UPDATED INSIGHT ON FOAM BINDER GRANULATION

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ABSTRACT

To have updated handy reference as source of outstanding knowledge on foam binder granulation process in granulating the material(s). Granulation considered being important unit operation for producing pharmaceutical oral dosage forms. Revolutionising binder application methodology as advancement of wet granulation process best owed said process. It is a modified version of atomised spraying method and gaining wide acceptance. Product and process development calls for method of optimisation involving multidisciplinary activity and creates difficulties as several rudiments needed to be achievable, associated with umpteen features. Depth knowledge on process and formulation properties, monitoring granulation behaviour and its performance, is prerequisite. In this regard, information collected and presented as a handy note. Presented note will give insight on associated technicality and will assist researchers in getting optimised granule, having applicability in product evolution. This considered being offering outstanding knowledge and helping hand for getting granule with excellent feature.

Keywords: Binder, evolution, foam, granulation, process, technology.

INTRODUCTION

Granulation is a vital unit operation of pharmaceutical technology where small powdery particles agglomerated into larger entities called granule¹. This executed for improving flow ability, appearance and mixing; reducing segregation; eliminating dustiness and detrimental properties; and improving physical or chemical properties of fine powders²⁻⁴. Granulation achieved through incorporation of binder (as solution or melt) onto powder or compressing them, to ensure their coalescence and growth¹. This traditionally executed with wet-/dry-granulation process. Novel and modified processes includes fluidized-bed granulation, foam binder granulation (FBG), freeze granulation, melt/thermoplastic granulation, moisture activated dry granulation, pneumatic dry granulation, steam granulation, thermal adhesion granulation, and so on. All of these have limitations and superiority over each other⁴. Section of wet-granulation process calls for application of aqueous/non-aqueous solution of binder (SoB) and or polymer onto powder mass including instant release and controlled release products. Controlled release product uses release controlling polymers and in elevated quantity⁶. In production-scale, wet-granulation process uses spray technology for incorporating binders into powders, moving within granulator bowl. Type, geometry and location of nozzle, sprays geometry, spray rate, and droplet size influences performance of sprayer and hence efficiency of granulation process and granules⁷. The process of FBG developed abolishing many process-problems of sprayer in conventional spray method, considered substitute, and was acquiring wider acceptance⁸. FBG is advanced and refined method for incorporating binders in high-/low-shear granulator (HLSMG), extruder granulator, or fluid-bed processor (FBP), invented by The Dow Chemical Company (Midland, MI, USA). Said process designed to reduce complexity of spraying step and forefend plugging problems of spray nozzles⁹. Here aqueous SoB is added continuously or in batches to powdery particle bed in the form of foam, generated with foam generator⁹⁻¹². Foam penetration involved in FBG method is less dependent on powder hydrophobicity

comparing drop penetration, involved in spraying method¹³. It recognised as faster, simpler, and safer process. Being consider replacement for conventional atomised liquid spray technology gaining wider recognition¹⁴. Said process employs preferable and well recognised polymer (as binder) like hydroxypropylcellulose (KLUCEL™), ethyl cellulose (ETHOCEL™), poly(ethylene) oxide (POLYOX™), hydroxypropyl methylcellulose (hypromellose or METHOCEL™), hydroxypropylcellulose, methylcellulose, modified hydroxyethyl methyl cellulose (WALOCCEL™), sodium carboxymethyl cellulose, and so on^{11,14}. Matrix system based controlled release tablets, instant release tablets, and disintegrating tablets formulated with said process. Several formulations successfully scaled up from laboratory-scale to pilot-scale with good process control^{9,10,15}. In setting of above, strong need felt to focus updated information on FBG. Present works project information on background, issue, technicality, and current practice. Presented information has applicability in product evolution and predicting technical issues.

Advantages

- eliminates use of spray nozzle and eradicates plugging effects¹⁰;
- accomplishes consistent binder distribution⁹;
- demands low amount of binder for granulation;
- renders a low soak-to-spread ratio and achieves efficient binder delivery and particle coverage¹⁶;
- eradicates over wetting problem with diminished in-process water requirement¹⁰;
- cost effective, fast, robust and reproducible processing¹⁰;
- lowers processing cost through reducing drying, processing, and equipment clean-up time. Besides eliminates need of attendant for attending spray nozzles, and all other variables like nozzle configuration, distance from moving powder bed, spray patterns, clogging, droplet size, and droplet distribution¹⁰;
- need not require new equipment or drastic changes in processing steps. Requires general equipments even in

- small-scale laboratory setting or full-scale production settings¹⁰;
- processes flexibility for adopting continuous or batch process¹⁰;
- yields lower proportion of coarse saturated lumps (> 2 mm) comparing spraying method, even during vigorous agitation of powder¹¹;
- utilises proven and familiar water soluble binders like hydroxypropylcellulose, hypromellose, and so on¹⁰;
- immediate- and matrix-system based controlled-release, and orodispersible products can be easily scaled-up^{11,15}, and
- Possess approval from several regulatory authorities³.

Applications

- suited for products with very low drug concentration¹⁰ or drug level (in mg or µg per tablet) resulting better drug distribution¹³,
- able to carry active ingredients at a very low concentration or level with generated foam^{10,17},
- suited for very water-soluble or very poorly water soluble drugs and water sensitive formulations², and
- Able in handling historically proven difficult materials including natural ingredients, the components of nutritional supplements³.

Process and Technology

FBG process enables granulation employing HLSMG, or twin-screw extruder (TSE) granulator, or FBP in both laboratory-scale and production-scale settings. This process involves step-batch, or batch, or continuous mode of adding SoB (as aqueous foam) onto previously blended powder bed contained in HLSMG^{9,10} or fluidized powder bed contained in FBP, kept in operation^{10,18,19}. In TSE granulator, it applied through foamed binder application port, while in operation¹². After attaining granulation endpoint wet mass is subsequently wet-milled. Resulting wet granules subsequently dried in FBP until attaining desired moisture content level⁹⁻¹². Dried granules milled, sized, and characterised. Flow chart of FBG process is provided with Figure 1.

Principle

Conventional method of applying SoB involves encounter of spray droplet with a porous solid surface (powdery particle). This prevents its further travel from initial point of contact unless collision with another powder particle causes total/partial transfer of droplet onto the surface of colliding particle³. In FBG SoB applied as foams. Applied foams are capable in flowing through porous media by the “breaking and remaking process”. In the process of breaking and remaking bursting of foam bubbles may lead to bridging of lamellae and powder thus can regenerate foam as lamellae gets contacted by free gas or foam. This mechanism improves ability of foam to spread rather than to get soaked on encountering particles. Which in turn coats surface of powder, before absorption of liquid from the foam will be effective. As foams replace water with air, process possesses “low wet pickup property”^{13,16,20,21}. Here, distribution of SoB throughout powder bed gets improve associated with tremendous increase in surface area of liquid and foam volume of polymeric binder. Generated liquid droplets (foam) from foamed SoB had a high spread-to-soak ratio thus

got spread on the surface of particles to coat it and place binder where actually needed. This makes binder distribution more consistent^{5,9,10,22}. In case of extruder mechanical dispersion dominated nucleation mechanism is involved^{12,13}. The FBG process involves mechanical dispersion type of nucleation mechanisms that differs from spray which tends to incur early liquid penetration type of nucleation mechanisms^{5,13}.

Foam Generation and Application

Foam generator used, is a modified version of early design. Modification is incorporation of an air intensifier that intensifies and generates air pressure ≤ 150 psi from in-house air supplies of 40–80 psi. Intensified air pressure enabling foaming of viscous fluids²³. Laboratory-scale foam generator used for laboratory-scale and pilot-scale production, but heavy duty one used for manufacturing-scale^{9,10}. Foamed binder pumped via a plastic pipe into granulator bowl at suitable location where the blades will not be foul by pipe. Said pipe simply inserted through any convenient port accessing in to granulator bowl. Pumping carried out following any one of three distinct modes (i.e., batch, step-batch, and continuous) at a rate of 75 to 300 g/min, depending on product^{9,10}.

Quality of Foam

Concentration, molecular weight, and substitution-type of the polymer impart greatest flexibility to nature of aqueous phase and foam quality (FQ), and monitor stability of foam. Requisite stability of foam is highly process dependent. Viscous solutions with viscosity 150-300 cP generally produce highly elastic foams having high yield stress. These foams tediously produced, often have lowest FQ, having very low tendency to spread. Low viscosity having viscosity of 3-100 cP very conveniently foamed and can result very high quality foams with low density⁹.

Foams quantified in several ways while FQ calculated from penetration time and nucleation ratio. Said values used to determine range of acceptable FQ needed to get granules with wished quality^{9,11,24-26}. FQ is determined from volume of liquid (VLiq) and volume of gas (VGas) following the relation⁹:

$$FQ = V_{Gas} / (V_{Gas} - V_{Liq}) \times 100 \text{ at NTP}$$

Higher FQ value indicates higher surface area. Improvement in surface area of foams improves binder efficiency and its potentiality to carry various components (like highly potent and low volume drugs) into powder mass. FQ presented from wet foam (FQ < 70) to dry foam (FQ > 70). Wet foam has physical characteristics and flow similar to a liquid and exhibit a low rheological yield stress. Dry foam has a high air-to-liquid ratio and moves like solid with comparatively high rheological yield stress. They exhibit solid-like flow properties below their yield stress, tend to flow in pipes by wall slippage, and recommended for granulation^{9,10}. Increasing FQ through decreasing SoB concentration or liquid-to-solid ratio decreases average granule size²⁷. Improvement in surface area of foam improves binding efficiency of binder with same liquid and liquid-to-air ratio.

Figure 1: Flow Chart of Foam Binder Granulation Process

Said parameter of foam calculated from thickness of foam lamellae (H), surface area of foam (A), and volume of liquid (V_{Liq}) using given relation⁹.

$$H = 2 V_{Liq} / A$$

Foam density (ρ_F) readily calculated from density of liquid phase (ρ_{Liq}), volume of liquid (V_{Liq}) and volume of foam (V_F) employing given equation⁹.

$$\rho_F = \rho_{Liq} (V_{Liq} / V_F)$$

Value of FQ and foam density, and thickness of foam-lamellae indicate foam stability. Stabilisation of foam is done with incorporation of non-aqueous liquids²⁸ and solids²⁹ in formula. Cellulose ethers were effective foam stabilisers enabling in preparing foams of various stabilities⁹.

Penetration Kinetics of Foam

Nucleation and binder distribution plays critical role in determining size distribution of granule in FBG processes²¹. Penetration and nucleation kinetics data of foam indicates its penetrability through loosely packed powdery particle bed. It is determined from specific penetration, penetration time and nucleation ratio. Value of nucleation ratio and penetration time is useful in quantifying liquid distribution efficiency and nuclei formation kinetics^{20,24-26,30}. Specific penetration (t_{ps}) is penetration time (t_p) per unit mass of binder (m) while penetration time is time required for a drop or foam to penetrate completely into powder bed³⁰. Value of t_{ps} is invulnerable to variations in dispersed foam mass, a limitation of t_p ³⁰.

$$t_{ps} = t_p / m$$

Nucleation ratio (K_m) reflects distribution efficiency of binder through powder mass to create granule. It is amount of powder nucleated per unit mass of SoB^{16,20,24,30}. K_m calculated from ratio of nucleus mass (M_n) to SoB mass (M_b).

$$K_m = M_n / M_b$$

Foam's t_p depends on formulation while roping powder flow and agitation is crucial in rapidly dispersing foam¹⁶. K_m depends on foam addition method²⁰. Drop penetration time decreases with decrease in proportion of hydrophobic component whereas hydrophobicity strongly influences same³⁰. Wettability of powder mixture had a pronounced affect on granule properties. Whilst hydrophobicity of it proportionately decreases granule strength and granule size³⁰.

Effect of Processing Parameters on Granule Size

Flow rate and screw speed are most significant factors affecting particle size and granule fracture strength. Binder molecular weight had a minor influence on granule properties and FQ have insignificant influence when extruder is used¹². Increasing FQ, and decreasing concentration of binder-solution and liquid-to-solid ratio decreases average granule size, but effect is interrelated with impeller speed²⁷. Foam delivery tends to create a narrower nuclei size distribution during early stage of wet granulation. Nuclei formation influenced by foam properties and powder flow conditions within granulator. Narrowest size distribution of nuclei obtained with high-quality foam and intensive powder mixing conditions. Coarser nuclei formed with low-quality foam and sketchy powder mixing condition²⁷.

FBG with the HLSMG

Small-scale laboratory setting

In small-scale laboratory setting, granulation carried with a 10-L to 20-L HLSMG. Foamed binder delivered in to powder bed contained within HLSMG under running condition through port located on granulator lid. It dispersed in powder by operating side chopper blades between 300-1,800 revolutions per minute (RPM) and main blade speed between 30-300 RPM³. Step-batch mode of foamed binder addition involves addition of aliquot amount of foam to powder bed for specified time at preset liquid flow rate while granulator is in operation. Granulator run until foam got disperse homogeneously into powder bed. Then degree of wetness and granularity of granules examined visually and manually. Process of foamed binder addition and subsequent evaluation of granules for degree of wetness and granularity repeated until an acceptable wetness and granularity attained. Granules deemed to acceptable at a point when a compressed handful of granules holds loosely together and easily breaks over again into agglomerated particles³. Batch mode involves placing entire amount of foam on top of powder at any suitable flow rate before HLSMG set into operation. Continuous mode involves continuous addition of foam into powder bed while granulator is in operation. This is resulting homogeneous dispersion of foam in powder as added³. Damp mass had to be wet-milled employing multi-mill equipped with suitable screen, holes, and an impeller, operated at suitable speed. Granules air dried or dried with FBP at suitable temperature. Dried granules is sized using multi-mill with higher size screens while size of opening and speed of impeller tip to be kept same^{10,31,27}. During initial stage of development step-batch mode followed and also for granulating unfamiliar powder system. It is also follow for determining relative proportions of foam and powder to be employing in successive batch or continuous granulation processes for processing of equivalent formulation.

Pilot-scale setting

Granulation in pilot-scale setting done with a 50-L to 150-L HLSMG operated with main blade speed of lower RPM and a chopper speed of same RPM, comparing small-scale settings. Foam added via a 0.5-1.0 inch tube through a porthole on lid of bowl, in continuous mode. The damp mass wet-milled employing multi-mill operated at similar operational conditions, comparing small-scale settings. Granules air dried or dried with FBP at similar operational conditions, comparing small-scale settings. Dried granules sized using multi-mill with higher size screens while size of opening and speed of impeller tip to be kept same^{10,11}.

Manufacturing-scale setting

Granulation in manufacturing-scale setting can be done with a 500-L to 600-L HLSMG operated with main blade speed of lower RPM and a chopper speed of same RPM comparing pilot-scale settings. Foam added via a 1.5-2.0 inch tube through a porthole on lid of bowl, in continuous mode. The damp mass wet-milled employing multi-mill operated at similar operational conditions comparing pilot-scale settings. Granules air dried or dried with FBP at similar operational conditions comparing pilot-scale settings. Dried granules sized using multi-mill with higher size screens while size of opening and speed of impeller tip is kept same¹⁰.

FBG with TSE

Here granulation of material done continuously between 20-40 kg/h and 220-320 RPM using co-rotating TSE while controlling extruder barrel temperature to 25-40°C using a cooling system. Addition of binder fluid is done by pumping it, after foaming to 75-95 % FQ using a mechanical foam generator, through injection port of extruder. Foamed binder metered accurately into extruder using a side stuffer (auxiliary feeder affixed to the extruder), at all operating conditions¹². Thermo Fisher Scientific Inc. (Waltham, USA) has several ranges of TSE granulators ranging from lab-scale to plant-scale (Pharma 11, Pharma 16 TSG and Pharma 24 TSG)⁴.

FBG with FBP

FBP used for granulating material using foamed binders^{10,18,19}. Addition of binder fluid is done by pumping it (after foaming it to 75-95 % FQ using a mechanical foam generator) through pipe that is used for spraying purpose after removing atomising nozzle assembly¹⁰. FBP based granulators ranging from lab-scale to plant-scale are available from several manufacturers⁴.

Evaluation of Granules

Granulations evaluated for loss on drying, flow property, density, and particle size and size distribution³³; morphology by Scanning Electron Microscopy³²; and surface area, median pore diameter (volume), total intrusion volume, and bulk density following mercury porosimetry method⁸.

In vitro dissolution study

In vitro drug release profile of granules studied with IP/BP/USP dissolution (basket type) apparatus operated at 37°C ± 0.5°C and suitable RPM containing discriminatory dissolution medium. Granules kept in basket (wrapped with suitable cloth) of dissolution apparatus. Aliquot quantity of dissolution medium withdrawn at preset periods, and immediate replacement with equal volume of fresh one. Drug content in withdrawn sample analysed suitably and result presented in percent referring actual drug content value³³.

In vitro release kinetic study, statistical evaluation, and data fitting

A mean value of three determinations at each time point used to fit *in vitro* drug release profile to different kinetic models for finding their release exponents, while the mean value of twelve determinations used for estimating difference factor, similarity factor, and two indices of Rescigno. Statistical analysis of percent released data and other data performed using one-way analysis of variance at a significance level of 5 %. *In vitro* release kinetic studies, statistical evaluation, data fitting, nonlinear least square curve fitting, simulation, and plotting done with suitable software for determining parameters of each equation^{32,33}.

FBG Equipment**Laboratory-scale equipment**

Vertical high-shear granulator model FM-VG-10 (Glatt Air Techniques, Ramsey, NJ, USA), FBP based MP-MICRO™ (GEA Process Engineering nv, Wommelgem, Belgium) and MIDI-LAB (DIOSNA Dierks and Söhne GmbH, Osnabrück, Germany); TSE based Pharma 11; and laboratory-scale foam generator (Corrosion Fluids Inc., Midland, MI, USA)⁴.

Pilot-scale equipment

Top-drive high-shear granulator model GMX-150 (Vector Corp., Marion, IA, USA); FBP based MULTI-PROCESSOR™ (GEA Process Engineering nv), Pilot Fluid Bed Dryers/Granulators (Ohara Technologies Inc., Richmond Hill, Ontario, Canada) and Fluid Bed Processor-50 (Umang Pharmatech, Mumbai, India); TSE based Pharma 16 TSG; and a laboratory-scale foam generator (Corrosion Fluids Inc.)⁴.

Manufacturing-scale equipment

Top-drive high-shear granulator (GEA Niro Pharma Systems, Columbia, MD, USA); FBP based Fluid Bed Processor – 125/500/750/1000/1500 (Umang Pharmatech), Production Fluid Bed Dryers/Granulators or Multi Processor (Ohara Technologies Inc.); TSE based Pharma 24 TSG; and a production-scale foam generator model Top Mix type 100 (Hansa Industrie-Mixer GmbH and Co., Stuhrl-Heiligenrode, Germany)⁴.

CONCLUSION

The FBG process is very controllable and results granules with acceptable properties. Better understanding of flow patterns, mixing behaviour and impact velocities in different types of granulation equipment also needed. FBG process can be successfully used to get diversified product including controlled-release and immediate-release granules of several drugs, including water sensitive formulations. Application of FBG technique by pharmaceutical and other industries will be a function of inherent conservatism and statutory limitations, a major challenge to overcome. Processing process, desired FQ, processing equipment should be judiciously selected to get granules with desired characteristics and robustness.

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