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REVIEW ON NOVEL GRANULATION TECHNIQUES

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ABSTRACT

Tablets are the generally use dosage form, suitable to long-suffering observance, stretch in dose routine as well as design of dosage form. Pharmaceutical tablets be process every one in excess of the humanity use direct-compression, wet and dry granulation. The process choose depends on the ingredient entity description also aptitude towards surge suitably, compact, throw out with collapse. Selecting correct granulation way require systematic study of every component into the method, mixture of ingredient and their interaction. Exhaustive research is going on different novel granulation techniques that are able of replacing traditional granulation techniques as they have advantages of being cost-effective and high yielding. The object of their article is towards centre of attention lying on the novel granulation tools similar to pneumatic dry granulation, freeze granulation, Granurex® technology and so on.

KEYWORDS: Pneumatic dry granulation, melt granulation, nucleation, Granurex®.

INTRODUCTION

Granulation procedure have be broadly use into pharma manufacturing use high-quality the research of objects used for tableting. Other method which involve the particle formation includes microencapsulation, multi-particulate method designed for customized liberate instrument as well as towards get ready granule use in patient directly. mostly granule be

ready towards get better surge as well as solidity character of the blend but there are many other reasons and sometimes multiple reasons for granulation such as-

- Getting better flow property of the combine also the equivalence of the dose.
- Growing bulk density of a product.
- volumetric dispensing.
- Controlling the rate of drug release.
- Decrease dust generation and reduce worker contact near drug product;
- Improving product appearance.[1]

According to Tardos ‘‘Granulation is a part procedure with little fine particle be agglomerate in bigr entity call granule. fine particles with covering be complete towards get better flow, appear with combination property, towards let pass dustiness also decrease separation with, common, towards any reduce unwanted property otherwise get better the chemical and physical property of fine powders.’’ Tardos elaborate additional mainly frequent process of granulation powder be other use fluid binder into type of a melt or solution, with employ pressure to insure coalescence and growth.’’[2]

Together controlled-release (CR) and immediate-release (IR) solid-dose formulation are commonly use a wet granulation process make easy fine particles run into severity-feed drug manufacturing. usually, immediate release formulation be granulate with addition in to fine particles accumulation an aqueous solution of a binding polymer. Controlled release formulation granulate with addition a binder polymer solution.[3]

Granulation be a single mostly significant component operation into manufacturing of oral dosage forms in pharmaceutical industry. Granulation procedure get better compression and flow quality, get better comfortable consistency with reduce unnecessary quantity of well element. The result be there better yield, reduced drug defects and improved efficiency. Pharmaceutical production be process all over the earth use a direct-compression, dry-granulation and wet granulation techniques. Which technique be selected depend going on ingredient character with capability to correctly run, disintegrate, compress with eject. decide a technique require systematic examination of every element within the method, mixture of ingredient, also job by everyone. The correct granulation procedure is apply. purpose of this article be focus on novel granulation technologies.[4]

Table 1: Frequently used granulation techniques and subsequent processing

	Process	Drying techniques
Wet granulation	Low-shear mixer High-shear mixer High-shear mixer Fluid-bed granulator Spray dryer Extrusion/spheronization Continuous mixer granulat Fluid bed—continuous or batch Continuous fluid-bed granulator	Tray or fluid-bed dryer Tray or fluid-bed dryer Vacuum/gas stripping/microwave Fluid-bed granulator/dryer Spray dryer Tray or fluid-bed dryer Fluid bed—continuous or batch Fluid bed (continuous)
Dry granulation	Continuous fluid-bed granulator process Direct compression Slugging Roller compactor	granulator Fluid bed (continuous) Blend and process further Mill slugged tablets/blend Compacts milled/blend/process further

TECHNOLOGY OF PNEUMATIC DRY GRANULATION

It is base on a pneumatic dry granulation procedure, a new process used for semi-automatic or automatic production of granules which enable stretchy change of granules fill, dissolution period as well as tablets hardness.[5]

Process flow technology of PDG

Granule particles are prepared by powder apply a power among two roll so make a compressed band in conservative roller compactor. The band in granulated using a suitable milling system. The resultant combination of dissimilar size granule be separate with a fraction machine system to small particle or granules be detached from coarser one with entrainment flow of gas. The flow of gas is provide by proper resources, example for, a vacuity pump. The gas stream, for example, air or nitrogen, is concentrating during the chamber of fractionating. The stream of gas divided well granules and small particles for larger one. Mostly, the gas stream into the way differing towards the progress of roller compacted granulate. The separated small granules and fine particles entrained in the streamof gas are transferred from the fractionating chamber to a separating device, example for, a cyclone, in which they be divided to carrier gas. The material is return in the direction of the system for immediate re-processing (i.e., they are re-circulated for compaction) or they may be placed into a container for later re-processing. For suitable protection of the system and environment, the gas inlet of the vacuum pump is provide by filtering system to remove any particles from the gas stream before they pass through the pump (Fig. 1).

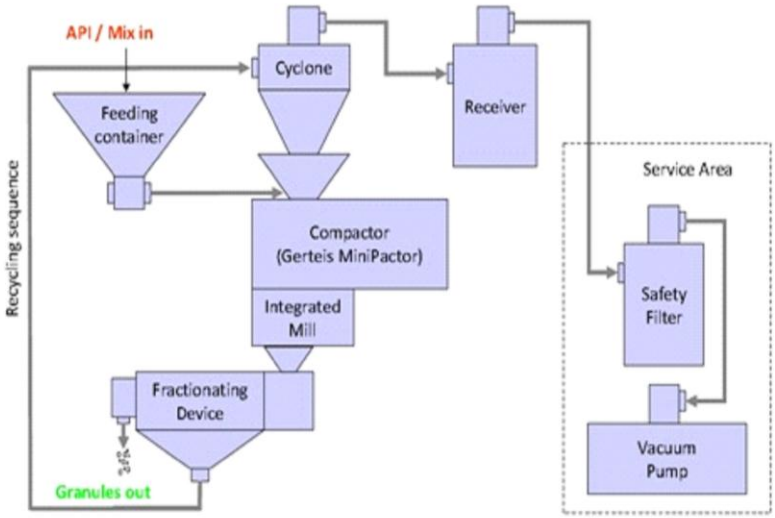

Fig. 1: process flow for pneumatic dry granulation.

Major dissimilarity compare towards conservative compaction roller be, suitable optimally roller compaction controlled procedure with a particularly mild parting of pneumatic fine smutty particle, jointly by further granulating result inside the fractionators, distant minor force of compaction be necessary to get a flowable granulate, thus preserving most binder ability of granule.[6, 7, 8] The Technology of pneumatic dry granulation produce fine granules by outstanding flowability and compressibility quality.

Today, frequently used a wet granulation technique. Team of formulation will frequently intention a dry granulation and direct compression formulation everywhere probable except about 80% case finish by a wet granulations formulation due to processing issues (Fig. 2).

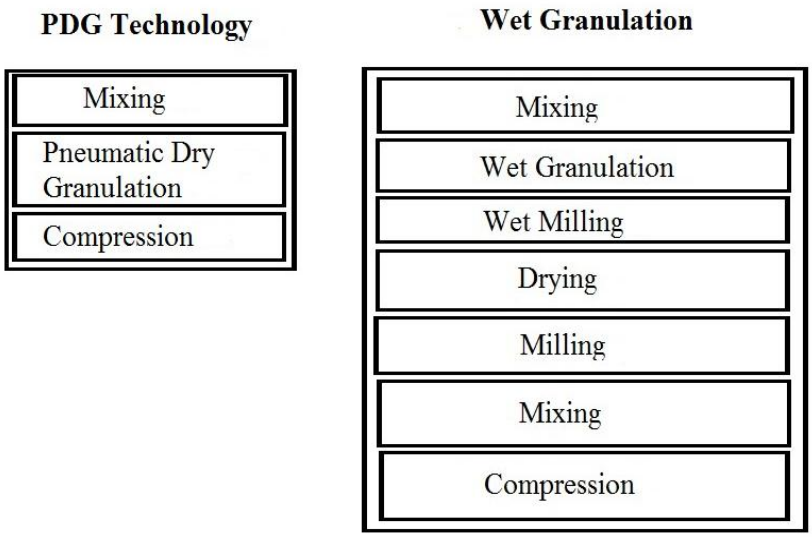

Fig. 2: Comparison between PDG technology and wet granulation method.

Compare towards a PDG Technology™, wet granulation is complex and difficult to control. Wet granulations is inappropriate used for heat responsive and moisture responsive drug, it is additional costly than other granulation methods. There be a huge quantity of method steps with every steps need requirement, of cleaning validationg. High matter lose can be incur as move among stage with around be a require for extended dry time. Extent awake frequently concern and there significant assets requirements. PDG Technology™ solves these problems.[5]

Advantages of PDG Technology™

1. high-quality results of granulation still at higher drugs loaded have been achieved even with materials known to be difficult to handle,
2. Properly suitable for moisture sensitive and heat labile drug.
3. Quicker speed of compare by wet granulation manufacturing,
4. Minor cost of compare by wet granulation manufacturing.
5. The finish good products are extremely stable - shelf life may be enhanced,
6. Little or no waste of material,
7. The tablets and granules produced show quickr dissolution and disintegration property, and

Applications for technology of pneumatic dry granulation.

The techniques have been effectively use for produce

- Orally disintegrating tablets (ODT) and quick release tablets
- Sustained release tablets,
- Fix combination tablets.

A unique capabilities, technology of pneumatic dry granulation can be utilize in developing new products or for managing the life cycle of existing products.[5]

FREEZE GRANULATION TECHNOLOGY

Which enable conservation of homogeneity from suspension to dry granule. With spraying fine particles suspension into fluid nitrogen, the drops (granules) are instantaneously frozen. freeze drying granule be dry with sublimation of the frost with some separation result in case of conservative dry in air as shown in Fig. 3. The result will be sphere, gratis flow granules, by best homogeneity. FG provides optimized form successive proces of granules, for example simple crush to homogeneous and dense powder compacts in a pressing operation

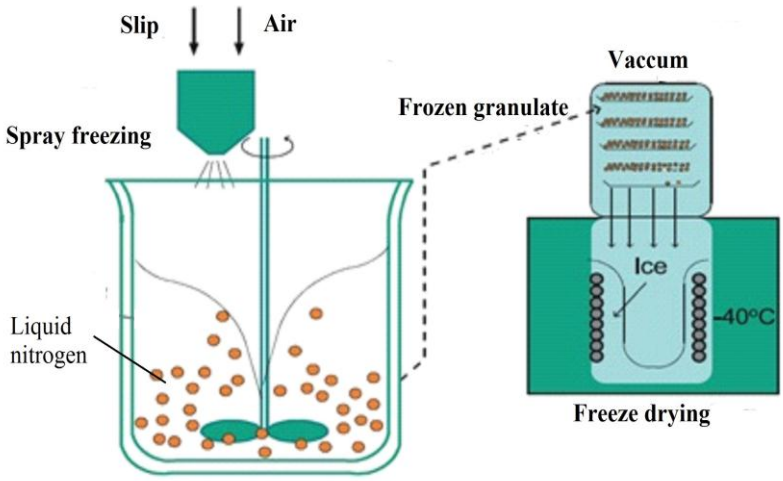

Fig. 3: Freeze granulation technology.

Advantages for technology of freeze granulation

1. Granule density is controlrd with solid contented of suspension.
2. Mild drying prevents highly corrosion of nonoxides and metals.
3. No cavity within the granules.
4. high yield and low matter waste
5. Large and small granule quantity can be produce the same quality.
6. Latex binder can be used for equipment are easily clean.
7. opportunity to reprocess of organic solvent.

Disadvantages for technology of freeze granulation

1. Two process steps: freezing and batchwise freeze-drying.
2. Restriction in the option of solvent, freezing properties base on a freezing point among 20 and +10 °C is recommended.
3. Large-scale equipment with a capability away from 35-45 kg granule for every day wants to be more development.[9]

TECHNOLOGY OF FOAMED BINDER (FBT)

Foam granulations technology involve adding of fluid binder as foam. of aqueous. Binder foamed techniques from The Chemical industry be able to assist to achieve simpler, safer and faster wet granulating process,. Using familiar, proven methocel polymers, this technology greatly improves binder distribution inside formulation mix and yields a remarkable collection of process compensation. compare to conservative spray process, technology of foamed binder can shorter process in time with reduce water requirements. It can improve

productivity in consistent distribution of binder. Moreover, it eliminate nozzle spray with their several variable in granulation process apparatus. Foam process is offer improved finish point determination and reduced equipment clean-up time. whereas process of foamed binder offers various benefits , this technology doesn't demand new equipment or radical changes in processing techniques. You can very simply apply by familiar low shear, and high shear, granulation apparatus in lab and manufacture level setting.[10, 11, 12]

TECHNOLOGY OF MELT GRANULATION

Process of melt granulation a powder is agglomerate by the assist of a binders, in also a or solid state or melt state to melt through the procedure. The equipment of option is a high shear blender, Temperature of a powders can be raise over the meling point of a melt able binders by also frictional forces generated by the impeller blades. Liquid binding is possible by the molten binder, thus melt granulation does not require utilize of solvents. The choice of the melt able binder play an significant task into the process. It has to melt at a relatively low temperature of 50–80°C. Hydrophilic binder are used for that melts in low temp will aid in the rapid release of drug. Passerini and co-workers[18] used a copolymer of propylene glycol and ethylene glycol as the surface active agent, to get faster release ibuprofen granules.

Dissolution profile of granule be establish to be superior physical mixture of same compositions and the pure drug. Gupta and co-workers[20] employed a variation of the above method. They first formed a melt mixtures of drugs and polyglycolized glycerides, which was the surface active agent employed, before adding this to a surface adsorbent such as magnesium alumino silicate. The utilize of a exterior adsorber is to form granule with superior flow and compressibility properties.

Table 2: List of binders

Hydrophilic meltable binders generally used in the melt granulation techniques	**Hydrophilic Meltable Binder Typical Melting Range (°C)**
Gelucire50/13	44-50
Poloxamer188	50.9
Polyethyle glycols	
PEG 2000	42-53
PEG300	48-63
PEG600	49-63

TECHNOLOGY OF STEAM GRANULATION

Steam Granulation: Steam granulations are derivative of wet granulation techniques, which involve the utilize of steam instead of traditional liquid binder. Instead of spraying the liquid

binder, steam is emitted into the wet massing chamber.[37] Steam injection technique, employ vapour on a temp about 150°C, tend to extreme wet of the particle into vicinity of the nozzles steam, thereby causing the configuration of lumps in the granulated product.[38] The dispensation period is small because less moisture is needed as steam has a superior distribution speed by mass of powder, achieving a higher distribution of the binder. Another reason is the more favourable during thermal stability the drying step. This is because steam condensation of the powder mass, forms of water a hot thin film and this requires only a little quantity of energy for vaporization as compared to evaporating the wet from area temperature.

This process was proposed by Rodriguez et al.[39] and they successfully produced diclofenac-polyethylene glycol 4000 acted as the water-soluble carrier. The authors compared the granules with granules manufactured from wet granulation technology and found that the granules produced were more spherical. The larger surface area was proposed to enhance drug release. This group of researchers also used steam to complex piroxicam with β-cyclodextrin as the complexing agent, forming steam granulated granules simultaneously, thus carrying out two processes in a single step to produce granules having dissolution profiles better than the original drug or a physical mixture of the two.[38]

MOISTURED ACTIVATE TECHNOLOGY OF DRY GRANULATION

Dry granulation moisture activated procedure consists of two steps, wet agglomeration of the powder mixture followed by moisture absorption stages. A little quantity of water (1–4%) is added firsts with agglomerates the combination of the API, a binder and excipients. Material are absorbing of moisture such as starch of potato and MCC is then added to absorb any excessive moisture. After mixing with a lubricant, the resultant combination can be compacted directly into tablets.[40] Hence, this process offers of wet granulation advantages, but eliminates the must need used for a drying step as revealed in . The applicable of 25-30 litre high-shear blender for dry granulation of moisture activated phenobarbital was investigated by Christensen et al.[41] MCC, potato starch. The results of the study showed that the actually property of tablets were primarily affected by the water content, the moisture absorbing material, and the compression force.[42]

Introduced of biopolymer has two novel excipients produce of Pharmaceutical market: Avicel HFE-102, which are based on already existing excipients but have been generated to make a different entity with improved benefits.[43] Microcrystalline cellulose is based on(MCC), has

been formulated to reduce the water quantity added to the granulation process Biopolymer's Avicel PH-200 which had a moisture level of five per cent. The new product has a moisture level of no more than 1.5 per cent soak up approximately three to four times more water from the granule. This benefit, beside with enable the utilize of MADG, meant the utilize of Avicel could eliminate the extra steps of milling, drying and screening, thus reduced energy used and manufacturing price. The process also produced a larger particle size for optimal flow, this increases efficiencies to the manufacturing process.

Advantages

- It utilizes very little granulating fluid.
- It drying time decreases and granules are produces with superb flow capacity.
- High shear granulator single manufacture equipment
- No equipment change
- Lower tablet capping
- No over and under granulation[45]

GRANUREX® TECHNOLOGY

The Granurex® precisely and consistently performs both powder layering and coating processes. In the following Fig. 4, powder (ingredient) and multiple coating layers demonstrate the accuracy and control of a Granurex® rotor processor.

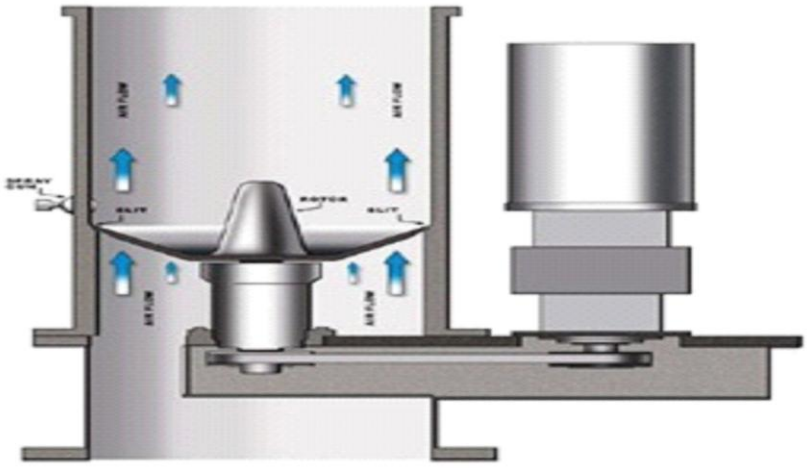

Fig. 4: Rotor processing for Granurex® technology.

The rotor imparts energy to produce for granule formation, in various ways very similar to high shear granulation. Less emphasis is placed on fluidization for product movement. The geometry of the stator and rotor combined with the angular momentum of rotor to produce

the characteristic helical product movement specific to rotor processing. This helical product movement provides order to the flow past the gun spray creating the environment for high efficiency and excellent uniformity.

Granurex® process consist of following steps like, Spherical granulation, powder layering and solution/suspension spraying.

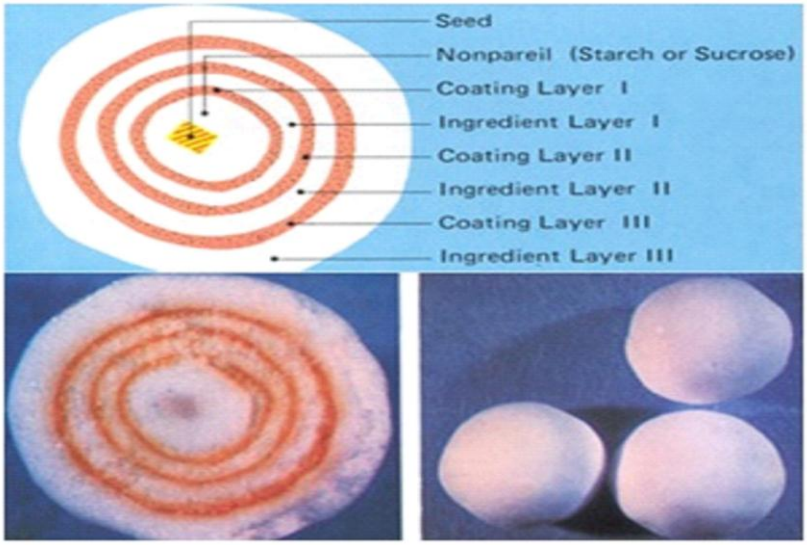

Fig. 5: Granules obtained from Granurex® technology.

1. Spherical granulation

Process that is a hybrid of a top spray granulation starts with a powder blend inside the rotor disc, and sprayed a solution of binder onto the powder to granulate it. The rotor imparts force onto the powder, forming a more spherical granule than a top spray process would. During the granulation phase, very low airflow is required (5-10 CFM in small units). Desired size of final particles determines several parameters such as spray rate, atomization pressure and temperature. faster the rotors speed, the more round the finished granules will be. It is possible to go too fast, however, causes over sticking and wetting of the product.

Advantages of spherical granules: Spherical granulation creates a very fine size of particle distribution; more spherical granules can have up to 97 % active content, a small amount of excipient are required. It can achieve excellent content uniformity from granule to granule.

2. Powder layering: Process starts with a core material, usually a sugar/starch or salt crystal or sphere, which is placed inside the machine on the rotor plate. The active drug is feed into the machine using a precision powder feeder. The active powder is dispersed directly in the

material of core via a powder gun port. A solution of binder is sprayed onto material opposite of the active powder is being introduced. The binder solution sticks the active powder to the outside of the core material and the powder begins to coat the core, similarly to how a snowball is formed.

Critical step in the process of granulation, very low amount of airflow are required balancing the powder feed rate and spray rate is mainly critical parameters for powder layering. If these parameters are out of balance, both overwetting and agglomeration will occur, or inefficient of the powder and losses will occur.

Advantages of powder layering

Significant time saving by adding the active in powder form rather than by dissolving/suspending it into a liquid and spraying it on. Most, if not solvents of organic are eliminated. It is able to achieve upwards of 80 % coating in a relatively short time. It has ability to create a multi-layer bead with multiple actives in similar bead.

Dry powder layering

Same process as active powder layering, except a polymer powder is feed on the cores instead of an active powder. A plasticizer solution is use to plasticize and bind the polymers to the outside core instead of a standard binder solution. As by powder layering process, the mainly significant parameters to monitor is the balance between the polymer powder feed rate and spray rate. In general, this process is identical to the active layering process, only the materials are different.

3. Solution/suspension spray

This process involves spraying an active or polymer that is dissolved or suspended into a liquid onto a multi-particulate core, similar to what is done in a Wurster coater. Doing this process in a rotor offers the unique ability to add any required glidants (talc, magnesium stearate) as dry powder via the powder feeder/powder gun system, thereby removing them from the solution. These very much reduce problems with spray gun/solution line plugging and allows for increased spray rates while reducing the required amounts of glidants.

Critical parameters are, unlike the other processes done on a Granurex®, the solution/suspension spray process does require significantly more airflow for drying purpose. Other parameter as rates of spray, temperatures, atomization pressure and rotor speed are

largely variable, depending on the specific solution being applied,core size being used. For coatings that required glidant addition, the rate of glidant application will mostly depended on the polymer type and spray rate.[47,48]

CONCLUSION

Majorly focus in this review article on the innovative granulation techniques to produce granules and pellets. Every techniques have merits and demerits. Selection of method mainly depends on the individual ingredient's characteristics, sufficient flow properly, eject, disintegrate and compresses, accurate process of granulation necessarily uses the knowledge of every ingredients in the method, the combination of ingredient, and how they work with each other.

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REFERENCES

1. Ennis BJ. Theory of Granulation: An Engineering Perspective. In: Parikh DM, editors. Handbook of Pharmaceutical Granulation Technology. 2nd ed. New York: Marcel Dekker INC; 1997.
2. Tardos GI. Preface. Powder Technol 2001; 117: 1-2.
3. Ritala M, Jurgersen O, Holm P, Schaefer T, Kristensen HG. A comparison between binders in the wet phase of granulation in a high shear mixer. Drug Dev Ind Pharm 1986; 12: 1685-1700.
4. Alderman DA. A review of cellulose ethers in hydrophilic matrices for oral controlled-release dosage forms. Int J Pharm Technol Prod Manuf, 1984; 5(3): 1-9.
5. http://www.atacamalabs.com/technology_specialty.
6. Hancock BC, Colvin JT, Mullarney MP. The relative density of pharmaceutical powders, blends, dry granulations and immediate release tablets. Pharm Technol. 2003; 274: 64-80.
7. Rowe RC, Roberts RJ. Mechanical properties. In: Alderborn G, Nystrom C, editors, Pharmaceutical powder compaction technology. Volume 71. New York: Marcel Dekker; 1996.
8. Nkansah P, Wu SJ, Sobotka S, et al. A novel method for estimating solid fraction of roller-compacted ribbons. Drug Dev Ind Pharm, 2008; 34(2): 142-48.

9. Rundgren K, Lyckfeldt O and Sjöstedt M. Improving Powders with Freeze Granulation. Ceramic Industry, 2003; 40-44.
10. www.dow.com/dowexcipients/resources/application/app_granulation.htm.
11. Paul J, Shesky R, Colin K. New foam binder technology from Dow improves granulation process. Pharmaceutical Canada, June 2006; 19-22.
12. Sheskey P. Foam Technology: The Development of a Novel Technique for the Delivery of Aqueous Binder Systems in High- Shear and Fluid Bed Wet-Granulation Applications. poster presented at AAPS Annual Meeting and Exposition, Salt Lake City, UT, Oct. 2003; 26-30.
13. Sheskey P. Scale-Up Trials of Foam Granulation Technology—High Shear. Pharm. Technol. 2007; 31(4): 94-108.
14. Thompson MR, Weatherley S, Pukadyil RN, and Sheskey PJ. Foam granulation: new developments in pharmaceutical solid oral dosage forms using twin screw extrusion machinery Drug Dev Ind Pharm. 2012; 38(7): 771-784.
15. Keary CM, Sheskey PJ. Preliminary report of the discovery of a new pharmaceutical granulation process using foamed aqueous binders. Drug Dev Ind Pharm. 2004; 30: 831-845.
16. Fry JF, French RJ. A mechanical foam generator for use in laboratories. J Appl Chem. 1951; 1: 425-429.
17. Keary CM, Sheskey PJ. Priliminary Report of the Discovery of a New Pharmaceutical Granulation Process Using Foamed Aqueous Binder. Drug Dev. Ind. Pharm, 2004; 30(8): 831-845.
18. Passerini N, Albertini B, Gonza´lez-Rodrı´guez ML, Cavallari C, Rodriguez L. Preparation and characterization of ibuprofen-poloxamer 188 granules obtained by melt granulation. Eur J Pharm Sci., 2002; 15: 71-78.
19. Perissutti B, Rubessa F, Moneghini M, Voinovich D. Formulation design of carbamazepine fast-release tablets prepared by melt granulation technique. Int J Pharm. 2003; 256: 53-63.
20. Gupta MK, Goldman D, Bogner RH, Tseng YC. Enhanced drug dissolution and bulk properties of solid dispersions granulated with a surface adsorbent. Pharm Dev Technol 2001; 6(4): 563–572.
21. Gupta MK, Bogner RH, Goldman D, Tseng YC. Mechanism for further enhancement in drug dissolution from solid-dispersion granules upon storage. Pharm Dev Technol, 2002; 7(1): 103-112.

22. Gupta MK, Tseng YC, Goldman D, Bogner RH. Hydrogen bonding with adsorbent during storage governs drug dissolution from solid-dispersion granules. Pharm Res 2002; 19(11): 1663-72.
23. Schaefer T, Holm P, Kristensen HG. Melt granulation in a laboratory scale high shear mixer. Drug Dev Ind Pharm, 1990; 16: 1249-77.
24. Schaefer T, Holm P, Kristensen HG. Melt pelletization in a high shear mixer. II. Power consumption and granule growth. Acta Pharm Nordica, 1992; 4: 141-148.
25. Schaefer T, Holm P, Kristensen HG. Melt pelletization in a high shear mixer. I. Effects of process variables and binder. Acta Pharm Nordica, 1992; 4: 133-140.
26. Schaeferand T, Mathiesen C. Melt pelletization in a high shear mixer. IX. Effects of binder particle size. Int J Pharm, 1996; 139: 139-148.
27. Schaeferand T, Mathiesen C. Melt pelletization in a high shear mixer. VIII. Effects of binder viscosity. Int J Pharm, 1996; 139: 125-138.
28. Schaefer T, Taagegaard B, Thomsen LJ, Kristensen HG. Melt pelletization in a high shear mixer. V. Effects of apparatus variables. Eur J Pharm Sci., 1993; 1: 133-141.
29. Schaefer T, Taagegaard B, Thomsen LJ, Kristensen HG. Melt pelletization in a high shear mixer. IV. Effects of process variables in a laboratory scale mixer. Eur J Pharm Sci., 1993; 1: 125-131.
30. Iveson SM, Litster JD, Hapgood K, Ennis BJ. Nucleation, growth and breakage phenomena in agitated wet granulation processes: a review, Powder Technology., 2001; 117: 3-39.
31. Zhaib H, Lia S, Andrewsb G, Jonesb D, Bella S, Walkera G. Nucleation and growth in fluidised hot melt granulation. Powder Technology, 2009; 189(2): 230-237.
32. Passerini N, Perissutti B, Monoghini M, Voinovich D, Albertini B, Cavallari C, Rodriguez L. Characterization of carbamazepine–Gelucire 50/13 microparticles prepared by a spray congealing process using ultrasounds, J Pharm Sci., 2002; 91(3): 699-707.
33. Maejima T, Osawa T, Nakjima K, Kobayashi M. Application of tumbling melt granulation method for preparing controlled release beads coated with hydrogenated castor oil, Chem Pharm Bull. 1997; 45(5): 904-910.
34. Kidokoro M, Sasaki K, Haramiishi Y, Matahira N. Effect of crystallization behavior of polyethylene glycol 6000 on the properties of granule prepared by fluidized hot melt granulation (FHMG), Chem Pharm Bull. 2003; 51(5): 487–493.

35. Chokshi R, Zia H. Hot melt extrusion technique: a review. Iranian J Pharm Res. 2004; 3: 3-16.
36. Heng WS, Wong TW. Melt processes for oral solid dosage forms. Pharm Tech. 2003; 1-6.
37. Cavallari C, Abertini B, Gonza´lez-Rodrı´guez ML, Rodriguez L. Improved dissolution behaviour of steam-granulated piroxicam. Eur J Pharm Biopharm, 2002; 54: 65-73.
38. United States Patent 4489504 - Steam granulation apparatus and method.
39. Rodriguez L, Cavallari C, Passerini N, Albertini B, Gonza´lez-Rodrı´guez ML, Fini A. Preparation and characterization by morphological analysis of diclofenac/PEG 4000 granules obtained using three different techniques. Int. J Pharm. 2002; 242(1,2): 285–289.
40. www.vectorcorporation.com/news/papers.asp, optimization of binder level in moisture activated dry granulation (MADG) using absorbent starch to distribute moisture.
41. Christensen LH, Johansen HE, Schaefer T. Moisture-activated dry granulation in a high shear mixer. Drug Dev Ind Pharm, 1994; 20: 2195–2213.
42. Ullah I, Wang J, Chang S, Wiley GJ, Jain NB, Kiang S. Moisture Activated Dry Granulation—Part I: A Guide to Excipient and Equipment Selection and Formulation Development, Pharm Tech. 2009; 33(11): 62-70.
43. Ullah I, Wang J, Chang S, Guo H, Kiang S, Jain N. Moisture Activated Dry Granulation Part II: The Effects of Formulation Ingredients and Manufacturing-Process Variables on Granulation Quality Attributes, Pharm Techn. 2009; 33(12): 42-51.
44. Gerhardt AH. Moisture Effects on Solid Dosage Forms Formulation, Processing and Stability, Journal of GXP Compliance Winter. 2009; 13(1): 58-66.
45. www.colorcon.com/literature/marketing/mr/Extended%2520Release/METHOCEL/English/ads_invest_mag_v1_01.2010.pdf Investigation of Moisture Activated Granulation of Hydrophilic Polymer Blends in Verapamil HCl Extended Release Matrices.
46. http://www.freund-vector.com/technology/granurex.asp.
47. Shoung Y and Hungting Y. United State Patent Application: Process for the preparation of direct tableting formulation and aids; 20030017198; 2003; 23(1).
48. www.pharmcast.com/Patents100/.../6761905_Tabletting071304.htm.