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Melt electrowriting with additive manufacturing principles

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Abstract

The recent development of electrostatic writing (electrowriting) with molten jets provides an opportunity to tackle some significant challenges within tissue engineering. The process uses an applied voltage to generate a stable fluid jet with a predictable path, that is continuously deposited onto a collector. The fiber diameter is variable during the process, and is applicable to polymers with a history of clinical use. Melt electrowriting therefore has potential for clinical translation if the biological efficacy of the implant can be improved over existing gold standards. It provides a unique opportunity for laboratories to perform low-cost, high resolution, additive manufacturing research that is well positioned for clinical translation, using existing regulatory frameworks.

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Introduction

Tissue Engineering (TE) is a field of research that aims to safely manufacture implantable materials (scaffold & non-scaffold based) to treat injuries and diseases [1]. It is an inherently multidisciplinary field that promises to deliver a significant benefit to humanity, yet has long-standing limitations, notably in the translation of university-based research through to an implantable product that can be widely accessed by patients. Most recently, the adoption of automated processes in TE has given rise to biofabricated products, which address reproducibility and delivers a capacity to customize medical devices and tissue constructs [2].

There are many challenges in developing TE constructs for treating injury and disease, including for manufacturing methods which have recently trended towards additive manufacturing (AM) approaches [3–6]. This review on electrostatic writing technologies is focused on using polymer melts, since this provides the fastest way to clinically translate research and develop products for TE [5,7]. Most people consider electrospinning (derived from the term "electrostatic spinning") to be a dynamic manufacturing technology that produces ultra-fine diameter fibers in a chaotic deposition pattern [8–10]. Instead, *what if* the placement of every single electrospun fiber could be predetermined? *What if* the manufactured construct could reach milliliter volumes while maintaining accurate fiber placement? And, finally, *what if* the diameter of the electrospun fiber could be automatically controlled by over a magnitude, using the during scaffold manufacture? This review shows that electrostatic direct-writing technologies can deliver all the above, using polymers that have a history of use in clinical settings [11,12] and moreover, can achieve this with a solvent-free manufacturing approach.

Development of electrospinning for TE

Electrospinning was first reported as a method for manufacturing a biomaterial in 2001 by Bowlin and colleagues, on the basis that the small diameter filaments (including those made from collagen) mimic fibrillar structures found in extracellular matrix [13,14]. Since then, the use of electrospinning in TE research as a scaffold has significantly expanded, driven by numerous advantages of the technique [8]. These include the 1) low cost and 2) simplicity of establishing the process within a research laboratory, the 3) diversity of polymers (both synthetic and natural) compatible with the process [15] and 4) capacity to handle the resulting non-woven fabrics manufactured using electrospinning. A strategy, however, is required to induce porosity within a solution electrospun mesh, since randomly depositing sub-micron diameter fibers does not produce a material with sufficient pore size for cell invasion. In 2005, Mikos and colleagues demonstrated that when using a single collector configuration, electrospun fibers needed to be at least 3 μm in diameter, to generate pore sizes (20 μm) sufficient for cell penetration into the material [16].

Electrospinning as a technology that developed quite separately to AM (often described in the media as 3D

printing). In 2008, electrospinning was first used in combination with fused deposition modelling (FDM) to create a "bimodal" scaffold that contained both small diameter and large diameter elements [17,18]. In this instance, the ordered scaffold structure is still provided by the FDM component, while the electrospinning filled up the pores between each deposition layer to aid in cell-seeding. For the most part, electric instabilities that electrospinning researchers rely on to generate sub-micron diameter fibers is fundamentally incompatible with the need for accurate deposition required for AM. The first description of direct-writing using electrospinning was in 2006, where the term "near-field" electrospinning was introduced to the community [19]. In this configuration, the collector distance is very short, and a single layer of fibers could be deposited onto a substrate and controlled using stage movement. As shown later in this review, scaffolds with 200 layers can be direct written when the fluid used is a polymer melt.

Melt electrospinning is neither a new nor an unknown concept within the electrospinning community [8,9,20], however it remains an area of under-investigation [21]. Melt electrospinning was first described in a 1936 patent [22], in publications from 1981 [23–25], and first described post-1995 by Reneker and colleagues in 2001 [26]. Yet, to date, less than 1% of the electrospinning publications use solvent-free configurations [21,27]. While the first melt electrospinning publications described larger microfibers [23], there have since been numerous reports where sub-micron filament diameters are generated [28–30].

Up to 2015, 20 years after Reneker first published his key paper reintroducing "electrostatic spinning" to the research community [31], over 16,000 peer-reviewed journal articles have been published on this topic. However, even after considerable electrospinning research with polymers that have a history of use in clinical applications, there are a surprisingly low number of medical electrospun clinical products available for implantation (currently only Restorex for heart valves, produced by Xeltis, the Netherlands). While high quality electrospinning devices are now available to manufacture within a controlled environment, the inherent issue of solvent removal (and proving the solvent is removed) results in additional cost for medical device manufacture. As outlined here, switching from a polymer solution to a molten fluid with different electrorheological properties to polymer solutions improves the direct writing performance and stability.

Electrospinning versus electrowriting

The principle underlying controlled direct writing with electrified polymer jets is outlined by Sir Geoffrey Taylor in his seminal 1969 paper [32] on electrically-charged jets. To fully appreciate the distinction between "electrowriting" and "electrospinning", a different starting point to electrospinning is required to describe the method. It is well-known that a non-electrostatically charged falling fluid breaks into droplets – we see this every day, when a water tap is opened (Figure 1A) or honey is allowed to fall from a spoon (Figure 1B). Also well-known is that the location of these (Plateau-Raleigh) instabilities is influenced by the flow rate of the fluid column, and the height at which this non-charged fluid is falling from. In the context of a polymer solution (such as Golden syrup) falling as a column, the flow rate required before Plateau-Raleigh instabilities is significantly lower. However prior to Plateau-Raleigh instabilities, this fluid can be direct-written onto a moving collector (Figure 1C) [33].

What is less appreciated in the electrospinning community, is that the application of a voltage between the nozzle and the landing point of the fluid *stabilizes* the falling fluid (Figure 1D), preventing Plateau-Raleigh instabilities and permits a continuous column of liquid [32]. When the voltage is increased, the electrical instabilities (and corresponding non-predictive path) often associated with electrospinning are achieved (Figure 1D). Interestingly, once an applied voltage has reached a sufficient threshold to stabilize the falling fluid, then the voltage can be reduced, to a level well below the initial threshold (Figure 1E).

While in electrospinning, the electrical instabilities (often termed "whipping") are required to draw out the fiber to its final dimensions, electrowriting uses applied voltage in a different manner – *to permit continuous fluid deposition at low flow rates*. Depending on the configuration and fluid properties, these flow rates can be extremely low, with sub-micron fibers achieved even in the absence of whipping. While the difference between electrowriting and electrospinning is effectively the magnitude of applied voltage, the physical effect that is established is vastly different. Instead of sub-micron diameter electrospun fibers being generated due to "whipping", they are achieved in electrowriting by lowering the fluid flow rate and sustaining this with the application of an applied voltage.

Electrostatic writing today

The underlying principles of controlled fluid deposition at low flow rates can be applied to many liquids, including polymer solutions and melts [34]. However, to generate a fixed structure after the direct writing, this fluid must be solidified. Solvent evaporation, coagulation baths and cooling are three approaches to achieve this fiber solidification that will be described in this review.

Solvent evaporation

First described in 2006, "near-field" electrospinning direct-writes polymer solutions onto a substrate aided