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Research paper

Development of drying-induced stresses in pharmaceutical granules prepared in continuous production line

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ABSTRACT

The phenomenon of development of drying-induced stresses has been given a through consideration in the literature on drying of many products. At the same time, to the best of our knowledge, the open published sources contain no information on drying stresses in pharmaceutical granules prepared by continuous manufacturing methods. To study the appearance and evolution of drying-induced stresses in pharmaceutical granules during their production, in this work a theoretical model of drying of single wet pharmaceutical granule has been developed and successively validated by published experimental data obtained on ConsiGma™ continuous from-powder-to-tablet production line (GEA Pharma Systems). The results demonstrate that elevated temperatures of drying air result in faster drying process (which reduces the specific cost of the final product), but, on the other hand, quick drying leads to substantial drying-induced stresses which may damage the granule microstructure, resulting in cracking or even breakage of granules. The drying-induced stresses increase with drying temperature, porosity and size of dense non-hollow granules. The negative effects promoted by the drying-induced stresses should be taken into consideration when choosing operating conditions of continuous production lines including drying of pharmaceutical granules.

1. Introduction

In pharmaceutical science and industry the strategic vision is nowadays changing from batch processing to continuous and semi-continuous tableting production methods [1–3]. Such technique requires development and implementation of in-line real-time quality control systems, which should rely on the knowledge of the process specifics and the effect of process variables on the product quality [4]. Therefore, model-based design of pharmaceutical processes and products becomes highly important [5].

Presently, there are several continuous tablet manufacturing lines in the market; one of them is ConsiGma™ (GEA Pharma Systems). This installation consists of wet high-shear granulation, fluidized bed drying, evaluation and compression units. Recently, Mortier et al. [4] applied the mechanistic model [6], originally developed for evaporation of droplet of suspension/solution, to describe the drying behavior of a single wet granule of pharmaceutical material in a fluidized bed of ConsiGma™ setup. The calculated granule parameters were in good agreement with experimental data. The results of investigation [4] testify on high versatility and universality of the fundamental modelling approach, and feasibility of comprehensive theoretical description of transport phenomena attributed to the fabrication of pharmaceutical granules.

The phenomenon of development of drying-induced stresses has been given a through consideration in the studies devoted to drying of wood [7–15], paper and paperboard [16–19], clay and ceramics [15,20–26], concrete [27–29], soil [30–32], polymer and colloidal films and coatings [33–39], corn kernels [40–43], composite food [44], gel [45], leather [46,47] and others. An extensive review on phenomena of drying-induced strains and stresses is available [48]. Author's previous investigations [49,50] have demonstrated that drying-induced stresses in wet particles can develop during the second drying stage as a result of internal temperature and pressure gradients. The outcomes of these earlier studies suggest an idea that appearance of drying-induced stresses in wet granules produced for the range of process parameters offered by ConsiGma™ system should be investigated. Drying-induced stresses developing in granules during the continuous tablet manufacturing may affect the essential properties and quality of the granules, their tableting ability and, in some cases, lead to cracking/rupture of the obtained product.

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Nomenclature

B_k	permeability of granule crust (m^2)
c_p	specific heat (J/kg/K)
d_p	granule diameter (m)
D_{eff}	effective diffusion coefficient (m^2/s)
D_v	vapor diffusion coefficient (m^2/s)
E	Young's modulus (Pa)
h	heat transfer coefficient (W/m^2/K)
h_D	Mass transfer coefficient (m/s)
h_{fg}	specific heat of evaporation (J/kg)
k	thermal conductivity (W/m/K)
m	mass (kg)
M	molecular weight (kg/mol)
$\dot{m}_v$	mass transfer rate (kg/s)
p	pressure (Pa)
r	radial coordinate (m)
R	radius (m)
R^2	coefficient of determination
$\Re$	universal gas constant (J/mol/K)
t	time (s)
T	temperature (°C)
u	velocity (m/s)
X	moisture content (dry basis) (kg_w/kg_s)

Greek letters

α	thermal diffusivity (m^2/s)
α_T	coefficient of thermal expansion (1/K)
ε	granule porosity (–)
γ	empirical coefficient (–)
μ	dynamic viscosity (kg/m/s)
ν	Poisson's ratio (kg/m/s)
σ	stress (Pa)
σ_t	tensile strength of granule (Pa)
ρ	density (kg/m^3)

Subscripts

a	air
cr	crust
diff	diffusion in pores
f	final point of drying process
flow	forced flow in pores
g	drying gas
i	crust-wet core interface in wet granule
m	air–vapor mixture
p	granule (particle)
r	radial direction
s	solids or surface
v	vapor
w	water
wc	wet core of granule
0	initial point of drying
θ	tangential direction
∞	bulk of drying gas

In the present contribution, we give a theoretical method predicting the drying-induced stresses in wet pharmaceutical granules and perform parametric investigations of influence of granule size, granule porosity and process temperature on the behavior of the drying-induced stresses.

2. Theory of drying of wet granules

2.1. General background

The theoretical modelling of drying process of wet granules in technological equipment is based on description of drying kinetics of single granule (called also particle). The drying kinetics of a wet granule, containing liquid and solids, is usually divided in two drying stages. In the first drying stage, wet granule having excess of liquid is subjected to a stream of drying gas (air, steam, nitrogen, etc.), gains sensible heat and then liquid vaporization begins on the entire surface of wet granule. The process of evaporation from the granule surface results in decrease of the wet granule size and increase of solid concentration on its surface. Eventually, the entire surface of wet granule dries out and becomes covered with a dry porous layer called crust. From this moment, the front of liquid evaporation moves under the crust, into the wet granule interior, and the second stage of drying commences. In the second stage, the drying of wet granule interior (intra-granule liquid evaporation and vapor transfer to the ambient) is hindered by the surrounding crust layer. Pores in the crust layer can be considered as channels allowing the generated vapor to pass from the wet granule core toward the outside ambient. The second stage of drying continues until the granule moisture content reduces to equilibrium with the drying medium. After this point the drying process actually stops and the dry granule is heated up to a thermal balance with drying medium.

Typical evolutions of temperature and moisture content of wet granule during drying process are outlined in Fig. 1. In this figure,

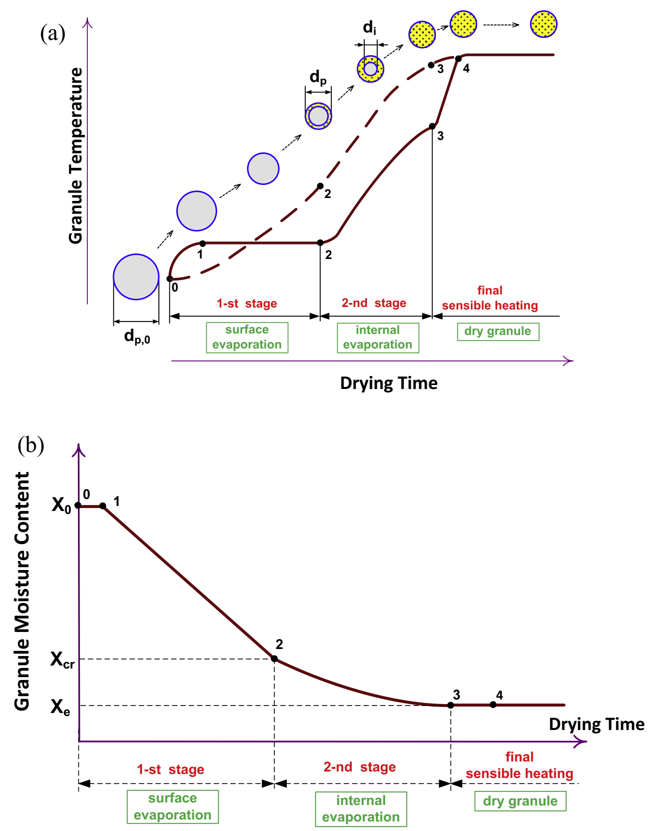

Fig. 1. Characteristic drying curves of: (a) – wet granule temperature (solid line – wet granule with suspended solids, dash line – wet granule with dissolved solids) and (b) – wet granule moisture content. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)