ELECTROSPINNING: A PROMISING APPROACH TO CONTINUOUS MANUFACTURING FOR PHARMACEUTICALS

Here, Blair Brettmann, PhD, Assistant Professor, Georgia Institute of Technology, discusses the present advantages and challenges, as well as the future potential, of electrospinning as a continuous manufacturing technique for the pharmaceutical industry.

INTRODUCTION

Continuous manufacturing of pharmaceutical products has generated significant industrial and academic interest in recent years. Most current pharmaceutical manufacturing processes operate in batches, with each operation occurring in discrete steps and equipment being fully restarted between each batch. Continuous manufacturing, already employed in many industries including chemicals, paper and plastic, and food products, can streamline the process, moving material through all stages without stopping.

Pressure to decrease manufacturing costs and increase capability for in-line process analytics has driven the establishment of research centres at universities, including the MIT-Novartis Center for Continuous Manufacturing of Pharmaceuticals, the Center for Structured Organic Particulate Systems based at Rutgers University, and the University of Strathclyde Centre for Continuous Manufacturing and Advanced Crystallisation. Well-publicised commercial ventures, such as Janssen's Prezista®, have used continuous manufacturing for industrial production, and other, less publicised, ventures are being explored throughout the industry.

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Continuous manufacturing has significant benefits as compared with batch throughout the production process, including high production efficiency, low physical footprint, capability for in-line real-time process analytics, and translatable know-how from other industries. The Brettmann Lab at the Georgia Institute of Technology specifically focuses on downstream continuous manufacturing; starting with the synthesised and purified drug and finishing with the final drug product. Continuous manufacturing provides additional benefits for downstream processing and formulation, in particular providing platforms to reduce solids handling and make better use of designer excipients.

DOWNSTREAM CONTINUOUS MANUFACTURING TECHNOLOGIES

Three promising technologies for downstream pharmaceutical manufacturing are very familiar in the polymer processing field:

- Melt extrusion
- Film formation
- Electrospinning.

These typically take a mixture of polymer excipient and active pharmaceutical ingredient (API), with solvent added for film formation and electrospinning, and process them together as a liquid (melt or solution). The liquid is solidified in the process, be it by cooling or drying, to obtain a final solid form (Figure 1). These technologies minimise or eliminate the need for handling solids and improve the degree of mixing between the polymeric excipient and the API, at times resulting in molecular-level mixing. This is in contrast to traditional blending and

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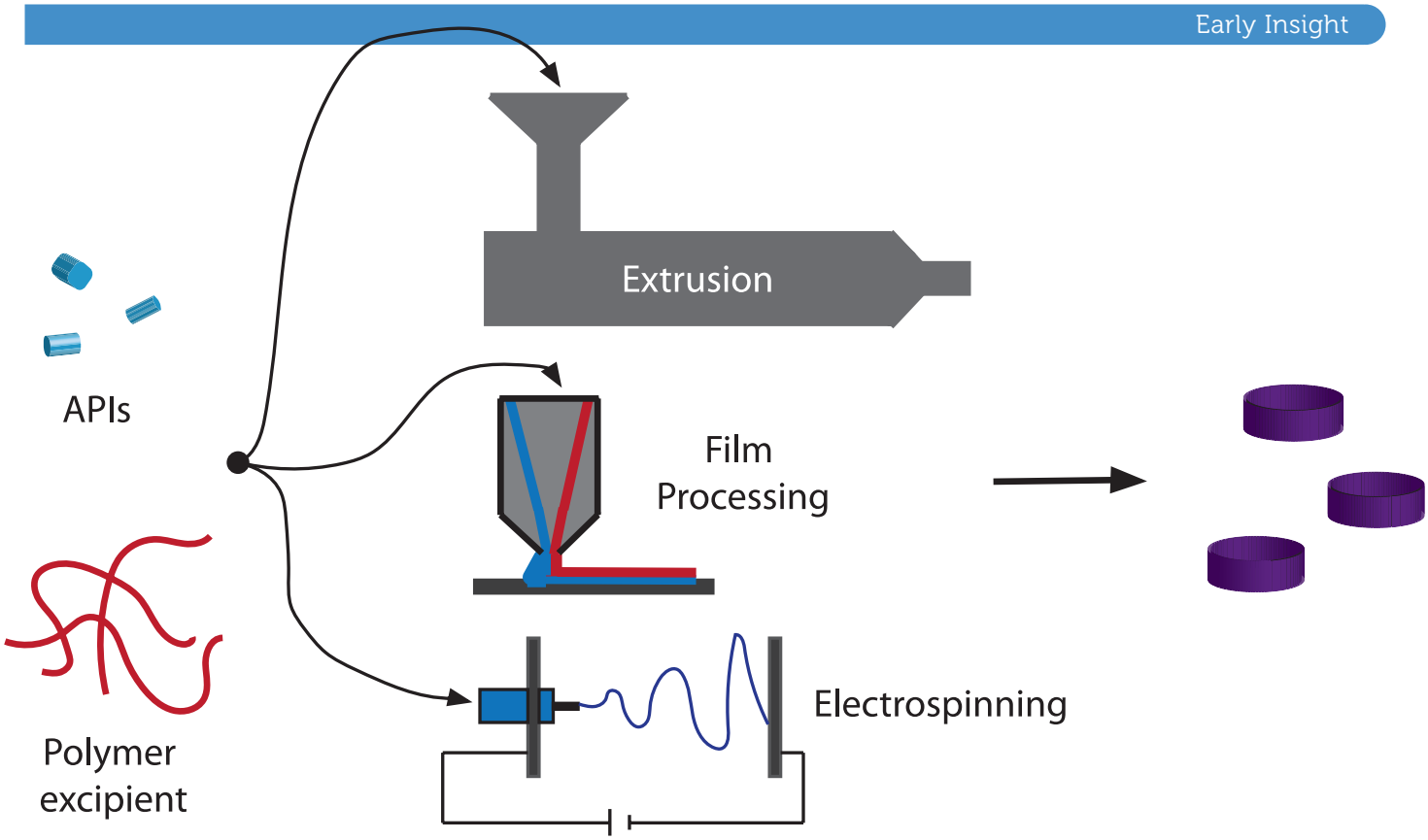

Figure 1: Downstream manufacturing processes for drug products inspired by polymer processing.

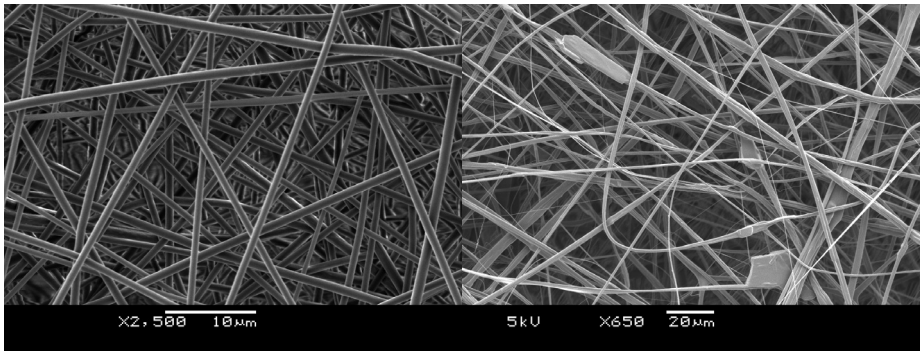

Figure 2: Electrospun fibres containing APIs: A) Amorphous API and B) Crystalline API.

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granulation processes, where micron to millimetre sized powder particles are mixed.

Of these processing methods, electrospinning is particularly exciting, as it results in fibres of 100-1000 nm in a non-woven mat. The high surface area of the fibres is advantageous for rapid dissolution and the morphology is of interest in drug delivery beyond oral dosage forms. The scale of the electrospun fibres is similar to that of the extracellular matrix, potentially making them viable scaffolds for tissue engineering. Furthermore, the surface chemistry of the fibres is readily adaptable, providing unique potential to modify the material to be compatible with any environment.

In addition to the high surface area fibres, electrospinning provides advantages to downstream pharmaceutical manufacturing through its exceptionally high evaporation rate, which freezes the mixture as it is mixed in solution state. It is also readily performed at many scales, from 0.05 g/hr for a single needle to 200 g/hr for a 1 metre electrode using free surface electrospinning, which can be further increased to larger production scales using many electrodes in series. The end product of electrospinning is a non-woven fibre mat (Figure 2), which can be delivered as a film-based dosage form or can be chopped and pressed into tablets.

OVERCOMING THE CURRENT DRAWBACKS OF ELECTROSPINNING

Electrospinning has been developing as a production technology in recent years, with great progress being made in scale-up and process understanding. Commercial products from electrospun fibres are on the market for applications such as air and water filtration, cell culture scaffolds and sound-proofing materials. While large companies such as Samsung, Toray and Boeing have incorporated it into their R&D programmes, pharmaceutical manufacturing is still lagging behind, in part due to drawbacks unique to small-molecule pharmaceutical drug products.

- **Limited materials are "electrospinnable":** Electrospinning requires a significant amount of high-molecular-weight polymer to maintain fibre shape during spinning. In the Brettmann Lab at Georgia Tech, we work to improve electrospinning of high loadings of particles, expanding the functional material types that are amenable to electrospinning applications.

- **Controlling the API form:** Due to the high evaporation rates during electrospinning, the API is typically in the amorphous form following electrospinning, altering its resultant physicochemical properties. A particle electrospinning process is able to to electrospin crystalline API, however traditional solution electrospinning can still be used to prepare amorphous solid products.
- **Importance of API-excipient interactions:** The molecular interactions between the API and excipient will impact the performance of the drug product, and with electrospinning these interactions are enhanced due to the intimate level of mixing. In a well-understood system, this can be an advantage, as the polymers can be used to improve drug performance, but a thorough consideration of molecular behaviour with respect to processing is essential to control the therapeutic effect and mitigate potential side effects.

The Brettmann Research Group at Georgia Tech takes an integrated approach to product development, considering chemical molecular behaviour and microstructural effects in developing new processes for a variety of applications. Fundamental studies are performed to look at how the drug molecule interacts with the polymer excipient, going as far as to design and select polymers to have desired interactions for both processing and dissolution properties. Beyond that, technology solutions are designed to broaden the applicability of electrospinning in downstream pharmaceutical processing, examining the effect of the process on the solid drug form, the stability and the functionality.

ELECTROSPINNING AMORPHOUS SOLID DISPERSIONS

A large number of newly-discovered drugs are poorly water soluble, inhibiting their development as pharmaceutical products. One approach to improve the solubility of these APIs is to formulate them as amorphous solids, where the molecules are arranged in a disordered fashion, rather than in crystalline lattices. The amorphous form is in a higher energy state, thereby exhibiting higher solubility, but it also has a tendency to crystallise over time during storage and delivery. Rational formulation with a polymeric excipient as an amorphous solid dispersion can help stabilise the amorphous form, maintaining the higher solubility for an acceptable period of time to use as a drug product.

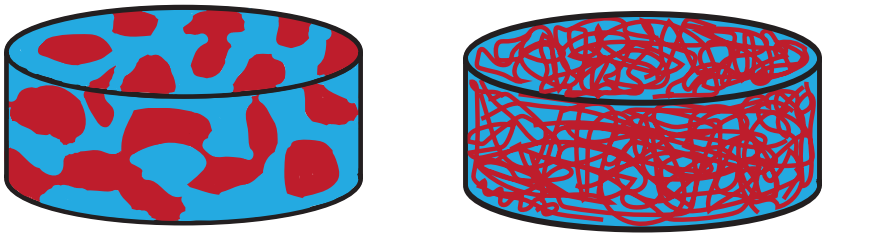

Figure 3: Melt extrusion results in phase separation of the polymer and API, while electrospinning results in homogeneous mixtures down to a 10 nm length scale.

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One challenge in preparing amorphous solid dispersions is achieving sufficient mixing between the polymer excipient and the API to provide good stability. More physical separation between API molecules and a greater occurrence of molecular interactions, such as hydrogen bonding, between the API and polymer will improve stability, but this is difficult to achieve via powder blending. Some improvements have been made using twin screw extrusion, where the API is melted and mixed with the polymer, but in many cases this has not been sufficient.

Due to the extremely rapid evaporation during electrospinning, the degree of mixing between the API and polymer is higher than with other methods. It has been shown that, following melt extrusion, a 4:1 Aliskirin:polyvinyl pyrrolidone mixture was phase separated with domains of at least 40-80 nm, while the same formulation prepared by electrospinning was homogeneous with no measurable domains larger than about 10 nm, as illustrated in Figure 3.[1] Processing into a solid form via electrospinning demonstrated improved mixing of the drug with the polymer excipient, which has been shown to improve amorphous form stability.

In addition to providing a greater barrier to diffusive ability of drug molecules and rearrangement from the amorphous to crystalline form, the increased surface area provided by electrospun fibres makes them particularly valuable for poorly water soluble drugs. The dissolution rate of the API will also be enhanced with greater exposure to the solvent, and the very high surface-to-volume ratio of electrospun fibres provides a distinct advantage over compressed powders, which are typically prepared from particles that are tens of microns in size.

Adding the advantages conferred by

ABOUT THE AUTHOR

Blair Brettmann received a BS in Chemical Engineering at the University of Texas at Austin and a PhD in Chemical Engineering at MIT, focusing on continuous manufacturing of pharmaceuticals. Following her PhD, Dr Brettmann was a Senior Research Engineer at Saint-Gobain, where she worked on polymer-based coatings and dispersions for commercial applications. Later, Dr Brettmann served as a postdoctoral researcher in the Institute for Molecular Engineering at the University of Chicago. Her lab at Georgia Tech designs and studies new processing and characterisation technologies, focusing on linking molecular- to micron-scale phenomena to product performance, with a specific interest in applications for pharmaceutical product development.

"Adding the advantages conferred by continuous processes in general to the unique advantages of electrospinning makes this a particularly exciting approach for preparation of amorphous solid dispersions."

continuous processes in general to the unique advantages of electrospinning makes this a particularly exciting approach for preparation of amorphous solid dispersions. While the feasibility of using electrospinning to prepare amorphous solid dispersions has been demonstrated, the future of the process as a commercial manufacturing method will rely on two key challenges:

1. **Integration into manufacturing:** Applying scale-up principles from other electrospinning applications and developing the best downstream processing of the fibre mats into deliverable dosage forms.
2. **Formulation of products with desired performance:** Developing a fundamental understanding of API-polymer molecular interactions and determining the performance of the materials, particularly when additional excipient compounds are added, such as surfactants and disintegrants.

ELECTROSPINNING CRYSTALLINE DRUG PRODUCTS

Drug products containing crystalline API make up a majority of oral solid dosage forms on the market today and are likely to remain important in the industry. Though electrospinning has specific advantages for amorphous solid dispersions, the technology can also be applied as a continuous manufacturing process for crystalline drug products, rendering it a highly versatile approach for APIs of interest developed in the drug discovery pipeline.

For the amorphous products, the API is dissolved in a common solvent with the polymer, promoting molecular-level mixing. To obtain fibres containing crystalline API, a suspension of drug particles must be prepared, where the API is insoluble in the solvent and API crystal particles are dispersed throughout the polymer solution. The suspension is then electrospun, an approach referred to as "particle electrospinning".

Using two model crystalline APIs, albendazole and famotidine, it was shown that the particles can be electrospun into fibres at a 1:2 particle:polymer ratio.[2] The fibres encapsulated the crystalline API particles in the centre of the fibre and, since the particle size (approximately 10 µm average diameter) is larger than the fibre size (approximately 2 µm average diameter), they appeared as protrusions along the length of the fibre (Figure 2B). When the fibres were pressed into tablets, they showed significantly higher dissolution rates than compressed powder tablets due to the distribution of the particles throughout the fibres; the encapsulation of the crystals in the polymer prevented aggregation and, since the polymer is hydrophilic, allowed release and rapid dissolution of the crystals.

Recent work has explored particle electrospinning further, particularly examining the effect of large particles on electrospinnability and morphology at loadings ranging from 1:5 to 2:1 particle:polymer. Three factors were found to strongly impact the process:[3]

1. **Particle density:** Particles with a high density will settle out of the electrospinning solutions, resulting in lower loadings than expected in the fibres.
2. **Particle aggregation:** If the particles aggregate prior to electrospinning, the entire aggregate will be electrospun, resulting in a "bunches of grapes" morphology.
3. **Fibre to particle diameter ratio:** When the size of the fibres is much smaller than the particle, the particles may be entrapped within the fibre mat in a net-like structure rather than encapsulated within the fibres.

Particle electrospinning is a promising method for downstream continuous manufacturing, maintaining the benefits of high surface area and solution processing, while allowing for crystalline APIs in the final drug product.

FUTURE OUTLOOK

Continuous manufacturing has the potential to transform pharmaceutical manufacturing, particularly in downstream manufacturing where additional benefits, such as reduced solids handling, can also be readily integrated. Building off of current polymer processing technologies, melt extrusion, film processing and electrospinning are particularly ripe for development into the pharmaceutical space. Amorphous solid dispersions produced via electrospinning provide higher degrees of mixing between an API and polymer excipient, resulting in improved therapeutic products, while crystalline API can be incorporated into the fibres using a particle electrospinning process.

To be ready for integration into pharmaceutical manufacturing lines, further development is needed to adapt scale-up methods from established electrospinning applications and to determine the ideal methods to transform fibre mats into tablets. To take maximum advantage of further benefits of electrospinning, fundamental studies need be conducted to fully understand polymer-API interactions during electrospinning and during dissolution of the final products. New studies for rational design of polymers as advanced excipients[4] can readily be integrated into the formulation for electrospun drug products. These advances will lay the groundwork for electrospinning to be a highly competitive downstream manufacturing process for the pharmaceutical industry.

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