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Melt-processed polymeric cellular dosage forms for immediate drug release

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ABSTRACT

The present immediate-release solid dosage forms, such as the oral tablets and capsules, comprise granular matrices. While effective in releasing the drug rapidly, they are fraught with difficulties inherent in processing particulate matter. By contrast, liquid-based processes would be far more predictable; but the standard cast microstructures are unsuited for immediate-release because they resist fluid percolation and penetration. In this article, we introduce cellular dosage forms that can be readily prepared from polymeric melts by incorporating the nucleation, growth, and coalescence of microscopic gas bubbles in a molding process. We show that the cell topology and formulation of such cellular structures can be engineered to reduce the length-scale of the mass-transfer step, which determines the time of drug release, from as large as the dosage form itself to as small as the thickness of the cell wall. This allows the cellular dosage forms to achieve drug release rates over an order of magnitude faster compared with those of cast matrices, spanning the entire spectrum of immediate-release and beyond. The melt-processed polymeric cellular dosage forms enable predictive design of immediate-release solid dosage forms by tailoring microstructures, and could be manufactured efficiently in a single step.

1. Introduction

Pharmaceutical dosage forms are formulations of biologically active drug substances and drug carriers or excipients. They can be solids, ranging from a few nanometers to several millimeters in size, semi-solids (such as ointments), liquids, or even gases [1–6]. For decades, the most prevalent dosage forms have been the solid, immediate-release oral tablets and capsules. Typically, they consist of a granular material structure compounded by blending and compacting drug and excipient particles. The microstructure and solid-state properties are critical, for they determine the rate of drug release in the gastrointestinal tract, affecting the concentration profile of drug at the biological target [7–11]. Upon ingestion, the granular, immediate-release dosage form is percolated by gastric fluid and the bonds between the particles are severed resulting in rapid disintegration of the dosage form into its particulate constituents. The small drug particles with large surface area-to-volume ratio then release drug molecules and are dissolved almost immediately [12–19].

Manufacture of the granular dosage forms, however, is fraught with several problems [20]. Mixing and compacting the drug and excipient particles is hampered by particle segregation [21,22], uneven flow [23–26], and aggregate formation resulting in poor dissolution characteristics [27,28]. Therefore, drug and excipient particles are usually combined with a solvent and a binder prior to compaction to form granular agglomerates that exhibit improved granular flow and uniformity [29]. This entails resource-intensive and time-consuming batch processing: mixing, granulating, drying, milling, and screening followed by tableting, coating, and so on [30]. Even then, a robust process that consistently provides dosage forms with the desired properties is difficult to achieve. The reason is that the theories elucidating the behavior of granular media are far from complete [31,32], which limits the adoption of deterministic approaches in manufacturing process control, product and process development, and manufacturing scale-up [33]. As a consequence, large batch-to-batch variations are not uncommon in drug manufacturing, resulting in out-of-specification product waste and expensive off-line quality control [34]. Furthermore, the lead-times to develop and scale-up a formulation are long, which limits the flexibility in product development and in the supply of materials for clinical trials [35–37].

By contrast, manufacture of the dosage forms by casting or molding could mitigate many such limitations. The material is fluidized either by a solvent [38] or by melting [39] and is handled in liquid form, thus imparting reproducible, predictive microstructure and properties. Numerous studies have shown, however, that such cast dosage forms are appropriate only for long-term or sustained release, particularly if they consist of the biologically inert and chemically and physically stable polymeric materials [40–42]. They are unsuited for immediate drug release because cast matrices resist percolation of the dissolution

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medium, giving a much slower rate of drug release compared with the granular counterparts. Recently, it has been reported that dosage forms based on solid foam matrices release drug faster than cast structures [43,44]. However, also such dosage forms were developed for the sustained release of drug. The increase in drug release rate, accordingly, was only a factor of two compared with the cast forms, not enough for immediate-release.

Thus the objectives of this work are to design, prepare, test, and model new immediate-release solid dosage forms prepared by a predictable liquid-based process. We primarily focus on microstructures fabricated by the solidification of mixtures of molten polymeric excipients and solid drug particles which are not degraded by the applied heat treatment. Because the kinetics of melting and solidification are inherently faster than solvent addition and removal, the process rates are correspondingly greater in a melt process, in addition to avoiding solvent handling and waste.

2. Dosage form requirements and design considerations

The most basic requirement of an immediate-release solid dosage form is the conversion of the solid drug content into molecularly dissolved units within a specified time after ingestion (generally between 3 to 15 min, but no longer than 30 min). Additional specifications are: geometry, esthetics, chemical purity, long-term stability, and mechanical strength, among others [45]. In conformity with these requirements, polymeric cellular dosage forms comprising skeletal structures of non-toxic, stable solid polymeric excipient with drug embedded either as individual molecules or as solid particles are proposed. The gas-filled cells or voids can be isolated (closed cells), partially interconnected (partially open cells), or fully interconnected (open cells).

Cellular solids are abundant in nature and are widely employed as engineering materials [46], but their drug release behavior has not been systematically investigated so far. It is expected that drug release can be controlled by tailoring the excipient material properties and the topology of the cells. If the excipient is insoluble, diffusive transport [47] of either the dissolution medium into or the drug molecules out of the dosage form are rate-determining. The distance that an individual drug molecule in solution travels by diffusion in the time required for immediate drug release, however, is much shorter than the characteristic length-scale of a typical dosage form (several millimeters). Therefore, such cellular dosage forms that consist of an insoluble excipient are unsuited for immediate drug release. Shorter dissolution times can be achieved if the excipient is soluble so that erosion of the excipient dominates. In this case, excipients that resist the penetration of dissolution medium, or the drug from diffusing out, are just eroded away. The drug release rate of dosage forms using erodible excipients is greatest if the surface area-to-volume ratio of the solid material exposed to the dissolution medium is largest. The surface area-to-volume ratio is increased, for example, in open-cell structures that take advantage of capillary effects for rapid percolation of the dissolution medium to the core of the dosage form. We show that such open-cell structures with drug embedded in an erodible excipient can give drug release rates within or even greater than the present immediate-release specifications.

3. Materials and methods

3.1. Preparation of cast and cellular dosage forms

Acetaminophen powder was first sieved using a stainless steel mesh with a nominal opening of 53 μm (size No. 270). The drug particles were then combined with solid polyethylene glycol 8000 (PEG 8000) flakes to give a formulation of 63% Acetaminophen and 37% PEG 8000 by weight. The mixture was then heated to 90 °C and kneaded manually until a uniform paste was formed. Subsequently, an aliquot of the paste was put in a stainless steel mold held at 25 °C. The aliquot was compressed and cooled in the mold at 25 °C to give a cast disk with diameter 13 mm and thickness 2.5 mm. This disk was used as reference of the unfoamed (cast) samples.

For preparation of the cellular dosage forms, the cast disk was placed in a sample holder with an inside diameter of 13 mm. The sample was then soaked in a high-pressure oven for 50 min at a temperature, T_s, and a pressure, p_s (T_s was between 70 °C and 130 °C and p_s was 4.1–6.9 MPa). The gas used in the oven was nitrogen and the pressure was applied using a Trexel Supercritical Fluid System (Trexel, Inc.). Subsequently, the pressure was released in a time τ_r, which was either 3 s or 1 min. The oven was then opened and the temperature of the disk reduced to room temperature using an industrial fan.

Thus the cast and cellular dosage forms prepared here just consist of a single polymeric excipient and the drug substance, whereas the foaming agent (nitrogen) is volatile and chemically and biologically inert. No residues are left behind that could potentially be toxic or impair the stability of the dosage form.

3.2. Scanning electron microscopy (SEM)

A cross sectional surface of the dosage form that shows its microstructure for SEM imaging was obtained by first scoring the sample with a razor blade and then breaking it manually along the score. A Zeiss Merlin High Resolution SEM with a GEMINI column was used to image the microstructure of the cross sectional surface. Imaging was done with an in-lens secondary electron detector. An accelerating voltage of 5 kV and a probe current of 95 pA were applied to operate the equipment. The magnification of the images taken is 50×.

3.3. Dissolution testing

The dosage form was first attached to a ring disk using a drop of glue (Loctite Super Glue) to avoid floating of the dosage form in the dissolution medium. The sample was then placed at the bottom of a dissolution vessel (within a Sotax dissolution bath) which was filled with 900 ml of 0.05 M phosphate buffer solution (using sodium phosphate monobasic and sodium phosphate dibasic) at a pH value of 5.8 and a temperature of 37 °C. The solution was stirred using a paddle rotating at 50 rpm. Concentration of the dissolved drug was measured versus time by UV absorption at 244 nm using a fiber optic probe (Pion, Inc.).

3.4. Rotating disk experiments

A 2.2 mm thick cast disk consisting of 97% PEG 8000 and 3% Acetaminophen by weight was attached to the center of rotation of a flat stainless steel surface connected to a rotator. The sample was then immersed in a dissolution vessel (a Sotax dissolution bath) which was filled with 900 ml of 0.05 M phosphate buffer solution (using sodium phosphate monobasic and sodium phosphate dibasic) at a pH value of 5.8 and a temperature of 37 °C. The disk was rotated at rotation rates between 50 rpm and 250 rpm and the concentration of dissolved drug was measured versus time by UV absorption at 244 nm using a fiber optic probe (Pion, Inc.).

The data so obtained was used to estimate the concentration of the eroding polymer at the solid/liquid interface, c_0. If it is assumed that the dissolution medium is a dilute solution and behaves as a Newtonian viscous fluid, the flux of the polymer eroding from a flat rotating surface can be expressed, provided the concentration boundary layer is at steady-state, by Levich's equation [48]:

$$j = 0.62\left(\frac{\rho_f}{\mu_f}\right)^{\frac{1}{6}} D^{\frac{2}{3}} c_0 \Omega^{\frac{1}{2}} \tag{1}$$