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APPLICATION OF ADDITIVE MANUFACTURING THROUGH MICROFLUIDICS AND SOLUTION BLOW SPINNING TO FORMULATE DERMATOLOGICAL DELIVERY SYSTEMS

Keywords: *3D printing; nanotechnology; skin delivery; cosmetics*

Introduction

Additive Manufacturing (AM) has become one of the most innovative technologies over the past two decades and it has certainly proved to be a technique capable of revolutionizing the manufacturing processes of many industries thanks to its adaptability and low cost, ability to produce complex partes saving time and materials.[1,3]

AM is a manufacturing technology that produces 3D objects from a design made with CAD software using layer-by-layer deposition of material. It has already found application in the healthcare and pharmaceutical industries, but its use in topical delivery is equally interesting, especially its potential and current use in the cosmetic field.[2]

Skin is a protective barrier that isolates and defends the body while interacting with the external environment. This role is primarily performed by the stratum corneum, composed of corneocytes, surrounded by lipid lamellar regions and tightly adhered to each other via protein structures limits or even block the penetration of external agents, ensures maximum resistance and limits the speed of percutaneous absorption.

So far numerous technologies have been developed to increase the permeation of actives through the skin such as penetration enhancers, supersaturation and a wide range of skin delivery systems (liposomes, niosomes, transfersomes, lipid nanoparticles, polymeric nanoparticles and patches).[4,5]

One of the most recent approaches involves using AM to produce manufacturing devices able to formulate lipid based nanovesicles or polymeric-based nanofibers.[2]

The importance of these delivery systems arises from the need to reversibly overcome the skin barrier, with numerous desirable benefits, including the ability to trap substances favoring their dispersibility, optimizing performance and release, ensure the protection of sensitive and volatile actives, improve specific site penetration and ensure prolonged contact in the target layer. Lipid nanovesicles appear to be promising delivery systems thanks to their biocompatibility, low toxicity and prolonged release capacity, they are also perfectly comparable to the cellular membranes of our organism and scientific studies have confirmed that they are able to alter the fluidity of cell membranes and to fuse with them, penetrating into the deeper layers of the skin and releasing the delivered ingredient. [6,7]

Another interesting innovative technology is Solution Blow Spinning (SBS) for the production of polymeric and nanocomposite materials. The advantages of SBS over other spinning methods are the fast generation of fibers and the simplicity of the experimental setup capable of releasing embedded active agents.[8]

Nanofibrous patches can be easily designed and fabricated by SBS and they can be loaded with different active ingredients for different cosmetic application, such as *acne vulgaris*.[9]

AM has led to important developments in the medical and pharmaceutical fields, serving as inspiration for potential applications of 3D printing in cosmetics. This indicates a large potential in developing efficient cosmetic delivery platforms using 3DP technology; certainly, needs further investigation.[2]

Aim of the Project

The main goal of the project is to use emerging technologies such as AM to develop engineer devices (microfluidics chips and SBS nozzles) able to manufacture innovative nano formulations for the release of functional molecules into the skin. The proposed research will focus on the creation of formulation systems for the release of molecules of dermatological interest and above all on the development of simple, inexpensive and easily scalable techniques at an industrial level. Particular attention will be paid to their environmental impact, for example by avoiding the use of organic solvents harmful to humans and the environment and employing low energy impact processes.

The production process will be engineered, and the best set up for scale up will be identified. Highly innovative formulations will also be designed, formulated and characterized both in the form of colloids and patches for dermatological use, reaching the final development of the product including the regulatory aspects.

More specifically the project aims to:

- CAD design of manufacturing devices (microfluidics chips and SBS nozzles)
- Optimization of the 3DP parameters to be print prototypes by Fused Deposition Modeling (FDM)
- Design of Experiment set up to predict formulative development of the nano-based delivery systems
- Loading of selected functional molecules
- Chemical-physical characterization of the formulations (DLS, SEM, HPLC, DSC, Rheology)
- In vitro characterization on cell culture and Franz Cells testing models
- Industrial scale up manufacturing studies

Methodology

Product design and manufacture

In the first phase, the activity involves the use of 3D printing techniques such as FDM to obtain microfluidic devices useful for the formation of colloidal systems. The use of customized and 3D printed microfluidic chips will enable the formulation and production of nanometric vesicles based on phospholipids to encapsulate molecules of dermatological interest. A low-cost production process will be engineered, using peristaltic pumps and easily scalable microfluidic systems. The produced colloidal systems will be used to prepare dermatological formulations applicable the skin level for treating specific skin alterations.

At a later stage the 3D printing techniques will then be used to create devices for setting up SBS useful for the production of nanofilaments and patches for skin application. A 3D printed system capable of obtaining nano and micrometric polymer filaments, onto which functional active molecules will be loaded and conveyed, will be engineered through CAD development. In addition to the 3D printed device, the process involves using of compressed air and a pressure system to convey the polymeric matrix fluid. The objective of this production technique is to formulate and produce skin patches.

Product Characterization

The formulation will be characterized by:

- Dynamic light scattering (DLS): to determine the vesicle size and polydispersity index (PDI)
- Scanning Electron Microscopy (SEM): to study the morphology (nano and micro fibers)
- High Performance Liquid Chromatography (HPLC): used to quantify the incorporation efficiency and to evaluate the amount of the molecule during the release studies
- Differential Scanning Calorimetry (DSC): to assess the thermal behaviour of the product
- Texture analyzers can be used to evaluate the mechanical properties
- Rheology: to study the viscoelastic properties of the final dermatological formulations

In vitro studies

- Franz Cells coupled with artificial or *ex-vivo* membrane will be used to evaluate the release profile
- *In vitro* cell culture studies determining biocompatibility (keratinocytes and fibroblast)

Expected Results

The proposed research activity aims to set up simple, easily scalable, low-cost and low-impact industrial processes, thanks to the use of emerging technologies in both formulation and production fields, such as 3D printing, microfluidics and SBS. The use of microfluidic processes in developing nano and micro technological platforms, such as liposomes, ethosomes, transferosomes, nanoparticles, micelles etc., is currently the most important approach and the one that allows the widest process scalability. Additionally, it is proposed to use AM technology to engineer custom, low-cost chips capable of serializing multiple chips to scale the process and simplify production. Furthermore, it is proposed to set up technologies such as SBS, again using 3D printing, which will enable the production of devices capable of spinning polymeric matrices, loadable with functional molecules, for the production of patches for skin delivery. The setup of these processes will allow us to design and produce innovative formulations capable of delivering various types of functional molecules to the skin level in the most appropriate and effective way.

The creation of highly efficient platforms for the preparation of nano and microparticle systems, filaments and patches made of biodegradable and biocompatible materials, will allow the creation of libraries of delivery systems adaptable to the specific needs of pathologies or blemishes.

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Feasibility of the 3-years project:

Time period	**Activities**
First Year (Nov 2024–Oct 2025)	■ Knowledge acquisition about: ✓ Additive Manufacturing, Microfluidic and Solution Blow Spinning ✓ Biocompatible Materials ■ Engineering and development of 3DP devices for microfluidic and Solution Blow Spinning processes ■ Optimization and characterization of the developed devices
Second Year (Nov 2025-Oct 2026)	■ DoE and formulation of functional substance loading ■ Physicochemical characterizations ■ Visiting period abroad
Third Year (Nov 2026-Oct 2027)	■ Final *in vitro* and scale up studies ■ Final thesis