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3D printing of nano-cellulosic biomaterials for medical applications

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Abstract

Nanoscaled versions of cellulose viz. cellulose nanofibers (CNF) or cellulose nanocrystals (CNC) isolated from natural resources are being used extensively since the past decade in the biomedical field e.g. for tissue engineering, implants, drug delivery systems, cardiovascular devices, and wound healing due to their remarkable mechanical, chemical and biocompatible properties. In the recent years, 3D printing of nanocellulose in combination with polymers is being studied as a viable route to future regenerative therapy. The printability of nanocellulose hydrogels owing to their shear thinning behavior and the possibility to support living cells allows 3D bioprinting using nanocellulose, a recent development which holds tremendous potential.

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Introduction

3D printing also known as additive manufacturing (AM) or rapid prototyping (RP) follows a bottom up process and has been applied in medicine since the early 2000s to make dental implants and customized prostheses [1–3]. AM technologies such as direct ink writing (DIW), standard lithography, laser-based polymerization, or epitaxial assembly techniques can be employed in order to create 3D structured objects [4]. This review is focused on the DIW process, which is an extrusion-based technique that enables programmable assembly of three-dimensional periodic architectures.

An advantage over the other techniques is that a broad range of materials can be printed at the micrometer scale by DIW. The main challenge related to this DIW is assigned to the development of inks possessing optimum rheological behavior [5].

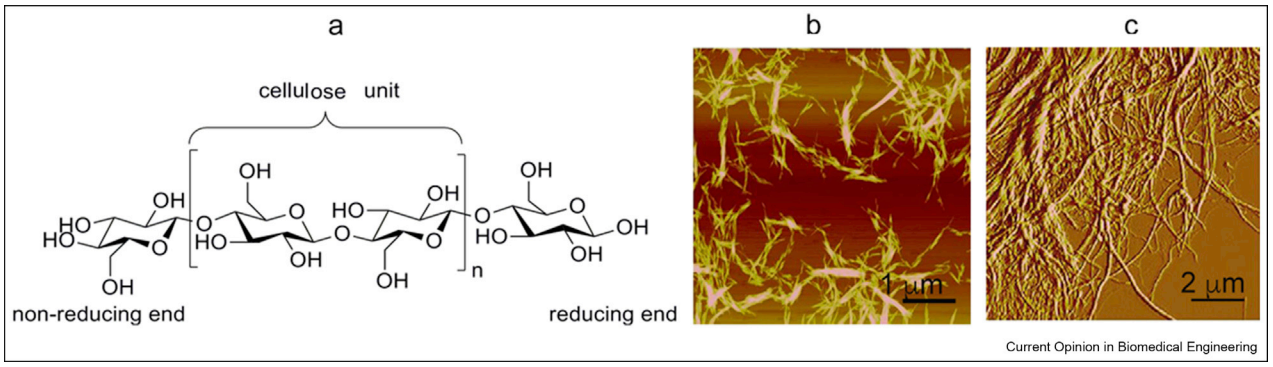
3D printing technology used in biomedical field, involves collecting accurate information of tissues and organs for designing the model, transferring the information into electrical signal to control the printer, and developing a printing process that maintain the cell viability during the fabrication process.

Cellulose is a linear carbohydrate polymer with long chains of β-(1 → 4)-linked D-anhydroglucopyranose moieties repeating units (Fig. 1a), it is made up of sugar monomers and is hence a polysaccharide. Nanocelluloses are isolated from diverse cellulose sources via a top down approach and known to have different nomenclature for the same type of nanocellulose as described below [6–8].

- Cellulose nanocrystals (CNC) (Fig. 1b), with other designations such as nanocrystalline cellulose, cellulose (nano)whiskers, rod-like cellulose microcrystals; which are the ordered regions in cellulose chains, isolated via acid or enzymatic hydrolysis and having diameters in the range of nanometers
- Cellulose nanofibers (CNF) (Fig. 1c), with the synonyms of nanofibrillated cellulose (NFC), microfibrillated cellulose (MFC), cellulose nanofibrils; comprising of the ordered and disordered regions of cellulose chains, usually isolated via mechanical disintegration, having diameters in nanoscale and lengths in micron range.

Abundance, wide availability, insolubility in water/solvents, biocompatibility etc are the reasons why nanocellulose is being considered in biomedical application. In the recent years, research activities in the field of "biomedical application of nanocellulose" has grown exponentially [6] and the use of 3D printing is one of the most recent and promising developments in this field. The specific reasons why nanocelluloses are used in 3D printing are that they can be utilized as rheological modifiers for the inks, ensuring the viscoelastic response required for filament printing; their specific mechanical

Fig. 1



a) Repeating unit of cellulose chemical structure and images of b) cellulose nanocrystals and c) cellulose nanofibers.

properties; their ability to support cells and the possibility to accurately control pore structure and shape in scaffolds and implants.

Compared to traditional fabrication approaches, the 3D printing technology allows fabrication of more complex structures by integrating layer by layer (bottom to top) slices of the designed and desired objects [9,10]. Moreover, it provides substantial liberty to fabricate new and untested geometric designs where, for instance, well-organized nanoscale building blocks can be assembled in a specific fashion to bridge structural length scales from nano-to-macro [11]. Hydrogel formation capability of nanocellulose at low concentrations (1–2 wt%) also has facilitated the design of inks for 3D printing.

The nomenclature in 3D printing of nanocelluloses for biomedical application is not standardized yet and different terms are being used to represent the techniques. In this review article, some terms are defined below for ease of comparison.

- Any biocompatible ink/hydrogel mixed with living cells is defined as **Bioink** and 3D printing of bioink is referred to as **3D Bioprinting**

In this review we aim to give a brief overview of factors to consider while 3D printing nanocellulosic inks and summarizes the recent research and commercial developments in 3D printed nanocellulosic systems for biomedical applications.

Factors affecting 3D printing

Majority of the current manufacturing processes using 3D printing is overwhelmingly based on single material printing, typically with a limited range of commercial and often proprietary resins compatible with commercial printers [10]. To overcome this issue and extend the application of 3D printing to biomedical products, researchers are adapting commercial printers and developing new inks based on naturally based polymers (including alginates, hyaluronic acid, gelatin, chitosan, collagen) [9] or synthetic polymers (polyethylene glycol; PEG) [12]. Materials that can be thermally crosslinked at body temperatures and/or that need short curing time, low photoinitiator concentrations, and low-intensity UV light to minimize possible adverse side effects on cells caused by creation of free radicals are generally considered attractive materials for 3D printing [13,14].

The selection of materials for 3D printing for biomedical applications and their performance are dependent on several characteristics; the most relevant are listed below:

- *Printability*: the importance of this parameter lies on the specific rheological behavior required for the inks used. For example, the ink has to be sufficiently fluid to be extruded through the micro nozzles under ambient conditions without demanding prohibitively high pressures (e.g. >4 bars). When shear ceases, the ink should exhibit enough elastic modulus (G'), typically higher than few kPa, and yield stress in the order of few 10^2 Pa, to maintain its filamentary shape thus preventing single filament deformation. One possible approach to meet the rheological requirements is the designing of the inks that display non-Newtonian viscoelastic response, generally evidenced by its high storage modulus (G') over the loss modulus (G'') at low shear stresses [5,15].
- *Biocompatibility*: the selected material should be compatible if it is aimed to coexist with endogenous tissue without causing undesirable effects in the host; [9].
- *Biodegradability*: since major part of developed scaffolds and constructs are not intended as permanent implants; [16].
- *Structural and mechanical properties*: the choice of materials should be based on the final mechanical properties required for the specific anatomical site into which it is intended to be implanted; [9,16].

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