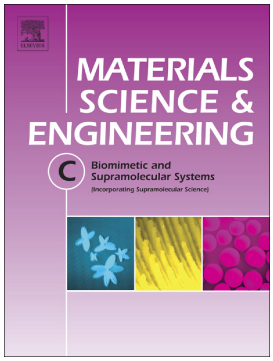

3D-micro-patterned fibrous dosage forms for immediate drug release

Aron H. Blaesi, Nannaji Saka

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3D-micro-patterned fibrous dosage forms for immediate drug release

Aron H. Blaesi* and Nannaji Saka

Department of Mechanical Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

A B S T R A C T

At present, the most prevalent pharmaceutical dosage forms, the orally-delivered immediate-release tablets and capsules, are porous, granular solids. They disintegrate into their constituent particulates upon ingestion to release drug rapidly. The design, development, and manufacture of such granular solids, however, is inefficient due to difficulties associated with the unpredictable inter-particle interactions. Therefore, to achieve more predictable dosage form properties and processing, we have recently introduced melt-processed polymeric cellular dosage forms. The cellular forms disintegrated and released drug rapidly if the cells were predominantly interconnected; yet preparation of interconnected cells relied on the coalescence of gas bubbles in the melt, which is unpredictable. In the present work, therefore, 3D-micro-patterned fibrous dosage forms with intrinsically interconnected void space are presented. It is demonstrated that such dosage forms can be readily prepared by melt extrusion of the drug-excipient mixture, followed by patterning the fibrous extrudate on a moving surface. The resulting fibrous structures are fully predictable by the extruder nozzle diameter and the motion of the surface. Drug release experiments show that the specific drug release rate from single fibers scales roughly in proportion to the fiber curvature or specific surface area. Furthermore, the disintegration time of the fibrous dosage forms is of the order of that of the corresponding single fibers, well within immediate-release specification. Finally, models of dosage form disintegration and drug release by single fibers and fibrous structures are developed. It is found that drug release from fibrous dosage forms is predictable by the physico-chemical properties of the excipient and such microstructural parameters as fiber radius, inter-fiber spacing, and the volume fraction of water-soluble excipient in the fibers.

1. Introduction

As shown schematically in Fig. 1a, the present immediate-release pharmaceutical tablets and capsules are porous, granular solids of drug and excipient particles. Both the choice of the excipient and the design of the microstructure are aimed at promoting rapid disintegration of the dosage form into its constituents upon contact with gastrointestinal fluid. This provides a large surface area-to-volume ratio (specific surface area) of the solid exposed to the fluid and thus effects immediate dissolution of drug particles after ingestion [1-3].

Despite their ability to release drug rapidly, and their widespread use and application, the microstructure and manufacture of the granular dosage forms are difficult to predict because processing granular matter is fraught with numerous difficulties [4-8]. For example, mixing drug and excipient particles uniformly is hampered by particle segregation and agglomeration, and dispensing and compacting particulates is complicated by the uneven flow of granular matter [9,10]. As a consequence, the design, development, and manufacture of granular dosage forms rely heavily on inefficient statistical or empirical methods [11].

Dosage forms prepared by a predictable process could open opportunities to achieve faster product development, deterministic and tightly controlled properties, and faster manufacture of products with repeatable quality [12-14]. Predictable dosage form manufacture could be achieved by liquid-based processing, as the streamlines in laminar flow follow deterministic pathways, and the flow rates can be calculated from "constitutive" models [15].

As the manufacturing process is changed from granular to liquid-based processing, however, the resulting microstructures are changed, too. The solidification of a melt, for example, yields a minimally-porous, solid microstructure as shown in Fig. 1b. The specific surface area of the minimally-porous structures is much smaller than that of the porous, granular solids, and thus the rate at which such structures disintegrate is too small for typical immediate-release applications.

Therefore, we have recently introduced cellular dosage forms prepared from polymeric melts [16-20]. The cell structures were prepared by the nucleation and growth of gas bubbles in a drug-laden polymer melt, and by injection of the bubbles in a micro- or

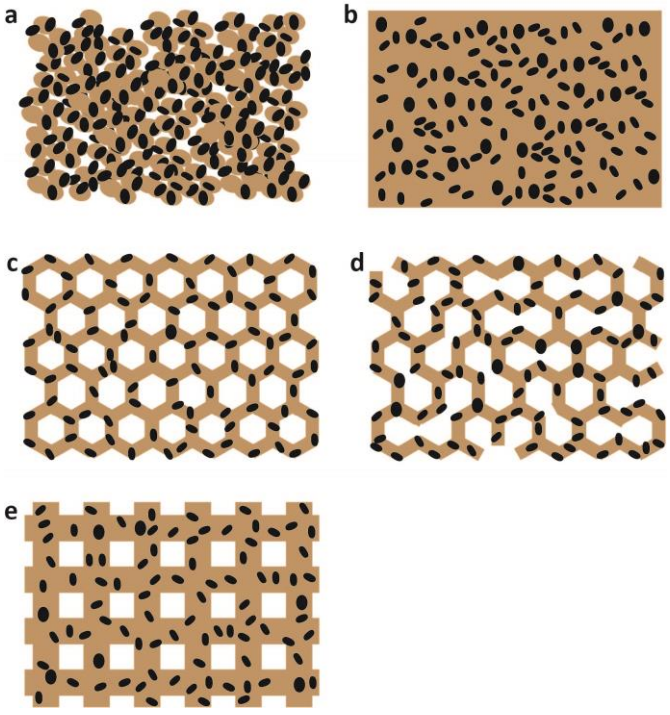

Fig. 1. Microstructures of granular and melt-processed dosage forms: (*a*) granular, (*b*) non-porous, (*c*) cellular with closed-cells, (*d*) cellular with partly open cells, and (*e*) fibrous dosage forms.