UNIVERSITY OF URBINO CARLO BO
Department of Pure and Applied Sciences
Doctoral Program in Research Methods in Science and Technology
Chemical and Pharmaceutical Sciences curriculum
Academic year 2023/2024
XXXIX Cycle

Under the PNRR funds referred to ***D.M. 118, 2 March 2023***

Bounded Topic: ***Additive manufacturing technologies for the development of advanced drug delivery systems***

Applicant: Costanza Fratini

THE VERSATILE EMPLOYMENT OF ADDITIVE MANUFACTURING IN THE DELIVERY OF ACTIVE PHARMACEUTICAL INGREDIENTS

Background

Additive Manufacturing (AM) represents a big step forward in the pharmaceutical and biomedical field. AM includes novel techniques that allow the creation layer-by-layer (LbL) of three-dimensional (3D) objects from a computer-aided design (CAD) model [1-3]. This technique allows prototyping, which traditionally takes several months, to be completed in a matter of days or hours, saving both time and money [3]. Over the past few decades, AM has changed numerous areas of human activity and is one of the cornerstones of the fourth industrial revolution [4]. This is because AM technology offers unique benefits in manufacturing fields when compared to traditional methods. With AM personalized pharmaceutical forms with flexible dosages, different shapes, multiple APIs (even incompatible ones), and modulated release kinetics can be designed [4]. Unlike conventional medicine, which uses a "one-size-fits-all" standard, personalized and precision medicine focuses on patient-centric treatments considering the differences among individuals, including genetics, lifestyle, and pharmacokinetics, and has shown improved results [5]. Precision medicine is a cutting-edge method to handle personalized care that gives a person the proper therapy at the right moment [5]. One of the key features of AM is indeed the ability to simply customization [6]. Furthermore, it is sustainable from an environmentally friendly point of view; chemicals are not always necessary, it uses less energy and produces less material waste. However, because of various restrictions, such as the limited build size, post-processing, and lack of regulation, its real-life application is restrained [6].

AM methods allow to easily produce several medical devices and dosage forms such as tablets, dermal adhesives, microneedles, vaginal rings, and implantable scaffolds. Furthermore, the potential use of different materials helps to choose the most suitable one according to the desired final product and technique employed.

Recently, the most advanced application of AM technology has been the production of biocomponents for humans, capable of reproducing living tissues [7]; bone scaffolds and wound dressings have gained popular interest. The constructed scaffold should support specific requirements, such as promoting cell migration, proliferation, and differentiation, removing waste components, and promoting neovascularization, to support tissue repair [8]; meanwhile also release active molecules.

Aim of the Project

The main goal of the project is to explore and acquire further knowledge on AM techniques in the fabrication of advanced and personalized drug delivery systems, including medical devices, with better properties and advantages, also from a "green" point of view.

The project will focus on:

- Identify the best AM technique to involve;
- Investigate APIs, biocompatible materials and formulation parameters to obtain the most suitable mixture according to the goals;
- Characterize the final product evaluating its morphology, surface properties, and stability;
- Asses the cytocompatibility *in vitro*;
- Evaluate the *in vivo* behaviour.

Methodology and Expected Results

Starting from a selection of different drugs and materials such as natural or synthetic polymers and depending on the material properties and the compatibility of the process, different AM techniques will be studied until finding the most suitable one. Once optimized the manufacturing process, the final product will be analyzed to confirm the shell stability of the materials and the kinetic of the drug release.

Product Characterization

- *Scanning Electron Microscopy:* to evaluate the morphology and surface of the product;
- *FT-IR spectroscopy:* to chemically characterize the product and explore the interactions between the materials employed;
- *Texture analyzer:* to verify the mechanical properties of the product;
- *Differential Scanning Calorimetry (DSC)*: to assess the thermal behaviour of the product;
- *HPLC:* to quantify the amount of drug loaded or released.

Cytocompatibility in vitro and in vivo studies

The *biocompatibility* and *bioactivity* of the product can be assessed on different cell lines representative for the desired target, the aim is to evaluate the possible toxicity and if the drug release is effective to treat the selected disease.

Overall, at the end of the project a successful development of advanced systems that prove themselves to be stable, biocompatible both *in vitro* and *in vivo* and that demonstrate a potential role to improve health care will be expected.

References

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8. Habib A, Sathish V, Mallik S, Khoda B. 3D Printability of Alginate-Carboxymethyl Cellulose Hydrogel 2018.

A Provisional PhD Research Milestone

Period Time	Activities
1st Year *(Nov. 2023 - Oct. 2024)*	Knowledge acquisition about: - Different 3DP and *nano*- and *micro*-fibers preparation methods - Biocompatible materials - Applications Starting the development of advanced drug delivery systems or medical devices
2nd Year *(Nov. 2024 - Oct. 2025)*	Optimization and Characterization Evaluation of drug loading and release profiles Visiting period abroad (6 months)
3rd Year *(Nov. 2025 - Oct. 2026)*	Final *in vivo* and *in vitro* studies Final Thesis

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Abstract

Additive Manufacturing (AM) can be considered a cornerstone of the fourth industrial revolution and has transformed many fields of human activity over the past few decades. AM include a variety of different cutting-edge techniques, among which one of the most well-known consists of the deposition of fused material layer-by-layer (LbL) while constructing a three-dimensional (3D) object reproducing the virtual computer-aided design (CAD) model. The world of pharmaceuticals and biomedicine, for example, has advanced significantly because of AM that allow to reach the goal of precision medicine, because prototyping, which ordinarily takes several months, may be finished quickly and affordably and because of easier customization. Contrary to conventional medicine, which adheres to a "one-size-fits-all" standards, personalised and precision medicine places an emphasis on patient-centric treatments that take into account individual differences such as genetics, lifestyle, and pharmacokinetics and has demonstrated improved outcomes. However, its real-life use is constrained due to a number of limitations, including the small build size, post-processing, and a lack of regulation. For this reason, it is imperative to focus the research and implement the knowledge on AM in order to develop drug delivery systems or medical devices to handle personalized care that gives a person the proper therapy at the right moment.
The research will be focused on investigating AM techniques for creating advanced and personalised drug delivery systems, including medical devices, with improved qualities and benefits, also from a "green" perspective. Different AM approaches will be investigated until the most appropriate one is found, starting with a variety of various pharmaceuticals and materials like natural or synthetic

polymers and depending on the material qualities and the process compatibility. The final product will be examined after the production process has been optimised to verify the shell stability of the materials and the kinetics of the drug release; along with other useful studies such as the *biocompatibility* and *bioactivity* of the innovative drug delivery system or medical device.