A graphical review on the escalation of fused deposition modeling (FDM) 3D printing in the pharmaceutical field

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Keywords:	Printing (3D), Solid dosage form(s), Controlled release, Polymeric drug delivery system(s), Drug delivery system(s)

A graphical review on the escalation of fused deposition modeling (FDM) 3D printing in the pharmaceutical field

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Keywords: 3D Printing; Solid dosage form; Controlled release; Drug delivery system; Polymeric drug delivery system; 4D printing, Fused deposition modeling.

Abstract

Fused deposition modeling (FDM) 3D printing is currently one of the hot topics in pharmaceutics and has shown a 2000% increase in the number of research articles published in the last 5 years. In the prospect of a new era of FDM focused on the industrial development of this technique applied to the fabrication of personalized medicines, a conceptual map to move through the evolution of the design of the printed dosage forms/drug delivery systems was conceived and mainly discussed by means of graphical tools.

1. Introduction

Starting from 2014, fused deposition modeling (FDM) 3D printing has become a hot topic in the pharmaceutical field. This technique makes use of a filament, generally obtained starting from a thermoplastic polymer by hot melt extrusion (HME), as starting material. The filament is driven, through a geared system, into the heated block of the printer for softening or melting. In this way, subsequent layers of material could be deposited, through a nozzle, onto the 3D printer build plate. The overlaid layers fuse and, following cooling, bond to each other, thus allowing one to obtain the final 3D object. As FDM involves the deposition of subsequent layers obtained by the extrusion of molten/softened formulations, it is characterized by strong similarities with other hot-processing techniques that have already found application in the pharmaceutical field, such as HME.

FDM moved from just appearing in the experimental section of published papers to become the true key player of research. With respect to the former application, it was tested as a rapid and economical method to produce plastic prototypes of different shapes for casting molds having specular cavities[1-5]. These were then used for the fabrication of drug-containing systems following assembly and welding of different parts previously manufactured *via* other techniques and placed within the mold cavity. On the other hand, the real first attempts to demonstrate feasibility of FDM for direct fabrication of printed dosage forms / drug delivery systems (DDSs) were carried out in parallel by several research groups[6-11]. Following these essential inputs, the overall research activity of subsequent years exhibited the full potential of this technology and its main advantages. However, many challenges have yet to be addressed for enabling the actual printing of personalized medicines safe for human administration, thus launching a new FDM era.

Aware that any advancement requires a deep knowledge of the relevant background, we used the graphical tool and a language made of images to highlight the evolution of FDM in the pharmaceutical field and the variety of the applications proposed so far in the scientific literature, in terms of design and route of administration. An attempt was made to consider all journals, not only those belonging to the pharmaceutical area, and to include all the research groups currently working on FDM. A schematic overview of the critical parameters impacting the quality of the FDM process, and therefore of the final product (*i.e.* starting materials, hardware and software characteristics, and manufacturing environment), are collected in Figure 1. Research and review articles specifically focused on FDM, published from 2014 to the present date, were employed for the construction of a graphical discussion, *i.e.* to visually display and quantify:

i) the key-factors associated with the developments of the technique in the field of pharmaceutical research (Figure 2),

ii) the times and sources chosen for dissemination (Figure 3),

iii) the different applications taken into consideration over time (*e.g.* administration routes proposed) (Figure 4),

iv) the complexity of the systems proposed, especially in terms of design (Figure 5).

In this way, we aimed to provide the readers with a concept map of the DDSs manufactured by FDM since the beginning of its application in the pharmaceutical field.

Images are supposed to reflect meanings more directly than words and to be easier to recall. As they can also generate a verbal label (while words are not likely to generate image labels), a few highlights are summarized for each figure in the form of bullet points[12-17]. Moreover, for each category identified in the concept map, a choice was made to develop schematic representations of the main DDSs proposed, highlighting similarities and differences relevant to their geometry / design (Figure 6-16). By way of example, in a few cases, details were also reported (indicated with the magnifying glass symbol) providing insight into the internal structure, content or working mechanism of the systems. Formulation issues, such as the choice of technological and performance aids, and the addition of active ingredients, either during or after the fabrication process (*e.g.* by soaking), were necessarily omitted as they cannot be easily described by images. Indeed, this topic has already been covered in depth elsewhere[18-35]. The selected approach would make the readers take advantage of any possible picture superiority effect. In this respect, showing the design of the systems proposed would fulfill different objectives, such as making the audience curious about specific articles, easily recognizing possible similarities in the research work, enabling identification of groups that are facing the same challenges, and laying down the bases for new applications of this technique.

2. Graphical discussion

Figure 1

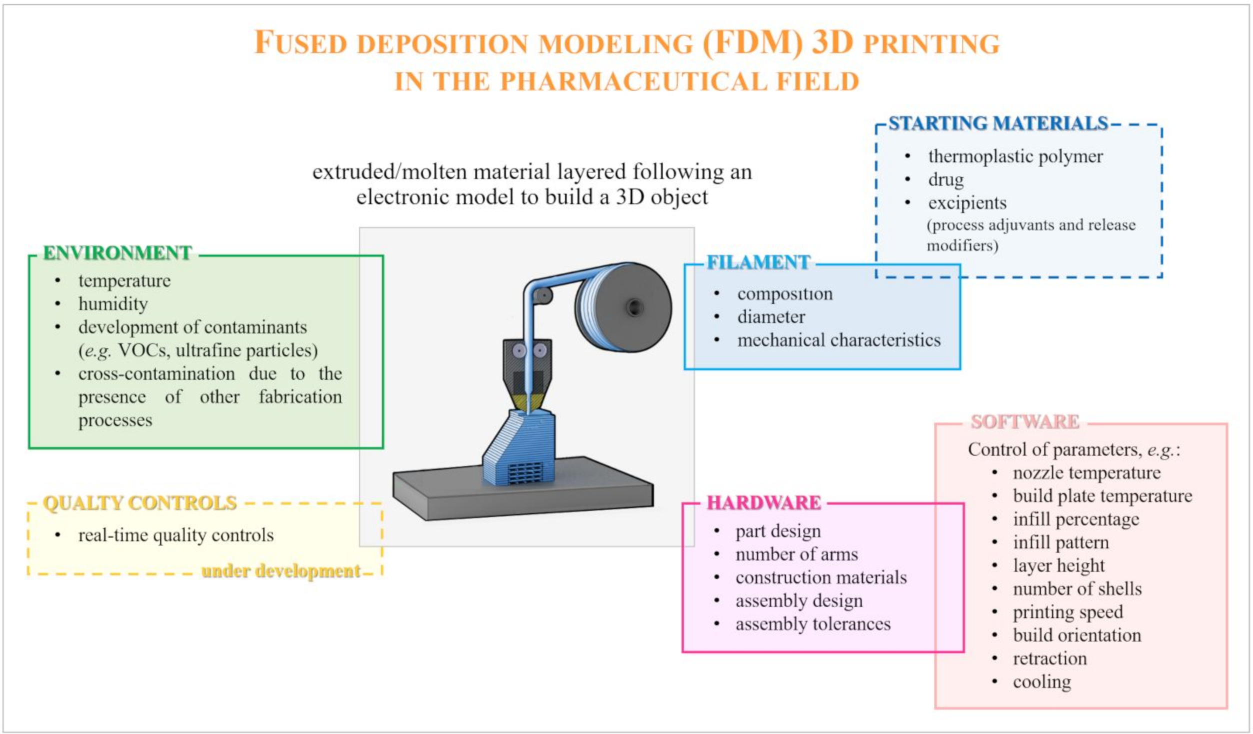

Figure 2

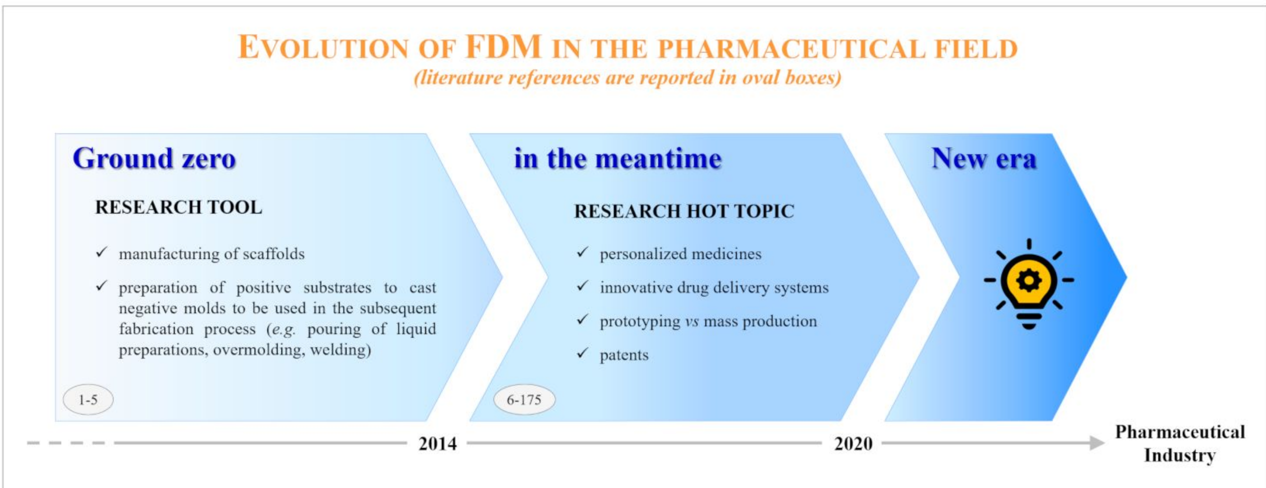

Figure 3

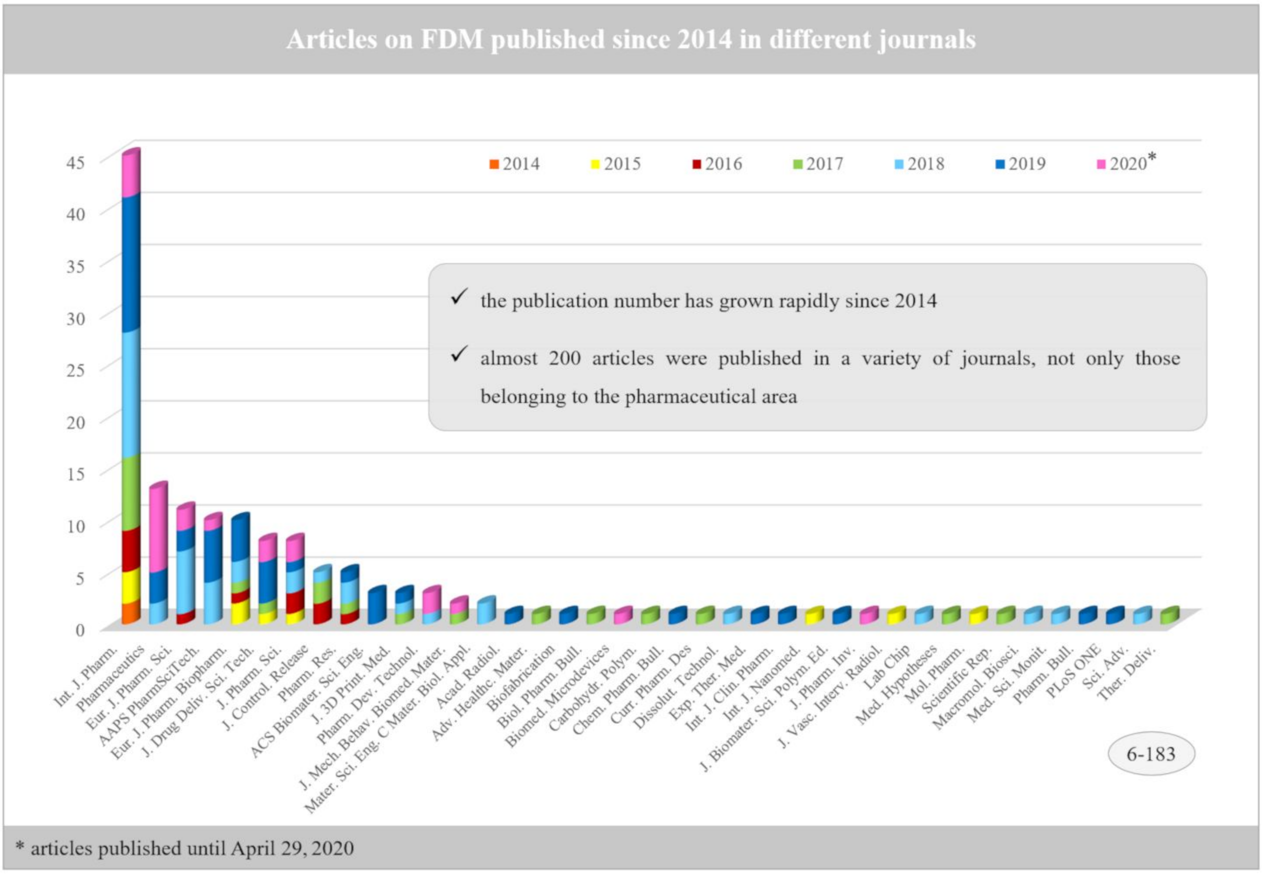
Articles on FDM published since 2014 in different journals
2014
2015
2016
2017
2018
2019
2020*
the publication number has grown rapidly since 2014
almost 200 articles were published in a variety of journals, not only those belonging to the pharmaceutical area
6-183
* articles published until April 29, 2020

Figure 4

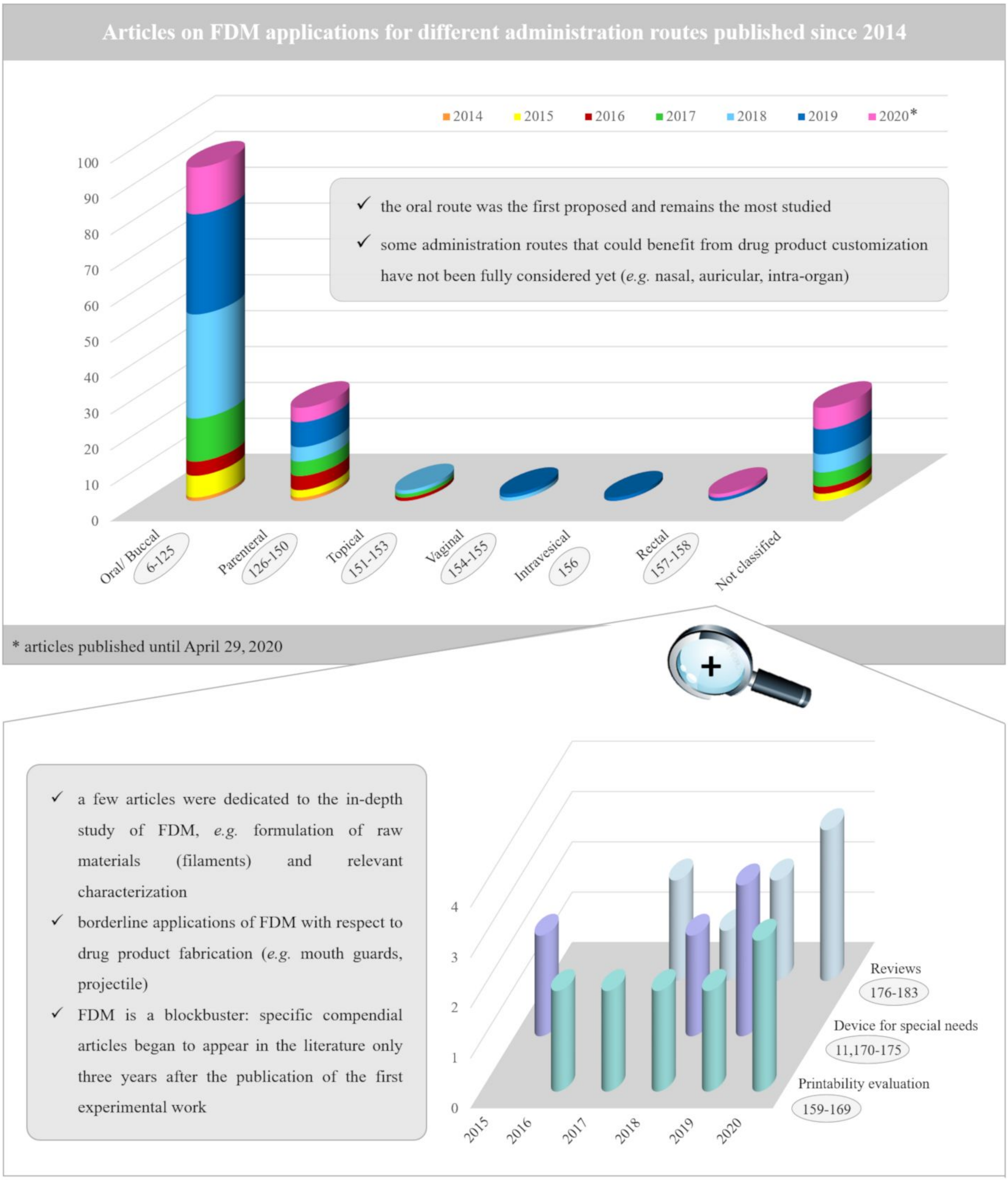
Articles on FDM applications for different administration routes published since 2014
2014
2015
2016
2017
2018
2019
2020*
100
90
80
70
60
50
40
30
20
10
0
the oral route was the first proposed and remains the most studied
some administration routes that could benefit from drug product customization have not been fully considered yet (e.g. nasal, auricular, intra-organ)
Oral/ Buccal
6-125
Parenteral
126-150
Topical
151-153
Vaginal
154-155
Intravesical
156
Rectal
157-158
Not classified
* articles published until April 29, 2020
a few articles were dedicated to the in-depth study of FDM, e.g. formulation of raw materials (filaments) and relevant characterization
borderline applications of FDM with respect to drug product fabrication (e.g. mouth guards, projectile)
FDM is a blockbuster: specific compendial articles began to appear in the literature only three years after the publication of the first experimental work
4
3
2
1
0
2015
2016
2017
2018
2019
2020
Reviews
176-183
Device for special needs
11,170-175
Printability evaluation
159-169

Figure 5

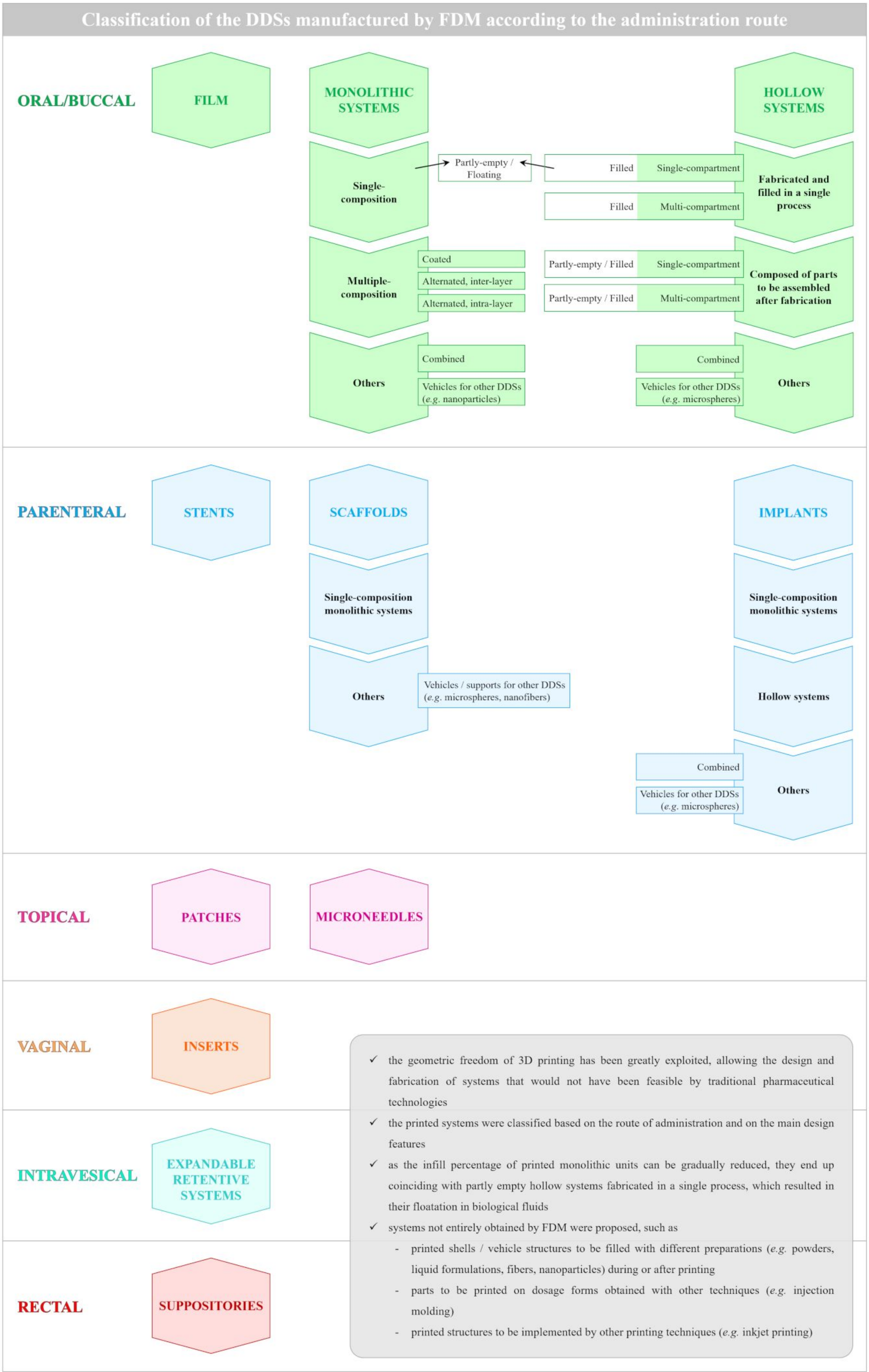
Classification of the DDSs manufactured by FDM according to the administration route
ORAL/BUCCAL
FILM
MONOLITHIC SYSTEMS
HOLLOW SYSTEMS
Single-composition
Partly-empty / Floating
Filled
Single-compartment
Filled
Multi-compartment
Fabricated and filled in a single process
Multiple-composition
Coated
Alternated, inter-layer
Alternated, intra-layer
Partly-empty / Filled
Single-compartment
Partly-empty / Filled
Multi-compartment
Composed of parts to be assembled after fabrication
Others
Combined
Vehicles for other DDSs (e.g. nanoparticles)
Combined
Vehicles for other DDSs (e.g. microspheres)
Others
PARENTERAL
STENTS
SCAFFOLDS
IMPLANTS
Single-composition monolithic systems
Single-composition monolithic systems
Others
Vehicles / supports for other DDSs (e.g. microspheres, nanofibers)
Hollow systems
Combined
Vehicles for other DDSs (e.g. microspheres)
Others
TOPICAL
PATCHES
MICRONEEDLES
VAGINAL
INSERTS
INTRAVESICAL
EXPANDABLE RETENTIVE SYSTEMS
RECTAL
SUPPOSITORIES
✓ the geometric freedom of 3D printing has been greatly exploited, allowing the design and fabrication of systems that would not have been feasible by traditional pharmaceutical technologies
✓ the printed systems were classified based on the route of administration and on the main design features
✓ as the infill percentage of printed monolithic units can be gradually reduced, they end up coinciding with partly empty hollow systems fabricated in a single process, which resulted in their floatation in biological fluids
✓ systems not entirely obtained by FDM were proposed, such as
- printed shells / vehicle structures to be filled with different preparations (e.g. powders, liquid formulations, fibers, nanoparticles) during or after printing
- parts to be printed on dosage forms obtained with other techniques (e.g. injection molding)
- printed structures to be implemented by other printing techniques (e.g. inkjet printing)

Figure 6

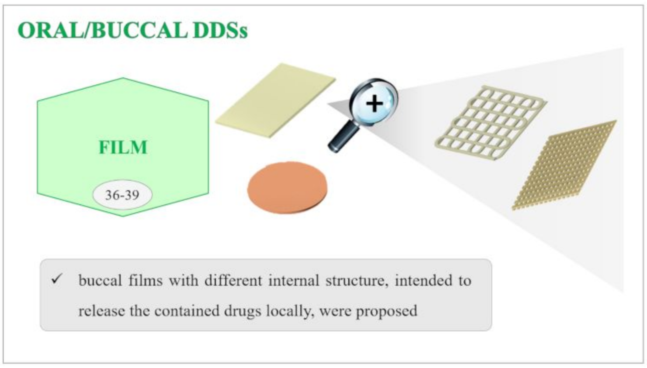
ORAL/BUCCAL DDSs
FILM
36-39
buccal films with different internal structure, intended to release the contained drugs locally, were proposed

Figure 7


ORAL/BUCCAL DDSs
MONOLITHIC SYSTEMS
✓ the first printed systems were monolithic units; published articles cover different compositions, shapes, internal structures (e.g. infill percentage), and performance (e.g. immediate, prolonged release)
✓ by using improved (e.g. two-arms) / modified printing equipment coated systems and units with alternated composition were obtained, leading to the achievement of different and more complex release performance (e.g. delayed, pulsatile release and combined kinetics)
✓ a mass-customization approach for the fabrication of combined systems was proposed, involving the printing of additional personalized layers over standard units obtained by mass-manufacturing techniques
✓ a solution for mix-up issues associated with the production of personalized drug products was proposed, involving the application - via inkjet printing - of unique QR codes on FDM units to make their traceability easier
✓ monolithic complex units were proposed as vehicles for other DDSs (e.g. nanoparticles)
✓ the feasibility of 4D printing - entailing shape modification of the 3D printed units over time, the latter being the 4th dimension - was demonstrated and employed for the development of gastroretentive DDSs
Single-composition
6,9,40-86
Partly-empty / Floating
4D printing
shape enabling oral administration
shape enabling gastric retention
shape recovery
Multiple-composition
87-99
Coated
Alternated, inter-layer
Alternated, intra-layer
Others
100-104
Combined
Vehicles for other DDSs (e.g. nanoparticles)

Figure 8

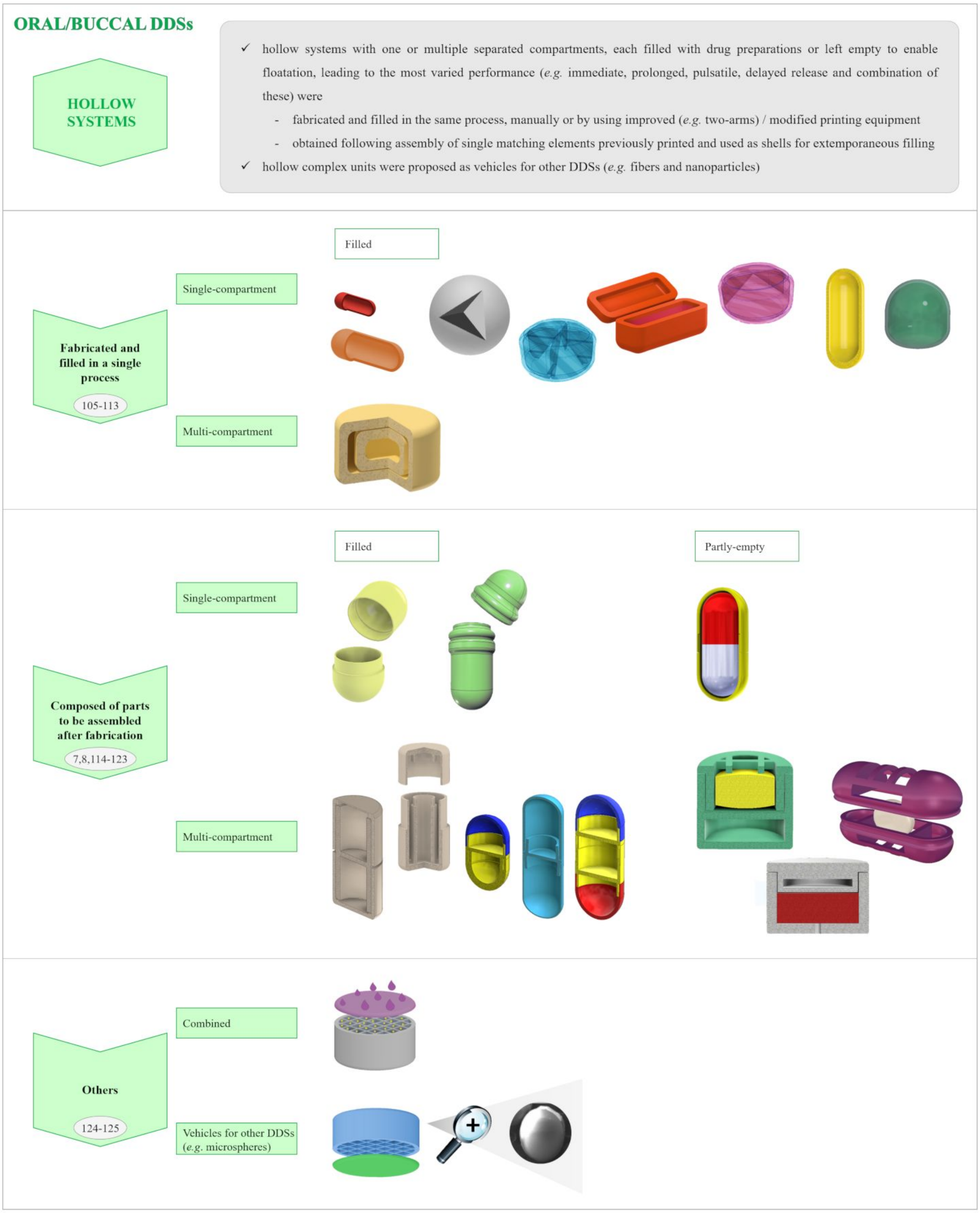
ORAL/BUCCAL DDSs
HOLLOW SYSTEMS
✓ hollow systems with one or multiple separated compartments, each filled with drug preparations or left empty to enable floatation, leading to the most varied performance (e.g. immediate, prolonged, pulsatile, delayed release and combination of these) were
- fabricated and filled in the same process, manually or by using improved (e.g. two-arms) / modified printing equipment
- obtained following assembly of single matching elements previously printed and used as shells for extemporaneous filling
✓ hollow complex units were proposed as vehicles for other DDSs (e.g. fibers and nanoparticles)
Fabricated and filled in a single process
105-113
Filled
Single-compartment
Multi-compartment
Composed of parts to be assembled after fabrication
7,8,114-123
Filled
Partly-empty
Single-compartment
Multi-compartment
Others
124-125
Combined
Vehicles for other DDSs (e.g. microspheres)

Figure 9

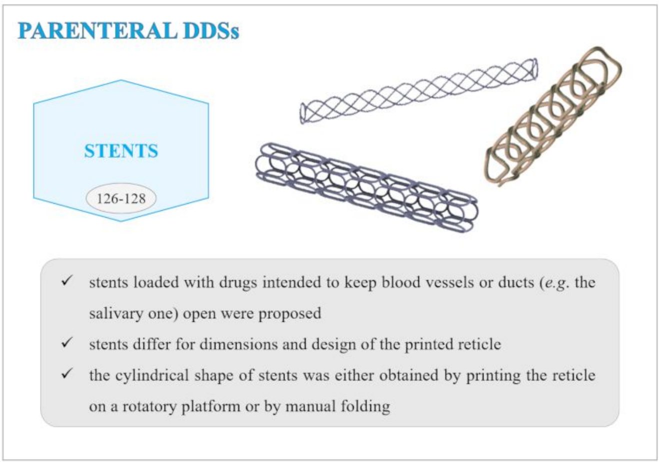

Figure 10

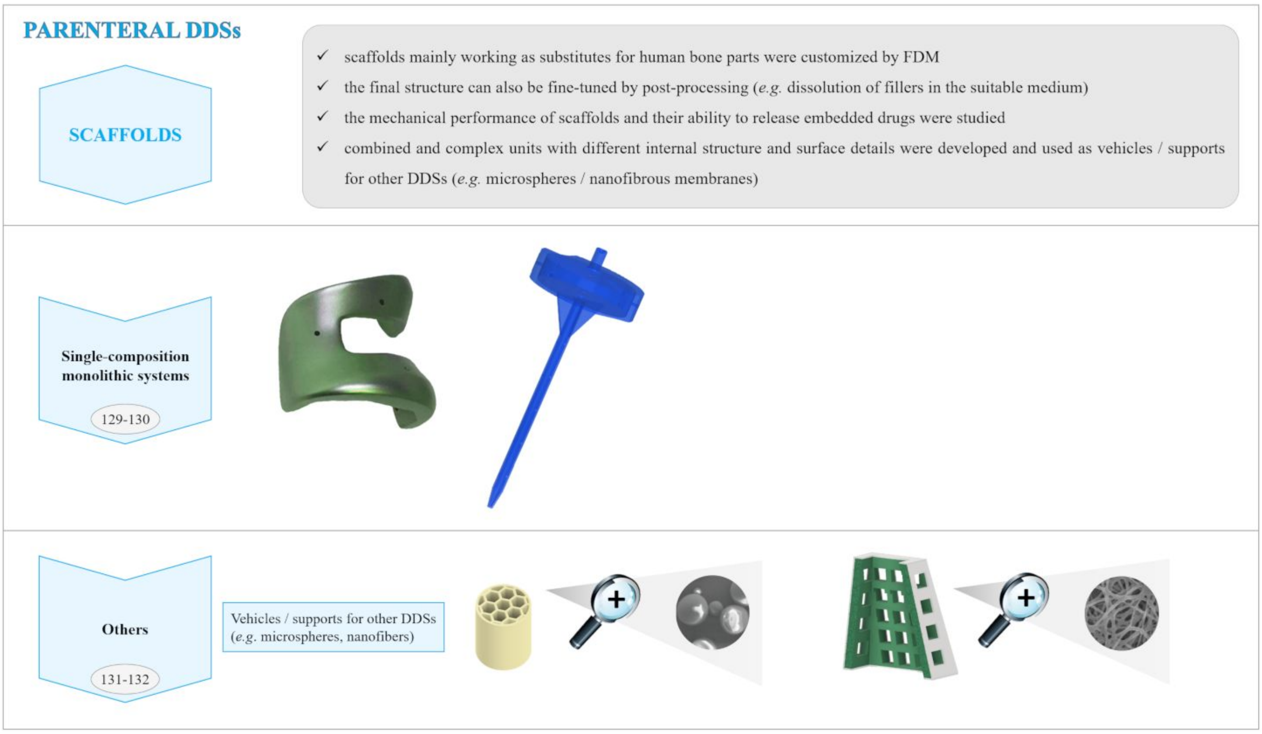

Figure 11

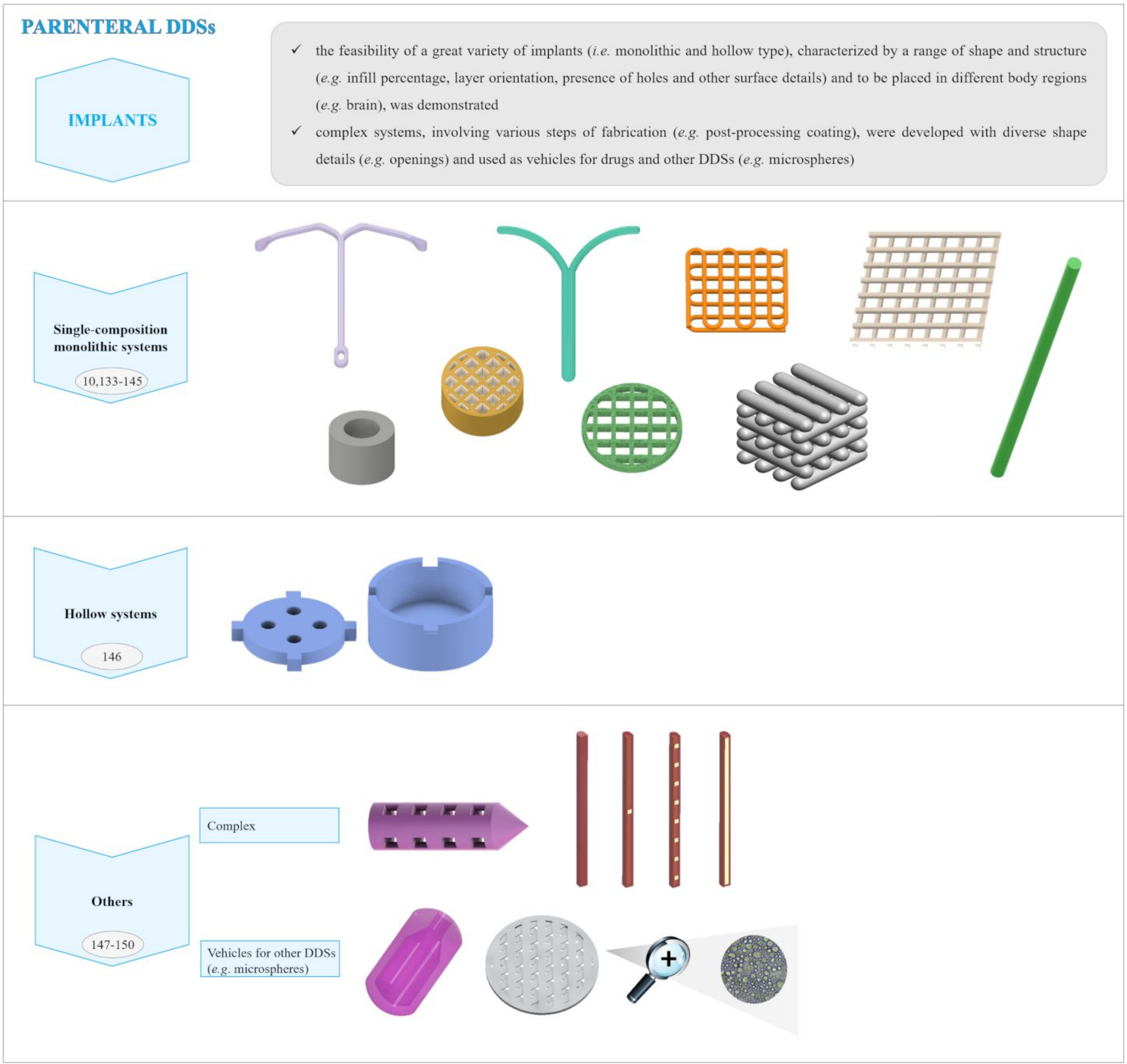
PARENTERAL DDSs
IMPLANTS
✓ the feasibility of a great variety of implants (i.e. monolithic and hollow type), characterized by a range of shape and structure (e.g. infill percentage, layer orientation, presence of holes and other surface details) and to be placed in different body regions (e.g. brain), was demonstrated
✓ complex systems, involving various steps of fabrication (e.g. post-processing coating), were developed with diverse shape details (e.g. openings) and used as vehicles for drugs and other DDSs (e.g. microspheres)
Single-composition monolithic systems
10,133-145
Hollow systems
146
Others
147-150
Complex
Vehicles for other DDSs (e.g. microspheres)

Figure 12

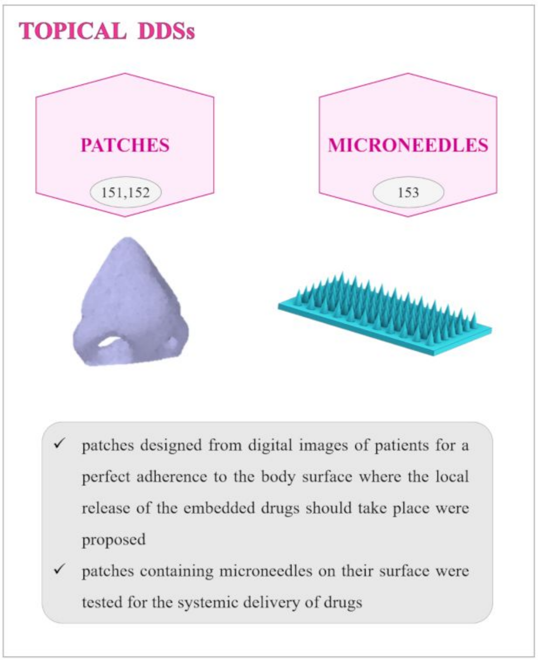

Figure 13

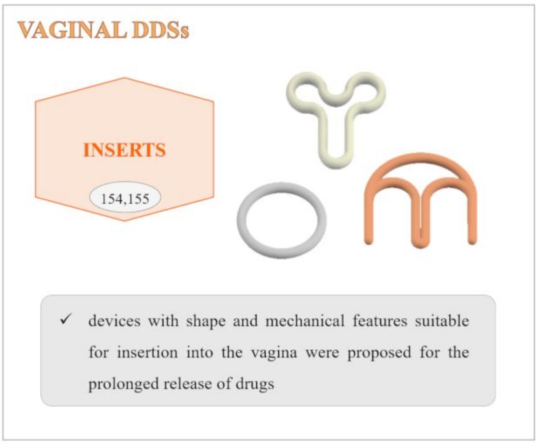

Figure 14

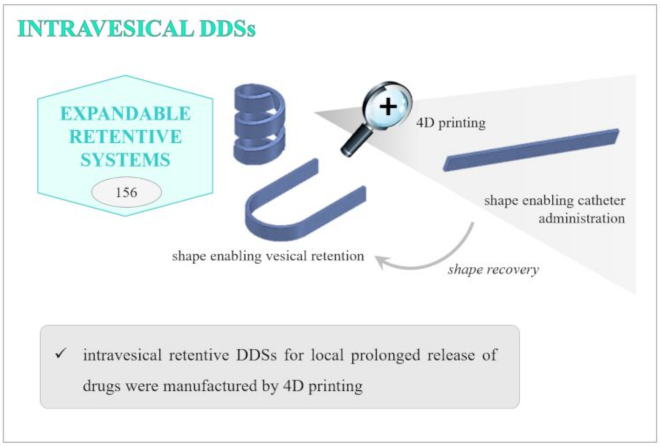

Figure 15

Figure 16

3. Conclusions

Since 2014, dosage forms / DDSs fabricated by FDM have rapidly grown in number and complexity in terms of shape, composition and use, covering different routes of administration and performance targets. An insight into the literature relevant to pharmaceutical applications of FDM, other than those described in patents or concerning the fabrication of casting molds[184,185], was provided through the use of graphics and images. These were effective in visualizing the common aspects, but also the peculiarities / details that gradually promoted small and greater advances in the field. However, both quality assurance and quality control topics, as well as formulation choices still represent limitations, especially with regard to the expected performance and resolution goals. For the same reason, no drug products manufactured by FDM have been approved yet. Relying on the experience gained thus far, this manuscript could help to develop ideas to consolidate the results obtained to date and open up inspiring perspectives in the use of FDM in the pharmaceutical industry, possibly inaugurating a new era for such a technique.

The data that support the findings of this study are available from the corresponding author upon request.

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