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Recent developments in micro- and nanofabrication techniques for the preparation of amorphous pharmaceutical dosage forms☆

Sheng Qi [a,*], Duncan Craig [b]

[a] School of Pharmacy, University of East Anglia, Norwich, Norfolk, NR4 7TJ, UK
[b] UCL School of Pharmacy, 29-39 Brunswick Square, London, WC1N 1AX, UK

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ABSTRACT

Nano- and microfabrication techniques have been widely explored in the textile, polymer and biomedical arenas, although more recently these systems have attracted considerable interest as drug delivery vehicles with concomitant considerations of physical characterization, scalability, stability and drug release. In this review, the current thinking with regards to the manufacture of solid amorphous pharmaceutical materials using electrohydrodynamic and gyration-based approaches, melt-spinning approaches, thermal moulding, inkjet printing and 3D printing will be examined in the context of their potential and actual viability as dosage forms. A series of practical examples will be discussed as to how these approaches have been used as means of producing drug delivery systems for a range of delivery systems and treatments.

Contents

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* Corresponding author.

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1. Introduction

Solid amorphous pharmaceuticals have a particular advantage in being able to provide rapid dissolution in comparison to crystalline materials, however they have the intrinsic disadvantage of physical instability, particularly for low molecular weight drugs [1]. A wide range of industrial processes can be used to produce amorphous solids, such as freeze drying, spray drying, hot melt extrusion, melt granulation and film casting. As with pharmaceutical products containing crystalline drug materials, the amorphous material may be compressed into conventional tablets or filled into capsules as dry powder/granule forms. Although amorphous forms of the active ingredient often address the dissolution difficulties of the crystalline form of the drug, the issue of patient adherence associated with physically taking such bulky solid dosage forms still remains. For example, recent research revealed that more than 55% patients from all age groups have difficulties swallowing such dosage forms [2]. There is therefore interest in exploring alternative approaches to dosage form design which overcome the issues of both the need for improved dissolution and practical dosage form viability, including the methodologies outlines in this review. However, any such approaches must be scalable in an industrial setting and, very preferably, be affordable for a global market, especially with a view to usage in countries where healthcare needs and economic flexibility are mismatched. The movement towards personalized or stratified medicine also requires flexible dosing tailored for individual patients [3], dosage forms that can in themselves be easily administrated to the patient [4], and advanced formulation innovations for maximizing therapeutic effectiveness and minimizing side-effects (particularly for potent and/or cytotoxic drugs) [5].

One family of approaches that is attracting considerable interest is the use of micro- or nanofabrication techniques in order to develop structured systems, either in terms of external shape and size or alternatively containing complex internal micro- or nanostructures, that may either be delivered in themselves or else be incorporated into more conventional dosage forms with enhanced performance characteristics. Such systems have demonstrated the potential to facilitate one or all the required improvements of a drug delivery system described above [6–8]. The recent FDA approved 3D printed levetiracetam tablets by Aprecia Pharmaceuticals for treating seizures is an excellent example. The 3D printed tablets have a highly porous internal environment, with the micron scale pore size providing a large surface area leading to ultra-rapid drug dissolution (within few seconds) and release after administration [9].

A key characteristic of many of these fabrication approaches (henceforth referred to as nanofabrication for simplicity) is that the products tend to be amorphous in nature, hence there is an alignment between the manufacture, the performance and the fundamental physical structure of these systems. It is this alignment that the current review will address. More specifically, the focus will be on outlining the basic approaches to scalable manufacture that are currently being explored with a particular focus on the amorphous characteristics of the associated materials, particularly by using case studies to demonstrate principles of structure-performance relationships. Indeed, every approach described here represents a very large area of study in their own right, hence it is necessary to be selective rather than inclusive in terms of the work cited. Nevertheless, an interesting development across all these field is the exploration of these methods as a means of producing amorphous dosage forms as opposed to scaffolds, inserts and other biomedical platforms. By examining the literature through the prism of the production of viable amorphous dosage forms, the viability of the different approaches and their possible future utilities takes on a new perspective.

The micro- and nanofabrication methods discussed in this review can be loosely divided into two categories based on their basic working principle of forming solid structures, these being either solvent evaporation-based or thermal melt and solidification-based methods. Solvent based electrohydrodynamic methods, electrospraying and electrospinning, spin coating, pressurized gyration and solvent based inkjet printing rely on the removal of solvents which are used to dissolve the carrier materials/excipients and drugs. In contrast to conventional pharmaceutical solvent evaporation based processes, such as film casting and spray drying, the formation of micro- and nanostructures using these methods mainly relies on the micro- and nanoscale dispensing volumes and an ultra-fast solvent evaporation rate. The thermal melt and solidification processes discussed in this review are melt electrospinning, thermal inkjet printing, extrusion based 3D printing, and thermal moulding. These methods are used for processing polymeric based drug delivery systems. As a result of the higher viscosity of a polymer melt in comparison to polymer solutions used in the solvent-based fabrication methods mentioned previously, the dimensions of materials produced by thermal based methods are usually in the micron rather than nano range. Nevertheless, these approaches have the concomitant advantage of the absence of solvent use and removal, while the requirements for nanoscale manufacture may vary according to the application. In all cases, consideration will also be given to the scalability of the approach in question as this is a key consideration for product development.

2. Electrohydrodynamics for micro- and nano-structure fabrication

Electrohydrodynamics refers to the dynamics of a fluid under an electrically charged field. There are two main electrohydrodynamic processing techniques, electrospraying and electrospinning [10]. Following Lord Rayleigh's theoretical estimation on the limit of charge a liquid droplet could carry before forming a liquid jet in 1882 [11], John Zeleny first published experimental work in 1914 on electrospraying [12]. In the 1920s, Geoffrey Ingram Taylor described the formation of a liquid cone with convex sides and a round tip which had a semi-vertical liquid cone angle of 49.3° (a whole angle of 98.6°) when a threshold electrical voltage was applied to an electrically conductive liquid [13]. This was later named as Taylor's cone in the field of electrohydrodynamic research. These two manufacturing processes work on same principle, but are distinguished by the physical form of the liquid when leaving the Taylor's cone, more specifically droplets for electrospraying (leading to particles) and a continuous stream for electrospinning (leading to fibers), as shown in Fig. 1.

The best-known and earliest application of electrospraying involves the ionization process that occurs in a mass spectrometer [14]. The adoption of both processes by the biomedical and pharmaceutical field is rather recent and is mainly associated with the ability of the techniques to fabricate micro- and nano-structures including particles, fibers and beaded fibers, which are of interest for both drug delivery and tissue engineering [15–17]. This review will only focus on their applications in amorphous drug delivery systems. The readers are directed to other comprehensive reviews on the applications of these techniques in other biomedical fields such as tissue engineering [15–17].

2.1. Basic working principles of electrospraying and electrospinning

The basic set-ups of electrospraying and electrospinning are very similar as shown in Fig. 1. The sample liquid feeds into the nozzle at a