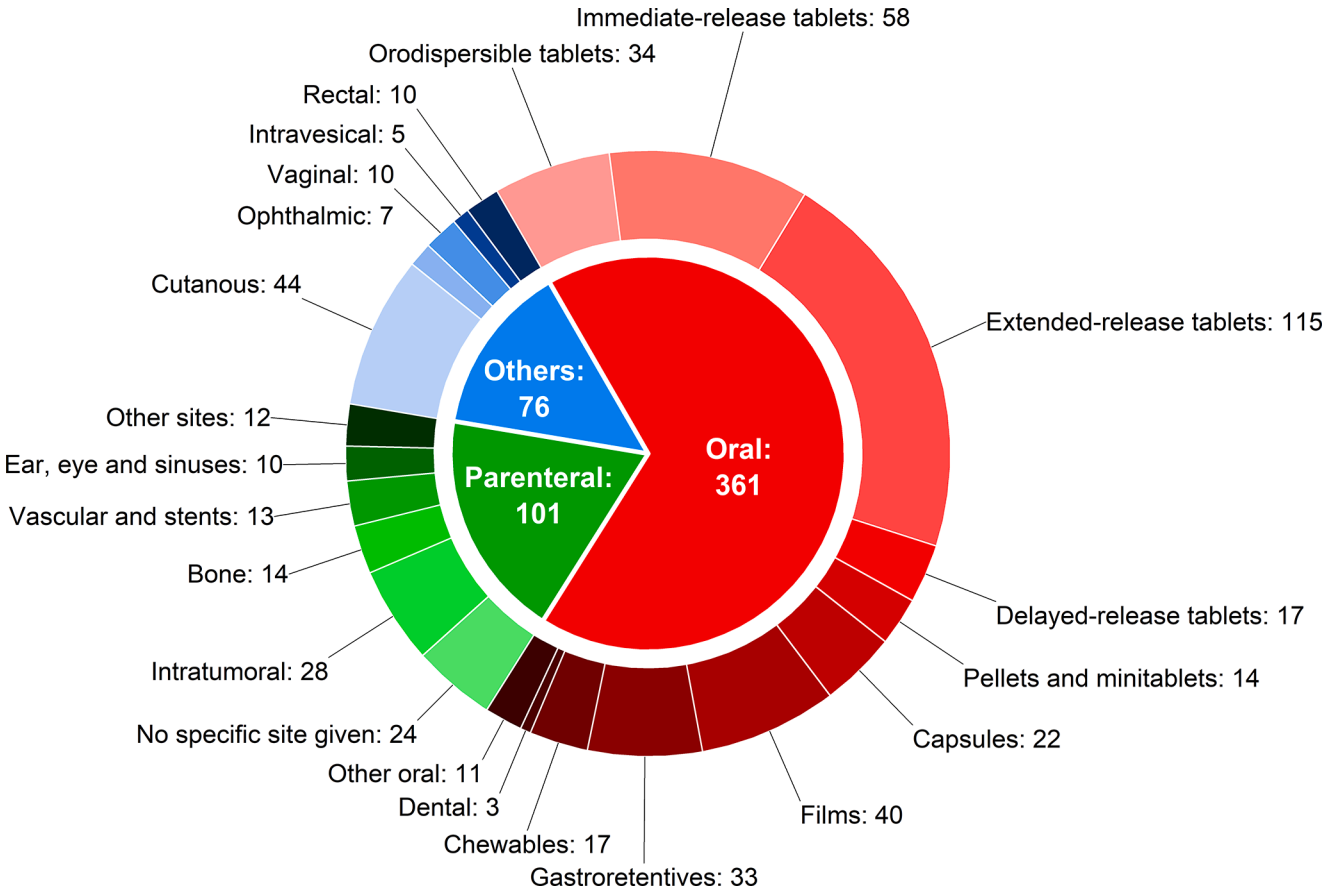

Fig. 1. Distribution of the topics of the 538 included manuscripts in the categories oral, parenteral, and other dosage forms in general (circle) and in the individual sub-categories (ring).

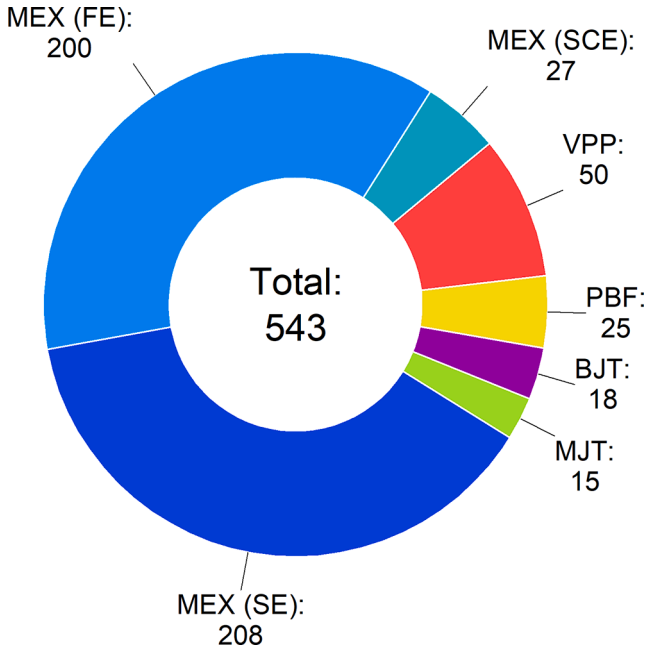

Fig. 2. Distribution of the reported printing techniques among the manuscripts; material extrusion-based on filaments (MEX (FE)), material extrusion-based on syringe extrusion (MEX (SE)), material extrusion-based on screw extrusion (MEX (SCE)), material jetting (MJT), binder jetting (BJT), powder bed fusion (PBF), vat photopolymerization (VPP).

oral dosage forms are often classical excipients that are also used with established production methods. An exception from this was the printing of capsule shells, for which mainly poly(vinyl alcohol) (PVA) was used as an excipient as opposed to traditional capsules typically made from gelatine.

2.1. *Tablets*

Tablets are solid dosage forms containing a single dose, often derived from powders or granules via compression, but also other techniques, such as molding or extrusion, can be used. Tablets often have a cylindrical shape with either flat or convex end surfaces. Several characteristics regarding the disintegration and/or drug release behavior, as well as other properties or methods of administration, may be used to differentiate among different types of tablets. The Ph. Eur. distinguishes between immediate-release and modified-release, whereas the latter group is further divided into prolonged-release (often also referred to as extended-release), delayed-release, and pulsatile-release. For the purpose of this review, the following categories will be distinguished: orodispersible tablets (ODT), immediate-release (IR) tablets, extended-release (ER) tablets, and delayed-release (DR) tablets. Delayed-release tablets for this purpose are defined as tablets in which the onset of release has been modified. This group includes gastro-resistant tablets. The differentiation between IR and ER tablets was based on the Ph. Eur. recommendations on dissolution testing [34], which specifies a typical acceptance criterion for IR tablets of 80% release within 45 min for the first test level. In addition, the Ph. Eur. describes an IR dosage form as one „that is not deliberately modified by a special formulation design and/or manufacturing method“ [35]. It also mentions that for a solid dosage form, the dissolution profile of the active ingredient essentially

depends on its intrinsic properties. This means that even comparatively slow releases can be classified as immediate-release dosage forms if they contain, for example, active ingredients that possess a low dissolution speed. Some examples of developed tablets found in the screened manuscripts are depicted in Fig. 3 highlighting the diversity of the proposed tablet formulations.

2.1.1. Orodispersible tablets

ODTs are uncoated tablets that are placed in the oral cavity, where they disintegrate quickly before being swallowed. The disintegration time requirements vary depending on the legal framework. The Ph. Eur. demands a disintegration time of less than 3 minutes, while the FDA asks for a disintegration time of 30 seconds or less [39–41]. ODTs are usually produced by compression, lyophilization, or molding [42,43].

The only 3D printed drug approved to date, Spritam®, is an ODT, supposed to be taken with a small volume of liquid. It is produced via the ZipDose® technology, which is basically a type of BJT on a conveyor belt. The high porosity of the dosage form due to the manufacturing method and the use of highly soluble excipients support a claimed average in vivo disintegration time of 11 seconds [7]. As an innovative product in the field of 3D printing, the choice of this BJT manufacturing process and the choice of excipients is certainly leading the way for research in this field, which also explains the high proportion of publications using this printing method. Other printing techniques have also been investigated for the production of ODTs. Table S1 provides an overview of all included manuscripts that fulfill the requirements of the European Pharmacopoeia for ODTs, including their printing method and their disintegration times.

BJT research often involves screening the starting materials. Both the powder bed [44–49] and the jetting fluid [44,47,48,50,51] can be modified to determine the properties of the final dosage form. For the production of ODTs using BJT, the use of easily water-soluble powder mixtures based on mannitol and lactose is just as suitable as for conventional production methods [36,45–48,50–55]. The choice of these

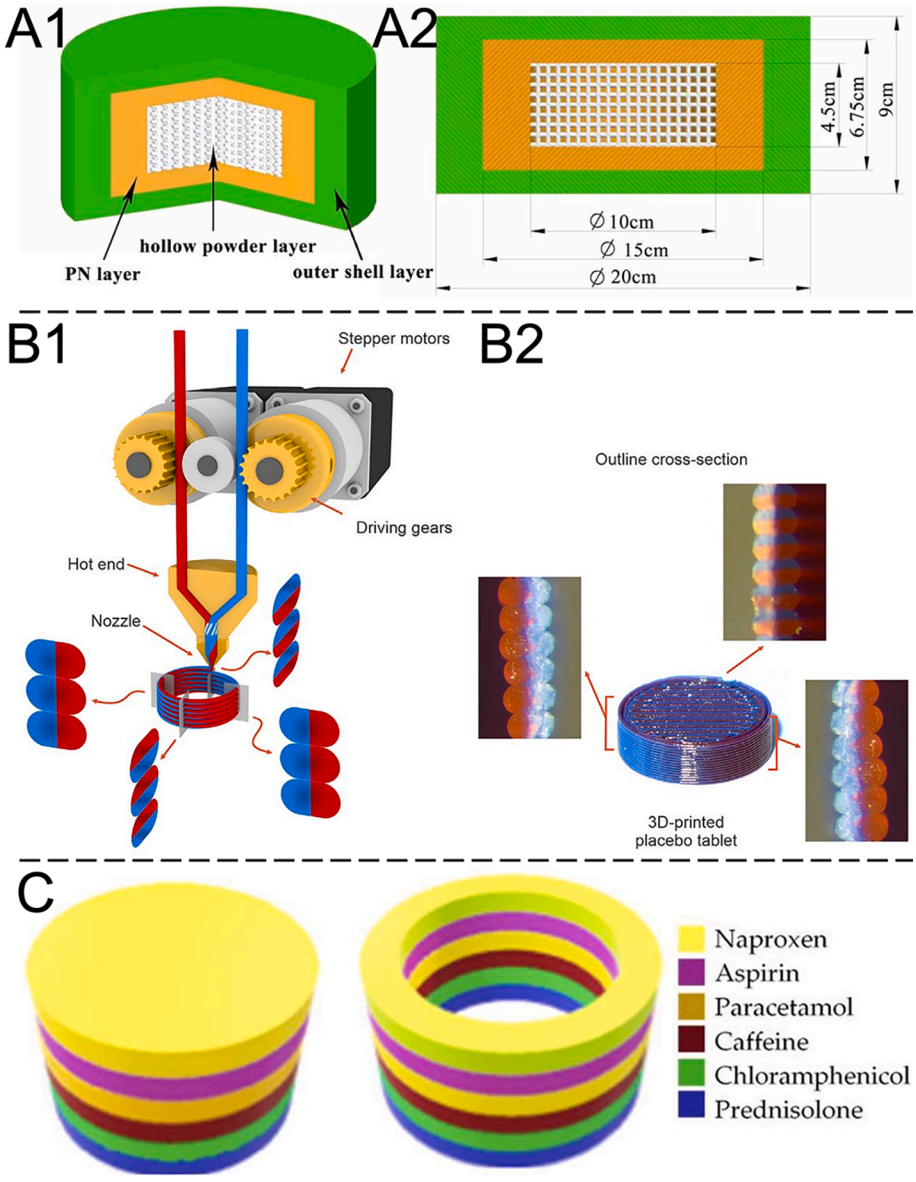

Fig. 3. Different 3D printed tablet dosage forms, A: orodispersible tablet, the green layer was impregnated with drug-free jetting fluid, the orange layer was sprayed with jetting fluid containing a photosensitive drug, the white-structured core was not sprayed; 3D section view (A1); side view (A2) (Reproduced with permission from [36], published by MDPI, 2021), B: 3D printed tablet for extended-release; two-material co-extrusion print head (B1); printed tablet with two materials within the same strand (B2) (Reprinted from [37], with permission from Elsevier), C: cylindrical and ring-shaped VPP printed polypill with six different water-soluble drugs (Reproduced with permission from [38], published by MDPI, 2019), all figures were modified.

excipients also enables compliance with the FDA's disintegration time requirements for ODTs of 30 seconds or less [36,45–48,50,51,53,54] in addition to their sweet taste.

Research projects also involved the modification of the primary particles in the powder mixture e.g. by coating or co-processing with the binder in order to simultaneously reduce the disintegration time of the dosage form while improving its mechanical stability [45] or to improve the printability of the powder [44]. Higher binder content can increase the mechanical stability and lead to longer disintegration times [45,54]. The chain length of the binder can also influence the disintegration and release time, as was shown in the case of hydroxypropyl cellulose (HPC), where of those tested, only the one with the shortest chain length resulted in tablets that fulfilled the requirements of the Ph. Eur. for ODTs [49].

The 3D printing of core-double-shell tablets by Hong et al. is particularly interesting. Two different jetting fluids were used for the process, one containing a photosensitive drug and the other free of drugs. The outer shell, which was impregnated with the drug-free jetting fluid, is intended to protect the photosensitive drug in the inner shell from degradation. The latter was applied with the drug-containing jetting fluid. The powder core of the tablet was not impregnated with any jetting fluid and is thus intended to promote even faster disintegration of the ODT. In addition, a second drug was included in the powder bed and was therefore also incorporated in all compartments of the tablets [36]. A schematic of the ODT design is given in Fig. 3A.

MEX (SE) of pastes can also lead to tablets with low disintegration times. Yi et al. evaluated different excipients in different proportions for their development of loratadine ODTs. For their best-performing formulation, they achieved disintegration times of 30 seconds and less. However, this FDA-compliant disintegration time could only be achieved for infill percentages of 40 and 60%, while tablets with 80 and 100% infill only met the Ph. Eur. requirements. However, a lower infill resulted in a higher friability and also reduced the maximum drug loading [56].

The development of orodispersible minitablets (ODMT) that met the requirements of the Ph. Eur. with less than 90 seconds disintegration time has also been reported by using high proportions of the superdisintegrant sodium starch glycolate as well as povidone (PVP) as a binder and lactose as a filler [57]. The Ph. Eur. compliant disintegration time is undoubtedly also supported by the small size of the minitablets and their high specific surface area. The authors also investigated croscarmellose sodium as a disintegrating agent. The resulting minitablets disintegrated on average in just under 3 minutes. This excipient was also used in other publications [58–60]. It is striking that this superdisintegrant was partly used in atypically high concentrations, which suggests that it could also act as a binder in the moistened mass [57–59]. The excipient can also be used for the aqueous outer phase in emulsoid systems. The formulation by Johannesson et al. disintegrated in less than a minute for infill percentages of 25 and 50% so that the incorporated, dispersed lipid-based formulation was subsequently liberated [61].

BJT and MEX (SE) usually do not work without solvents such as water. This may reduce the activity of added disintegrants and superdisintegrants, which in turn can have a negative effect on the disintegration time [62,63]. The use of solvent-free printing methods is, therefore, an obvious alternative. In this context, publications using solvent-free methods like MEX (FE) and PBF, were identified for the period under investigation. Besides BJT, PBF is also particularly suitable for printing highly porous objects [64,65].

Copovidone seems to be the polymer of choice of many authors here [66–74]. It can be processed with pigments, that are usually used to absorb the energy of the laser, and drug to form tablets that disintegrate in less than 5 seconds. Additional features that have been reported include the printing of Braille on tablets for identification, although friability tests would have been interesting here in order to assess the durability of the writing on the tablets [66]. Gueche et al. demonstrated that it is even possible to print ODTs with copovidone without pigments [69,72].

Also macrogol poly(vinyl alcohol) grafted copolymer (PEG-PVA) [75–77] and PVP [78] are suitable to formulate ODTs via PBF. It is also interesting to note that the speed of the fusing laser in the process can influence the density of the tablet and thus also its hardness and most importantly in this context the disintegration time [67].

For MEX (FE) printed ODTs Pyteraf et al. describe an interesting case in which a higher proportion of a slightly soluble drug can shorten the disintegration time. Fluconazole-containing PVA tablets with drug contents of 70% disintegrated in less than 3 minutes, while the same geometric structures with 40 and 20% drug load did not. The authors attribute this effect to the lower weight of the high-dose tablets and the lower PVA content. In addition, analyses of the filament showed that a higher PVA content makes the filament more mechanically stable [79]. By producing amorphous solid dispersions with PEG-PVA, disintegration times can also be reduced to values of around one minute. The 3D printed tablet with 100% infill is also superior to the pure drug and its physical mixture with the polymer in terms of release behavior [80].

Currently, it seems challenging for printing methods based on MEX to fulfill the specified disintegration time of the Ph. Eur., even if macroscopic surface enlargements such as reduced infill or smaller dosage forms are already being used. Therefore, it is reasonable to assume that BJT or PBF are the better choice for the production of orodispersible dosage forms. The publications in the period under review that used the latter methods were often able to meet the requirements of both the Ph. Eur. and the FDA. This is presumably due to the high porosity of the dosage forms resulting from these processes, which in turn promotes wetting by the disintegration media.

2.1.2. Immediate-release tablets

In this chapter, 3D printed tablets whose drug release is not prolonged or delayed will be discussed. An IR tablet can be defined as a tablet for which the release of the drug has not been intentionally modified by a special formulation design or manufacturing process [35,40]. However, 3D printing, particularly MEX, partly challenges this definition, as dosage forms produced with excipients that typically exhibit relatively good dissolution properties in the dissolution medium can still show an extended-release. This becomes particularly clear with FE, where the melting process leads to densely fused products and the polymers themselves can also often show release-delaying effect, as already stated by Kempin et al. [81]. The dense packing and reduced porosity of 3D printed tablets are particularly apparent when a high infill is used. Therefore, the tablets often show ER kinetics, which might explain the high number of screened papers in that chapter (see Extended-release tablets). One challenge in 3D printing lies in the production of IR formulations, which is to be illustrated in the following.

For the period analyzed, 60 manuscripts were identified that fit into this category. More than 87% of the publications used MEX processes for the production of IR tablets. Within the MEX processes, FE dominates with 50% of all publications within this chapter, as also visible in the manuscript overview in Table S2.

Among the reported MEX (FE) dosage forms, the most prominent excipient was PVA, which was used in the majority of publications [82–95]. Sometimes as the only polymer [82,84,92,93,95], sometimes in combination with other polymers [86] and sometimes in comparison with other polymers [90,91].

In addition to the "generally recognized as safe" (GRAS) status of the polymer, this is probably also because its printability is well-studied, as it is also commercially available as a filament. These marketed PVA filaments can be loaded with drugs by placing them in drug-containing solutions [82,84]. However, the drug loading of the PVA filament depends highly on the solvents and drugs used. Another way of loading drug substances can be realized by extruding PVA together with the drug substance [92,93]. For PVA filaments, the effect of changed mechanical properties due to the drug loading is apparent due to its comparability with commercially available filaments [84,92,96]. The mechanical

properties of PVA filaments can also be modified by adding other excipients, e.g., plasticizers like sorbitol [89,95], triethyl citrate (TEC) [83,88], macrogols [85,89], mannitol [85,91] , or glycerol [90].

A noteworthy approach was reported by Pereira et al. in their addition of water as a "temporary plasticizer" [94]. This allowed them to extrude the filaments at lower temperatures of 90 °C compared to their approaches without water, which were extruded at temperatures of 170 °C. However, it is worth mentioning that there are also reports in which the unintentional addition of water (for example due to high humidity) can influence the printability of the PVA filament [92,97].

The relatively slow drug release from PVA tablets can be modified by the addition of other polymers such as copovidone [86] or disintegrating agents such as crospovidone [85,86], croscarmellose sodium [85] , or sodium starch glycolate [98,99].

Water-soluble cellulose derivatives are also suitable for printing IR tablets using MEX (FE). Hypromellose [100,101] and short-chain HPC [88,90,98,99,102] were predominately used here.

The utilization of other polymers, which are soluble in water or gastric fluid, can also be applied for the 3D printing of IR tablets. Examples include basic butylated methacrylate copolymer (bbMA, e.g., Eudragit® E) [88,99,101,103–108], PEG-PVA [102,109] , or copovidone [86,91,99,100,102,104,109–112]. Even the production of filaments and tablets solely from short- and long-chain macrogols (also sometimes referred to as polyethylene glycol (PEG)/polyethylene oxide (PEO)) is possible [113]. However, systematic comparisons of the polymers are hard to find. Okwuosa et al. carried out a larger screening regarding the question of whether and under what conditions filaments are stable under storage - at least for the filaments examined. While the drug content decreased by no more than 1.3% within 6 months, even at elevated temperatures of 30 °C, some of the filaments could no longer be printed after storage. This mainly affected the more hygroscopic filaments made of PVP and HPC [88].

Without filament as an intermediate product, MEX (SCE) technologies can also be used to produce IR tablets. The excipients used can be the same as those used for FE printing. Examples of this are the use of copovidone [114–117], bbMA [114,118,119], PEG-PVA [115] or cellulose derivates. The latter was used by Mendibil et al. who printed HPC together with starch and guar gum as well as paracetamol at 90 °C by incorporating water. This is especially interesting as the thermal burden on the drug and the excipients are lower in comparison to water-free MEX (SCE) or even MEX (FE) [120]. MEX (SE) techniques have already been investigated with polymers of natural origin, semi-synthetic polymers, and synthetic polymers, but emulsions can also be successfully printed as outlined in the following.

The biopolymer gelatine can be used for both IR tablets and ER dosage forms. For this purpose, Yang et al. modified the design of the dosage form and added hypromellose for ER [121].

Among the semi-synthetic cellulose derivates, hypromellose, which is able to form gels with water [122,123] or ethanol-water mixtures [124], was mainly used for manufacturing IR tablets via MEX (SE). Here too, rapid release was often supported by an increase in the surface-area-to-volume ratio (SA/V). For example, the naftopidil tablets printed by Tagami et al. were less than or equal to 2 mm thick [123]. Even liquid-free production of IR tablets was possible by MEX (SE) of cellulose derivatives such as HPC at temperatures above 150 °C, whereby the release rate can be increased by adding a further water-soluble polymer and plasticizer [125].

The binding properties of PVP and its related substances are already well-known from conventional tablet manufacturing methods [126–129]. PVP was also used several times in MEX (SE) of IR tablets. It is noticeable that in this context, it was apparently only used together with other binders or swelling agents [122,130]. This also applies to its copolymer with vinyl acetate, copovidone [125,131]. The binding properties of starch have also been investigated for SE [132]. Already mentioned above in the category of FE printlets is the copolymer of PVA and macrogol. PEG-PVA was primarily investigated by El Aita et al. to formulate levetiracetam into IR tablets [131,133]. Macrogol is often added as a plasticizing or pore-forming additive, as already mentioned for FE printing. However, macrogol itself can also be the main excipient. In addition to the macrogol suppositories described in the section for Rectal dosage forms, macrogol can also be printed directly with drugs [134] or in combination with other excipients [135] leading to IR tablets due to its good water solubility.

Similar to the extrusion of macrogol for the production of tablets, whose printing temperature is usually below 70 °C [136], some lipids can also be melt-extruded at relatively low temperatures. They also have the potential to improve the bioavailability of some drugs [137]. Macrogol-32 stearate, for example, can be printed at temperatures below 45 °C [138,139]. However, the storage conditions for dosage forms with ingredients with a relatively low melting point, such as macrogol or macrogol-32 stearate, are critical parameters.

The extrusion of emulsoid systems represents a combination of the extrusion of classic hydrophilic components, such as the cellulose derivatives and lipids that have already been described. In this field, Johannesson et al. published three papers on the lipid-based inner phases of emulsion gels. The water-containing outer phases were dried after printing so that the gel formers contained therein formed a stable, manageable framework for the dispersed lipids [61,140,141]. This resulted in a short disintegration time of the tablets and a supersaturation of the release medium or the lipolysis medium. While the 3D printed capsular, self-emulsifying drug delivery systems are only filled (see Capsules), Algahtani et al. formulated them directly as a printable formulation for the manufacturing of tablets [142].

MJT has also been reported for the production of IR tablets. As with any 3D printing process, it is only possible to build up another layer if the previous one has solidified sufficiently (e.g. by drying). As only liquid printing inks build up the dosage form in the MJT process, the method is of limited suitability for printing thicker tablets. Due to the need to allow the solvent to evaporate and the low layer height, the process is relatively slow. The printing of 10 tablets with a thickness of about 1 mm consisting of 250 layers took more than 8 hours in Cader et al.'s experiments [143]. It can be assumed that this is a possible reason why only one publication with MJT IR tablets could be identified for the period analyzed.

As already discussed for ODTs, BJT and PBF are printing methods that can be used to achieve rapid disintegration of the dosage form and, in some cases, also rapid release. It is therefore logical to use BJT [144,145] and PBF [146–148] for producing IR tablets. The reason why so many publications are not listed here is that many of the tablets produced with this method also fulfill the requirements of the Ph. Eur. for ODTs and are therefore listed there. For PBF in particular, copovidone was again the most important excipient [146–148], but combinations with PVA were also analyzed [146,147]. In addition, it was shown for both BJT and PBF that the disintegration time or release time of HPC tablets correlated with the molecular weight of the polymer [49,149].

IR tablets can also be 3D printed using VPP technologies, even if not much research has been published with only one publication in the investigated time period. The rapid release of zolpidem tartrate was here accelerated by the SA/V of the 3D printed flat tiles and minitablets as well as by higher content of macrogol and water within the poly (ethylene glycol) diacrylate (PEGDA) formulation [150]. However, due to the small number of publications, it could be hypothesized that VPP is not necessarily the method of choice for the production of IR tablets at the present time.

In most of the identified publications on IR dosage forms, a material screening of various excipients and combinations of excipients was carried out. Changing the SA/V appears to have been utilized by the majority of authors to further investigate and improve release from their 3D printed tablets. This was done, for example, by adapting the infill, printing thinner dosage forms or by choosing printing methods that can produce dosage forms with high porosity, such as BJT and PBF. In some

cases, it has also been shown that lower drug loading can accelerate release [116,150]. However, this is highly dependent on the drug and the polymer used and can also be the other way around, as already described for fluconazole in the ODT section [79]. Overall, it was hardly possible to identify any truly innovative approaches that accelerated the release from 3D printed tablets.

2.1.3. Extended-release tablets

According to the Ph. Eur., ER tablets are classified as a type of modified-release tablets. They can be coated or uncoated and are designed to modify the rate, place, or time at which a drug is released. Within the Ph. Eur., ER, tablets are labeled as prolonged-release tablets [151]. Those and other terms like controlled-release, sustained-release or long–acting tablets can be used synonymously. The definition of modified-release also includes tablets with delayed-release kinetics, which are addressed in a separate section of this article (see Delayed-release tablets). The utilization of ER tablets offers numerous advantages for certain drugs: the controlled release of the drug facilitates a more consistent therapeutic effect, reduces the frequency of administration, and can enhance patient adherence. By avoiding the high peaks in drug concentration associated with IR formulations, ER tablets can potentially decrease the incidence of adverse effects [152]. The controlled ER of the drug is typically achieved through various mechanisms. Conventional ER tablets are classified into matrix, reservoir (membrane), or osmotic systems [153]. Deviating from the description of IR dosage forms in the Ph. Eur., dosage forms are included in the ER category of this review that are “not deliberately modified by a special formulation design and/or manufacturing method” [35], but which have a dissolution rate far below the threshold value of the recommendations on dissolution testing of 80 % release in 45 min [34]. However, this was not done if the dissolution behavior essentially depended on the intrinsic properties of the particular drug. Furthermore, studies that investigated different release kinetics (e.g., broad polymer screenings resulting in both IR and ER kinetics) were included in this category. Strictly separating into well-defined categories is challenging in this complex topic due to frequent overlaps.

3D printed ER tablets form the largest category in this article, with 115 papers identified after the final screening process (see also Table S3). All 3D printing methods according to the classification presented in the introduction are represented within this category. More than half of the articles employed MEX (FE), followed by VPP and MEX (SE) methods. As all printing processes are represented, the used polymers and other excipients are diverse: e.g. from water-soluble polymers such as PVA [154–158] to water-insoluble polymers such as polycaprolactone (PCL) [159–163] and cross-linkable PEGDA [164–168]. Many studies about the effects on the release behavior of proposed ER tablets followed similar approaches. For example, the composition of the formulation was often varied [169–173] or multiple polymer types were screened [174–178]. In addition, the internal structures were often changed, e.g., the proportion or pattern of the infill was investigated in regard to the release behavior [179–183]. Model variations of the tablets e.g. in terms of shape, size or number of printing layers were also frequently used in the investigations [184–188]. In addition, the combination of different 3D printing processes, e.g. MEX (FE) with PBF, was also researched [158]. To highlight the diversity of the used printing methods, five different publications were chosen exemplarily and will be highlighted in the following paragraphs.

Jamróz et al. employed MEX (FE) utilizing a two-material co-extrusion print head. Instead of using two separate print heads, each assigned to a different polymer with distinct solubility properties, they utilized a single nozzle that co-extruded drug-loaded water-soluble PEG-PVA alongside drug-free water-insoluble polylactic acid (PLA). This approach resulted in single printing layers comprising two materials within the same strand (Fig. 3B). The authors investigated various tablet designs, infill parameters (50% and 100% infill, rectangular, and honeycomb infill patterns), and different layer compositions. For instance, by increasing the proportion of water-insoluble PLA in the strand composition (0%, 25%, and 50% PLA) for a one-compartment tablet, they were able to extend the release of bicalutamide from 30 minutes to several hours (50% PLA: 36% drug release after 6 hours, total amount within one tablet around 7 mg) [37]. This specialized approach highlights the possibilities achievable through variations in software (printing settings) and hardware (different print head) configurations. However, the benefit of drug printing of this print head compared to multiple standard print heads for a single FE was not evaluated within the publication.

MEX (SE) was used by Alayoubi et al. to print a polypill comprising metoprolol succinate and atorvastatin calcium dihydrate within a single tablet, utilizing two distinct compartments made from different materials (lactose, starch, and/or hypromellose) and various formulations for each compartment. The objective was to produce a polypill with dual-release kinetics: an IR compartment for atorvastatin and an ER compartment for metoprolol. The IR compartment was designed as a cylindrical tablet with defined gaps between the printing layers to facilitate rapid water penetration. The ER compartment was structured as a core-shell tablet with diverse formulation compositions beneath the IR compartment. A separation layer was printed between the IR and ER compartments. Using different formulations and geometric parameters, only three formulations for atorvastatin achieved IR, whereas all formulations resulted in ER for metoprolol in the printed polypills [189]. This is an excellent example of how much more effort is sometimes needed to create MEX immediate-release tablets than extended-release ones as already described in the chapter about Immediate-release tablets. It also shows that efforts are made to print tablets with multiple drugs to reduce the pill burden and enhance patients’ adherence.

Duranovic et al. provide another example of the challenge of printing IR tablets. Despite reducing the filling to 20 % and incorporating various disintegration-promoting excipients into the PVA filament used, the complete release of the active ingredient paracetamol still took at least 2 hours and was therefore categorized as an extended-release tablet [190].

Another approach was to use a PBF printer, as done by Trenfield et al., to print methacrylic acid-ethyl acrylate copolymer (1:1) (MA-EA; e.g., Eudragit® L 100-55) tablets containing theophylline and to investigate the release behavior when using different scanning speeds (100-180 mm/s). The authors showed that with higher laser speeds, a faster drug release was achieved. With the highest laser speed of 180 mm/s, approximately 80% were released after 60 minutes. With a laser speed of only 100 mm/s, only about 30% were released after 8 hours. The reason for those differences was the production of less porous and more dense objects when using lower printing speeds due to the higher energy input per tablet of the laser. Apart from the printing process, the prediction of the tablet’s density and release behavior using a near-infrared spectroscopy method was addressed [191]. This manuscript shows that similar to changing infill patterns for MEX, the scanning speed of lasers is a crucial parameter to control the drug release from dosage forms produced via PBF.

Robles-Martinez et al. used VPP and were able to print a polypill with six different water-soluble drugs. As this is quite challenging when using resin tanks for printing instead of for example multiple print heads with different filaments, the tanks had to be exchanged frequently throughout the printing process by stopping and continuing the printing process (multi-resin printing). Two different tablet geometries (cylindrical and ring shape) were tested, and the release behavior was investigated (Fig. 3C). The authors showed that printing polypills with VAT photopolymerization in general is possible and that ER for the different drugs can be achieved (after 20 hours, 22-80% of drugs released) [38]. This publication shows that new methods are consistently developed to broaden the horizon of possibilities for 3D printing.

A relatively new method of rotatory volumetric 3D printing was used by Rodriguez-Pombo et al. [167]. This VPP technique differs from other techniques as the entire object was printed simultaneously and not in a layer-wise manner as was the case for all other above-mentioned papers [38,189,191,192]. Rodrigues-Pombo et al. printed two objects

simultaneously and used different shapes (cylindrical and ring-shaped), and analyzed different formulations. Dissolution testing proved that an ER for several hours is possible. This paper used a promising new printing method that can create objects within seconds (12 to 32 seconds for two objects), which might be beneficial regarding higher throughput of products.

As mentioned above, the ER tablets category accounts for the largest proportion of screened papers. The reason for this is probably that the usual initial workflow for 3D printing dosage forms starts with screening of various potentially suitable polymers or conducting infill tests. The results of such investigations are often tablets with ER, probably due to the often-used printing process of MEX. In general, 3D printing is very well suited for producing ER tablets. The large selection of polymers, for example, or the almost infinitely variable software printing settings, provide an ideal basis for scientific research with promising results in adjusting the release behavior.

2.1.4. Delayed-release tablets

DR tablets are tablets in which the onset of release is adjusted by the formulation design. This includes gastro-resistant dosage forms, which typically show a pH-dependent drug release. Gastro-resistance can be beneficial as some drugs are not stable inside the acidic environment of the stomach or even harm the stomach mucosa [193]. Other DR formulations aim at releasing drugs at a specific, more distal portion of the intestine, e.g., the colon. This is often also called targeted release. Targeting of specific regions, for example the colon, can have a positive effect especially when a local treatment at a specific site is desired as smaller doses are typically required which can lead to fewer adverse effects [194]. Gastro-retentive dosage forms can also be understood as a type of targeting approach. Nevertheless, papers focusing on gastro-retention in general are discussed separately in the chapter about Gastro-retentive dosage forms.

Strictly separating some of the tablets in the screened manuscripts into these categories is difficult, especially when different release kinetics are evaluated within one paper. Therefore, overlaps with other categories are possible. Furthermore, the categorization depends on the chosen methods for dissolution testing of the printed dosage forms. Different media with pH values ranging from ~1.0 - 1.2 (stomach environment) to ~6.8 - 7.4 (small intestine) specify the in vitro release behaviors. If for example only water was used for dissolution testing, a possibly existing gastro-resistance could not be detected. In Table S4-7, the manuscripts on delayed-release tablets are categorized according to the targeted region in the gastrointestinal tract (GIT).

MEX (FE) and (SE) techniques were used to print DR tablets. Dual extrusion printing was sometimes used to print different polymers within the same dosage form [195–198]. The most used materials were polymers with different swellability/solubility at various pH values, such as hypromellose acetate succinate (HPMCAS) [195,198–202] and/or different polymethacrylate types [196,197,203].

Chung et al. used dual MEX (FE) to create core-shell tablets of two different polymers. The shell was made of hypromellose, and the core of HPMCAS contained indomethacin. The idea was to create an oral dosage form releasing the drug after a defined lag time for morning stiffness in rheumatoid arthritis. The authors printed tablets with different shell thicknesses for different lag times and analyzed their release behavior in pH 1.0 and 6.8. With increasing shell thickness (0.4, 0.6 and 0.8 mm), a lag time of 4, 5 and 8 hours, respectively, was achieved. The drug release after the lag time was completed within 3 hours, independent of the shell thickness [195]. This design of an inner structure and an outer protective structure is a reoccurring approach to achieve delayed release.

The research group with Melocchi et al. went one step further and used a complex dual extrusion MEX (FE) method to produce a multi-component core-shell system for colon targeting. The authors created a PVA core containing caffeine and two shells with different formulations. The first shell around the core was made of HPC, and the second (outer) shell was made of MA-EA. The aim of using two instead of only one shell was to withstand the stomach's acidic environment and, once the small intestine is reached, to target the colon region by inducing a lag time with the second shell. Dissolution testing at pH 1.2 and 6.8 showed a lag time of approximately three hours after reaching the higher pH values [197]. The printing procedure is quite complex as different parts had to be printed independently of each other and then manually inserted into the surrounding shell. For this, the printing process had to be paused temporarily. Such an approach is extremely challenging regarding the printing parameters as the smallest deviations in the height of the object that is placed within the shell during printing may lead to problems in the following layer due to the close proximity between the core and the nozzle and may result in instability of the shell as reported by Kempin et al. [204].

By designing tablets with different parts and assigning different polymers with different incorporated drugs to those parts, targeting of two sites can be achieved. This approach was tested by Tabriz et al. with a bilayer tablet containing two drugs. One layer incorporated isoniazid embedded in HPC. The second part of the tablet was made of HPMCAS and contained rifampicin. The idea was for the isoniazid to be immediately released pH-independent most likely inside the stomach while rifampicin would be released later inside the small intestine. This was supposed to decrease the degradation of rifampicin and to reduce drug-drug interaction. Dissolution testing was conducted at pH 1.2 and 7.4. An independent release of the two drugs depending on the pH value mimicking the stomach or the small intestine was observed [201].

3D printing of DR tablets seems to be a promising approach. Especially the concept of core-shell structures is often used, and the idea can be successfully achieved by choosing suitable polymers. This concept attempts to mimic the idea of a coating, as is done for conventional tablets. Because printing thin, fully closed layers with MEX techniques might be difficult, thicker layers are often printed, resulting in a thick shell. Gaps or pores within the shell resulting from bad printing results might be problematic in regard to achieving DR [198]. On the other hand, a perfect but thick shell might take a long time to dissolve compared to thin film coatings. Since at least two different polymers are required, the overall manufacturing process is quite complex and must be well understood in order to achieve good printing results.

2.2. Pellets and minitablets

While pellets and minitablets describe different dosage forms and their conventional production is very different, they will be described together in this review due to their similar dimensions and the resulting requirements and challenges. The related manuscripts are also listed together in Table S8 in the supplementary material to this review. Fig. 4 (A and B) shows two examples of dosage forms belonging to this category.

According to the Ph. Eur., pellets (spheroids) are classified as granules. They are spherical objects, usually between 200 and 2800 μm in diameter, with a smooth and uniform surface and generally have an increased mechanical strength and flow behavior compared to conventional granules [35,209–211]. Pellets are produced conventionally by rounding segments of extrudates or granules.

Minitablets are tablets with a diameter smaller than 3 mm, according to Lennartz and Mielck [212]. Oblong minitablets with a length of 6 mm have also been described [213]. Regardless of these definitions, this chapter also lists those tablets that were described as minitablets by the respective authors. For a better overview, the dimensions of the 3D printed tablets are included in the supplementary material in the list of manuscripts for this chapter (see Table S8). These tablets offer several potential advantages, including improved dosing accuracy and increased adherence in patients who have difficulty swallowing larger tablets, e.g. children [214–217]. Minitablets are usually produced by using conventional tablet presses equipped with single- or multi-tip punches [217,218].

The 3D printing of pellets and minitablets is an alternative, additive

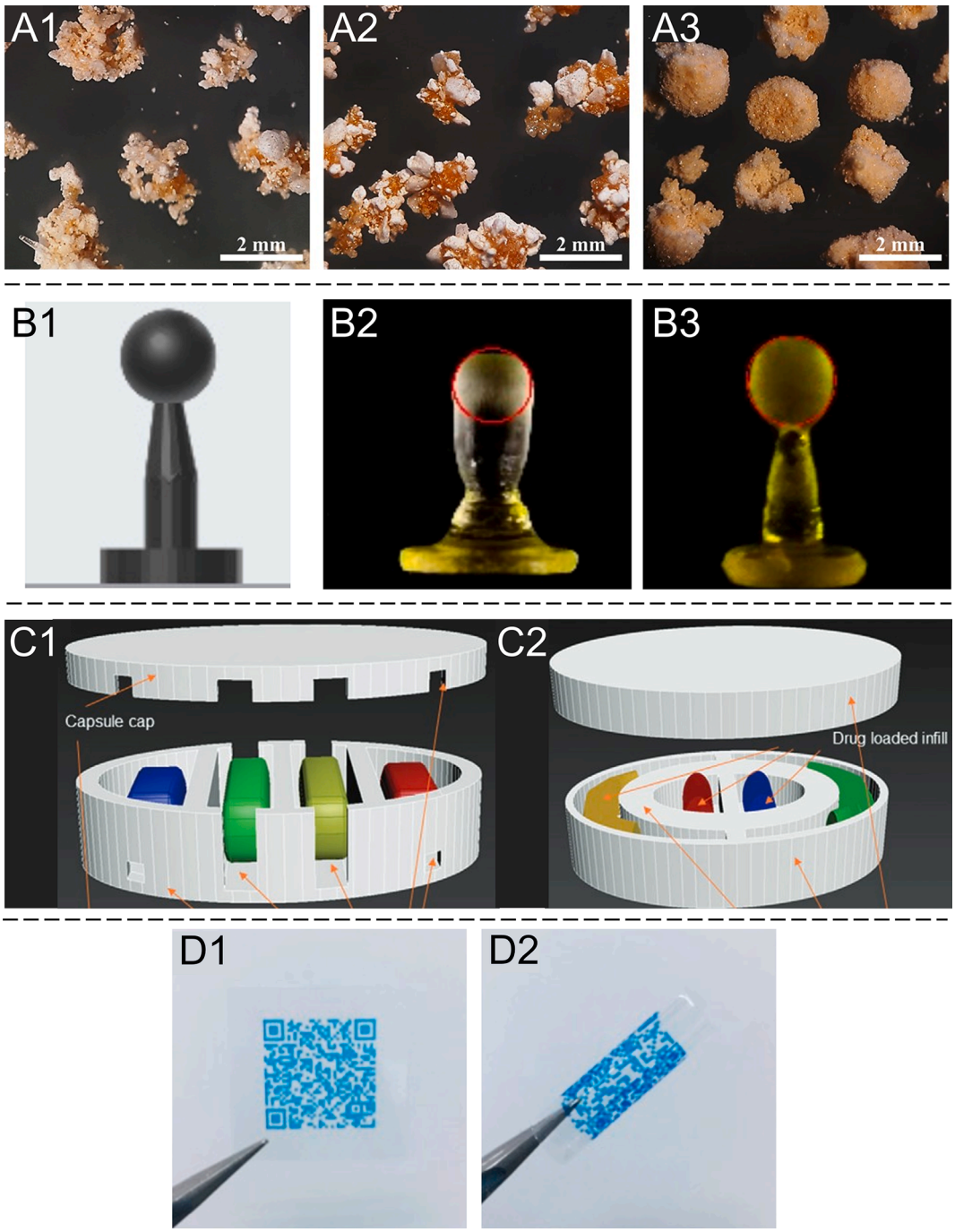

Fig. 4. 3D printed pellets, capsules and orodispersible films, A: Ibuprofen pellets made from PEO (A1), EC (A2) and MA-EA (A3) (Reprinted from [205], with permission from Elsevier), B: VPP printed pellets with support structure; CAD model (B1), non-optimal formulation (B2), optimal formulation (B3) (Reproduced with permission from [206], published by MDPI, 2021), C: Model of multicompartmental capsules with (C1) and without (C2) pores (Permission granted by [207], published by John Wiley and Sons, © 2020 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim), D: MEX (SE) printed film with QR Code labeling containing various information, view of the plain film (D1), rolled-up film, visualizing its flexibility (D2) (Reproduced with permission from [208], published by MDPI, 2019), all figures were modified.

manufacturing method. The size of the dosage forms is a challenge for the process depending on the additive manufacturing technique chosen. Sizes of less than 2 mm, for example, which are required for unimpeded passage through the pylorus even in the fed stomach state with given mechanical stability, pose challenges for some printing methods [219–222]. Nevertheless, besides VPP and PBF also MEX methods have been described.

The spatial resolution of the light or laser-based printing systems supports their use in the production of small structures such as pellets.

Using PBF, Awad et al. were able to produce pellets with diameters of 1 and 2 mm and different release kinetics. To achieve IR properties, they utilized PEG-PVA while to extend the release ethyl cellulose (EC) was used. The authors were also able to combine both release properties in dual-layered pellets [223].

The excipients and drugs used in the production of pellets by PBF also appear to have a decisive influence on the morphology of the particles obtained. Comparatively smooth particles were obtained with MA-EA, while 3D printed particles containing EC were relatively sharp-

edged. PBF of macrogol, which was also investigated in this research work, is interesting because only comparatively low processing temperatures of 50 °C were needed. The macrogol and EC pellets shown seem to possess a rougher surface than those made of MA-EA (Fig. 4A) [205].

In contrast, relatively smooth ibuprofen particles with ER can be produced from a mixture of PEG 400, PEGDA 600, diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide and tartrazine using VPP. Even if the particles obtained are printed very precisely, particularly in the x-y direction, an increase in size was seen in the z direction depending on the resin composition. In addition, the support structures required for the printing process must be removed after printing (Fig. 4B) [206] which complicates the process.

Minitablets can also be produced with VPP, as shown by Adamov et al. Here too, the dimensional deviations from the CAD model are larger in the z-direction than in the x- and y-directions. The printed minitablets were always flatter than they should be. For almost all models, the complete release of the drug was achieved in less than an hour [150].

The resolution of the MEX (FE) and MEX (SCE) processes appears to be sufficient for minitablets. Recently, cellulose derivatives like hypromellose [224,225], HPC [224,226,227] and HPMCAS [228,229] have mainly been investigated for MEX.

Krause et al. printed hypromellose and HPC tablets with a 0.25 mm nozzle and investigated the influence of the size of the minitablets (diameters of 1.5, 2, 3, and 4 mm) on the release of the model drugs. The release of the entire drug took between approx. 1 and 4 hours depending on the size of the minitablet [224]. Similar results were also shown for oblong minitablets made of PVA [230]. Structural adjustments, that appear to be primarily of a cosmetic nature, such as star shapes, heart shapes or rings, are also an option for 3D printed minitablets [231].

Ayyoubi et al. studied the impact of excipients and geometry on nifedipine dissolution from minitablets. The authors printed solid and porous, spherical minitablets with PVA, HPC, EC, and copovidone filaments. The effect of the excipients used exceeded the influence of the geometry [226].

Due to observing high drug degradation (> 30%) with MEX (FE) printing, Malebari et al. switched to MEX (SCE) printing methods for printing minitablets, which reduced the degradation to less than 5%. This is probably also due to the process parameters, as temperatures of 120 °C were required for the production of the filament, whereas only 80 °C was needed for printing with MEX (SCE) [228].

Sanchez-Guirales et al. used MEX (SCE) to produce minitablets with a nifedipine loading of 25% to enable the printing of materials which are usually difficult to process into filaments. The authors observed that a higher proportion of the plasticizer PEG 4000 improved content uniformity, while higher proportions of HPC further extended drug release [229].

The only MEX (SE) printed minitablets identified for the investigated period are already described within the ODT section [57,59].

Dose adjustments for drug products formulated as pellets or minitablets can usually be made by weighing or counting the dosage form. 3D printing of these dosage forms is possible and can also be used to influence their properties, but the throughput is still too low for meaningful medication production, especially for pellets, particularly if they still have to be post-processed as with VPP methods.

2.3. Capsules

According to the Ph. Eur., capsules are single-dose, solid pharmaceutical dosage forms, which are usually intended for oral administration. The Ph. Eur. distinguishes between hard and soft capsules [232]. Traditionally, capsule shells for hard capsules are usually manufactured industrially using the dipping pin process. The animal product gelatine is mainly used, but vegan and vegetarian alternatives such as hypromellose and pullulan are also used [233–235]. Soft capsules are formed and filled in a single production step [232,236].

In this analysis, research articles that repurposed 3D printers as dosing devices to fill non-3D printed capsules were excluded. Manuscripts were included in the capsule section in which the printing of an outer envelope and a non-3D printed filling is described. This filling material can also be a tablet [237]. For this chapter, 3D printed capsules were also included in which the active ingredient itself was not printed and was only filled into the capsule, as this is also more common in conventional processes. Thus, most of the examined studies on 3D printed capsules focus on the production and functionalization of capsule shells. A distinction is also made between one-piece and two-piece capsules. This information is also included in the list of manuscripts on printed capsules in Table S9. Two-piece capsules can be filled after manufacture, whereas this is not possible with most one-piece capsules. With the latter, filling takes place during the process, which is usually made possible by pausing the printing process. The predominant printing method is MEX (FE). PVA in particular is currently used for the printing of capsule shells. Even though PVA is water-soluble, its swelling and dissolution process can lead to a higher lag time in dissolution curves and a slower dissolution compared to regular gelatine capsules. This effect can be increased by using PVA-hypromellose-mixtures [238]. In their comparison, however, Gaurkhede et al. mention but do not discuss the influence of different capsule wall thicknesses. The gelatine capsules had a lower thickness (approx. 100 μm) compared to the printed PVA capsules (approx. 390 μm). An even thicker, uninterrupted PVA capsule shell of 0.9 mm was printed by Cotabarren et al. to successfully delay drug release [239]. The influence of printing settings such as wall thickness and infill of 3D printed PVA capsules on their release was investigated. Single and multi-compartment capsules with different filling materials were intended to provide customized ER profiles [240]. 3D printed, pure PVA shells have also been used to encapsulate filling materials like spray-dried solid dispersions and drugs which were applied via inkjet printing [241,242].

No lag time was observed when holes were incorporated into the model of the capsule shell so that the filling material was immediately in direct contact with the release medium. This was utilized, for example, by Alganthano et al. for the release of a cyclosporin containing self-nanoemulsifying drug delivery system. They observed that the release rate was slower when the substance was only released through the capsule hole. However, after approximately 30 minutes, the release rate increased notably when the 0.8 mm thick PVA shell ruptured, exposing a larger surface area of the filling to the media. In addition, a larger hole size slightly increased the release rate [243].

Another option to achieve direct contact of the drug to the release medium is to incorporate the drug directly into the PVA capsule shell as shown by Palekar et al. Here, the one-piece capsule itself was filled with an aversion liquid to prevent possible misuse of the drug, which could theoretically also be an opioid, for example, through manipulation of the dosage form, e.g. by crushing or extracting the drug with solvents which would also lead to release of the aversion liquid [244].

A broad variety of delayed and both delayed and sustained release profiles with PVA-based capsules was achieved by Pereira et al. The authors also varied the wall thicknesses of their 3D printed, multi-compartmental “polypill” for this purpose, while filling each compartment with a mixture of macrogols of different chain lengths, lactose monohydrate and either lisinopril, rosuvastatin, indapamide and amlodipine. Furthermore, the water-insoluble, thermoplastic polymer PLA was utilized for a modified, multicompartmental capsule model with pores of different sizes in order to achieve IR- as well as ER profiles for the four drugs incorporated (Fig. 4C) [207].

PVA- and PLA-based filaments not only promise a certain potential for the printing of dosage forms for humans in addition to their already established application in technical 3D printing but could also be used for the production of veterinary medicines. The mono- and multi-compartmental capsules for ruminants developed by Gallo et al. measured up to 106 mm in length and were so large that the authors had

to modify the USP 2 apparatus for dissolution testing. The drug urea was released from the capsule after the PVA-printed parts dissolved [245].

PLA can also be used in conjunction with pharmaceutical polymers. PLA improved the mechanical and adhesive properties of the MA-EA filament which was used by Nober et al. to produce enteric capsules. It was also found that a higher layer height can cause premature release from the capsules in this setting [246].

The enteric properties of MA-EA were also utilized for two-chamber polypills. Also here, filaments made of the pure polymer were reported to be too brittle if not enough plasticizer was added [247].

Other filaments and 3D printed dosage forms made from pure methacrylate copolymers were also reported to be brittle [185,248–250]. The fact that this property can also be used to create pressure–sensitive capsules was demonstrated with the use of pure ammonio methacrylate copolymer (type B) (amMA-B; e.g. Eudragit® RS) [251,252].

Various processes such as banding and sealing have become established in conventional production for the gapless closure of liquid-filled hard capsules [39,253]. For their 3D printed capsule shell, Zhang et al. tested different formulations based on HPC and evaluated the sealing of the capsule to ensure prolonged release of the drug inside the capsule. While formulations without plasticizers were either not printable or the printed capsules had pores, the addition of high-molecular macrogol and amMA-B enabled a delayed release from the encapsulated, directly compressed tablets by up to 3.5 hours. Sufficient sealing of the capsule is also ensured by the seamless fit of the two capsule parts into each other and their large overlapping area [254].

Another methacrylate copolymer-based material, bbMA, was used together with TEC and talc to 3D print an ER capsule. Since bbMA is soluble in acid media the capsule was enteric coated with MA-EA after printing using the dip-coating method [250].

A one-piece capsule filled with a self-nanoemulsifying drug delivery system for an ER of lansoprazole and curcumin was achieved by Kulkarni et al. using HPC and polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer (Soluplus®) as capsule shell materials. The authors were also able to increase the delaying effect by varying the thickness of the capsule shell [255].

Other enteric-coated polymers, such as the cellulose derivative hypromellose phthalate, have also been used for the production of gastro-resistant or pH-responsive capsule shells using MEX (FE) printing. The bronze-colored capsule printed by Eleftheriadis et al. contained macrogol as a plasticizer and showed a strong acceleration of drug release during the transition from simulated intestinal fluid (pH 6.8) to phosphate buffer (pH 7.4). There was no release of the model substance in the gastric medium [256].

To date, little research has been reported in the field of 3D printing of capsules with laser-based systems. Nevertheless, prolonged releases from capsule shells have been achieved with VPP and PBF printing processes [257,258]. Two-piece capsules were printed in both approaches.

Capsules intended for colon targeting release the drug even later in the GIT. For this targeting approach, the capsule shell can be functionalized, e.g. by using polymers that are expected to dissolve in the colon at pH values above 7.0. Asadi et al. printed capsules made of 80% poly (methyl acrylate, methyl methacrylate, methacrylic acid) (7:3:1) (MA-MMA-MA, e.g. Eudragit® FS 100) and 20% PLA. By using this approach, the authors showed that no drug was released at pH 1.2 and less than 20% was released at pH 6.8. Once pH values of 7.4 were reached the drug was released from the hydrogel within 29 hours [259]. Another approach for colon targeting is the use of an insoluble, open capsule shell made of PLA and fill it with a drug-loaded ink based on colon release polymers. This was done by Almeida et al. by also using an automated filling approach for their camptothecin-loaded MA-MMA-MA-based ink [260].

Interestingly the literature research for this review did not identify a research article utilizing gelatine to 3D print capsule shells. So far, it seems that PVA in 3D printing of capsules is the analogy to gelatine in conventional manufacturing. It is most likely widely used because it is cheap and easily available. A certain functionalization of the capsules, e.g. by adjusting the geometric structures, seems to offer advantages over regular capsules. The chapter on gastro-retentive dosage forms, for example, provides further insights into this (Gastro-retentive dosage forms). However, from the authors' point of view, a simple, 3D printed capsule shell, e.g. made of PVA, offers no general advantage over regular capsule shells.

2.4. Films

While the Ph. Eur. only mentions orodispersible films (ODF) and mucoadhesive buccal films in the context of preparations for use in the oral cavity, the USP names films as an independent pharmaceutical form. In addition to buccal films, sublingual films are also intended to facilitate the absorption of the drug through the mucosa. Oral films, on the other hand, are intended to achieve a local effect or absorption via the GIT [39,261].

Based on the various definitions of films, they are classified into these different types hereinafter:

- ODF: Film that disintegrates rapidly in the oral cavity (less than 3 minutes, limit for ODT according to Ph. Eur. [40])
- Oral film (local): Films applied in the oral cavity to deliver the drug locally.
- Oral film (GIT): Films that are intended for absorption via the GIT and are not ODF.
- Buccal/sublingual film: Mucoadhesive film designed for prolonged systemic absorption of the drug through buccal or sublingual mucosa.

This classification was also applied to the dosage forms listed in Table S10.

Conventionally, films are produced via hot-melt extrusion and solvent-casting methods [262]. Theoretically, the dose of a film can be adjusted by cutting it to size if the drug distribution within the film is homogeneous. Here, 3D printing of films could be a solution to provide accurate dosing directly for individual patients. 3D printed films containing solvents have a production advantage over many other geometries with a lower SA/V. Due to their large surface area, films allow rapid evaporation or vaporization of solvents, so that they can dry quickly after the printing process or sometimes even during the process [263]. In a majority of the identified manuscripts (15 out of 40), ODFs were reported, followed by local oral films (10 manuscripts) and buccal/sublingual films (8 manuscripts). Most often, MEX (SE) printing was employed (26 times).

2.4.1. Orodispersible films

ODFs are designed to disintegrate quickly in the oral cavity [261]. In addition, ODFs promise good swallowability and are, therefore, also promising dosage forms for use in pediatrics [264]. In contrast to orally disintegrating tablets, neither the Ph. Eur. nor the USP have regulations for the disintegration time or release time of ODFs. As a result, publications often follow the disintegration guidelines for orally disintegrating tablets, which are 3 minutes for the Ph. Eur. and 30 seconds for the FDA Guidance for Industry, respectively [40,41]. Various approaches for suitable test methods have already been published [265–267]. However, these methods differ from one another and make it difficult to compare the results.

Most 3D printed ODFs are produced by the precise deposition of liquid, highly viscous or semi-solid preparations using MEX (SE). The solidification of the liquid or semi-solid formulations after deposition can occur, for example, through drying, freezing, or sol-gel transitions. Hypromellose is primarily used as the film-forming excipients [268–273]. These hypromellose formulations can contain only a

plasticizer in addition to the drug and the cellulose derivative in the dried state [270,273]. Similar to conventionally produced films, 3D printed hypromellose films can also contain other additives such as fillers and sweeteners [268]. But also, the combination with other gelling agents and thickening agents to modify the film properties has been studied. This involved examining both, the combination of film formers in a multilayer film, where each layer contained one film former, and the mixture of multiple film formers for use within one layer [269,271]. Panraksa et al. evaluated hypromellose as well as other cellulose derivatives and polysaccharides, examining their effects on rheology, printability, disintegration time, and other film properties. They achieved a rapid in vitro disintegration within 2.1 ± 0.3 seconds with films containing carmellose sodium [272]. The cellulose derivative hydroxyethylcellulose (HEC) was also used in various grades for the production of multilayer ODFs [263,272], while HPC films were used to customize the dosage of the drug warfarin, which has a narrow therapeutic range [208,263]. The latter was also compared with MJT-printed films and also labeled with a quick response (QR) code by MJT (Fig. 4D).

In further investigations HPC was superior to PVA, whose dried, drug-loaded films did not exhibit the required mechanical properties without further additives [274].

Although cellulose derivatives dominate ODF printing with MEX (SE), other polymers can also be used. Sublingual films made from sodium alginate and macrogol with insulin disintegrated in less than 6 seconds and released the entire drug in 30 seconds, reducing blood glucose levels by about 60% in rats within 30 minutes [275]. Melt syringe extrusion below 100 °C was used to produce maltodextrin-based films that disintegrate within 80 seconds [276].

The syringe extrusion of molten macrogol and poloxamer has been investigated in two studies, of which one also included QR codes for digital information access [277,278]. This utilization of 2D and 3D printing can also be found in other dosage forms and is certainly a beneficial use of the technology, as it can contribute to drug and therapy safety by providing any type of information, starting with general information such as the drug substance and dosage to more specific data such as the patient's name and individual instructions for use.

While MEX (SE) methods are widely used for 3D printed ODFs, MEX (FE) is also usable. Printing macrogol filaments follows a relatively simple approach in terms of the materials used. Macrogol with a relative molecular weight of 100,000 was printed into films at temperatures of 135 °C. The addition of the model drug cannabidiol had a softening effect on the film and reduced the hardness and elastic modulus with increasing proportion [279].

Comparing films printed using MEX (FE) with those produced by conventional solvent casting using HPC and PVA with aripiprazole showed faster release from printed films. The publication further illustrates the resulting surface structures of the different manufacturing techniques. However, the solvent-casted films exhibited higher puncture strengths [280]. Also, structure related is the approach to print mesh-like structures instead of thinner but uninterrupted films. This can decrease disintegration times by about half [281].

2.4.2. Oral films (local)

Oral films that are intended to exert a prolonged local effect should be mucoadhesive to avoid their accidental swallowing and to ensure greater patient compliance. The fields of application are, for example, the treatment of inflammation [282–285] and candidiasis [286] or for local pain therapy [287,288]. To achieve this, the majority of researchers utilize the mucoadhesive properties of hypromellose [283,285–291] and carbomer [291,292] by MEX (SE) methods. But also, the printing of molten polymers can lead to mucoadhesive films [282,285,288].

VPP was also used to print flexible films for local intraoral therapies, even if the number of publications is very low - as is the case with many intraoral and peroral dosage forms [283].

2.4.3. Oral films (GIT)

Cellulose derivatives are the predominant film formers for the production of films that are intended to be swallowed as well [293–298]. The polymers were printed by MEX (FE) [293,297] or as hydrogels using MEX (SE) [294,295,299]. The research group led by Ming-Wei Chang used electrohydrodynamic printing to print cellulose acetate IR- [296] and ER [296,298] films. The method is reminiscent of a mixture of classic inkjet printing and electrospinning and is intended to deliver a high resolution while minimizing the thermal burden. The authors also printed a film in the form of a hollow cylinder with various release properties, which they call a capsule. However, as the dosage form cannot be filled, it is listed here [300].

2.4.4. Buccal films

Buccal films are intended to deliver the drug over a longer period of time via the oral mucosa and therefore require mucoadhesive properties. The incorporated drug is intended to bypass the GIT and thus the first-pass effect and leads to a systemic effect [39,261].

Buccal films usually contain hydrophilic polymers that form hydrogels with saliva, which adhere to the oral mucosa [261]. Here too, MEX (SE) of hydrogels made from these polymers was the most frequently used 3D printing method for the production of buccal films in recent years. Unfortunately, not every publication that claims to develop a mucoadhesive dosage form actually investigates this mucoadhesiveness. Occasionally, reference is made to the mucoadhesive properties of individual excipients without proving that these can also exert this property in the given concentration or in combination with the other components of the film. In addition to the synthetic polymers, PVA [301,302], natural and semi-synthetic substances such as gelatine [302], alginates [301] and cellulose derivatives [293,301,303–305] are used as film formers.

In addition to simple films, more complex structures can also be printed into films with special properties. The two-layer, hormone-containing film produced by Abdella et al. is intended to reduce the leaching of the drug through the saliva with its backing layer. The influence of the pattern of the drug layer on the release was also investigated. The rectangular pattern released the drug most quickly, while a plain film led to the slowest release. The release rate of the films with honeycomb pattern was in between [305]. The mesh-like film developed by He et al. contained three layers designed to improve the bioavailability of the drug, the local pH value, and the mechanical stability of the film. MEX (FE) of mucoadhesive substances for the production of buccal films also seems possible, even if it is less popular [306,307]. It can be coupled with MJT to deposit heat-sensitive drugs [306].

2.5. Other oral dosage forms

2.5.1. Gastro-retentive dosage forms

GRDFs are advanced peroral medications designed to enhance the retention of the dosage form in the stomach and release the drug there, thereby improving the drug's bioavailability and therapeutic efficiency. Drugs that are absorbed primarily in the upper small intestine and with a narrow absorption window are expected to benefit from gastro-retention [308,309]. Several strategies have been proposed to avoid gastric emptying of dosage forms, including high and low density dosage forms, expanding dosage forms, and mucoadhesive dosage forms. Conventional GRDFs are often floating drug delivery systems (FDDS). They are usually divided into effervescent or non-effervescent floating systems. Effervescent tablets used for gastric retention create gases which make the dosage form float [309,310]. Turac et al. recently published a review article where they listed the different types of GRDFs and also included recent research of such 3D printed devices [311]. GRDFs are not specifically listed in the Ph. Eur. 3D printing of GRDFs is an interesting approach as it opens up completely new possibilities for dosage forms. By adapting the printing parameters (especially infill parameters), air-filled spaces can be created. Those air pockets can make the dosage

form swim on top of the gastric fluids, which is called buoyancy. Other essential parameters for GRDFs are the floating time, the floating onset (lag time of floating mechanism) and the release kinetics.

This chapter focuses on the different shapes and approaches of 3D printed GRDFs (see also Table S11-13). It is essential to point out that many 3D printed dosage forms contain air-filled spaces because of the general printing build-up process of three-dimensional objects (shell and infill). Changing infill patterns or percentages is often done to modify the release kinetics of dosage forms, as seen in the chapter on Immediate-release tablets and Extended-release tablets. But also capsules frequently contain air pockets. Therefore, the floating of such objects on liquids is always a possible property. Unfortunately, many papers do not check for buoyancy of the final printed dosage forms. It depends on where the research focus is put. Furthermore, even if buoyancy is achieved in vitro this is no guarantee for in vivo gastroretention. The manuscripts screened within this chapter focused on the implementation of potentially gastro-retentive properties and often claimed this attribute already in the paper's title. It is possible that some papers listed here also fit into a different category (e.g. capsules) of this article.

Most of the screened papers used the concept of FDDSs. For example, air-filled sections were created by changing the tablet's infill [312–318], predetermined air-filled chambers were designed in the computer model [319–322] or capsule-shaped devices with air-filled sections and incorporated tablets were manufactured [323–326]. In the case of tablet-filled capsules, typically, the shell designed to promote gastroretention was printed while tablets were incorporated that were produced using conventional manufacturing processes. Nevertheless, these manuscripts are included in this category. Completely different approaches of 4D printing and mucoadhesion were also utilized to a certain extent [327–329]. 4D printing incorporates the dimension of time, enabling the printed object to change its shape [26]. For mucoadhesive dosage forms, the tablet is supposed to stick to the stomach's mucosa therefore increasing the gastric residence time [330].

The 3D printing techniques used were MEX (FE) and (SE). For MEX (FE), most of the authors combined the method with a preceding HME to manufacture drug-loaded filaments [313,331,332].

The most used materials were hypromellose, HPC, PLA, different polymethacrylate types, and PVA. Water-soluble materials which can swell or erode, such as hypromellose or PVA, were often used [333–335]. Water-insoluble materials such as PLA were also used e.g. to print cavities for manufactured incorporated IR tablets [336]. The used drugs were versatile, and often, model drugs were used for a proof-of-concept.

One example of 3D printed FDDSs is the work of Chen et al.. By changing the infill parameters (infill percentage) within the slicing software, (rectangular) multiple air-filled pockets were created, which can presumably lead to gastric retention. Chen et al. extruded propranolol hydrochloride containing PVA filaments and used them to print ellipsoid-shaped tablets. They used two different infill percentages, 15 and 25%, respectively, and analyzed the in vitro gastric floating. Floating of their printed tablets, without any lag time, was achieved but with a relatively short floating time of 2.11 ± 0.05 hours (15 % infill) and 1.96 ± 0.04 hours (25% infill) [318]. Changing infill parameters can lead to floating dosage forms because of air-filled pockets, but the choice of material is also crucial for longer floating times.

Another design approach was implementing one big air chamber inside the tablet. Zhao et al., for example, designed a core-shell tablet with one big air chamber on one side and a drug-releasing hole on the other. The shell consisted of water-insoluble PLA, and the core was made of hypromellose and loaded with venlafaxine hydrochloride. The authors used a dual extrusion MEX (FE) approach to print FDDSs. They also analyzed the drug release behavior with changing hole diameters (3 to 9 mm). Because of its insoluble PLA shell, the tablets floated for the tested 24-hour period without any lag time. It is reported that the tablets always faced down towards the release medium with its drug-releasing window. With a diameter of 9 mm, a drug release over 24 h was achieved [319]. Unfortunately, the paper does not state the size of the final dosage form, but it is probably at least 11 mm in diameter. After the hypromellose core is dissolved, the PLA shell stays inside the stomach, which might be problematic with respect to potential intake frequency as opposed to the presumed slow degradation.

Chen et al. also designed a core-shell tablet but used a dual nozzle MEX (SE) instead of a dual MEX (FE) approach. One print head was used to print a clarithromycin-loaded low-density hypromellose shell, and another was used to print a gas-creating floating core mainly consisting of EC and carbomer. Interestingly, the core structure of the dosage form incorporated two different floating approaches. Instead of one big air-filled chamber, as seen by Zhao et al., it had multiple microcavities. Those irregular microcavities were created between the print layers by changing their alignment. These grew into small round cavities as the ethanol contained in the formulation evaporated during production. On top of that, the authors incorporated $CaCO_3$ into the core, which generated CO_2 once the tablet came into contact with water. This combinational effect led to a floating time of more than 10 hours without a lag time [337].

Another overall design approach is manufacturing capsule-shaped devices with an air-filled space inside. Jeong et al. designed a complex PLA capsule with two integrated magnets, two different incorporated tablets, perforations for water influx and drug-releasing holes (Fig. 5A1-2). The design aimed at controlling the drug release of an incorporated commercially available IR baclofen tablet by the capsular floating device around it through drug-releasing holes. The second placebo tablet was incorporated to dissolve faster than the baclofen tablet. When this happens, the two magnets would get closer together, closing the previously opened windows which were intended to allow for initial water influx. The components of the baclofen tablet were then released through the still-opened drug-releasing hole. Floating of the capsular device for more than 24 hours was achieved (Fig. 5A3) [324]. This approach also results in a quite large insoluble capsular device. Moreover, the basic idea is quite complicated. However, it shows the potential of designing complex geometries and what is already possible with filament-based 3D printing.

A completely different idea is the design of shape-changing GRDFs over time by using 4D printing. Such an expandable drug delivery system was designed by Uboldi et al. They used 3D printing and melt casting to manufacture a collapsible and expandable device. The metformin-containing core was melt-casted with PCL, and the flexible arms were 3D printed and made of polyurethane (PU). After assembling both parts, the device was collapsed and put into a capsule. This transformative process is supposed to keep the devices inside the stomach by expansion after oral intake of the capsule [327]. Once again, printing techniques were only used to print the device responsible for gastric retention, not the drug itself. In addition, a rather large capsule with a size of 25.3 mm has to be swallowed, in order to realize a dosage form with the doses required for the treatment of type II diabetes (500 - 1000 mg).

In summary, using 3D printing processes (especially MEX (FE) and (SE)) offers a lot of potential for complex, previously unrealizable shapes of GRDFs often used for proof-of-concept studies. Air-filled spaces can be flexible and easily adapted during the design phase or when adapting infill parameters, and they offer the potential for floating dosage forms. The use of 3D printing for potentially gastro-retentive dosage forms seems to be reasonable; however, quite large dosage forms are often manufactured and in vivo performance has not been evaluated.

2.5.2. Chewables

There are various preparations that can or must be chewed or crushed by the patient prior or during administration, which can be found in different parts of the Ph. Eur. and the USP. Both Pharmacopoeias describe chewable tablets and gums, while the USP also mentions chewable gels [39,40,342]. The Ph. Eur. also lists soft capsules for use in

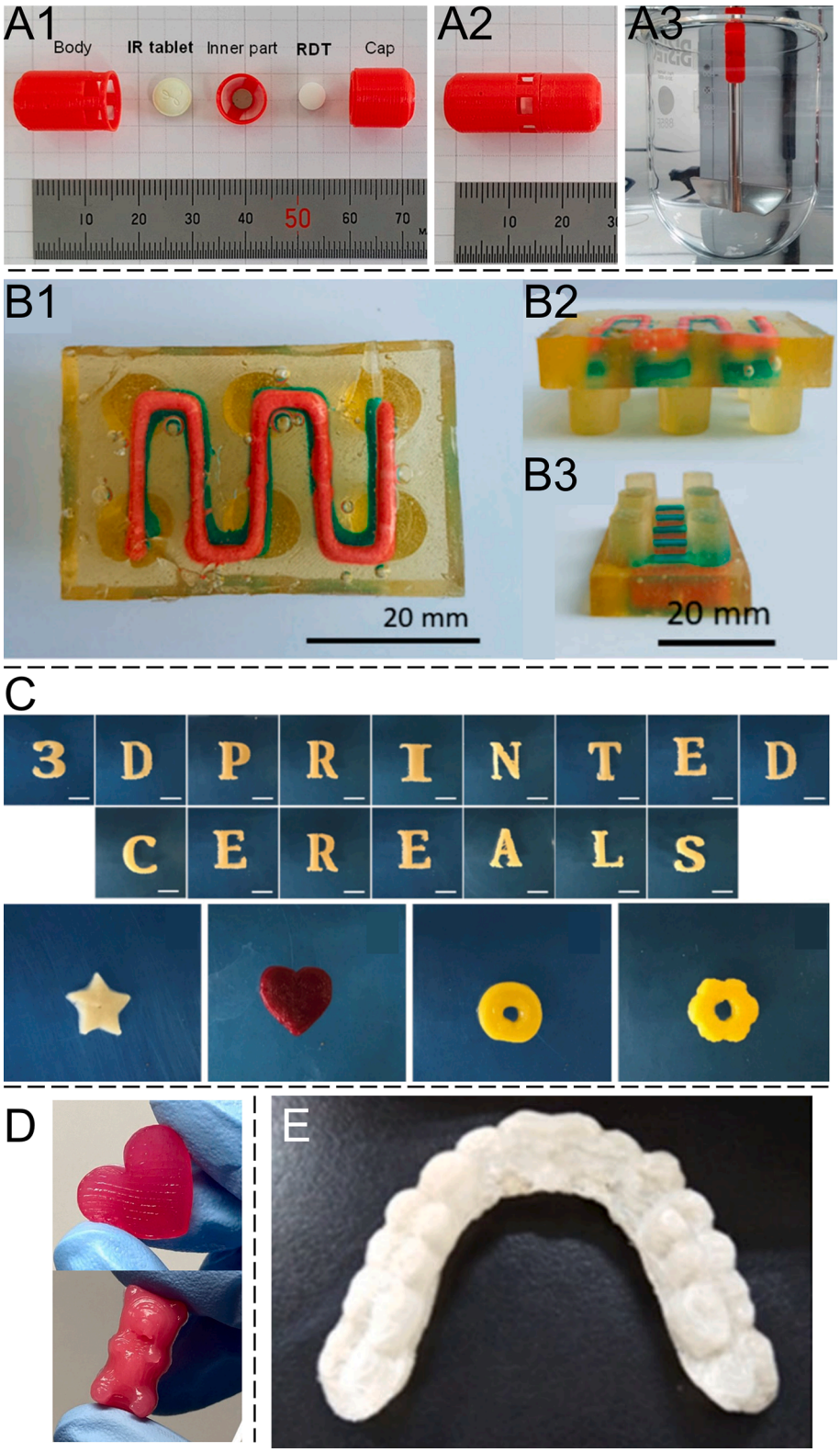

Fig. 5. 3D printed gastro-retentive dosage form, child friendly chewable gels and food-like chewables and dental dosage forms, A: Gastro-retentive 3D printed capsular device, components of capsular device with integrated tablets and magnets, (IR: immediate-release, RDT: rapidly dissolving tablet, A1), final dosage form after assembly (A2), floating capsule on the surface of a filled vessel (A3) (Reproduced with permission from [324], published by MDPI, 2020 B: molded, LEGO brick-like gummies with embedded, 3D printed, drug-containing strands (Reproduced with permission from [338], published by MDPI, 2019), C: 3D printed food-like, chewable cereals in various shapes (Reprinted from [339], with permission from Elsevier), D: heart and bear shaped gummies (Reprinted from [340], with permission from Elsevier), E: Clonidine-HCl loaded 3D printed dental retainer (Reproduced from [341], Springer Nature, 2019, reproduced with permission from SNCSC), all figures were modified.

the oral cavity, which are intended to be chewed or sucked [261]. For this chapter as well as for the overview in Table S14, these classifications have been adopted and also the category of food-like medicines is briefly described and discussed.

Chewable tablets are tablets that must or can be chewed before swallowing to ease swallowing or for faster release. Hard chewable tablets are generally produced by compression, usually using easily soluble and good tasting excipients such as sugar and sugar alcohols as binders and fillers. Soft chewable tablets are usually produced by a molding or extrusion process. The chewability and taste of the chewable tablets are decisive criteria [39,40].

Taste masking also plays a role for 3D printed chewable tablets. Tabriz et al. aimed to produce personalized, taste-masked dosage forms of ibuprofen using polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer (Soluplus®), copovidone, and bbMA. All polymers effectively masked the taste in vivo. bbMA achieved nearly 90% drug release in gastric acid within 15 minutes, copovidone showed slower release at pH 7.2 [343]. The authors further optimized the bbMA formulation for faster release and better taste masking and tested child-friendly shapes like hearts and bananas to enhance pediatric acceptance [344].

Han et al. investigated a multiphasic formulation with solid, liquid hydrophilic, and lipophilic components. The influence of three excipients on breaking strength, friability and release was examined. Subsequently, an evaluation of different amounts of sweetener and flavoring agents was performed. Different dose levels were realized by different child-friendly geometries [345].

In the field of veterinary medicine, chewable tablets are quite common, although it cannot be assumed with certainty whether the animal really chews the tablet or not. In order to make the dosage form more palatable to the recipient animal, different flavor enhancers are added depending on the species. In case of the theophylline and gabapentin-containing chewable tablets printed by Sjoholm et al., liver powder was added for dogs and cats. The compositions of the two formulations used were identical except for the drug [346,347].

Chewable gels, also known as “gummies,” usually consist of gelling agents, sugars, water, sweeteners, and flavorings. These gels retain their shape, are elastic, and are meant to be chewed before swallowing. They are typically produced via molding [39].

3D printed chewable gels are also mostly based on hydrogels. Therefore, the obvious printing method here is the semi-solid extrusion of gels. Chewable gummies printed by other methods could not be identified. Gelatine [338,340,348–350], hypromellose [348,351] and carrageenan were used in particular [340,349,350,352], but also the use of other well-known hydrogel formers such as xanthan gum [340,350], pectin [353,354] and agar [351] has been reported.

Whereas in the production of chewable tablets the added water was always dried out if present, there are reports on different processes for chewable gels in which an additional drying step was sometimes carried out [348,353] or not [338,340,349–354]. Shrinkage has occurred, when drying was performed [353]. The addition of various polyols not only usually improved the taste of the dosage form, but also acted as a plasticizer and humectant [338,352–354]. Two different shaped 3D printed child friendly gummies can be seen in Fig. 5B and D.

Rouaz-El Hajoui et al. came up with the idea of incorporating omeprazole pellets into a chewable gel in order to formulate the drug in a child-friendly way while retaining the enteric properties of the pellet coating. In order to simulate the influence of the chewing process on the release, the gels were divided into eight fragments. However, whether this can simulate to chewing by a child and how a chewing process can influence the integrity of the pellet coating was not investigated [350]. Overall, this type of oral dosage form could be particularly interesting for children, as it is visually and haptically reminiscent of familiar sweets and therefore shows good acceptability [354]. However, it should be mentioned that this similarity also represents a potential risk that should not be underestimated.

Several publications also investigated 3D printed dosage forms that resemble ordinary foods. These food-like medicines are usually chewed just like normal food products. Due to their nature, these dosage forms are difficult to categorize. A completely different approach to the ones mentioned so far is the production of 3D printed chewable tablets using commercially available cereals and milk as excipients. While the choice of milk with a higher fat content led to an improved release of ibuprofen, this effect was less pronounced with paracetamol. The authors hope that this formulation will increase the acceptance of medicines by children in hospitals (Fig. 5C) [339]. Other food materials are also being investigated for oral dosage forms. The 3D printing of chocolate was established in the food sector and several printing systems designed for this purpose are already on the market [355]. Chachlioutaki et al. dispersed paracetamol into a ready-to-print chocolate formulation and compared the printed dosage forms with molded dosage forms. The printed dosage forms showed a faster release of the drug in comparison to the molded cubes. The reason for this behavior is not discussed by the authors [356]. Also, Karavasili et al. used chocolate and corn syrup to incorporate analgesics into child-friendly oral dosage forms [357].

In both cases, however, there is a risk of confusion between the pharmaceutical form and foodstuffs without active ingredients, especially if they are inadequately labeled or stored within reach of children. Furthermore, the polymorphisms of the cocoa butter which is contained in the chocolate can probably complicate the formulation and production of chocolate printlets [358].

Overall, it can be said that MEX (SE) is probably the method of choice for most researchers to produce chewables by 3D printing. This is probably not least due to the fact that dosage forms produced using other techniques (e.g. MEX (FE)) can be too hard to chew. However, it is remarkable that no approaches to PBF or BJT-printed chewables were found for the time period analyzed. Most publications mention the supply of pediatric patients as the intended main area of application. Here, the 3D printing of chewable preparations should increase the acceptance through good taste and candy-like appearance, while precise dosing for these patients should be ensured by the 3D printing process as such.

2.5.3. Dental

Traditional dental devices, such as dental trays and orthodontic retainers, have primarily been used for maintaining teeth alignment after orthodontic treatment. These devices are typically custom fitted to the patient’s dentition and are made using molds taken directly from the patient’s teeth. However, 3D printing offers a transformative approach to the design and production of these dental devices, enabling greater customization, more efficient manufacturing processes, and the potential for drug delivery directly from the device itself.

Three manuscripts have been identified that explore the application of 3D printing in dental dosage forms, specifically focusing on dental trays and orthodontic retainers (see Table S15). These studies demonstrate the potential for these devices to deliver both local and systemic treatments.

Jiang et al. investigated the incorporation of clonidine hydrochloride into a 3D printed orthodontic retainer designed for long-term drug administration. The study utilized a previous mold of a volunteer’s teeth to capture the individual teeth orientation, which was then scanned and transferred to a CAD file to produce a customized retainer (Fig. 5E). The retainer was printed using a combination of PLA and PCL in an 8:2 ratio to achieve the necessary mechanical strength, while small amounts of macrogol 4000 and polysorbate 80 were added to modify printability and drug release characteristics. Drug release was sustained over a period of a few days, though the exact amount of drug released depended on the duration of wear, highlighting a challenge in the application of drug-loaded retainers. Unlike traditional orthodontic retainers, which are worn multiple times, often overnight, this drug-loaded retainer was designed for single use only due to the one-time release of the drug [341].

Berger et al. developed an individualized dental tray for the localized delivery of urea, aimed at preventing tooth decay. This tray was designed to release the incorporated drug unidirectionally, targeting the teeth directly without releasing the drug into the oral cavity. While this controlled release behavior was successfully demonstrated in printed objects with other forms, the effectiveness of the printed dental tray itself in achieving similar release characteristics was not confirmed [359].

Further expanding on these innovations, another study explored the use of 3D printing to create a controlled fluoride delivery system. This study demonstrated the feasibility of using 3D printed dental devices to provide sustained fluoride release, thereby offering a promising method for continuous prevention against dental caries over extended periods. The fluoride-releasing devices were created using a specific polymer blend that allowed for controlled release, ensuring that the therapeutic agent was delivered directly to the teeth surfaces over a prolonged period of time [360].

2.5.4. Others miscellaneous

The flexibility of 3D printing has enabled the development of oral pharmaceutical forms that could not be categorized in previous sections, either due to a limited number of publications or because they do not align with traditional pharmacopeia classifications. This chapter focuses on these rarely investigated or novel 3D printed oral dosage forms. Due to the diversity of these dosage forms, an analysis of preferred methods and materials only makes limited sense. A list of these dosage forms is given in Table S16.

Sublingual tablets are applied under the tongue to achieve a systemic effect. Their shape is adjusted to the place of application [261]. Lopez-Vidal et al. used MEX (SE) to modify the shape of sublingual tablets to fit into the sublingual cavity and to adjust the dose. The formulation is primarily based on easily soluble macrogol and contains domperidone nanocrystals as drug [361].

Dispersible tablets are tablets that are dispersed in a dispersion medium before use. Rapid disintegration in the medium is therefore an advantage and is also explicitly demanded in the Ph. Eur.. This dosage form is particularly suitable for dysphagic patients and is usually more stable than aqueous dosage forms during storage, especially regarding hydrolysis and microbiological contamination. The concept of Panraksa et al. of the 3D printed tablet in a syringe aims to be able to adjust the dose precisely and at the same time offer a rapidly dispersible dosage form [362].

As already described for chewables, hydrogels can also be used for peroral drug delivery. However, hydrogels that are not chewed and do not match the typical appearance of tablets are mentioned here. In addition to MEX (SE) [363–366], VPP was also used to produce oral hydrogels [367]. Koshovyi et al. printed IR, nanoemulsified eucalyptus extracts in grid patterns and investigated their antimicrobial activity. De Oliveira et al. incorporated nanocapsules into cylindrical printlets and analyzed their release in an ethanol-containing release medium [363]. Vadivel et al. examined the influence of pH on the release from their biopolymer-based hydrogels. The release from the carrageenan-based 3D printed hydrogels occurred fastest in acidic conditions. In summary, 3D printed hydrogels for peroral use are currently rather rare and the areas of application are few.

3. Parenteral dosage forms

Parenteral dosage forms according to the USP include injections and implants and are administered through an external barrier to allow for direct administration of drug substances [368]. The monograph lists special tests for the following specific parenteral dosage forms: solutions, sterile powders for solutions, suspensions, liposomes, sterile powders for suspensions, emulsions, implants, and drug-eluting stents. The Ph. Eur. [369] defines parenterals as sterile preparations designed to be administered via injection, infusion, or implantation and distinguishes between injections, infusions, concentrates for injections or infusions, powders for injections or infusions, gels for injection, implants and intravitreal preparations. Parenteral dosage forms include liquid, semi-solid and solid dosage forms – for 3D printing applications solid dosage forms are relevant, even though during the printing process often semi-solid states are necessary. Solid parenteral dosage forms are typically intended for a sustained drug release over long periods of time either to act locally at the site of implantation or systemically after drug release and absorption into the blood. Traditional production methods for implants include HME, which is often used to produce rod-shaped implants, but also molding to produce specialized shapes. For very specialized local implants, e.g. vascular stents, the use of pharmaceutically unconventional methods such as laser cutting of the stent backbone and subsequent coating have been employed.

One of the most important requirements for parenteral dosage forms is sterility. Besides parenteral dosage forms, ophthalmics, preparations to be used during surgery, and preparations to be used on large open wounds are typically required to be sterile. Ophthalmic dosage forms are not covered in this chapter, however intravitreal preparations which belong the parenteral dosage forms are mentioned here.

The topic of 3D printed drug-eluting implants has been subject to reviews before, for example parts of our group gave an overview on this topic in 2021 [370]. However, quite a few new manuscripts have been published on the topic since then, therefore it is worthwhile to also revisit the topic here. In the meantime, passive loading of the implants with drug, for example by incubation of filaments or printed structures in drug solutions, has almost disappeared from literature reports. Sometimes it is still reported, especially when in research settings the use of highly potent drugs in non-dedicated equipment is problematic [371]. One of the reasons why these techniques are rarely considered is the fact that these methods are very limited regarding the loading capacity as well as the control of drug release. There are still many reports in which drug-containing coatings are applied to 3D printed structures, however, these studies have also been excluded here (see introduction for exclusion criteria). (Micro)-reservoir system approaches are also not discussed in this chapter. This includes systems which are filled with drug solutions or drug powders and control release via an external trigger, via a programmed release rate or via diffusion, even though several interesting approaches describing 3D printed devices have been published, e.g. [372–375]. Articles with the main focus on tissue engineering were not included either, even if they contained supplementary drugs.

Especially in the case of implants, it is also difficult to differentiate in some cases whether the 3D printed drug-eluting implants would be categorized as medicinal products or as medical devices. As the decision regarding this is up to the regulatory agencies, the authors of this review will avoid these terms for the drug-eluting implants and parenteral drug delivery devices described. Medical devices are also subject to a separate article in this special issue.

For implants, shape individualization plays a major role – not only because of its potential to influence the release characteristics by the SA/V or inner geometries (infill fraction and pattern) but also because implants for certain implantation sites should fit into the body orifice or defect into which they are implanted and the outcome for the patient is expected to improve if the implant has the dimensions to assure ideal fit. In traditional manufacturing approaches this problem is typically overcome by offering several sizes of implants that can be selected by the surgeon, however this approach has obvious limitations if the anatomical structures or defects show great interindividual variability that cannot be covered with several standard sizes. In these cases, an implant specifically designed and 3D printed for the individual patient based on the available imaging data might be suitable to optimize treatment. A challenge associated with such individualized shapes is, however, that drug release must also be expected to change as the shape of the implants varies. A potential approach to deal with this problem is prediction of drug release data, as for example attempted by [376–378].

Depending on the size of the implant and the degree of individualization, also different techniques to manufacture implants may have to be considered, as the resolutions that can be achieved using the available techniques greatly differ to-date. Techniques such as MEX (FE) or MEX (SE) may find their limitations when a very high spatial resolution is required and VPP or MJT seem to be promising methods in such cases. However, washing or rinsing processes which are often reported in products that were fabricated using polymerization reactions are typically to be avoided if drug is present at the outer surface of an implant as it is unclear how much of this drug will dissolve and thus be lost during the process. So far, these issues have not been systematically addressed according to the authors' knowledge.

Also, other aspects such as radial strength in case the implant also must fulfill mechanical support functions will greatly depend on the manufacturing technique and materials used. Therefore, also many new excipients are developed for use in 3D printed products and may provide great potential. On the other hand, the potential risk arising from an implant permanently in contact with the tissue and body fluids is also expected to be high. The studies necessary to achieve regulatory approval for new implant materials, such as PEGDA, which is often employed in VPP printing in combination with crosslinkers that also would require regulatory approval, are expected to be associated with high costs.

To the author's knowledge, there is no FDA-approved, or EMA-recommended marketed 3D printed drug-eluting implant or parenteral drug delivery device to date, and the current INDs (investigational

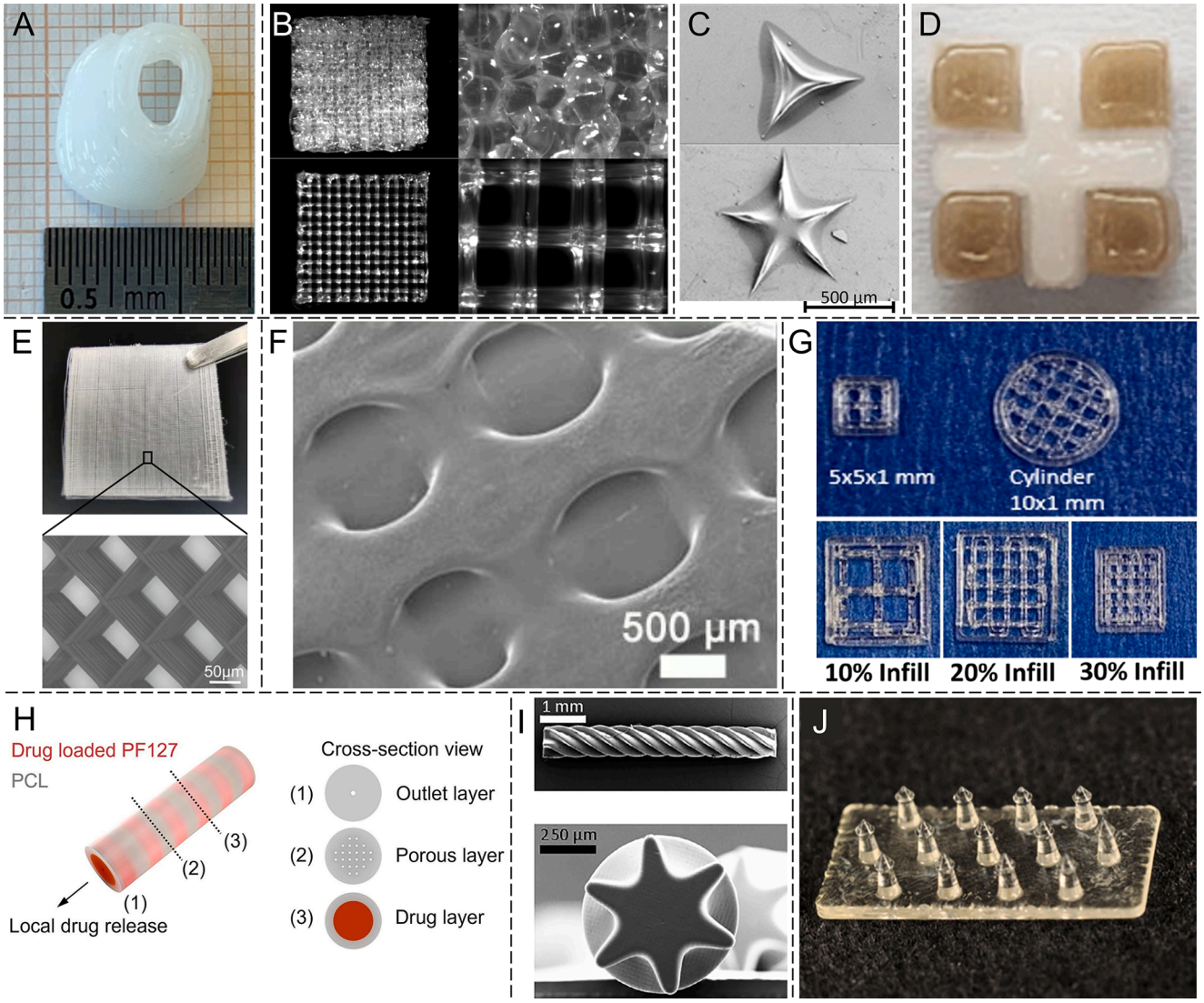

Fig. 6. Different 3D printed parenteral dosage forms, A: image of a 3D printed hollow implant for the outer ear canal used in an individual curative trial in a human (Reproduced with permission from [380], published by MDPI, 2022), B: microscopic images of ibuprofen-loaded polylactic-co-glycolic acid implants (meshes) prepared by droplet deposition modelling (MEX (SCE), top) or MEX (FE) (bottom) using the same materials and digital designs (Reprinted from [382], with permission from Elsevier), C: scanning electron microscopic images of printed microgels, scale bar 500 µm (Reprinted/adapted with permission from [383], © 2019 American Chemical Society); D: image of compartmental implant with individual near-infrared triggerable release of insulin (Reprinted from [384], with permission from Elsevier), E - F: different scales of printed meshes, E: photograph (top) and scanning electron microscopic image (bottom) of a scaffold composed of polycaprolactone, polyethylene glycol and roxithromycin (Reprinted from [385], with permission from Elsevier), F: scanning electron microscopic image of a nanocomposite specimens printed from polycaprolactone (Reproduced with permission from [386], published by MDPI, 2021), G: photographs of polylactic-co-glycolic acid scaffolds containing ketoprofen (Reproduced with permission from [387], published by MDPI, 2024), H: design of pulsatile release implant with drug containing and release controlling layers (Reprinted from [388], with permission from Elsevier); I: images of twisted star-shaped implant in side view (top) and cross sectional view (bottom) (Reprinted from [389], with permission from Elsevier), J: photograph of arrowhead array device (Reprinted from [390], with permission from Elsevier), all figures were modified.

medicinal products) are for peroral dosage forms (see introduction). However, drug-free implants used as replacement material for bone defects are available, for example, from Oxford Performance Materials, Inc. [379]. These implants are produced via selective laser sintering (SLS), a process belonging to the PBF techniques, from a polyetheretherketone (PEEK) – based material. According to Oxford Performance Materials Inc., they are the only company to have received FDA 510(k) approval to print patient-specific polymeric implants.

Furthermore, an individual curative trial using a 3D printed drug-eluting device has been reported in 2022 by Matin-Mann et al. [380] in which a shape-individualized hollow implant was printed in a MEX (SE) setup with a silicone elastomer with subsequent ultraviolet (UV) light curing for cross-linking. The implant contained dexamethasone and ciprofloxacin and was implanted into the outer ear canal of an eight-year-old child who suffered from restenosis of the external ear canal after a series of surgeries. An image of the implant is given in Fig. 6A. The drugs were chosen to prevent acute infection, reduce inflammation and to suppress the formation of granulation tissue. Such a product containing two different drug substances might still be a medical device if the support of the hollow structure preventing collapse of the opening is considered the main therapeutic concept. The implant was removed after 3 months as the materials were not approved for long-term implantation. 12 months post-surgery the outer ear canal showed good patency and no adverse effects were reported. However, it must be kept in mind, that this is not the result of a clinical trial with defined endpoints, parallel group design, etc. and the therapeutic approach as well as the manufacturing process will have to undergo further thorough evaluation. Nevertheless, it is to the author's knowledge the first report of a successful implantation of a 3D printed drug-eluting implant in humans. The study, however, also reveals that further effort is needed to develop products that can be marketed. In this case, for example, the implant was treated with UV light not only for the polymerization but also to reduce potential microbial contamination. In the performed sterility tests, no microbial contamination was detected. However, the method does not provide the same safety as a terminal sterilization process. There are other sterile products composed of dexamethasone and silicone that have been on the market for decades, e.g. lead tips for pace maker electrodes, so there must be an established procedure to manufacture sterile implantable medical devices of this composition. ELA Medical Inc., for example, reports that its pacing leads are sterilized with ethylene oxide [381]. Nevertheless, the topic of achieving sterility as well as the absence of pyrogens within parenteral products remains challenging, as many sterilization processes are expected to potentially impact on factors such as polymer chain length and drug stability. However, processes established for implants produced via traditional manufacturing methods such as HME should be transferable to 3D printed melt extrusion-based products as well.

The performed literature search yielded 101 manuscripts (see Table S17-22) that were classified to belong into this section. For systematic evaluation, the manuscripts were first divided into on the one hand manuscripts describing no specific implantation site or just a type of tissue (e.g. subcutaneous administration) but without a specific location and on the other hand dosage forms for placement in a specific part of the body (e.g. in the ear, in the vascular system, etc.). The latter implants are typically designed for a local drug therapy whereas in the first group also systemic therapy strategies were reported. Fig. 6 shows exemplary 3D printed parenteral dosage forms.

3.1. *Implantable drug delivery systems with no specific implantation site*

In the category of implants developed without a specific implantation site or just a type of tissue specified for administration, 24 manuscripts were identified with the described search parameters (see Table S17). A general problem concerning long-acting parenteral dosage forms is that the size of the implant to accommodate drug is limited, which also limits the amounts of drug that can be incorporated, especially if release controlling excipients amount to large fractions of the mass of the dosage form. This limitation is even more pronounced when the drug is expected to distribute in large compartments as intended in systemic therapy. Therefore, especially highly potent molecules should be considered as potential drug candidates for these types of dosage forms. Besides the use of classical small molecules as drugs for long-acting 3D printed dosage forms, also attempts to print proteins [384,391–394] or siRNA [395] have been reported. In addition to the immense variability concerning potential drug molecules, also a range of 3D printing techniques was used and accordingly also great variability regarding the materials used as excipients was observed. The described techniques included different MEX and VPP-based technologies, and one report also employed MJT-based printing. Solid (full infill) structures as well as meshes/ grids and other geometric structures such as rings were reported.

Two reports actually compared the manufacturing of the same formulation using different techniques. Muhindo et al. [396] compared a MEX (SE) process with a conventional HME process for production of implants composed of PCL, PEO and the drug raloxifene hydrochloride. The authors concluded that both methods were suitable to produce implants and report comparable data concerning the performed in vitro characterization. However, the authors stated the potential of 3D printing to easily adapt the release behavior and to personalize dosage forms. Bassand et al. [382] presented a study in which the same formulation consisting of poly(lactic-co-glycolic) acid (PLGA) and the model drug ibuprofen was printed using either a MEX (FE) process or the so-called freeforming droplet deposition modeling which is a MEX (SCE) process in which theoretically no continuous strand is extruded but a piezo actuator forms droplets at the nozzle outlet. However, the authors reported on a continuous droplet string caused by the high frequency of actuation. Nevertheless, the implants obtained with the two techniques which are depicted in Fig. 6B are optically quite different and also differences regarding the release profiles were reported. While the authors did not draw any general conclusions concerning the suitability of the compared methods, this publication emphasizes that processing parameters are extremely important in 3D printed products, especially when structured objects are produced, as the mechanical properties and the homogeneity of the material leaving the nozzle as well as its subsequent behavior (e.g. hardening upon and after deposition) will be of great impact for the resulting product. Therefore, understanding these processes is essential for further development and production. It is also interesting to note, that the authors of the above-mentioned manuscript avoided the filament fabrication with the MEX (SCE) process but nevertheless performed a HME with subsequent cutting of the extrudate to small cylinders prior to MEX (SCE) printing, presumably to assure homogenous material for feeding of the MEX (SCE) printer.

In other studies, the shape of the dosage form in general or the arrangement of different materials was in the focus of the studies, as the comparably easy control of these parameters is a clear advantage of the 3D printing techniques. It must be kept in mind though, that implants of complex shapes may be more challenging regarding the implantation procedure opposed to rod-shaped objects as typically produced via HME that can often be administered via a syringe with a large cannula or similar applicator.

Liaskoni et al. [397] showed how adding a drug-free printed coating layer (shell) using the same excipient (PCL) as for the drug-containing core dramatically slowed down release of the drug lidocaine (6% drug release opposed to 50 – 60% after 4 days) from discs produced using a MEX (SE) setup.

While MEX techniques were mainly used to produce macroscopic objects as the aforementioned discs with a diameter of several millimeters, VPP can also be used for very small objects. Liu et al. [383] presented a study in which microgels loaded with paclitaxel-containing nanoparticles were produced that possessed different shapes such as cylinders and cubes but also triangles and stars (Fig. 6C). The authors reported, that the microgels can be injected presumably upon immersion

in a fluid. In spite of the very small objects printed (from the provided images, the sizes seem to have been below 1000 μm) in which only fairly short diffusion path lengths can be achieved, the authors reported drug release data for 7 days. However, the used drug paclitaxel has a very low solubility in water and it was not reported whether sink conditions were maintained in the release experiments. The drug was incorporated into the gel embedded in nanoparticles, which is an approach that was chosen by several authors.

In peroral administration, amorphous state of the drug in the dosage form is often desired to achieve sufficiently fast dissolution and a high concentration gradient to increase bioavailability. In long-acting implants, this is typically not necessary. Nevertheless, if the polymer effectively controls release, amorphous state of the drug, if stable during storage, may also be desired. Manini et al. [398] published a study of embedding amorphous paliperidone palmitate obtained from cryo-milling in PCL and printing it using a MEX (SE) process. Drug release for more than 150 days was reported and the production of a filament, which typically includes two heating processes, was avoided. Nevertheless, for a thermostable drug HME during filament production might also be employed for the amorphization of the drug.

A triggerable release device was presented by Kim et al. [384] who designed an implantable reservoir with four drug-loaded regions separated by drug-free compartments consisting of PCL. The drug-eluting compartments contained PCL as well and in addition lauric acid and melanin as well as the model protein drug insulin. Drug release was triggered by near infrared (NIR) light which increased the temperature of the irradiated compartment and resulted in melting of the lauric acid. By placing an insulating compartment between the drug-loaded compartments it was possible to selectively trigger drug release from an individual compartment (Fig. 6D). An alternative trigger to initiate drug release was presented by Wang et al. [399] by using a magnetic field as an external trigger acting on magnetic hollow fiber scaffolds loaded with gels that contain drugs or proteins. However, triggered drug delivery systems will need a lot more investigations, for example to exclude unintentional triggering of drug release e.g. by physiological (e.g. fever) or external unintentional stimuli.

When implants are placed in tissue, sometimes implant migration is a cause for potential concern, which is why some marketed implants contain radiopaque materials to allow for localization such as barium sulfate. An alternative suggested by Muldoon et al. [400] in the context of 3D printed implants is to include iron oxide nanoparticles in printed implants to provide contrast for computed tomography imaging. However, the addition of barium sulfate should also be possible in MEX-based printed objects in many cases, as this is also used in marketed implants produced via HME.

3.2. Implants with specified sites of implantation

Among the drug-delivery devices for specific application sites, several manuscripts belonging to the following subcategories were identified, that are discussed below. These subcategories are implants placed in the vascular system and stents, implants for ear, eye and sinuses, bone implants, and intratumoral implants.

In addition, several reports concerned implants that do not fit into any of the categories mentioned above. However, to provide an overview of the large number of application sites and printed geometries, these are listed in Table S18, and selected publications are also mentioned here. Ponsar et al. [378] reported on a modular implant for intraarticular administration consisting of a drug-free shell and a core releasing triamcinolone acetonide. The authors reported that the shell could be adapted to the individual anatomy while the core could be personalized with regard to dose and release rate. The shell and the core polymer contained EC, TEC and fumed silica and the core in addition contained the drug triamcinolone acetonide and hypromellose as a pore forming agent. Three other manuscripts dealt with cartilage replacement and regeneration where most likely the mechanical aspect of the implant is predominant and the drug included might cause an adjuvant effect to prevent infection or protect the remaining natural cartilage. Another implant was designed to be implanted in close proximity to a mechanical implant (e.g. following / during joint replacement surgery) to prevent or treat infections that are a potential complication associated with the implantation. Furthermore, three publications were found in which VPP was used to produce tubes or rolled up self-adhesive films to be placed around an injured nerve to promote regeneration. Two manuscripts reported the printing of hydrogel implants for brain delivery and two manuscripts were identified in which 3D printed objects were designed to be used in combination with piercings / earrings to prevent or treat local infections.

3.2.1. Vascular application sites and stents

Among the drug-delivery systems placed in the vascular system, especially vascular stents and grafts as well as catheter systems were reported. Eleven publications were identified presenting systems to be placed in the vasculature (see Table S19). Therapy goals of the drugs incorporated included prevention of re-stenosis, promotion of re-endothelization and prevention or treatment of infections often as an adjuvant approach to a mechanical function of the implants. MEX (FE), MEX (SE) as well as VPP based processes were reported. In the case of drug-eluting vascular stents, an important question is, how much drug actually reaches the vessel wall tissue and how much is released to the blood flowing through the device. Another major issue besides controlling drug release is to find a balance between providing enough mechanical support of the vessel and achieving small struts, as strut thickness and stent geometric design seem to be a very relevant factor [401]. Ha et al. [402] showed the great variability of designs that is easily achievable with a 3D printing approach combining a MEX (SE) setup with a rotating rod that is used as the print bed in order to form the delicate cylindrical structures. According to the authors, the radial strength of at least one of the printed systems was comparable to a metal stent. The authors report on the in vitro release of paclitaxel from the PCL based stent for 1.5 years, however, in this study it is also unclear whether sink conditions were achieved for the extremely poorly water-soluble drug.

A comparable production setup in which MEX (SE) printing onto a rotating object was performed was presented by Kim et al. [403] who developed a stent for the treatment of inflammation occurring during obstructive salivary gland disease. The stent contained amoxicillin and cefotaxime in a PCL base. Compared to vascular stents, the amount of media flowing through the implant is expected to be lower, however a certain drug drainage from the intended site of action still may be expected. The development of stents for yet another site of application was reported by Prasher et al. [404] who designed a steroid-eluting esophageal stent for the treatment of eosinophilic esophagitis. The system was printed via a VPP technique and eluted fluticasone for at least 28 days. The local drug delivery to the esophagus is intended to increase the local tissue concentration while minimizing potential adverse effects often associated with systemic exposure and improving patient adherence through the long-term release.

3.2.2. Drug-eluting implants for ear, eye and sinuses (frontal neo-ostium)

Five reports were identified in the performed literature search in which systems for the ear were developed, of which one was designed as the ear piece of a hearing aid with adjuvant antimicrobial drug to prevent biofilm formation [405] (see also Table S20). This drug delivery system is not an implant, however as no further reports of comparable devices were found, it is listed here. Another device was the previously mentioned one for the prevention of re-stenosis of the outer ear canal [380] which was actually used in a human patient in an individual curative trial involving surgical opening of the stenosed ear canal. The other two publications [406,407] were aiming at therapy of the middle or inner ear which is challenging when administration in the outer ear canal is intended as the tympanic membrane and in case of inner ear

delivery also the round and/or oval window membrane have to be overcome. However, the exact site of administration is not clear. In case these delivery devices would be placed in the outer ear canal or at the auricle (as the ear piece mentioned above) sterility would not be required and it is not a parenteral application. Alternatively, implants might be placed in the middle ear or even in the cochlear, however the degree of invasiveness increases and the space available for implantation decreases. A concept for a 3D printed implant designed to be placed in the middle ear for inner ear delivery was reported by Mau et al. [408]. Even though this manuscript was not found in the performed literature search, it shall briefly be mentioned, as the topic is interesting for 3D printing of individualized implants. The implant is intended to be printed based on imaging data for the individual anatomy of a patient's round window niche and should deliver dexamethasone across the round window membrane. As the round window niche shows a comparably large anatomical variability but only a small size, a VPP method using PEGDA incorporating dexamethasone was used to print implants with dimensions of approximately 3 x 2.5 x 2 mm. While the formulation showed good printability, problems concerning drug stability were observed, which occurred during long-term storage but also directly after manufacturing in cases when post-curing in a UV light curing oven was performed. This publication shows how important it is to look into stability matters as well. Partially the same authors also published a manuscript [409] on the development of a hollow individualized implant to be implanted into the frontal neo-ostium in patients with surgical treatment of chronic rhinosinusitis. In this case a polymer based on trimethylammonium chloride monomers was printed in a VPP process and the model drug acetylsalicylic acid was used. There is another publication on an implant for the same site based on MEX (FE) by parts of our group, in which a hollow implant was printed with a drug-free luminal as well as a drug-containing abluminal layer [377]. The idea behind this concept was to allow drainage through the implant and deliver drug to the contacting tissue while preventing drug release into and transport from the site with the drained fluid. Ammonio methacrylate copolymer type A (amMA-A, e.g. Eudragit® RL) and amMA-B were used as polymers for the abluminal layer containing the model drug paracetamol and commercially available PLA filament was used for the barrier layer.

Three reports have been published on drug delivery systems for placement in or at the eye, namely 2 for intravitreal administrations and 1 for implantation into the conjunctival tissue. The very small size of the implants is challenging here. In all three manuscripts rod shaped objects were described in which the MEX (SE) printers were mainly used like a small extruder and apparently the added value of a printer of being able to determine the location of deposition was not used. In one of the manuscripts [410] in addition to rods also cuboids and rings were printed which showed different release kinetics. However, in this case it also has to be kept in mind that for intravitreal administration often an applicator is used to inject the implant into the vitreous, which is most likely not possible with implants that are not rod-shaped.

3.2.3. Drug-eluting bone implants

A great number of publications were identified dealing with implants to be placed in contact with or to substitute bone (see also Table S21). Most studies in this field dealt with the release of anti-infective or anti-inflammatory drugs in combination with promotion of bone regeneration. However, the topic of bone regeneration and tissue engineering is very diverse and many unconventional techniques and excipients are used in this field. For this reason, studies with a focus on tissue engineering were excluded here. There are several other reviews dedicated to this topic such as [411–413]. Only if the focus was on drug delivery e.g. for anti-infective drugs, the systems were included in this review. In total, 14 publications remained, of which 2 included drug-loaded surgical fixation devices in the shape of screws supplemented with an anti-infective drug. The other publications dealt with materials to be used in bone defects, e.g. after trauma or due to removal of infected bone. These materials would have to be personalized regarding the outer shape for the specific patient lesion. Benmassaoud et al. [414] and Ranganathan et al. [415] in their two publications on the topic printed a femoral implant with a specifically designed shape resembling two interconnected semi-circles using MEX (FE) technique. The implant was designed to be used in patients who suffered from an osteomyelitis following joint replacement surgery where the initial implant had to be removed due to a severe infection. Even though the implants were quite large, the shape of the printed object seemed to have optimization potential. The authors of those studies also evaluated alternatives including PBF-printing of a metal implant that can be filled with drug solution and act as a reservoir. In that case, the shape seemed to fit the designed object much better. In the majority of the identified publications, however, a specific shape was not printed, even though it should be a manageable task using 3D printing methods. Typically grid structures were printed opposed to filled designs as ultimately replacement by bone tissue was desired. Accordingly, the polymers used were preferably biodegradable such as PLA or PCL. However, the scales on which these meshes were produced were very different among the publications and it is conceivable, that this makes a great difference for bone regeneration as well as mechanical features of the implants. Fig. 6E and F show exemplary images of the material mesh structures obtained in different publications. Typically, the scale and resolution of the printed objects are directly connected to the printing technique. Nevertheless, in most published reports in this category MEX (SE) printing was employed but some reports on MEX (FE) were also identified. In the study in which the strand width was well below 100 μm [385] (Fig. 6G) a special deposition method was used employing electrohydrodynamic deposition. In several formulations hydroxyapatite was included as it is a natural component of bones and teeth. It has been reported to promote osseointegration in dental implants [416] and bone regeneration [417]. Because of its brittle nature, it has been used as a coating on metal implants but is also considered in combination with other materials. However, the mechanical aspects of composite materials will also need to be checked, and individualized shapes might impact these features of the implants.

3.2.4. Intratumoral drug-eluting implants

In the group of intratumoral implants, a comparably large number of manuscripts (28 in total, see Table S22) was published in the time frame chosen for the authors' literature research with the applied keywords. It is noticeable, that among the methods used for 3D printing MEX (SE) is the most prominent method used in this category. Only two published manuscripts used MEX (FE) setups and only two reports of VPP were identified. Some authors referred to specific tumor locations such as breast, brain, liver, ovarian or prostate tumors whereas others did not specify this. In most publications, authors assumed that a solid tumor was surgically removed and the implant would be inserted into the resurrection site in order to prevent tumor re-growth caused by incomplete tumor removal. The benefit of 3D printing for this site was generally described as the flexibility to adapt the implant size and shape to the operational space in combination with a flexibility regarding drug (s), doses and release rates. Some authors also aimed at a triggered release by an external stimulus, e.g. [418,419] or at an additional therapy option such as a layer containing particles intended to enhance radiation therapy [420]. As mentioned above, in most manuscripts from this category MEX (SE) processes were employed. In many of the formulations used for this purpose, sodium alginate solutions were used that were often crosslinked with calcium ions via immersion in calcium chloride solutions sometimes followed by washing processes. In the case of water-soluble drugs, this seems to be a challenging manufacturing method, as drug loss may be expected during the crosslinking and washing procedures. Internal gelation methods, as described by [421] might be an option here, however, in that publication the application site of the epirubicin-loaded hydrogel is not given, which is why it is not included respective table in the supplementary material section. An

unconventional approach to "3D print" directly during the operation into the region in which the surgery is performed was presented by [422], who used a hand-held device to extrude an alginate-based formulation which contained the drugs temozolomide and deferiprone in PLGA and PVA based microparticles. In this study, a co-extrusion method was used to bring the alginate vehicle in contact with calcium chloride solution for crosslinking thus also avoiding separate crosslinking and washing steps.

An interesting implant for application via a trocar to a tumor region has been reported by Myung et al. [423] and a prototype is depicted in Fig. 6H [388]. In the presented study the authors printed a PCL shell and also internal structures composed of the same material to control release and printed polyoxyethylene-polyoxypropylene triblock copolymer (Pluronic® F 127) gels containing the drug doxorubicin alone or in combination with cyclophosphamide in the center. A MEX (SE) method was used for this purpose. The shell of the implant layer was made of an eventually biodegradable material but drug release was intended to occur via an opening on one of the ends of the cylindrical implant prior to polymer degradation. By alternating drug-containing and drug-free, porous layers, pulsatile drug release was achieved and modulated via the design of the drug-free layers. This release behavior was considered to be beneficial with respect to efficacy and potential adverse effects according to the authors of that study.

Furthermore, some interesting implant shapes were reported in the manuscripts dealing with intratumoral drug-eluting implants. These include biodegradable 3D printed bilayer films loaded with two different drugs, 5-fluorouracil, and cisplatin, that were incompatible with each other and were therefore separated into individual layers [424]. By using this setup, the release properties may also be controlled separately by using different infill patterns and infill rates. Interesting shapes were also produced by Hagan et al. [389] who produced drug-loaded brachytherapy spacers intended for the therapy of prostate cancer with different surface patterns to control release of the adjuvant drugs incorporated. The implants loaded with docetaxel and dexamethasone were shaped as a regular rod, a star-shaped object (in cross-sectional view) and a twisted star-shaped implant (Fig. 6I) and were produced via VPP. VPP was also used by the same group to produce a so-called arrowhead array device that somewhat optically resembled a microneedle patch array to be placed within a tumor resurrection cavity (Fig. 6J) [390]. The printing of implants containing paclitaxel and/or cisplatin was reported and a first test in a mouse tumor model showed encouraging results. The authors also exemplarily printed individualized implants based on images of the resurrection sites. In contrast to the rigid appearance of these implants, Li et al. [425] described flexible meshes produced via MEX (FE) for glioblastoma treatment. The authors reported that a flexible, biodegradable and individually shaped 3D printed mesh might overcome limitations of the commercially available GLIADEL® wafer due to mechanical mismatches of that implant and by providing better coverage at the surgical margins.

4. Cutaneous dosage forms

Many dosage forms are administered onto the skin either for systemic delivery of drugs or for local drug delivery to certain layers of the treated skin section, or for protective or keratolytic effects on the skin surface. The Ph. Eur. has several monographs for dosage forms administered onto the skin, including liquid preparations for cutaneous application [426], semi-solid preparations for cutaneous applications [427], powders for cutaneous application [428], patches [429], and medicated plasters [430]. In case the dosage forms are intended for use on large open wounds or on severely injured skin, they are required to be sterile. As 3D printing is a manufacturing process for shaped dosage forms, 3D printing of patches and similar structures may be considered.

Patches, according to Ph. Eur., are applied onto unbroken skin. Depending on the intended site of action of the delivered drug (systemic or local) the monograph distinguishes between transdermal and cutaneous patches. Transdermal patches are designed to deliver drugs through the skin and into the systemic circulation [429]. These patches provide a controlled, sustained release of medication over time, making them suitable for long-term therapies such as pain management, hormone replacement, and nicotine withdrawal. One of the key features of transdermal patches is the ability of the drug to bypass the GIT, thereby avoiding first-pass metabolism and reducing potential adverse effects associated with oral administration. Those patches typically feature a backing layer, which protects the dosage form from external influences, enhances the occlusion effect, and facilitates packaging and secure application. The drug is incorporated in a reservoir or matrix as a solution or solid dispersion. Due to a pressure-sensitive adhesive, the patch adheres to the skin. Cutaneous patches may have some similar features but are intended for localized drug delivery directly to the skin, targeting specific areas without significant systemic absorption. These patches are ideal for treating localized conditions such as infections, inflammation, and dermatological disorders. The focus here is on delivering a high concentration of the drug at the site of application or in close proximity, which enhances efficacy and minimizes systemic exposure. Furthermore, the Ph. Eur. lists medicated plasters in an individual monograph. These can be administered onto intact or injured skin and are intended for a local protective, keratolytic, or antimicrobial effect [430].

Thirty-four manuscripts were identified in the literature search, investigating 3D printed cutaneously applied dosage forms, including dermal patches, films, and wound dressings, intended for local or systemic drug delivery. Often, a classification, according to the definitions given above, was not possible, e.g. because it remained unclear whether the reported systems achieved transdermal or cutaneous delivery. Many were also intended for the use on injured skin. The identified formulations were based on different technologies and excipients and can be divided into gel-based and non-gelled patches.

In addition, 12 manuscripts were identified that presented research on 3D printed microneedle patches (MNP), a dosage form administered onto the skin but not listed in the Ph. Eur. to date. MNPs represent a potentially cutting-edge technology in transdermal drug delivery systems, enabling the delivery of drugs through the skin by overcoming its natural barrier with minimal invasiveness. This method has garnered significant attention due to its potential to deliver a wide range of therapeutic agents, including highly potent drugs and proteins. The use of 3D printing in the fabrication of MNPs offers a highly customizable and precise approach to designing these devices, allowing for tailored drug delivery profiles and enhanced patient compliance. However, there are no marketed products (whether 3D printed or not) to date in Europe or the United States. The number of manuscripts in this category would have been even higher, but in several cases, the drug was not applied in a printing process, and therefore, these manuscripts are not discussed here. In the following sections, the categories of non-gelled patches, gelled patches, and microneedle patches will be addressed separately. Fig. 7 gives an overview of some of the 3D printed dosage forms discussed below.

4.1. Non-gelled patches

The printed non-gelled drug-releasing patches are typically flat and flexible objects. Some manuscripts describe printing the patch on a backing layer [431,438,439], on packaging material [440], or just on the build plate of the printer [441,442]. The materials used depended on the 3D printing method, but most of the basic compounds were matrix-forming and/or release-delaying polymers, as also apparent from Table S23. Taking this into account, drug release could be prolonged for a couple of hours up to a few days by incorporating the drugs into different polymers.

Some manuscripts dealt with antibiotic patches, such as a study presented by Altun et al., who printed a patch based on PCL and bacterial cellulose which contained 90° rotated strings, which form a

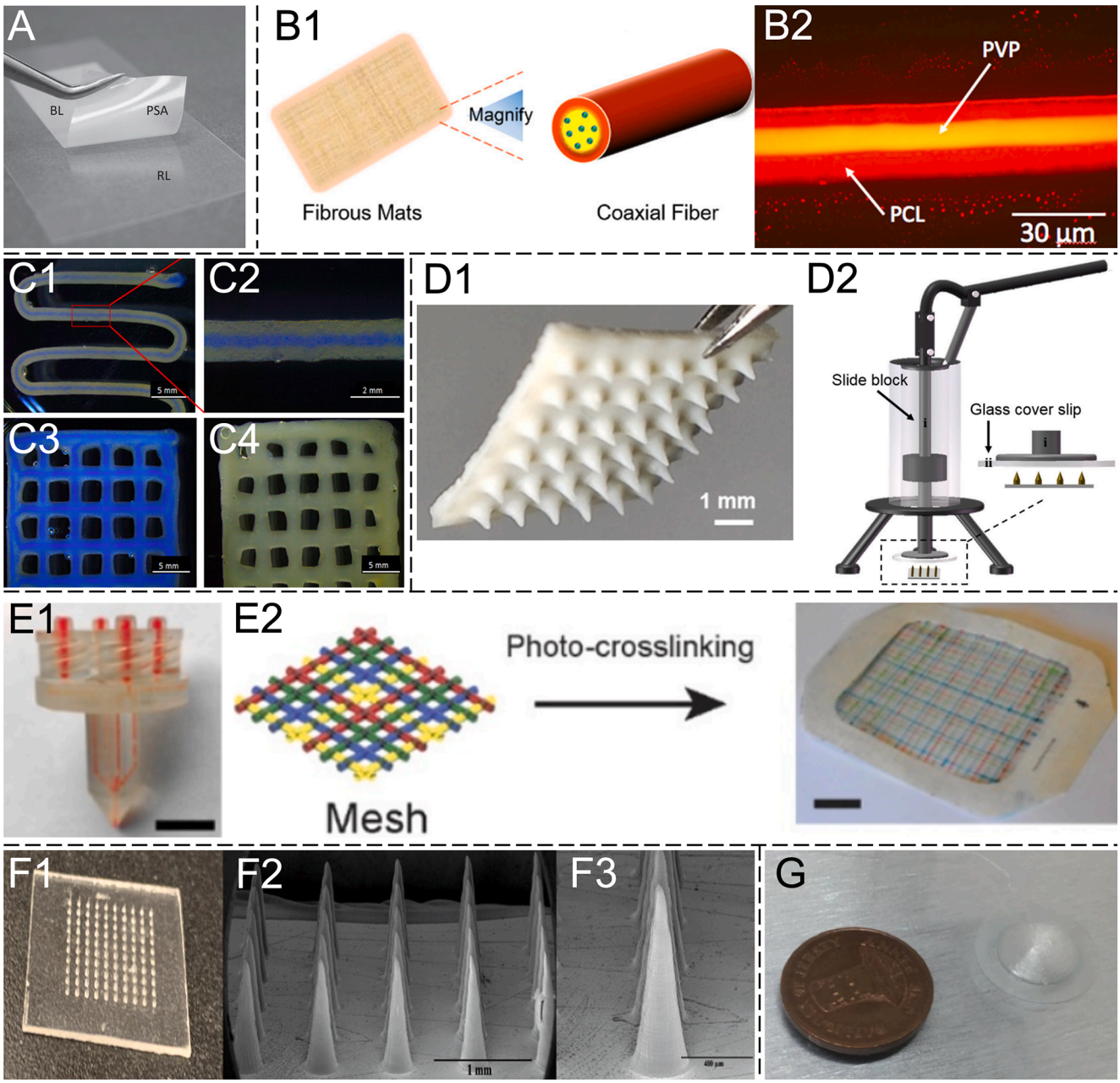

Fig. 7. Different 3D printed cutaneous dosage forms, A: ketoprofen-loaded patch with inter-fibrous pores, printed (trans)dermal patch during peeling off from the release liner (PSA: pressure-sensitive adhesive matrix; BL: backing layer; RL: release liner) (Reprinted from [431], with permission from Elsevier), B1-2: schematic of coaxial electrohydrodynamic (EHD) printed fibrous mats and individual fibers (B1), fluorescent micrographs of top view of coaxial fibers (B2) (Reprinted from [432], with permission from Elsevier), C1-4: 3D Core/shell (C/S) printing; C/S scaffold with the shell composed of alginate, methylcellulose and the core of 3% alginate, colored with blue ink for visibility, after 1 layer of 3D printing (C1); a magnified image of the C/S strand (C2); C/S scaffold of 4 layers after finishing the 3D printing (C3); a full strand (i.e., no core) 3D bioprinted scaffold of 4 layers (C4) (Reproduced with permission from [433], published by MDPI, 2021), D1-2: MEX (SE) printed microneedle patch containing insulin (D1), device for post stretching the needle tips to their final form (D2) (Reprinted from [434], with permission from Elsevier), E1-2: extrusion of the hydrogel ink using a microfluidic printhead (scale bar is 1 cm, E1), multifunctional wound dressings on a Tegaderm™ backing layer after UV irradiation (scale bar is 2.5 cm). Different filament colors (achieved by using food dyes) highlight the capability to print filaments loaded with distinct drugs (E2) (Reprinted/adapted with permission from [435], © 2021 American Chemical Society), F1-3: VPP-printed microneedle patch containing ibuprofen, patch after printing (F1), SEM image of patch showing individual microneedles (F2), magnified view of one row of the microneedles (F3) (Reprinted from [436], with permission from Elsevier), G: printed drug-eluting contact lens (Reprinted from [437], by permission of Oxford University Press on behalf of the Royal Pharmaceutical Society), all figures were modified.

network. The authors mixed their basic compounds with one of three antibiotic drugs to study the impact on the resulting patch. With the increasing molecular weight of the used drug, the diameter of the individual fibers increased as well, changing the optic of the printed mesh. However, this did not influence the in vitro dissolution behavior, leading to the same dissolution profiles for all three drugs, releasing them over 14 days. However, returning to the definition of a patch, adhesion to a backing layer or skin adherence was not tested by Altun et al., leaving questions regarding the successful application.

This topic was investigated by Musazzi et al., who took another approach with a dense MEX (SE) printed patch based on amMA-A and amMA-B and a high amount of plasticizers. The patch was printed

containing either ketoprofen or nicotine on a backing layer and sealed it with a release liner (Fig. 7A). The authors discussed that the viscosity of the extruded material was crucial for printing patches. High fluidity led to problems with the desired shape and size, while high viscosity led to matrices that were too stiff to adhere to the backing layer. With the developed composition, the authors were able to print patches with great adherence properties and influence the dissolution behavior with the ratio of the polymers.

Yao et al. investigated the control of drug release. Coaxial printing was used to create an antibiotic patch based on PCL and PVP (Fig. 7B1). The individual fibers of the patch consisted of an inner core containing the drug in a PVP matrix and an outer drug-free sheath of PCL (Fig. 7B2). The flow of the inner phase was changed to modify the speed of drug release. With a low flow, a coarser PCL sheath was obtained, leading to slower drug release, while a higher flow impeded the outer sheath, increasing the drug release. Considering this, tailored release profiles were obtained with 3D printing, contributing to a more personalized treatment [432].

4.2. Gel-based patches

The gel-based patches found for this category all included gelling agents that form a 3D network of hydrophilic polymers containing water or water-miscible liquid. They adhere to the skin due to their specific physical properties and are often used in wound care, burns, and other applications where maintaining a moist environment is beneficial. In most cases, the printed hydrogels were crosslinked by UV radiation or the addition of chemical components to form an applicable dosage form. For example, alginate-based hydrogels are crosslinked via contact with a calcium chloride solution, while photocurable hydrogels containing acrylamides are crosslinked through UV exposure. The respective gelling agents and further information on the included manuscripts are also listed in Table S24. The geometric structure of these 3D printed hydrogels typically were rectangular porous meshes or dense networks designed to optimize both the release of therapeutic agents and the physical characteristics of the hydrogels.

3D printed dermal hydrogels are emerging primarily as innovative wound dressings, particularly for managing diabetic wounds. These specialized dosage forms are designed to protect the wound, promote healing, and prevent infection, addressing the critical need for effective treatment in chronic wounds that result from the impaired healing process associated with diabetes. However, 3D printing offers significant advancements in wound dressing therapy by customizing dressings to fit a wound's specific shape and size. Furthermore, it allows for precise control over the release of therapeutic agents, which can be tailored to meet the particular needs of individual patients. Materials commonly used for 3D printed gel-based patches are alginates, chitosan, hyaluronic acid, and cellulose derivatives, which are non-toxic and ideally suited for cell contact. These materials can be loaded with antibiotics, growth factors, or other bioactive agents to improve wound healing outcomes.

3D printed wound dressings can be engineered to optimize mechanical strength and flexibility, which are critical factors in effective wound care. These dressings must provide sufficient mechanical support to protect the wound site while maintaining the flexibility needed to conform to various wound shapes and allow patient mobility. For instance, Glover et al. demonstrated that the mechanical properties of 3D printed wound dressings can be fine-tuned by adjusting printing parameters and the composition of biomaterials, ensuring that the dressings meet the specific needs of different wound types [443].

Antibiotic wound dressings are an advanced form of wound care that not only protect the wound site but also actively combat bacterial infections, a common complication in chronic and diabetic wounds. These dressings are designed to gradually release antibiotics over time, ensuring the wound environment remains free from harmful bacteria. However, since hydrogels often form a porous network, control of drug release seems challenging.

Akkineni et al. employed coaxial printing to produce hydrogels with a distinct separation between the core and shell. In their design, the core consisted of antibiotic drugs mixed with alginate, while the drug-free shell contained alginate mixed with methylcellulose and laponite. This method effectively reduced the burst release of drugs, thereby prolonging the antibiotic efficacy (Fig. 7C) [433]. A similar technique was used by Fratini et al., who printed thyme oil-liposome-containing hydrogels. The authors also utilized a coaxial printing approach to incorporate thyme oil into the core. The design was enhanced by adding free thyme oil to the shell to induce a burst release, providing an efficient drug level shortly after applying the wound dressing. This resulted in a biphasic drug-releasing hydrogel for wound healing [444].

Another significant advantage of 3D printing in hydrogel production was demonstrated by Alizadehgiashi et al., who developed a multichannel printhead capable of combining different drugs and materials within a single hydrogel (Fig. 7E1). This four-inlet printhead easily adapts the desired drug doses and release profiles, making it a versatile tool for creating customized wound dressings. In this study, multifunctional hydrogel meshes were printed with different drugs based on a chitosan-methacrylamide. With the 4-inlet printhead, alternating combinations of bovine serum albumin, silver nanoparticles, and vascular endothelial growth factor (VEGF) were printable (Fig. 7E2). To test the hydrogels in wound healing in vivo in mice, the dosage forms were printed on a Tegaderm™ film as a backing layer. Compared to a control group treated with only a Tegaderm™ film, faster wound healing was observed in the group treated with the printed hydrogel. Besides, good biocompatibility was shown by the authors [435].

Besides the potential application in wound healing, hydrogels intended for transdermal or topical drug delivery were investigated. Elshabrawy et al. developed a triple-layered system containing a 3D printed alginate/hyaluronate hydrogel combined with two layers of electrospun fibers for topical delivery of rosuvastatin [439]. Other approaches were made on topical drug delivery, for example, one from de Oliveira et al., which used a pectin-based hydrogel with incorporated clobetasol propionate. The drug was loaded onto mesoporous silica nanomaterials and added to the hydrogel mixture containing carboxymethylcellulose, pectin, and glycerin. Via MEX (SE) printing a dense gelled patch was printed releasing the drug over ten hours [445].

4.3. Microneedle patches (MNPs)

The 12 manuscripts identified in which the drug was 3D printed to produce MNPs can be further divided into studies in which a one-step MNP printing process was used where the drug was incorporated directly into the microneedles and two-step printed MNPs, where the needles were printed first and then coated with the drug using a second printing process (see Table S25).

MNPs offer an easy-to-apply system that penetrates the skin's different layers with small needles, enabling transdermal delivery of the drug. Due to the precision required in fabricating these structures, techniques such as VPP are commonly used, though other methods like MEX (SE) have also been employed. The individual tips of MNPs typically range from 500 to 1000 μm in height, with a peak diameter of less than 25 μm, making them small yet effective in breaching the skin barrier. The design of MNPs must ensure that the needles are sharp enough to penetrate the skin and mechanically stable enough to maintain their integrity during application, which often necessitates the use of rigid resins. However, due to the limited surface area and volume of MNPs, they are best suited for the delivery of highly potent drugs.

The first category of drug-printed MNPs discussed here involves coated microneedle patches. These MNPs are structurally stable and are designed to be removed after drug delivery. All studies in this category utilized VPP printing to create the finely detailed MNP structures [446–448]. However, a significant challenge with this method is that post-processing often involves washing the printed MNPs with organic solvents and post-curing, which can lead to the loss of the incorporated

drug (as previously discussed for parenteral dosage forms). To mitigate this, the drug is typically applied in a second step through coating techniques such as MJT.

For example, Economidou et al. prepared drug-free MNPs using VPP printing and subsequently coated them with insulin using MJT. This approach allowed for a highly defined and adaptable drug-loading process, with the amount of insulin applied to each microneedle precisely controlled by the number of coating cycles. In vitro permeation studies using Franz diffusion cells demonstrated rapid insulin release, with 90% of the drug released within 10 minutes. In vivo testing in mice further confirmed effective transdermal insulin delivery, with significant reductions in glucose levels observed, comparable to subcutaneous injections. However, scaling up this approach for human use and ensuring adequate drug loading remains a challenge [446].

The second category includes MNPs where the drug is incorporated directly into the microneedles during the printing process. These MNPs are designed to either dissolve after application or release the drug through pores as the needles penetrate the skin. Various 3D printing techniques and materials have been explored to achieve these designs.

Bagde et al. printed an ibuprofen containing dissolvable MNP via VPP printing (see Fig. 7F1-3), incorporating the drug into the resin. However, it is unclear, if parts of the drug were washed out while post-processing. To reduce the amount of resin used, the authors modified a standard VPP printer to a smaller build platform, decreasing the resin used to 10 mL. With this approach screening of different combinations of compounds was possible with a lower waste of material. After finding the best combination in terms of printing accuracy and mechanical stability, the resulting tips had a height of 750 μm with a diameter of 15 μm at the top. In vitro dissolution studies demonstrated drug release over 12 hours and the printed tips of the MNP had enough mechanical strength to pierce the skin of rats in an animal study [436].

A MEX (SE) approach to print MNPs was used by Wu et al. with an alginate/ hydroxyapatite hydrogel [434]. MEX (SE), usually not a method for high-precision printing, was used to print a more cylindric kind of tip, which was stretched to a sharp form afterward (Fig. 7D2). The resulting tips had a height of 643 μm with a diameter of approximately 25 μm at the top, showing nearly the same resolution as VPP-printed MNPs (Fig. 7D1). The MNPs were tested in an animal model, showing mechanical strength to pierce the skin. In this study the created notches disappeared after removing the MNPs in 45 minutes, showing that after application of the MNPs the skin regenerates quickly.

Li et al. used a special MEX (SE) printing technique called direct ink writing to print pointed MNPs [449]. The technique was used with different polymers like PEO, PVP, PLGA, or PCL and proved the ability to create multifunctional MNPs for various release profiles. Compared to other research, the authors reported the best resolution with a diameter of 5 μm at the top of the 700 μm high tips of a PLGA-MNP. Furthermore, the authors showed the possibility of creating bilayer tips to center the drug at the tip peak on a drug-free pedestal. Using PLGA as the carrier polymer, the drug was released for more than two weeks.

3D printing of MNPs offers a promising approach to creating highly precise, customizable, and minimally invasive transdermal drug delivery systems. The studies reviewed highlight the diverse techniques and materials that can be used to fabricate MNPs, each with its own set of advantages and challenges. Coated MNPs allow for precise drug loading and rapid release, while drug-incorporated MNPs offer the potential for sustained drug delivery. However, further research is needed to optimize these systems for clinical use, particularly in scaling up production and ensuring consistent drug release profiles.

5. Ophthalmics

Ophthalmic dosage forms, according to the Ph. Eu., include eye drops, eye lotions, semi-solid eye preparations, and ophthalmic inserts, which are often limited by their short duration of action, requiring frequent administration to maintain therapeutic levels. To address this issue, 3D printing has been explored as a means to create longer-acting dosage forms that could enhance patient compliance and improve treatment outcomes. In this review, various 3D printed ophthalmic dosage forms, including contact lenses, ophthalmic patches, inserts, and hydrogel scaffolds, were investigated (see also Table S26-27).

Recent research into 3D printed contact lenses has focused on developing lenses capable of delivering drugs directly to the eye, targeting indications such as local antibiotic or anti-inflammatory treatment, as well as the sustained release of beta blockers. Four manuscripts were identified that utilized liquid or semi-solid printing techniques to produce these lenses.

Two manuscripts used gelatine methacrylate mixed with hyaluronic acid or PEGDA in MEX (SE) printing to create clear, transparent, drug-eluting contact lenses [450,451]. Zidan et al. demonstrated that these lenses could release the incorporated drug dexamethasone for up to seven days, thus improving ophthalmic therapy. However, despite the promising duration of drug release, none of these studies addressed the potential impact of the lenses on visual clarity. Recognizing this gap, Mohamdeen et al. developed two different lenses using MEX (FE), one featuring an opening in the center to reduce visual impairment potentially (Fig. 7G). They incorporated timolol maleate for glaucoma treatment and showed drug release for three days [437].

While some progress has been made in developing 3D printed contact lenses, challenges such as biocompatibility and visual performance remain key areas for further research.

In addition to contact lenses, three manuscripts explored the development of ocular inserts, which are placed on the outside of the eye in the cul-de-sac. 3D printed ophthalmic inserts include different forms, such as patch-like inserts and punctual plugs.

Tagami et al. developed a hydrogel-based ophthalmic patch using hypromellose as the base material, incorporating the antibiotic levofloxacin. To stabilize the patch during freeze-drying, mannitol or xylitol were added. These rod-shaped patches demonstrated significant water absorption, increasing their mass by two to ten times within 15 minutes. Despite this rapid swelling, most of the drug was released within 60 minutes, providing only a marginal improvement over standard therapies in duration of action [452].

Xu et al. focused on the development of punctual plugs using VPP printing. Punctual plugs are small devices placed in the puncta or canaliculus to improve tear film stability in patients with dry eye disease. Xu et al. designed a plug with a diameter of 1 mm and a length of 1.9 mm, using PEGDA as the base material and adding macrogol 400 to accelerate drug release. By varying the drug and macrogol content, the authors were able to achieve different release profiles, ranging from 3 to 21 days [453].

In summary, 3D printing offers significant potential for developing advanced ophthalmic dosage forms, particularly in creating long-acting devices that could reduce the need for frequent administration. However, challenges such as ensuring biocompatibility, maintaining visual clarity, and optimizing drug release profiles must be addressed to fully achieve the potential benefits of these innovative dosage forms.

6. Vaginal dosage forms

Vaginal preparations traditionally include a variety of products such as semi-solid preparations, rings, inserts, ovules, suppositories, and tablets or capsules. These forms are widely used for localized treatment of infections, hormonal therapies, and contraception. In this review, ten manuscripts were identified that focus on 3D printed vaginal dosage forms, including vaginal rings, resorbable meshes, capsule-like scaffolds, and ovules, as also shown in Table S28.

The primary aim of the identified studies was to develop dosage forms that can provide prolonged therapies, thereby improving patient compliance and treatment efficacy. Many of the printed dosage forms were made from flexible materials to facilitate easier application and comfort during use.

Among the identified manuscripts, two studies explored the use of MEX (FE) to print intravaginal rings (IVR). These IVRs were designed based on marketed products but with the added benefit of customized drug release profiles. For example, Tiboni et al. developed an IVR containing the antifungal drug clotrimazole, which demonstrated a sustained release over several days when tested in a vaginal fluid simulant (Fig. 8A). This prolonged release effectively reduced the number of colony-forming units of Candida albicans in vitro, indicating potential for simplified antifungal therapy [454]. In contrast, de Carvalho's study produced IVRs capable of releasing drugs over several weeks, showcasing the versatility of 3D printing in extending the duration of drug delivery [455].

In addition to IVRs, three manuscripts focused on the development of vaginal meshes, which were designed to support inner tissues and strengthen the pelvic floor [460–462]. These elastic meshes, printed using MEX (FE) or MEX (SCE), were made from materials such as thermoplastic polyurethane (TPU) or PCL. Depending on the material used, the meshes were either biodegradable or non-biodegradable, providing sustained mechanical strength while releasing incorporated drugs like levofloxacin or estradiol over a period ranging from a few days to several weeks. However, it is important to note that none of these meshes were tested in vivo, meaning their clinical effectiveness remains theoretical at this stage.

Five manuscripts addressed the creation of other vaginal dosage forms, including discs, films, capsule-like scaffolds, and ovules, designed for localized drug delivery of immunosuppressants or antibiotics [456,463–466]. These forms were primarily produced using MEX (SE), but MEX (FE) was also employed. The materials used ranged from flexible silicones to alginate hydrogels, enabling the production of dosage forms with a prolonged drug release ranging from a few hours to a full day. This represents a significant improvement over traditional vaginal dosage forms, which often have shorter durations of action. For instance, Teworte et al. demonstrated that alginate-based 3D printed ovules (Fig. 8B) released the drug pirfenidone over a period of more than 8 hours. In ex vivo studies using porcine vaginal mucosa, these ovules exhibited better mucoadhesion compared to traditional dosage forms made of macrogol or hard fat. Over 24 hours, the printed ovules softened and formed an adhesive hydrogel, prolonging the contact time after application and leading to a potential improvement in vaginal therapy [456].

7. Intravesical dosage forms

Intravesical dosage forms are specialized pharmaceutical preparations designed for direct administration into the bladder, primarily used for treating bladder conditions such as interstitial cystitis, bladder cancer, and urinary tract infections. Traditional treatments typically involve either systemic drug administration or transurethral delivery via a catheter. Systemic treatments carry a higher risk of adverse effects, while transurethral applications are limited by short durations of action due to the frequent emptying of the bladder. Moreover, the use of catheters can lead to urinary tract infections, which presents additional challenges. Recent advances in 3D printing may offer promising new opportunities for enhancing intravesical drug delivery (see also Table S29). For instance, Archana et al. developed a 3D printed flexible catheter designed to mitigate the risk of infections. By incorporating secnidazole, the catheter demonstrated prevention of biofilm colonization and achieved drug release over two hours, potentially aligning with typical application intervals. However, this study did not test the application of fluids passing through the catheter, leaving some practical aspects unaddressed [467].

In addition to catheters, four research papers have explored 3D printed intravesical devices. The primary advantage of these 3D printed dosage forms lies in their ability to incorporate shape memory properties. This feature allows the creation of easy-to-apply dosage forms that can be retained in the bladder for extended periods, offering the potential for prolonged therapeutic action. Melocchi et al. utilized water-soluble PVA to create variously shaped specimens with shape memory capabilities (Fig. 8C). In vitro experiments demonstrated that these specimens could achieve shape memory within 120 minutes. However, while the dosage form can remain in the bladder longer, the drug release of the model drug caffeine was completed within the same 120 minutes, meaning no additional benefit was derived from the prolonged residence. Despite this, the study highlights the potential of shape memory to significantly advance intravesical drug delivery [457].

Further progress in this area was made by Rahman-Yildir et al., who developed a semi-solid foldable mesh containing three different drugs that are expected to unfold in the bladder and therefore remain there for longer periods of time (Fig. 8E). Using MEX (SE), they formulated a mesh with either nonbiodegradable ethylene-vinyl acetate (EVA) or biodegradable PCL. The drug release profiles varied depending on the properties of the incorporated drugs, ranging from a few days to several weeks [459]. The use of nonbiodegradable polymers raises concerns about the need for the removal of the dosage form after drug release is complete, highlighting an important consideration for future research and development in this area.

Overall, 3D printing of intravesical dosage forms presents a significant opportunity to improve the treatment of bladder diseases. By leveraging shape memory and customizable drug release profiles, 3D printed devices could provide sustained therapeutic effects, reduce the frequency of administration, and enhance patient outcomes. However, further research is needed to optimize these technologies, particularly in ensuring effective drug release over extended periods and addressing the practical aspects of dosage form retention in and removal from the bladder.

8. Rectal dosage forms

Rectal preparations, according to the Ph. Eur., encompass a range of liquid, semi-solid, and solid formulations, commonly used for both local and systemic drug delivery [468]. Among these, suppositories are the most studied in the context of pharmaceutical 3D printing. These dosage forms are particularly valuable for patients who cannot take oral medications or require localized treatment in the rectal area. Traditionally, suppositories are manufactured using a process where a solid base, often a hard fat, is melted, mixed with the drug, and then poured into molds to solidify. This conventional method is straightforward but has limitations in customization and shape flexibility.

Similar thermally based processes are employed in 3D printing, allowing for more precise control over the shape and dosage of the final product without the need for different molds. However, the potential benefits of 3D printing in this area are still being explored, with some challenges yet to be overcome. A total of ten manuscripts were identified which are listed in Table S30. The materials used in 3D printing of rectal dosage forms can be categorized into two main groups: fats and macrogols used in MEX (SE) printing [458,469–474] and more rigid polymers like PVA used in MEX (FE) [475–477].

Tagami et al. printed a water-soluble shell from PVA and filled it with a liquid containing ibuprofen as a model drug [477]. The shell was printed, sealed with glyceryl stearate, and capped with a 3D printed lid. Even if this is not the definition of drug printing, it's mentionable here because it showed a problem in the 3D printing of suppositories. During application, the suppository has to withstand the pressure from the sphincter. Tagami et al. showed that hollow-printed suppositories need a reinforced shell to withstand the same force as traditionally produced suppositories. A suppository in which the drug was incorporated within the shell was published by Wei et al. [475]. Again, a hollow cylinder based on PVA was printed with the incorporated drug mesalazine for local treatment of ulcerative colitis. The authors of this publication also faced problems with mechanical stability. To prevent the suppository from being crushed during administration, a 3D printed spring was inserted into the suppository. Additionally, two forms of suppositories

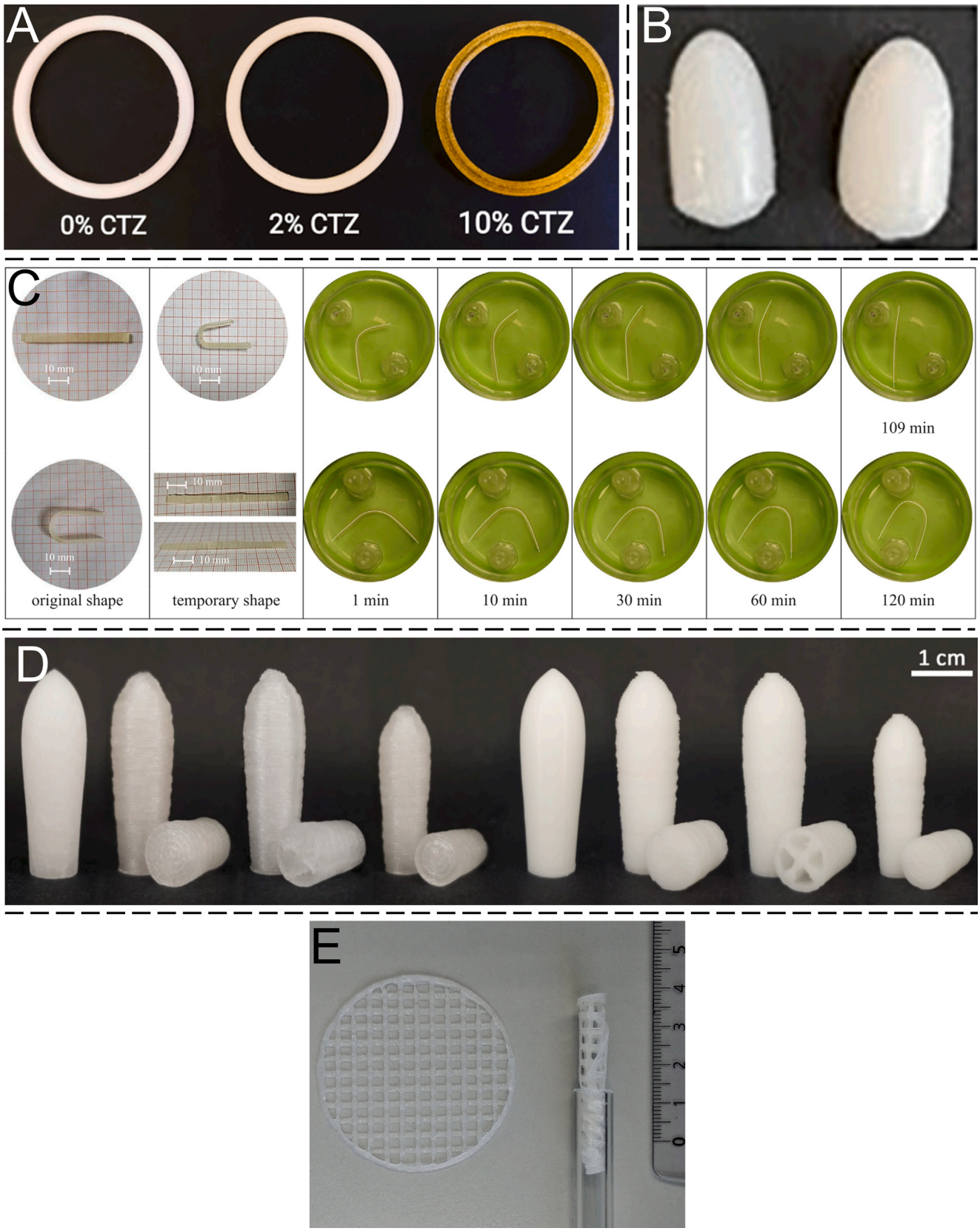

Fig. 8. 3D printed vaginal, intravesical, and rectal dosage forms, A: 3D printed intravaginal rings loaded with different amounts of clotrimazole (CTZ) (Reprinted from [454], with permission from Elsevier), B: alginate-based 3D printed vaginal ovule (Reprinted from [456], © 2023 The Author(s), CC BY 4.0, https://creativecommons.org/licenses/by/4.0/), C: photographs acquired during shape recovery experiments (room temperature) of PVA/glycerol specimens having original I- and U-shape obtained by MEX (FE) (Reprinted from [457], with permission from Elsevier), D: SE printed suppositories in different sizes and infills (Reproduced with permission from [458], published by MDPI, 2022), E: printed net-shaped inserts unfolded (left) and coiled up (right) for insertion via catheter (Reprinted from [459], with permission from Elsevier), all figures were modified.

were tested to improve the retention time in the rectum in an animal model. The authors found that a curved shape improved retention time from under 30 minutes to about 4.5 hours.

Regarding the MEX (SE) printed suppositories, most of the recently published work deals with the composition of macrogols and fatty components. Compared to the MEX (FE) printed suppositories, the MEX (SE) printed ones had a filled design, so there was no need for additional mechanical adaption. Some articles investigated the printing of suppositories based on lauroyl polyoxyl-32 glyceride and coconut oil using either one or two locally effective drugs [469–471,474]. Seoane et al. also investigated the influence of the positioning of the suppositories by printing them horizontally or vertically [474]. Vertical positioning was more advantageous for the surface quality. According to the authors, the reason for this was the lack of stability due to the round shape of the tip. In the horizontal approach, there was no supporting function of the lower layer, resulting in shape deficits. Some research has been done on the size and density of MEX (SE) printed suppositories. Domsta et al. printed suppositories based on either hard fat or macrogol. The size or the infill density of the printed dosage forms was changed, showing the benefit of 3D printing in adapting drug content and dissolution behavior of the suppositories (Fig. 8D). As described for other dosage forms, the drug release rate increased with lower infill [458].

Munoz-Perez et al. made another approach differing from the other manuscripts [473]. The authors printed a hydrogel-based suppository made of a combination of alginate and laponite. Different sizes of suppositories were successfully printed and tested in an animal model. In contrast to other printed and marketed suppositories, the hydrogel was not dissolving or melting at the application site, resulting in a non-degraded, form-stable suppository after application.

In recent years, significant progress has been made in developing 3D printed suppositories, with researchers exploring various techniques, materials, and drugs. Some potential advantages of 3D printing for dosage individualization and shape adaptation have been demonstrated. However, in the author's view, 3D printing has not yet demonstrated a substantial benefit over traditional molded suppositories.

9. Conclusion and outlook

In this review, published pubmed-listed manuscripts on the topic of 3D printing of dosage forms from 2019 to March 2024 were systematically evaluated. Of the more than 500 manuscripts identified, a large portion dealt with peroral dosage forms, but also solid dosage forms for almost any other site of administration, including parenteral, cutaneous, vaginal, rectal, intravesical, ophthalmic, and dental dosage forms, were identified. The range of printing techniques used also greatly varied. By far, most reports were on extrusion-based techniques, even though for some types of dosage forms, certain printing techniques seem to be favorable, e.g., jetting techniques to produce orodispersible dosage forms. The comparably high prevalence of the MEX techniques may also be connected to the relatively wide availability of extrusion-based printers at reasonable prices, making them more accessible to many research groups. From the author's point of view, techniques that can use approved pharmaceutical excipients are most promising regarding the potential to bring a 3D printed product to market since the approval process for new excipients poses additional challenges. Furthermore, substantial reasons to choose a specific printing technique include the properties of the processable excipients and their influence on drug release, the spatial resolution that is required, and the stability of the drug to withstand the stresses related to the processing parameters (e.g., temperature or moisture).

The chances that 3D printing holds for dosage form production have been discussed many times, as well as the challenges. The main benefit is the extraordinary flexibility in spatial arrangement with the potential to influence the dose, the drug release, the stability (in case of several drugs), the density, the shape, the looks, and many more parameters that might impact bioavailability and adherence and the therapeutic outcome in general. One of the main questions remaining concerning manufacturability compared to conventional dosage forms seems to be whether 3D printed medicinal products can be manufactured at a reasonable time and price. Some authors have addressed this topic, but in most publications, there are no reports of printing times. Other challenges, such as the availability of GMP-grade printers and files for the printing design, should be manageable, and the great number of publications show that it is technically feasible to 3D print dosage forms. If personalization is the goal, another challenge is how to deal with these dosage forms from a regulatory standpoint. If batches of only a few dosage forms or maybe even only single dosage forms in case of implants are produced for a specific patient, the typical approval and batch release procedures, e.g., regarding drug release specifications, will not be a feasible approach. First reports on predicting drug release from 3D printed dosage forms based on the design have been published which might be an option to solve such problems.

In spite of the large amount of literature published on the topic, there is only one marketed product to date, and little data on studies in humans has been reported. This is somewhat disappointing 9 years after the approval of Spritam® and considering how much research effort is put into advancing 3D printing of dosage forms. However, as manufacturers are not likely to publish data early and there is a growing number of medical devices that are 3D printed, it seems only a matter of time before more medicinal products are marketed. Several pharmaceutical companies are actively researching the 3D printing of dosage forms and promising approaches are in the pipeline. As already mentioned in the introduction, Triastek, for example, is currently developing several 3D printed products, one of which is intended for colon targeting. Also, it must be expected that as more knowledge is gained about the benefits of individualized medicine in the general population the demand to produce such products will also increase. The idea of producing personalized dosage forms in hospitals and pharmacies in-house and on demand also gives reason to hope for 3D printed dosage forms to be available to patients. It may be a few years before another 3D printed dosage form is approved, but the research efforts of recent years will hopefully soon bear fruit. Special patient groups such as children with medical needs that are currently not met by standardized doses, are expected to profit greatly if 3D printing of dosage forms becomes a standard of care in the future.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.addr.2024.115504.

Data availability

Data will be made available on request.

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