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A TECHNICAL NOTE ON GRANULATION TECHNOLOGY: A WAY TO OPTIMISE GRANULES

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ABSTRACT

To provide an updated technical note on granulation technology (GT), mostly on novel GT, that will help researcher working/engaged in designing an efficient GT for getting granules with desired features. Granules were most widely used in the production of pharmaceutical oral dosage forms. Advancement in GT had revolutionized the sphere and resulted in development of several processes. Each and every process had advantages and disadvantages, and limitations. Depth knowledge in GT was a prerequisite to process product for obtaining targeted granulation with desired product parameters. In this regards updated literatures were collected from data bases, studied and was presented for easy reference of scientists engaged in granule production, so that they can adopt appropriate and suitable GT. Presented handy note will help researchers in designing a robust GT for getting optimised granule.

INTRODUCTION: Granulation was a vital unit operation in the production of pharmaceutical oral dosage forms [1, 2]. Changing regulatory compliances that was directed towards enhancement of product quality came up with process validation of each unit operation, increasing product output, decreasing product throughput time, reducing labour and energy cost; had revolutionized the GT, since its introduction, thereby resulting in development of novel granulation technologies [3]. Each and every GT had its own limitations vis-à-vis possesses superiority over other.

Granulation method was selected not only on the basis of individual properties of the ingredients like their flow property, compressibility, eject-ability, and disintegrate-ability but also on the basis of compliance of the regulatory requirement for the product and employed technologies [3]. Pharmaceutical industry was very conservative with respect to application of new applications and new technologies associated with their required regulatory compliances with respect to the reproducibility of the process [2, 4]. Depth knowledge in the GT was essential to adopt proper granulation process during development stage of product to get a targeted granulation and final product parameters.

Present review was aimed to give an outline on technicality of GT while emphasis was put on to provide information related to advanced GT so that a suitable GT can be adopted for granulating a material. In this respect databases were extensively searched to gather data that were presented as a handy reference and the presented data will help scientists engaged in developing an efficient GT for the product in hand.

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Granulation: Granulation was a particle design process that involves gathering of small particles into large masses in which the original particles can still be identified. Granulation was done for improving flow and compression characteristics, improving content uniformity, reducing segregation, facilitating metering or volumetric dispensing, controlling/manipulating release rate, eliminating generation of excessive amounts of fine particles thereby increasing bulk density of the product, decreasing dust generation thereby reducing employee exposure to the product, and resulting in improvement of yield and productivity, reduced down time, and so on [1, 5].

Mechanisms of particle-particle interactions during Granulation: Mechanism of particle-particle interactions to be studied appropriately to select an efficient GT as this will provide an insight for the granule formation mechanism, an essential parameter for predicting not only energy requirement for the formation of granules but also its stability. Independent of the process employed, five discrete bonding mechanisms at the point of particle–particle interactions had been recognised that were enlisted as below [6, 7]:

1. Solid bridges: chemical reaction and/or sintering/heat hardening associated solid bridges were formed due to dissolution during granulation with subsequent solvent removal in the drying phase.

2. Immobile liquids: addition of speciality binder(s) solution in granulating solvent that softens, deforms, and adhere to particles, then hardens during drying.

3. Mobile liquids: liquid bridges, at higher fluid levels, which occupy void spaces thereby bonds particles.

4. Intermolecular and long-range forces: van der Waals forces, electrostatic forces results in bonding of the particles.

5. Mechanical interlocking: fracture and deformation due to pressure that results in shape related bonding or intertwining of long fibrous particles.

Granulation Technology: GT comprises the art and science for process and production of granules [1, 5, 6, 8]. All over the world granulation was done either by wet-granulation or by dry-granulation process. Technological breakthrough in the area of GT, over a period of time, as an urge to improve commercial output, had leaded to evolution of diverse newer and novel GT like moisture activated dry granulation (MADG), thermal adhesion granulation (TAG), pneumatic dry granulation (PDG), melt/thermoplastic granulation (MTG), fluidized bed granulation, freeze granulation (FG), foam binder granulation (FBG), steam granulation (SG), and so on.

Prerequisites of an Ideal Granulation Technology:

1. Must have potentiality to improve reproducibility in the product performance,

2. Must decrease variability in the process performance,

3. Must have potentiality to minimize post-approval process changes,

4. Must have potentiality to decrease cost and time, and

5. Should produce spherical granules with controlled size distribution, specific granule voidage (i.e., intragranular porosity), specific bulk density, good flowability and compact-ability, suitable structural stability and physical strength.

Classification of Granulation Technologies: Basing upon the type of processing, that had been involved, GT can be classified as follows:

1. Conventional methods
    - (i) Dry granulation
    - (ii) Wet granulation
        - (a) High-shear wet granulation
        - (b) Low-shear wet granulation
2. Novel/advanced methods
    - (i) Moisture activated dry granulation

(ii) Thermal adhesion granulation

(iii) Pneumatic dry granulation

(iv) Melt/thermoplastic granulation

(v) Fluidized bed granulation

(vi) Extrusion-spheronization granulation

(vii) Spray drying granulation

(viii) Freeze granulation

(ix) Foam binder granulation

(x) Steam granulation

Dry Granulation [1]: Dry GT, the cheapest method of granulation, was suitable for heat and moisture sensitive products that involve least processing steps. In dry GT the powder mixture was compressed into a compact mass without utilizing the heat and the solvent followed by milling the compact mass to obtain granules.

Compressed mass were obtained with two methods namely slugging and roller compaction. Slugging, the most widely used method, involves pre-compression of the powder to slug with a high duty tablet press while roller compaction involves pre-compression of the powder to flakes with pressure rolls using machines like Chilosonator.

Disadvantages:

1. Requires specialized heavy duty tablet press,
2. Does not permit uniform colour distribution,
3. Tends to create more dust with respect to wet granulation, and
4. Increases the potentiality of cross contamination.

Moisture Activated Dry Granulation [9, 10, 11, 12, 13, 14, 15, 16]: MADG was also called 'Single-Pot' granulation or moist granulation. In this process moisture was used to activate granule formation utilizing very little granulating fluid and eliminates drying step through utilisation of moisture absorbing material like microcrystalline cellulose (MCC), potato starch, a mixture of MCC and potato starch (50% w/w), silicon dioxide, Spress® B818 Pregelatinized Corn Starch NF [17], Maltrin® maltodextrins [18], to remove excess of moisture present in the granulate. MADG technology involves wet agglomeration of the powder mixture to form a tacky mass followed by moisture absorption to dry the granules. In this technology small amount of water (1–4%) was added to agglomerate the powder blend containing active, binder, and excipients using blender followed by addition of moisture absorbing material [11, 19, 20]. Impeller speed, chopper speed and time, spray rate and volume, droplet size, nozzle distance and position were the factors that influence the performances of the process [18, 19].

Advantages [9]:

1. A simple, clean, lean process that utilizes very little granulating fluid,
2. Produce granules with more uniform particle size distribution (particle size range of 150–500 µm) and excellent flowability,
3. Economical and time efficient, as requires less energy and eliminates drying step,
4. Suitable for continuous processing, and
5. Used for preparation of floating and sustained release products.

Disadvantages:

1. Unsuitable for thermo-labile, moisture sensitive, high moisture absorbing substances, and
2. Difficult to develop formulations with high drug loading.

Thermal Adhesion Granulation [21, 22]: TAG was a novel GT, patented by Wei-Ming Pharmaceutical Company (Taipei, Taiwan) [22] that involves granulation by adding very less amount of water or solvent. In this process the binder/diluent mixture was first moisturized by spraying water or ethanol (2.0–3.6%, by weight of the total mixture). Then the blend was placed in a pre-warmed glass bottle, sealed, and heated by an infrared lamp to raise surface temperature of the vessel to 90^0C –105^0C (in case of water) or 70^0C–90^0C (in case of ethanol) and mixed under tumble rotation for 3–20 min until granules had formed. Resulted granules were immediately sifted with proper sieve [22].

Advantages [21, 22]:

1. Utilizes less amount of water or solvent,
2. Granules with good flow properties and binding capacity were obtained even with substances having poor tabletting properties, and
3. Minimizes the dust generation during powder processing.

Pneumatic Dry Granulation [23]: PDG was a novel dry granulation method developed by Atacama Labs (Helsinki, Finland) following standard roller compaction method to compact material at very low compaction force with subsequent milling and fractionating milled material employing a newly innovated fractionating device that separates the granules and recycles rejected fraction. PDG was suitable for automatic or semi-automatic production of granules that enables flexible modification of drug loading, disintegration time and tablet hardness.

Advantages:

1. Can achieve high drug loading of traditionally proven difficult materials,
2. Faster development (within weeks) even with historically proven difficult materials
3. Decreases cost of product by minimizing waste through recycling and production cost,
4. Excellent stability with enhanced shelf-life,
5. Compatible with other technologies like coating, sustained release, fast release,
6. Suitable for thermo-labile and moisture sensitive drugs,
7. Taste masking and tailoring of release rate and time can be achieved,
8. Produce soft and porous granules with high compressibility and flowability,
9. Possesses potentiality to handle sterile products or toxic materials, and
10. Lowers scale-up cost and problems.

Melt/Thermoplastic Granulation: Melt or thermo-plastic GT was also called melt agglomeration where granulation was achieved with meltable binder that was in solid state (at room temperature) but preferably melts in the temperature range of 50^0C – 80^0C, and the melted binder acts like a binding liquid. Melt granulation was done either by the spray-on method that involves spraying of a molten binder onto the powders, or by the in situ melt granulation method that employs a solid binder which was heated above its melting point by hot air, when processed in the fluidised bed processor (FBP) [24, 25, 26] or by impeller frictional forces; and heating jacket, when processed in the high-shear mixer.

In spray-on method dried granules were obtained either by simple cooling the product at room temperature followed by milling or by hot melt extrusion technique [10, 27, 28, 29, 30, 31, 32, 33, 34, 35]. Hot melt extrusion technique involves extrusion of thermoplastic mass through a thermostatically controlled extruder [36, 37, 38, 39, 40, 41, 42] or nozzles [43, 44] at a temperature where its consistency was softer, followed by fragmenting the discharged plastic strand with the help of cutting blade or spheronizing the discharged plastic strand with spheronizer [28, 29, 30, 31, 45].

Processing parameters had to be optimized basing upon the equipment used associated with different mechanism of granule growth that influences particle size and size distribution, and morphology of granules [29, 30, 45, 46, 47].

Advantage:

1. Both aqueous and non-aqueous solvent were not used,
2. Time and cost effective as involves fewer processing steps and eliminates drying step,
3. Uniform dispersion of fine particle occurs,
4. Release profile of drugs can be controlled and modified,
5. Suitable for enhancing dissolution profile and bioavailability of poorly water soluble drugs by forming solid dispersion [48, 49],
6. Product exhibit good stability at varying pH and moisture levels and;
7. Higher degree of regulatory compliance.

Disadvantages:

1. Thermo-labile materials were poor candidates, and
2. Meltable binders with melting point in the specific range can only be utilized.

Requirements of MTG:

1. Meltable binder at a level of 10–30% w/w with respect to solid particles was used,
2. Meltable binder should be solid at room temperature and melt between 40^0c and 80^0c,
3. Meltable binder should be physically and chemically stable,
4. Meltable binder should have suitable hydrophilic-lipophilic balance to ensure the correct release of the active substance, and
5. The melting point of fine solid particles should be at least 20^oC higher to that of the maximum processing temperature.

Meltable binders in MTG: There were two types of meltable binder namely hydrophilic meltable binders and hydrophobic meltable binders. The hydrophilic meltable binders were used to prepare immediate-release dosage forms while the hydrophobic meltable binders were preferred for prolonged-release formulations. Meltable binders should be selected basing upon their melting point range. Polyethylene glycol 2000/3000/6000/8000, gelucire 50/13, poloxamer 188, etc. was used as hydrophilic meltable binders while stearic acid, cetyl or stearyl alcohol, paraffin wax, microcrystalline wax, bees wax, carnauba wax, cetyl palmitate, glyceryl stearate, mono-/di-/tri-glycerides, etc. were used as hydrophobic meltable binders [50].

Wet Granulation: Wet granulation was most widely used process of granulation in the pharmaceutical industry that involves addition of a liquid solution (with or without binder) to powder bed followed by mixing to form a wet mass and subsequent drying followed by sizing yields granules [1, 51]. Wet GT uses range of processing equipments like traditional double-cone blenders, shear mixers and pans; high speed or high-shear mixers/granulators with high tip speeds of the impeller and the chopper; FBP; etc [5, 51, 52, 53].

Advantages [51]:

1. Improves flowability and compressibility of the material [54],
2. Bioavailability improves as hydrophobic surfaces gets changed into hydrophilic surfaces,
3. Fast method to prepare controlled release granules [46],
4. Improves homogeneity of dosage forms with low active content, and
5. Adverse influence of poor electrostatic properties of powder can be avoided [54].

Disadvantages [5, 55]:

1. An expensive process associated with requirement for more labour, space, time, special equipment and energy,
2. Involves multiple processing steps thereby increases complexity,

3. Process loss of material was high,
4. Unsuitable for moisture sensitive, thermo-labile, and incompatible materials, and
5. Any incompatibility between the formulation components was aggravated during the processing.

High Shear Mixture Granulation: One-step high shear granulator (RMG) was simple and easily cleanable equipment that was developed to comply Good Manufacturing Practice requirements, to reduce the cross-contamination and the environmental hazards, and to get spherical and well-compacted granules in a relatively short time. RMG can be operated in a closed unit that involves mixing, primary and secondary granulation, and drying steps. Primary granulation step involves spraying of the binder solution onto the powder bed while the secondary granulation involves kneading of the wet product to produce and to enlarge the granules. Subsequent drying of final material was done suitably under low pressure at moderate temperature [45, 54, 55, 56, 57, 58].

Impeller speed, chopper speed, water addition method and rate, massing (mixing) time, load of the RMG, feed material characteristics, drug substance particle size [59] were the granulation process parameters that requires monitoring to get granules with desired characteristics [60, 61, 62]. Volume of load in RMG should be less than two-thirds of its capacity.

Advantages:

1. Short processing time,
2. Less amount of liquid binders required with respect to fluidized bed granulation technology, and
3. Highly cohesive material can be handled.

Disadvantages:

1. Mechanical degradation could take place in case of fragile particles,
2. Results in the uneven distribution of binder solution throughout moving powder bed during high-shear granulation,
3. Unsuitable for thermo-labile material, and
4. Over wetting can leads to formation of lumps and large size granules.

Fluidized Bed Granulation: Fluidized bed processing, an air suspension technique, of pharmaceuticals was first reported by Wurster to coat tablets that was later used for granulating and drying of pharmaceuticals [58, 63, 64] and particle/granule coating [65].

Fluidized bed granulation process involves spraying of binder solution onto the fluidized powder bed (FPB) to get finer, free flowing and homogeneous granules employing single equipment known as FBP [24, 25, 26, 66, 67, 68]. FBP contains air-handling unit, product container and air distributor, spray nozzle, disengagement area and process filters, exhaust blower or fan, control system, solution delivery system.

Advantages [66]:

1. Reduces dust formation during processing,
2. Improves housekeeping and worker safety,
3. Suitable for subsequent coating and controlled release products, and
4. Reduces product loss.

Disadvantages:

1. Cleaning was labour-intensive and time consuming, and
2. Assuring reproducibility was troublesome.

Extrusion-Spheronization Granulation: A multiple step process involving at least five-steps capable of making uniform sized spherical particles with narrow size distribution that were suitable for controlled release formulations by extruding the tacky mass through extruder [36] and subsequent pellatization or spheronization using pelletizer or spheronizer. Pelletizations were done employing wet extrusion technique or hot melt extrusion technique.

Wet extrusion technique involves extrusion of wet agglomerate (tacky mass) of the powder mixture [69, 70] through extruder [69, 71, 72]. Hot melt extrusion technique involves extrusion of thermoplastic materials through a thermostatically controlled extruder [28, 29, 30, 31, 37, 43, 44, 45, 73]. Processing parameters like extruder pore size, spheronization speed and operational conditions had to be optimized which influences particle size and size distribution, and morphology of granules [29, 30, 45].

Five fundamental steps of extrusion-spheronization process were:

1. Dry mixing of materials to achieve homogeneous dispersion,
2. Wet/thermoplastic granulation of the resulted mixture to form wet/thermoplastic mass,
3. Extrusion of wet/thermoplastic mass to form rod shaped particles,
4. Rounding off the rod shaped particles using spheronizer, and
5. Drying.

Advantages:

1. Can incorporate higher levels of active without producing excessively larger particles;
2. Can easily combine two or more active agents within the same unit, in any ratio;
3. Can modify physical characteristics of the active ingredients and excipients; and
4. Can produce spherical particles with high bulk density, low hygroscopicity, narrow particle size distribution and smoother surface.

Disadvantages:

1. Require more labour and time with respect to conventional granulation techniques, and
2. Unsuitable for moisture sensitive and thermo-labile materials.

Spray Drying Granulation [68]: It was a continuous process where a dry granular product was obtained by feeding a solution or a suspension of active agent with or without excipients to the drying system where the feed was atomised and dried with a heated gas stream followed by subsequent separation of granular product from the gas stream. Alternately particle agglomeration was brought about by spraying the binder solution onto bed of powder particles in fluidized state achieved with the passage of air followed by drying using hot air.

Advantages:

1. A rapid and continuous process,
2. Overall cost was reduced,
3. Minimizes operator exposure to dust of the product, and
4. Suitable for heat sensitive product.

Freeze Granulation [74, 75]: Integrated Biosystems, Inc. (California, USA) had patented freeze GT that results in spherical and free flowing granules with optimal homogeneity. FG involves spraying of suspension containing powder into liquid nitrogen where the drops were instantaneously frozen to form granules which upon subsequent freeze-drying yields dry granules [74, 75].

Advantages:

1. Granule density can be controlled by the solid contents of the suspension,
2. Non-oxides and metals can be handled as mild drying prevents their serious oxidation,
3. Results solid granules with no cavities,
4. High yield with low material waste,
5. Low to high quantities of granule can be produced with reproducibility,
6. Equipments can be easily cleaned up, and
7. Organic solvents can be recycled.

Foam Binder Granulation: FBG technology was developed by The Dow Chemical Company that enables faster granulation, which involves a simpler and safer wet granulation processing of materials and employs high shear or low shear RMG, or FBP in both laboratory-scale and production-scale settings using hydroxypropylcellulose or hypromellose as binder. This technology involves continuous addition of liquid binders in the form of aqueous foam (having consistency of shaving cream generated with foam generator) either onto the previously blended powder bed contained in RMG with variable speeds of impeller or chopper, or in FPB contained in FBP [24, 26]. After attaining granulation endpoint the wet granules were dried in FBP till desired moisture content was achieved [2, 4, 76, 77, 78, 79, 80].

Wet foam having physical characteristics and flow similar to a liquid, and dry foam having high air-to-liquid ratio that moves more like a solid were used for granulation; while dry foam was recommended. Foam quality was calculated from penetration time and nucleation ratio and the data was used to determine the range of acceptable foam quality that can be used to get granulated product with desired quality [2, 76, 81, 82].

Advantages [83, 84]:

1. Eliminates use of spray nozzle thereby eliminates plugging effects;
2. Requires low amount of the water and the binder for granulation;
3. Improves process robustness;
4. Binder distribution was uniform;
5. No over wetting;
6. Cost effective as reduces drying, manufacturing, and equipment clean-up time, and does not require new equipment or drastic changes in processing techniques; and
7. Immediate release and matrix controlled-release products can be easily scaled-up [76].

Applications:

1. Suitable for products with very low concentration or drug level (in mg or µg per tablet) as generated foam can carry active ingredients at a very low concentration,
2. Suitable for water sensitive formulations and, highly water-soluble and even very poorly water soluble drugs [83, 84] and;
3. Can handle historically proven difficult materials including natural ingredients used in nutritional supplements [85].

Steam Granulation [46, 47, 86, 87]: This technology was a simple modification of conventional wet granulation method in which steam was used as binder instead of water and involves injection of a jet of steam into the bed of fluidized particles to be granulated.

Advantages [5, 88, 89, 90]:

1. Higher binder distribution uniformity,
2. Higher binder diffusion rate into powders,
3. More spherical granule with large surface area were formed thereby increases dissolution rate of the drug from granules [89],
4. Favourable thermal balance results in rapid drying,
5. Time efficient as processing time was shorter, and
6. Employs stem as binding fluid thus was environment friendly, expensive safety precautions was not required [55] and does not results health hazards to the operator,
7. Possess regulatory compliance, and
8. Can control total micro organism count.

Disadvantages [5:]

1. Special equipments were required for steam generation and its transportation,

2. Requires high energy inputs,
3. Unsuitable for thermo-labile materials,
4. More safety measures were required,
5. Unsuitable for binders that cannot be activated by contact with stem, and
6. Uses steam at a temperature of about 150^0c, that tends to cause local overheating and excessive wetting of the particles in the vicinity of the steam nozzles resulting in the formation of lumps in the granulated product.

Principle of Steam Granulation: SG technology involves injecting steam through one or more jets onto the FPB contained in the FBP in hermetically airtight and thermo-stated condition. Enveloping and jacketing each jet of steam in a jet of gas that prevents premature condensing of the jet of steam into droplets thereby preventing lump formation of particle (due to powder aggregation at the water droplet formation site) in the FBP. Alternately gas stripping system can be used. The jets of steam and gas can be injected transversely and/or axially onto the bed of fluidized particles contained in the FBP.

Coaxially the jets of steam and gas can be injected through concentric nozzles that will communicate to the interior of the FBP. Choking of nozzle can be prevented by directing the nozzles downward or shielding or covering it, thereby inhibiting entry of fluidized particles into the nozzles which interfere with proper functioning of the apparatus. This technology permits formation of granulated product with close particle spectrum without any lumps. Hypromellose and pregelatinized starch were most frequently used binders [46, 47].

Advanced Granulation Equipments: Semiautomatic or fully automatic instrumentation systems had been developed and were used for optimizing each unit operation like granulation, slugging, compaction, and compression. Combining all or most of the unit operation in one system were also advanced approaches in granulation equipment technology that operates with greatest reliability [24, 26].

Fluidized Bed Granulator/Dryers/Processor [58]: FBP performs pre-blending the granulate including excipients by fluidizing them with fluidizing air, granulating the same by spraying adhesive/binder onto the FPB and drying the granulated product to the desired moisture level within a single piece of instrument. Marketed equipments were Glatt®-powder-coater-granulator, Vector® spir-a-flow granulator, etc.

Glatt®-powder-coater-granulator was available with process inserts like Rotor granulator, HS Wurster insert, and Top Spray product container. Rotor granulator contains a Glatt rotor systems that were designed for the production and coating of pellets and crystals. HS Wurster insert comprise a patented Glatt HS Wurster® technology that coats particles with size > 20 µm and works with unmatched efficiency in which charging and discharging was carried out manually (in case of standard design) or automatically (in case of total containment design). HS Wurster® inserts were suitable for batch volumes 4-780 dm^3. Fully automatic cleaning of the insert can be done as with SC SuperClean® design and removable nozzles can be used in the process. Top Spray product container was suitable for granulation, drying and powder coating in shortest possible process time. Standard sieve bottom designs to Glatt wedge wire bottom designs (suitable for clean in place) were available while right container bottom was selected basing upon the configuration and process.

Vector/Freund Spir-A-Flow Granulators was a modified full enclosed self contained FBP system with agitated hopper, rotor and stator, automatic loading and unloading, self contained filter, solution spray nozzles, pneumatic and electric control consoles.

Mixer-processor and mixer-granulator with Vacuum or Fluidized Bed Drying mechanism: Mixer-processor and mixer-granulator with vacuum or fluidized bed drying mechanism had potentiality for sequencing the unit operations of powder mixing/blending, wet massing, agglomeration and specialized granulation drying facilities. Littleford Day MGT™/Day Nauta™/Ploughshare™, CF Granulator™, Diosna Spiral Mixers™ and Topo Granulator™ were employed for mixing and/or granulation, with vacuum or fluidized bed drying facilities involving latest technologies.

Littleford Day Vertical Cone Day Nauta Mixer/Processor/Granulator was suitable for mixing, granulation and drying operation within a single assembly. The Day Nauta Processor was available in vacuum and hot-air deep bed drying facility. Littleford Day Horizontal Ploughshare® Mixer and Littleford MGT Vertical Mixer/Granulator were suited for mixing and granulation operation continuously or in batch and can be adapted for vacuum operation, if needed.

Topo granulator™ was employed for producing effervescent tablets following TOPO vacuum granulation technology, patented by Hermes Pharma (Pullach, Germany) [91]. TOPO vacuum granulation involves granulation under vacuum to prevent uncontrolled chain reaction. Topo granulator mixer-processor reduces the proportion of excipients and granulating fluid for intensified compaction. CF-Granulator™ was widely used for processing controlled-release pills that produce spherical granules. CF-Granulator™ involves spraying of coating/binder solution and adding primary ingredient/filler on to the nonpareils rolling along the cylindrical wall of this equipment. Diosna Spiral Mixers™ were suitable for mixing of material including all kind of dough materials.

Little ford Lodgie granulator and Collette UltimaGral™ with drying facility contains a high speed mixer blade for mixing and wet granulation, a high speed chopper blade system as a lump and agglomerate broker and a compatible fluidized bed drying facilities for facilitating drying. Collette UltimaGral™ was a high shear mixer and granulator that can be equipped with movable head to enhance flexibility. This feature allows operators to lower the closed bowl to enable better accessibility and easy loading.

Extruder-Spheronizer [38, 39, 40, 41, 42, 69, 70, 71, 72]: Spheronization was a technology of pellatization which refers to the formation of spherical particles from wet/thermoplastic agglomerate. Spheronization equipment extrudes wet/thermoplastic granulate into the cylindrical material of uniform size and narrower size distribution followed by breaking the segments and then rolling them into the solid spheres/granules in a spheronizer [29, 30]. Marumerizer™ (Fuji Paudal, Osaka, Japan) a spheronization equipment combines both roller compaction and spheronization mechanism.

Miscellaneous: The microwave processors were also used that employs mechanism to mix, wet, agglomerate and dry the granules within one piece of equipment and reduces the drying time considerably. This technique follows gentle mixing followed by vacuum and microwave drying with micro processor controlled operation and reduces the drying time by one fourth [92].

CONCLUSION: Technical breakthrough in the granulation field will came with latest technology. Depth knowledge was essential to adopt proper granulation process to get targeted granulation and final product parameters. While application of newer technique by the pharmaceutical and other industries will be a function of their inherent conservatism and regulatory controls.

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