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Microstructural effects in drug release by solid and cellular polymeric dosage forms: A comparative study

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ABSTRACT

In recent studies, we have introduced melt-processed polymeric cellular dosage forms to achieve both immediate drug release and predictable manufacture. Dosage forms ranging from minimally-porous solids to highly porous, open-cell and thin-walled structures were prepared, and the drug release characteristics investigated as the volume fraction of cells and the excipient molecular weight were varied. In the present study, both minimally-porous solid and cellular dosage forms consisting of various weight fractions of Acetaminophen drug and polyethylene glycol (PEG) excipient are prepared and analyzed. Microstructures of the solid forms and the cell walls range from single-phase solid solutions of the excipient and a small amount of drug molecules to two-phase composites of the excipient and tightly packed drug particles. Results of dissolution experiments show that the minimally-porous solid forms disintegrate and release drug by slow surface erosion. The erosion rate decreases as the drug weight fraction is increased. By contrast, the open-cell structures disintegrate rapidly by viscous exfoliation, and the disintegration time is independent of drug weight fraction. Drug release models suggest that the solid forms erode by convective mass transfer of the faster-eroding excipient if the drug volume fraction is small. At larger drug volume fractions, however, the slower-eroding drug particles hinder access of the free-flowing fluid to the excipient, thus slowing down erosion of the composite. Conversely, the disintegration rate of the cellular forms is limited by diffusion of the dissolution fluid into the excipient phase of the thin cell walls. Because the wall thickness is of the order of the drug particle size, and the particles are enveloped by the excipient during melt-processing, the drug particles cannot hinder diffusion through the excipient across the walls. Thus the disintegration time of the cellular forms is mostly unaffected by the volume fraction of drug in the walls.

1. Introduction

The orally-delivered immediate-release tablets and capsules, the prevalent pharmaceutical dosage forms at present, are porous, granular solids consisting of drug and excipient particles [1]. Upon ingestion, the pores between the granules are percolated by the gastro-intestinal fluid, and the bonds are severed resulting in rapid disintegration of the dosage form into its particulate constituents. The small drug particles then release drug molecules, which are subsequently absorbed by the blood stream and distributed to the disease-specific biological targets. As required by the large range of the potency of drugs, the drug content in the granular dosage forms can be varied in a large range, from a few micrograms to several hundred milligrams, without compromising the fast disintegration rate of the dosage form [2–7].

The primary drawback of the granular forms, however, is that their manufacture is fraught with difficulties inherent in processing particulate matter. For example, mixing, dispensing, and compacting the drug and excipient particles are inefficient due to particle segregation, uneven flow, and aggregate formation [8–15].

Such problems could be largely mitigated by transitioning from powder processing to the more predictable liquid-based processing. Therefore, we have recently proposed both minimally-porous solid and cellular dosage forms that can be prepared by melt-processing [16–19]. The minimally-porous solid forms are solid solutions or particle-dispersed composites of the excipient and the drug. The cellular dosage forms are solid frameworks of a drug-excipient solid solution or composite and, additionally, gas-filled voids or cells. The cells can be either closed or partially open.

We have demonstrated that the drug release rate of the dosage forms can be tailored by altering the cell volume fraction and the connectivity of the void space. For example, if the cell volume fraction is large and the cell structure predominantly open, the drug release rate of the cellular dosage forms can be an order of magnitude faster than that of their minimally-porous solid counterparts.

The drug release behavior of the minimally-porous solid and cellular dosage forms may also be changed, however, if the volume fraction of drug in the solid phase (or the drug content) is altered [20–23]. In this work, therefore, the volume fractions of the drug

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Nomenclature

b	bond length along polymeric chain
c_0	interfacial concentration
$c_{0,d}$	interfacial concentration of dissolving drug
$c_{0,e}$	interfacial concentration of dissolving excipient
c_d	concentration of drug in dissolution medium
c_e	concentration of excipient in dissolution medium
D	diffusivity of solute in dissolution medium
D_0	diameter of dosage form
D_d	diffusivity of drug in dissolution medium
D_e	diffusivity of excipient in dissolution medium
D_{eff}	effective diffusivity of dissolution fluid in cell wall
$D_{w,e}$	diffusivity of dissolution medium in excipient
$D_{w,d}$	diffusivity of dissolution medium in drug
d	drug particle size
d_{cell}	diameter of cells
E	erosion rate of dosage form
E_d	erosion rate of drug phase
E_e	erosion rate of excipient phase
$\overline{E}_e$	average erosion rate of excipient phase
f_d	weight fraction of drug in dosage form
f_{open}	fraction of open cells
H_0	initial thickness of dosage form
h_0	thickness of cell walls
j	flux of eroding material
j_d	flux of eroding drug
j_e	flux of eroding excipient
k_b	Boltzmann's constant
l_{pen}	penetration length
$M_{d,0}$	initial mass of drug in dosage form
m_d	mass of drug released from dosage form
dM_d/dt	drug release rate
N	number of bonds along polymeric chain
n	number of percolation-diffusion-exfoliation sequences to disintegrate dosage form
p	pressure
p_a	atmospheric pressure
p_s	sorption pressure
R	radius of drug particle
R_0	initial radius of drug particle
Re	Reynolds number
r, θ, φ	spherical coordinates
Sc	Schmidt number
T	temperature
T_0	room temperature
T_s	sorption temperature
t	time
$t_{0.8}$	time to dissolve 80% of the drug content
$t_{0.8,c}$	calculated time to dissolve 80% of the drug content
t_{cool}	cooling time
t_d	dissolution time of drug particle
t_{dis}	disintegration time of dosage form
$t_{dis,ex}$	disintegration time of an exfoliation
t_{ex}	time to exfoliate a fragment
t_{pen}	penetration time
t_{perc}	percolation time
t_r	pressure release time
t_s	sorption time
v_∞	far-field velocity of dissolution medium
x, y, z	cartesian coordinates
δ	height of protruding drug particles
$\delta_{c,e}$	excipient concentration boundary layer thickness of smooth surface
$\delta_{c,d}$	drug concentration boundary layer thickness
$\overline{\delta}_{c,d}$	average thickness of drug concentration boundary layer
δ_{eff}	effective concentration boundary layer thickness
δ_v	viscous boundary layer thickness
λ	inter-particle distance
μ	extensional viscosity of fluidized excipient
μ_f	viscosity of dissolution medium
μ_s	shear viscosity of fluidized excipient
ρ	density
ρ_d	density of solid drug
ρ_e	density of solid excipient
ρ_f	density of dissolution medium
ρ_s	average density of non-porous solid material
σ_0	initial stress applied on cell wall
φ_d	volume fraction of drug in solid phase
φ_d^*	percolation threshold of drug phase
φ_d^{**}	percolation threshold of excipient phase
φ_v	volume fraction of voids
Ω	angular velocity of basket

and the excipient in the solid phase are varied over a large range, and their effect on the drug release rate of both solid and cellular dosage forms is investigated.

2. Microstructural considerations: solid versus thin-walled cellular dosage forms

Fig. 1a is a schematic of a solid dosage form consisting of an erodible, polymeric excipient and a very small quantity of uniformly distributed dissolved drug molecules. Upon immersion in a dissolution fluid, the fluid diffuses into the dosage form. Concurrently, molecules of the excipient and the drug are transported away from the dosage form by diffusion, or by convection if the medium is stirred. Both processes are termed erosion. The diffusive flux of the dissolution fluid into the dosage form, and the erosion rate of the excipient and drug molecules, are determined by the physico-chemical properties of the excipient, the predominant component of the dosage form in this case.

Schematics of dosage forms consisting of randomly mixed excipient and drug particles are shown in Figs. 1b–d. In a random mixture, the drug particles form clusters ranging in size from that of a few particles to a large collection of particles, depending on their volume fraction. A cluster is considered interconnected if it extends from one face of the dosage form to the other. In a microstructure as shown in Fig. 1b, the volume fraction of drug particles is small. The excipient is interconnected, but the drug particles and clusters are isolated. Thus, if the diffusivity of the dissolution fluid molecules in the excipient is greater than that in the drug, the fluid can diffuse through the excipient to the interior. Similarly, if the erosion rate of the excipient is greater than that of the drug, the excipient can erode around the drug particles and wash them off. As the volume fraction of the drug particles is increased, as in Figs. 1c and d, however, the cluster size and connectivity of the drug phase are increased, and the connectivity of the excipient is decreased. At a large volume fraction of drug, as shown in Fig. 1e, the excipient is isolated. In such microstructures, passage of the dissolution fluid to the interior and excipient erosion around the drug particles are hindered by the drug phase.

Unlike the non-porous dosage forms where the drug particle size, $d \ll H_0$, the dosage form thickness ($d \sim 40$ μm and $H_0 \sim 5$ mm), the wall thickness, h_0, of the cellular dosage forms considered here is of the order of the drug particle size, d. Thus the cell wall may be considered a 2-dimensional sheet of the excipient-drug composite, as