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A Review on 3D Printing in Pharmaceutical Industries.

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ABSTRACT

Growing demand for customized pharmaceutics and medical devices makes the impact of additive manufacturing increased rapidly in recent years. The 3D printing has become one of the most revolutionary and powerful tool serving as a technology of precise manufacturing of individually developed dosage forms, tissue engineering and disease modeling. The current achievements include multifunctional drug delivery systems with accelerated release characteristic, adjustable and personalized dosage forms, implants and phantoms corresponding to specific patient anatomy as well as cell-based materials for regenerative medicine. This review summarizes the newest achievements and challenges of additive manufacturing in the field of pharmaceutical and biomedical research that have been published since 2015.

Keywords: International Standard Organization (ISO), Active pharmaceutical ingredients (APIs), Three-dimensional printing (3DP) , Moulding .

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INTRODUCTION

There is a constant motivation towards new concepts in drug design, better understanding of material properties, manufacturing technology and processes that assures high quality of dosage forms. The diversity of physicochemical and biopharmaceutical characteristics of active pharmaceutical ingredients (APIs) have to be considered and studied through each stage of product development. Auxiliary substances need to be examined as well in order to manufacture of the desired dosage form [1].

Within last decade the patient-centric drug product development has been under considerable attention. It was focused on novel dosage forms and technological processes. Growing demand for customized devices combined with an expansion of technological innovation drives the major progress in personalized medicine expressed e.g. by the production of small series of individually-selected doses and tailor-made prostheses meet the anatomical needs of patients. Within many discoveries introduced into pharmaceutical and biomedical market, three-dimensional printing (3DP) is believed to be the most revolutionary and powerful. This technique is recognized as a versatile tool of precise manufacturing of various devices. It serves as a technology for developing novel dosage forms, tissues and organs engineering as well as disease modeling.[2]

Nowadays, three-dimensional printing is one of the fastest developing branch of technology, art and science, and still broadens the applications. The term three-dimensional printing was defined by International Standard Organization (ISO) as: "fabrication of objects through the deposition of a material using a print head, nozzle, or another printer technology". In contrast to commonly used subtractive and formative manufacturing methodologies, this technique is one of the methods of additive manufacturing (AM) in which the parts are prepared from 3D model data in the process of joining materials layer by layer. The practical approach of AM is called rapid prototyping (RP) and its advantages include the reduction of prototyping time and costs, easy modifications of a product at a designed level, the possibility of manufacturing of small objects, individualized product series or structures impossible to be formed with subtractive techniques [3].

The application of 3D printing in the science and engineering has grown since 2012. The number of scientific papers recorded in Web of Science Core Collection containing a term "3D printing" or "3D printed" in the title increased from 59 in 2012 to 1573 in 2017. Moreover, the number of citations of these papers in the same period grown from 209 to 12,411. Narrowing the searching results to the category of pharmacy/pharmacology gives no result in 2012, however 77 records were found up to 2017, which also shows a great interest in the 3DP methods in pharmaceutical sciences.[4].

A Bit of History

The idea of 3DP has evolved from early 70′ of the twentieth century when Pierre A. L. Ciraud described the method of application of powdered material and subsequent solidification of each layer through the action of high energy beam. In this case meltable materials such as plastics or metals can be theoretically used for object preparation. In early 80′ in a patent entitles: "A molding process for forming a three-dimensional article in layers", Ross Housholder described an idea of sand binding by different materials and Carl Deckard developed a method of solidification of powdered bed by laser beam called selective laser sintering (SLS).[5].

The first commercially available technology created by Chuck Hull was stereolithography (SLA). This method was based on photopolymerization of liquid resin by ultraviolet light. At the end of 80's Scott Crump filed a patent for fused deposition modelling (FDM) – a technique which used thermoplastic material for object preparation. In the 90's Emanuel Sachs - MIT scientist with co-workers patented "Three-dimensional printing techniques" based on joining the selected regions of powder by inbinding material [6]. The most important achievements in 3D printing in pharmaceutical and biomedical applications are presented in Fig. 1.

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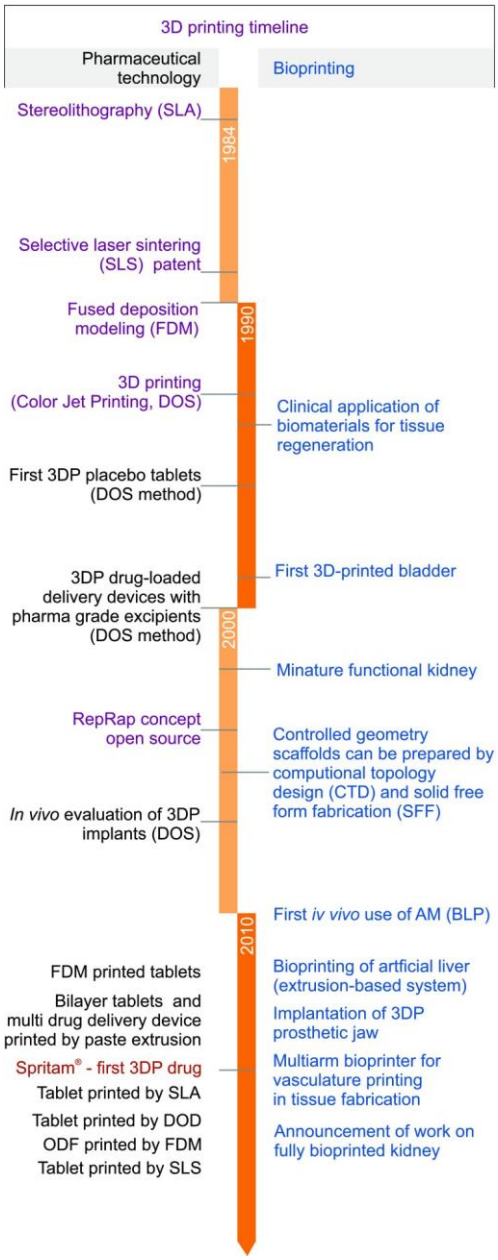

Fig. 1- The most important achievements in 3D printing in pharmaceutical and biomedical applications.

How it Works

Among almost 40 years of 3DP history many different techniques were developed and evolved with the technological progress.[7].

The main methods are based on:
- powder solidification,
- liquid solidification,
- extrusion.

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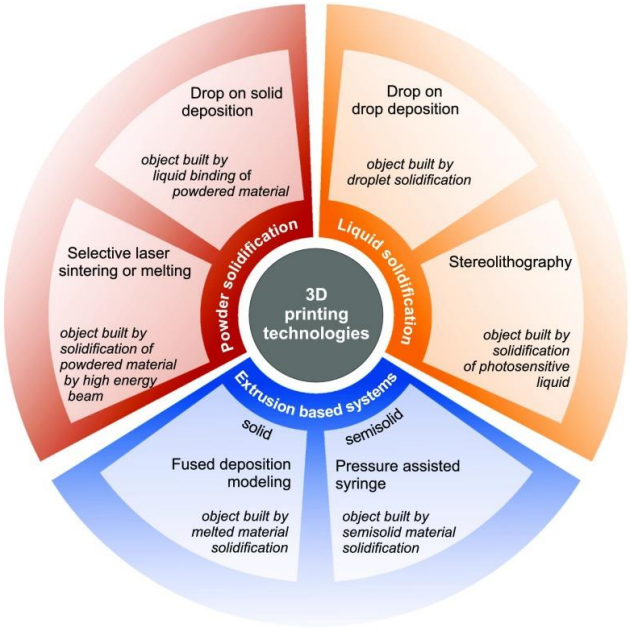

Fig 2- 3DP methods applied for drug formulation.

Despite of the diversity of 3DP methods, preparation of 3D-printed object includes several stages:

- the design of 3D object with computer-aided design software and optimization of the geometry according to printer specification,
- the export of 3D model to a common and printer-recognizable file format e.g. STL which l includes only 3D geometry in form of each vertex position data or OBJ in which additionally information about polygonal faces or color texture are coded,
- the import of the file to the software and generation of layers which will be printed; the height of the printed layer essentially influences the quality of the printed object as well as printing time,
- fabrication of the object by subsequent application (or solidification) of the material layers dedicated to the specific printing method.[8].

The development of 3D printed object is illustrated in Fig. 3.

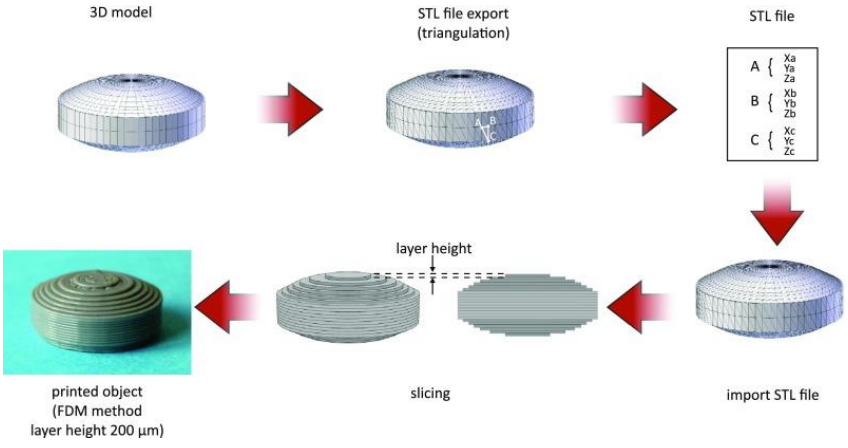

Fig. 3 The development of 3D printed object (from ref. (4) with modification).

The 3D printing methods gain an importance in the field of pharmaceutical and medical applications because of the possibility of rapid preparation of tailor-made objects which can be applied in personalized therapy or medicine. The introduction of 3D printing into the pharmaceutical technology particularly aims at the development of patient-centered dosage forms based on structure design. It is still a new research direction with potential to create the targeted release drug delivery systems in freeform geometries.[9].

From Powder it will Raise

The first 3DP method used in the development of pharmaceutical dosage forms was based on the idea presented in patent entitled "Three-dimensional printing techniques" .The printing process mode of action is similar to desktop inkjet printers and is called drop on solid deposition – DOS or powder bed jetting. Droplets of ink sprayed from print head bind the layer of free powder bed while unbound powder particles act as a support material preventing from collapsing of overhang or porous structures. After each step the formed object is lowered and a layer of free powder is applied by roller or powder jetting system and process is proceeded [10].

The first printers were equipped with commercially available thermal or piezoelectric print heads that delivered bonding agent. Active pharmaceutical ingredients as well as modifying agents can be either dissolved or dispersed in ink or distributed in powder bed. This method was used due to its similarity to classical formulation processes as wet granulation and the ability to apply the excipients commonly used in the field of pharmaceutical technology, especially in solid dosage form formulations [11].

Principles of Extrusion-Based Methods

Hot melt extrusion (HME) as well as extrusion of semisolid materials are well established processes in the field of pharmaceutical technology. Increasing popularity of printing methods based on this technical solution is related to progressive availability of compact size and relatively inexpensive equipment. Essentially two modes of printing method can be distinguished:[12].

- extrusion of semisolid, or semi-molten materials (gels, pastes) at room or elevated temperature,
- extrusion of molten thermoplastic rod-shape material (filament).

In both modes the material is extruded from the nozzle and spread in subsequent layers on the surface of build platform . Defined dimension of printed path is created by the distance of print head to the build plate and influenced by the nozzle orifice diameter. These two parameters and print speed affect the quality of printed object. Another layer is applied when print head or print platform moves along Z axis at the distance of layer height. The 3D printers technological solution are depending on printing material.[13].

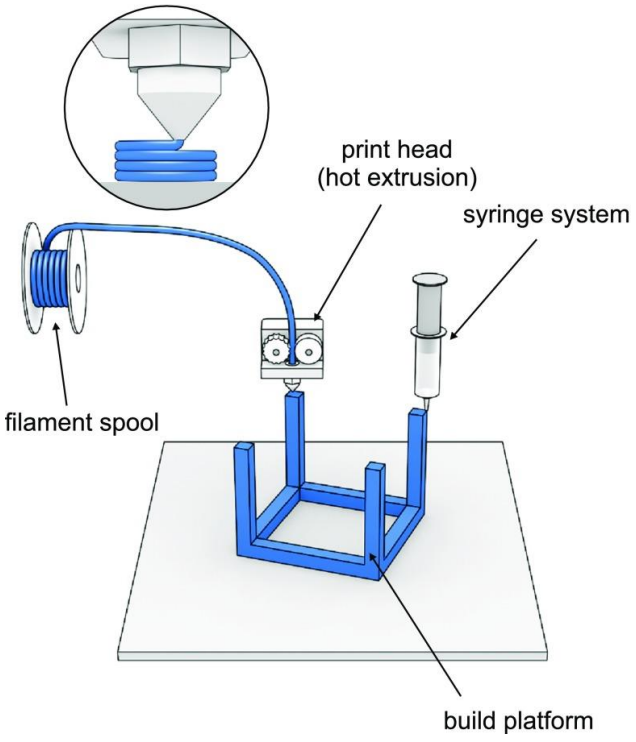

Fig 4: Extrusion-based techniques.

Filament – The Major Challenge The fused deposition modelling is based on extrusion of molten thermoplastic material. Dimensions of filaments in the range of 1.75 mm and 2.85–3 mm are adopted to standard commercially available print heads. Standard filaments are made of thermoplastic polymers such as acrylonitrile butadiene styrene (ABS), poly(lactic acid) (PLA), high impact polystyrene (HIPS), polyethylene terephthalate glycol-modified (PET-G), nylon. There are some commercially available high-quality filaments processed from medically grade polymers such as PLA, PVA, nevertheless the filaments prepared from pharmaceutical grade polymers and containing APIs are not commercially available so far. To prepare drug-loaded filaments the thermal stability of impregnated API must be considered. In FDM process the filament guided by gears is moved towards heat end where it is melted and pushed forward through the nozzle orifice by unmelted filament. The diameter of the nozzle orifice varies from 0.2 to 0.4 mm, and has an impact on resolution of printed object. Usually the printed path width is equal to the orifice diameter and the height of the path is a half of its width, however the final settlements can vary depending on the printed material and printer settings. The paths are organized in layers and formed into the object which resolution depends on layer height. The mechanical parameters of the printed object are related to number of outlines which build the external wall of the object and infill parameters ratio and type (e.g. honeycomb or rectilinear)[14].

Two Heads Are Better than One

In dual head extrusion process, the print head is equipped with two separate stepper motors and heating compartment which allows to carry out the process with two materials characterized by different melting temperature. Okwuosa et al. prepared the delayed release tablets with theophylline loaded core, based on PVP polymer, printed by one extruder and outer complementary shell of Eudragit® L with increasing thicknesses from 0.17 to 0.87 mm which was prepared by second printing extruder. The shell thickness which was required to achieve sufficient core protection in the acidic medium was ≥0.52 mm [15].

Extrusion of Semisolids- In case of printing of semisolid, or semi-molten materials (gels, pastes) at room or elevated temperature by extrusion process, some changes have been implemented in print head construction in comparison with FDM. The mass is extruded through orifice by compressed air pressure, syringe plunger or screw. This systems allow to fabricate high drug load dosage forms, nevertheless after printing the drying step is required what can influence the product integrity. Immediate release paracetamol tablets with 80% of drug load were prepared with pharmaceutical grade excipients that comply with pharmacopoeial standards. The systems with modified release were prepared as well. Li Q et al. developed gastro-floating tablets with dipyridamole to prolong the gastric residence time. In vitro buoyancy study revealed that 30 and 50% of infilling rate formulations floated up to 12 h. Multi-syringe printing system allows to prepare "polypill" as multi-active solid dosage form containing 3 or 5 APIs released with different kinetic characteristics [16].

Patient-Centric Therapy

Due to the possibility of various materials utilization, 3D printing methods have wide range of applications in medicine e.g. to build spatial systems used in tissue engineering as well as in pharmacy to prepare such dosage forms as tablets , capsules implants or orodispersible films .As already mentioned, tablets are the most frequently produced dosage forms. While they can be manufactured in several geometries, very few doses for one API are available on the industrial scale [17].

(Bio)Medical Applications

The impact of additive manufacturing on biomedical field has increased rapidly since the 3D printing was developed in the early 80′. It is due to the fact that the technique enables formation of individually developed materials of customized architecture and functionalities. It evolved into powerful tool for biomedical engineering providing formation of manufacturing implants that correspond to patient-specific anatomy, phantoms for education and surgical planning and disease models [18].

CONCLUSION

The 3D printing of drug delivery systems and medical devices serves as an attractive tool to produce customized product. Since few years the concept of 3D-printed drug formulation quickly evolved and was directed to enhance therapy by patient-centric medicine. The first FDA approval of drug manufactured by 3D printing technology caused an exceptionally rapid development of studies on oral, oromucosal and topical dosage forms. This promising technology offers formulation flexibility that is difficult to achieve with the conventional technological processes. Additional manufacturing allows to prepare different kind of dosage forms with high precision of API-excipients ratio, in totally new manner with comparison to traditional pharmaceutical manufacturing. The added value of the 3D printing is also opportunity to create multifunctional drug delivery systems, multidrug devices and drug formulations for personalized therapy with accelerated release characteristic. Therefore, future research should prioritize the development of pediatric and geriatric dosage forms in personalized dosing and dimension-specific drug formulations to ensure desired therapeutic effect.

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