Chemical Engineering Journal 328 (2017) 785–815

Contents lists available at ScienceDirect

Chemical Engineering Journal

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

Review

A comprehensive review on process and engineering aspects of pharmaceutical wet granulation

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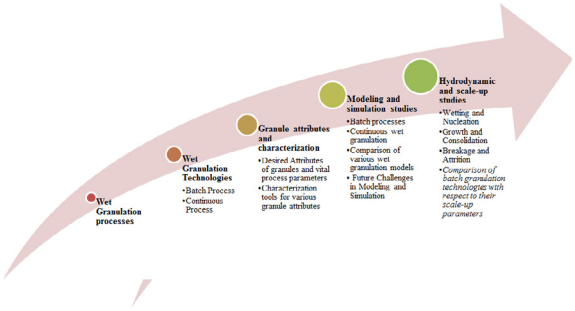
HIGHLIGHTS

- Granulators and their design.
- Granule attributes and their characterization.
- Process control and optimization.
- Modelling and simulation.
- Kinetics and scale up.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 21 April 2017
Received in revised form 13 July 2017
Accepted 14 July 2017
Available online 16 July 2017

Keywords:
Wet granulation
Granulator design
Modelling and simulation
Granule attributes and characterization
Process control
Kinetics
Scale-up

ABSTRACT

Wet granulation is a very important unit operation that finds applications in many industries mainly pharmaceutical and chemical industries. Various granulation technologies in batch and continuous modes were employed viz., high shear granulators, fluid bed granulators, twin screw granulators and the novel ones like foam granulators, steam granulators, dry granulators etc. In this review, various aspects of pharmaceutical granulation like technologies, characterization tools, process control, modelling and simulation, kinetics and scale up have been thoroughly analysed and discussed in terms of development trends and future challenges and prospects. The critical role played by various off line and inline characterization tools was highlighted along with their applications. Studies from PBM, DEM to hybrid models, CFD and ANN based models were presented in terms of their performance and challenges. Kinetic studies to understand the rate and influencing parameters of various steps involved in granulation process with controlling regimes were discussed along with the models used. The scale-up, a major challenge in granulation was also discussed in terms of the methodology and efficiency in retaining the granule attributes with proper control of process parameters was also presented. Process control protocols employed in the wet granulation process was discussed along with the relations of

Abbreviations: AE, Acoustic Emission; ANN, Artificial Neural Networks; API, Active Pharmaceutical Ingredient; BET, Brunauer–Emmett–Teller; CFD, Computational Fluid Dynamics; CIP, Constrained Interpolation Profile; CQA, Critical Quality Attributes; DEM, Discrete Element Model; ECT, Electrical Capacitance Tomography; EKE, Equipartition of Kinetic Energy; ETM, Equipartition of Translational Momentum; FBG, Fluid Bed Granulators; FBMG, Fluidized Bed Melt Granulation; FBRM, Focused Beam Reflectance Measurement; FDA, Food and Drug Administration; FG, Foam Granulation; GP, Granule Porosity; GSD, Granule Size Distribution; HPMC, Hydroxy Propyl Methyl Cellulose; HSWG, High Shear Wet Granulators; KF, Karl Fisher; LDV, Laser Doppler Velocimetry; LOD, Loss On Drying; LSWG, Low Shear Wet Granulators; MCC, Micro-Crystalline Cellulose; MPC, Model Predictive Control; MRI, Magnetic Resonance Imaging; MTR, Mixer Torque Rheometry; NIR, Near Infra-Red; PAT, Process Analytical Technologies; PBA, Pendulum Bridge Apparatus; PBM, Population Balance Model; PDPA, Phase Doppler Particle Analyser; PEPT, Positron Emission Particle tracking; PFR, Powder Feed Rate; PMMA, Poly Methyl MethAcrylate; PSD, Particle size diameter; PTFE, Poly Tetra Fluoro Ethylene; QbD, Quality by Design; ROM, Reduced Order Models; RPWG, Reverse Phase Wet Granulation; RTD, Residence Time Distribution; SCG, Super Critical Granulators; SEM, Scanning Electron Microscopy; SFV, Spatial Filter Velocimetry; SG, Steam Granulation; SI, Size Independent; SS, Stainless Steel; SSA, Specific Surface Area; TGA, Thermal Gravimetric Analysis; TSG, Twin Screw Granulators; XRPD, X-Ray Powder Diffraction.

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http://dx.doi.org/10.1016/j.cej.2017.07.091

different granule and tablet attributes to process and design parameters. The future challenges and prospects in the above mentioned aspects were listed for prospective researchers.

Contents

Nomenclature

ε	Porosity
W	Weight of liquid
ρ_l	Density of liquid
ρ_s	Density of the solid
h	Convective heat transfer coefficient of the particle
k_p	Conductive heat transfer coefficient of the particle
d_p	Diameter of the particle
λ	Latent heat of vaporization
L_{ht}	Entry length
T_g	Inlet gas temperature
T_l	Liquid temperature
A	Area of bed
m^o	Evaporation rate of liquid
ψ_α	Spray flux
V^o	Volumetric spray rate
A^o	Spray area
d_d	Average droplet diameter
τ_p	Drop penetration time
t_p	Time taken for a drop to fully penetrate the powder bed
t_c	Time taken for the exposed surface of powder to circulate back to the spray zone
$\vec{G}$	Gravitational acceleration
F_p	Sum of the forces on the particle caused due to other particles
F_w	Sum of the forces on the particle caused by walls
I	Inertia
$\vec{R}$	Position vector at current time
$\vec{V}$	Velocity vector at the current time step
$\vec{w}$	Rotational velocity vector at current time step
$\Delta\tau$	Length of the time step
$\vec{v_n}$	Normal collision velocity
$\vec{v_t}$	Tangential velocity
K	Spring constant
η	Damping coefficient
μ	Coefficient of friction
$\vec{\xi}$	Tangential overlap
$\vec{F_t}$	Tangential forces
$\vec{F_n}$	Normal forces
F(x,t)	F is the density of each particle and x is the vector
R_{form}	Birth rate of the particles having internal properties x
$R_{depletion}$	Death rate of the particles having internal properties x
F(s,l,g,t)	s, l, g are vectors which represent the solid, liquid, and Gas volumes in a granule
$R_{aggregation}$	Net rate of aggregation
R_{break}	Net rate of breakage
$R_{nucleation}$	Net rate of nucleation
X_{in}	Molar concentration of the in-flow properties
X_{out}	Molar properties of the out-flow properties
St_{def}	Stokes Deformation number
U_c	Representative collision velocity of Granules
P_d	Tapped density after vibration
A_d	Bulk density untapped
ρ_{EV}	Envelope density
ρ_s	Skeletal density
ρ_{bd}	Maximum compressed density
SSA	Specific Surface area