Chemical Engineering Journal 320 (2017) 549–560

Contents lists available at ScienceDirect

Chemical Engineering Journal

journal homepage: www.elsevier.com/locate/cej

Continuous manufacture of polymeric cellular dosage forms

Aron H. Blaesi *, Nannaji Saka

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

HIGHLIGHTS

- A continuous, microfluidic melt process for the manufacture of polymeric cellular dosage forms is presented.
- The size and volume fraction of gas-filled cells in the dosage forms are precisely controlled.
- Disintegration rate and density of the dosage forms can be tailored by altering the volume fraction of cells.

ARTICLE INFO

Article history:
Received 28 September 2016
Received in revised form 17 January 2017
Accepted 9 February 2017
Available online 11 February 2017

Keywords:
Continuous pharmaceutical manufacturing
Cellular dosage forms
Microfluidics
Pharmaceutical tablets
Cellular solids
Dosage form microstructure

ABSTRACT

The most prevalent pharmaceutical dosage forms at present are granular solids in the form of oral tablets and capsules. While effective in releasing drug rapidly upon contact with gastrointestinal fluid, their manufacture, which relies on particulate processing, is fraught with difficulties associated with the unpredictable inter-particle interactions. Such difficulties, however, could be easily overcome by transitioning to a liquid-based process. Therefore, we have recently introduced melt-processed polymeric cellular dosage forms. The drug release behavior of the cellular forms was tailored by altering the microstructure; yet their preparation relied on an inefficient batch method comprising gas dissolution, and nucleation and growth of microscopic gas bubbles in the melt. In this study, therefore, we present a continuous microfluidic melt extrusion and molding process. The cellular dosage forms are produced by injecting gas bubbles directly into the melt stream in a micro- or milli-fluidic channel, followed by molding and solidification of the cellular structure. A model is developed to illustrate the effects of the width, frequency, and pressure of the gas injection pulses, and the flow rate and viscosity of the melt, on the microstructural parameters of the dosage forms produced. Experimental results show that the size and volume fraction of gas-filled cells (or voids) are predictable. They also confirm that the dosage form disintegration rate and density can be tailored by altering the volume fraction of voids. It is thus demonstrated that polymeric cellular dosage forms with predictable drug release properties, and density, can be readily manufactured by a continuous process.

© 2017 Elsevier B.V. All rights reserved.

1. Introduction

For decades, the most prevalent dosage forms for delivering drugs, the oral tablets and capsules, have been compacted, granular solids [1]. A granular dosage form typically permits percolation of gastrointestinal fluid to the interior after ingestion, and then the bonds between the granules are severed so that the dosage form disintegrates into its constituent drug and excipient particles. If the drug particles are small, they have a large specific surface area, and thus rapid drug dissolution upon contact with gastrointestinal fluid is promoted. This enables that a large fraction of the ingested drug is absorbed by the blood stream, and available for distribution to the disease-specific target sites in the human body [2–6].

Although the granular dosage forms effect rapid drug release, their manufacture, which relies on particulate processing, is fraught with numerous difficulties [7–12]. For example, mixing drug with the carrier, or excipient, particles is hampered by particle segregation and agglomeration, and dispensing and compacting the particulates is complicated by their uneven flow. Moreover, because the theories elucidating particulate behavior are still incomplete it is difficult to predict and control manufacturing processes [13,14]. As a consequence, both resource-intensive and time-consuming batch processing (e.g., particulate mixing, granulating, drying, milling, screening, tableting, and coating) is required

* Corresponding author at: Department of Mechanical Engineering, Room 35-104, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

E-mail address: ablaesi@mit.edu (A.H. Blaesi).

http://dx.doi.org/10.1016/j.cej.2017.02.057
1385-8947/© 2017 Elsevier B.V. All rights reserved.

Nomenclature

A_p	area of syringe's piston
b	bond length along a polymeric chain
Ca	capillary number
c	specific heat
c_0	interfacial concentration of dissolving excipient
c_g	specific heat of gas phase
c_s	specific heat of solid phase
D	diffusivity of excipient in the dissolution medium
D_0	dosage form diameter
D_{cell}	diameter of a cell
D_{eq}	equivalent diameter of a sphere
f_{open}	fraction of open cells
g	acceleration due to gravity
H_0	thickness of dosage form
j	flux of eroding polymer
k	thermal conductivity
k_b	Boltzmann's constant
k_g	thermal conductivity of gas
k_l	lower-bound for thermal conductivity
k_s	thermal conductivity of solid material
k_u	upper-bound for thermal conductivity
L_c	channel length
L_{cell}	total length covered by the cells along test line(s)
L_m	length of melt-filled channel segments
L_n	length of hypodermic needle
L_{solid}	total length covered by solid along test line(s)
l_{cell}	average intercept length of a cell
dM_f/dt	mass flow rate of particulates in the syringe
N	number of bonds along a polymeric chain
N_{cell}	number of cells intersecting a test line
P_{atm}	atmospheric pressure
P_b	bubble pressure at hypodermic needle exit
P_{cap}	capillary pressure
P_g	gas pressure in the gas reservoir
$P_{m,F}$	melt pressure at point F
$P_{m,F}^{(0)}$	melt pressure at point F (melt-filled channel)
$P_{m,F}^{(1)}$	melt pressure at point F (channel filled with bubbles and melt)
$P_{m,H}$	melt pressure at point H
p	pressure
Q_g	volumetric gas flow rate
Q_m	volumetric melt flow rate at channel entrance
$Q_{m,0}$	volumetric melt flow rate in melt-filled channel
$Q_{m,1}$	volumetric melt flow rate at entrance of channel filled with bubbles and melt (during valve closing)
$Q_{m,s}$	volumetric flow rate of melt-filled channel segment
R_c	radius of the channel
Re	Reynolds number
Re_c	critical Reynolds number
R_n	radius of the hypodermic needle
S_{cell}	surface area of a cell
T	temperature
T_0	initial temperature
T_c	center temperature of the dosage form
T_w	wall temperature
t	time
$t_{0.8}$	time to dissolve 80% of the drug content
t_{dis}	disintegration time of dosage form
V_b	bubble volume
$V_{b,F}$	bubble volume at point F
$V_{b,H}$	bubble volume at point H
V_{cell}	cell volume
V_g	volume of gas-filled segment
V_m	volume of melt-filled segment
V_b	terminal rising bubble velocity
$v_{m,0}$	mean velocity of melt in channel
v_p	velocity of the syringe's piston
x	axial coordinate
γ	surface tension
λ	"free" distance between bubbles
λ_{cell}	mean free distance between cells
φ_d	volume fraction of drug in solid particle bed
φ_e	volume fraction of excipient in solid particle bed
$\varphi_{m,c}$	volume fraction of melt in the channel
φ_v	volume fraction of voids
ρ	density
ρ_d	density of solid drug
ρ_e	density of solid excipient
ρ_f	density of dissolution medium
ρ_g	density of gas
ρ_m	density of melt
ρ_s	average density of non-porous solid material
μ_f	viscosity of dissolution medium
μ_g	viscosity of gas
μ_m	viscosity of melt
τ_g	duration of valve opening
τ_m	duration of valve closing
Ω	angular velocity of basket

to produce granular dosage forms [15,16]. Additionally, the lead-times for developing and scaling up new formulations are unduly long, limiting flexibility in product development and timely delivery of dosage forms for clinical trials [17,18].

In contrast to the unpredictable processing of granular matter, mixing, dispensing and molding liquids in laminar flows are highly predictable and repeatable. The streamlines follow deterministic pathways and the flow rates are calculable from simple "constitutive" models [19–21]. Therefore, we have recently introduced cellular dosage forms prepared from polymeric melts [22–25]. A solid disk was first placed in a container in a high-pressure oven, melted for several minutes, and charged with an inert gas at a temperature of 70–130 °C and a pressure of 5–34 MPa. After saturation of the molten disk by the gas, the pressure was reduced to induce nucleation, growth, and coalescence of gas bubbles. Finally, the temperature of the mixture was lowered to solidify the cellular structure.

Though adequate for preparing experimental dosage forms, such a process is not optimal for continuous manufacture of pharmaceuticals for various reasons. First, the diffusivity of gas in the polymer at the process temperatures and pressures is of the order of 10^{-10}–10^{-9} m^2/s limiting the rates at which the several millimeters thick raw material can be charged with gas. Second, high pressure is required to add the required amount of gas to the material. Third, relatively high temperatures are needed to achieve the optimal rates of nucleation, growth, and coalescence of the gas bubbles. High temperatures degrade many kinds of drugs.

The above limitations could be overcome if the gas is delivered directly into the melt stream, eliminating the gas dissolution, bubble nucleation, and bubble growth steps altogether. For example, a gas-releasing blowing agent could be dispersed in the melt, as in the manufacture of foods and polymeric foams [26,27]. But the conversion of a small volume of a solid or a liquid blowing agent into a large volume gas bubble is difficult to control, and typically

Download English Version:

https://daneshyari.com/en/article/6466050

Download Persian Version:

https://daneshyari.com/article/6466050

Daneshyari.com