CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

https://zenodo.org/records/12620702

https://www.iajps.com/volumes/volume11-july-2024/01-issue-07-july-24/

Available online at: http://www.iajps.com *Review Article*

A REVIEW ON MELT GRANULATION TECHNIQUES

Anumula Chandra Kiran*, G Ramakrishna, M. V. Nagabhushanam, Malinedi Gowthami, Rompicharla Sushma, Tanniru Siva Pavani

Department of Pharmaceutical Regulatory Affairs, Hindu College of Pharmacy, Amaravathi Road, Guntur, Andhra Pradesh, India-522002.

Abstract:

In the process of creating pharmaceutical oral dosage forms, granulation is one of the most crucial unit processes. Granulation will enhance flow and compression properties, lessen segregation, increase content uniformity, and get rid of too many tiny particles. The outcomes will be better yields; fewer tablet faults, higher productivity, and less downtime. The collection of tiny particles into larger aggregates is referred to as an agglomeration or granulation. Agglomeration refers to the build up of small particles into larger aggregates with the help of a binding agent or mechanical force, such as water, starch paste, or roller compaction. Although both terms are similarly defined, inspection of the manufacturing process offers a simple method of differentiating the two aggregation phenomena. This analysis concentrates on the most recent developments.

Keywords: *Granulation, Agglomeration, Segregation.*

Corresponding author:

Anumula Chandra Kiran*,

IV/IV B.Pharmacy,

Department of Pharmaceutical Regulatory Affairs, Hindu College of Pharmacy, Amaravathi Road, Guntur, Andhra Pradesh, India-522002.

QR code

Please cite this article in press Anumula Chandra Kiran et al., ***A Review On Melt Granulation Techniques.,****Indo Am. J. P. Sci, 2024; 11 (07).*

1. INTRODUCTION[1-5]:

Granulation is the process or act of developing into grains during crystallisation. Depending on their intended purpose, granules can range in size from 0.2 to 4.0 mm. Prior to compressing tablets or filling capsules after granulation, the granules must be combined with other excipients. The two types of granulation methods are wet granulation and dry granulation. There are several novel granulation techniques, including pneumatic dry granulation, freeze granulation, foamed binder technology, hot melt granulation, and steam granulation. One of the most important unit processes in the production of pharmaceutical oral dosage forms is granulation. Granulation will improve flow and compression characteristics, reduce segregation, improve content uniformity, and remove an excessive amount of microscopic particles**.**

Higher productivity, fewer tablet failures, improved yields, and reduced downtime are the expected results. Agglomeration or granulation refers to the formation of smaller aggregates from smaller ones. A binding agent or mechanical force, such as water, starch paste, or roller compaction, is used to bind microscopic particles into bigger aggregates during a process known as agglomeration. Despite having identical definitions, the two aggregation phenomena can be distinguished by inspecting the manufacturing process. This review focuses on the most current advancements in the processes of thermal adhesion granulation, extrusion and spheronization, and moisture activated dry granulation. Pharmaceutical powders can now be efficiently aggregated for use in solid dosage forms with both immediate and prolonged release using a process called melt granulation.

The process utilizes materials that are eflective as granulating fluids when they are in the molten state. Cooling of the agglomerated powders and the resultant solidification of the molten materials completes the granulation process. The Fluidized hot melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by the use of a low melting point binder which is added to the other components of the powder.

Ideal characteristics of granules:

The following are ideal characteristics of granules.

- Spherical shape
- Smaller particle size distribution with sufficient fines to fill void spaces between granules
- Adequate moisture content [1-2 %]
- Good flow
- Good compressibility
- Sufficient hardness

The effectiveness of the granulation depends on the following properties:

- Size of the drug particle and excipients
- Types of binders
- Volume of binders
- Time of wet massing
- Amount of shear applied
- Rate of drying [Hydrate formation and polymorphism]

Reasons for conducting granulation process:

- To enhance the flow properties
- To prevent the problems of dust during compression
- To produce uniform size particles
- To improve drug compression ability
- For regulate the drug releasing from the tablet.
- It is usefull to densifying the material

Types of granulation technologies: The following are the types of granulation techniques.

1. Dry granulation
2. Moisture activated dry granulation
3. Pneumatic dry granulation
4. Wet granulation
5. Melt granulation (or) Thermo plastic granulation
6. Thermal adhesion granulation.
7. Steam granulation.

1. **Dry granulation**:

The Dry granulation process involved initially conversion of powdered blend tablet in to slugs (or) compact masess which are then screened to form uniform sized fine granules. The dry granulation process is suitable for

- Moisture sensitive drugs.
- Drugs undergo degradation at high temperature.

Advantage:

- Less time taking.

Disadvantage:

- It produces dust.

2. **Moisture activated dry granulation**:

In this method moisture is used for formation of granules. In this process the drying step is not necessary due to presence of moisture absorbing material such as micro crystalline cellulose (MCC).

Ideal characteristics of granules:

The ideal characteristics of granules include spherical shape, smaller particle size distribution with sufficient fines to fill void spaces between granules, adequate moisture (between 1-2%), good flow, good compressibility and sufficient hardness. The

effectiveness of granulation depends on the following properties. 2

♦ Particle size of the drug and excipients
♦ Type of binder (strong or weak)
♦ Volume of binder (less or more)
♦ Wet massing time (less or more)
♦ Amount of shear applied
♦ Drying rate (Hydrate formation and polymorphism)

2. MELT GRANULATION TECHNOLOGY[6-10]

Melt granulation is processes by which granules are obtained through the addition of either a molten binder or a solid binder which melts during the process. This process is also called melt agglomeration and thermoplastic granulation.

Principle of melt granulation:

The process of granulation consists of a combination of three phases:

I. Wetting and nucleation,
II. Coalescence step,
III. Attrition and breakage.

Wetting and nucleation step:

• During the nucleation step the binder comes into contact with the powder bed and some liquid bridges are formed, leading to the formation of small agglomerates.

Two nucleation mechanisms are proposed by Schafer and Mathiesen.

I. Immersion
II. Distribution Immersion

- Nucleation by immersion occurs when the size of the molten binder droplets is greater than that of the fine solid particles.
- Immersion proceeds by the deposition of fine solid particles onto the surfaces of molten binder droplets.

Distribution:

- In the distribution method a molten binding liquid is distributed onto the surfaces of fine solid particles.
- The nuclei are formed by the collision between the wetted particles.
- Generally, small binder droplet size, low binder viscosity, and high shearing forces are favorable conditions for nucleation by the distribution method

Coalescence step:

¬ It involves nuclei that have residual surface liquid to promote successful fusion of nuclei.

¬ The surface liquid imparts plasticity to the nuclei and is essential for enabling the deformation of nuclei surface for coalescence as well as promoting the rounding of granulation.

Attrition-breakage step:

¬ Attrition and breakage refer to the phenomenon of granulation fragmentation in that are solidified by tray cooling to ambient temperature without the need for drying by a tumbling process. ¬ Consequently, breakage is known to have a more essential role in affecting the resultant properties of the melt granulation during the granulation phase.

Requirements of melt granulation:

- Generally, an amount of 10–30% w/w of meltable binder, with respect to that of fine solid particles, is used.
- A Meltable binder suitable for melt a granulation has a melting point typically within the range of 50– 100_C.
- Hydrophilic Meltable binders are used to prepare immediate-release dosage forms while the hydrophobic Meltable binders are preferred for prolonged-release formulations.
- The melting point of fine solid particles should be at least 20°C higher than that of the maximum processing temperature.

Meltable binders:

- It must be solid at room temperature and melt between 40 and 80°C,
- Its physical and chemical stability
- Its hydrophilic-lipophilic balance (HLB) to ensure the correct release of the active substance.
- There are two type of Meltable binder

1) Hydrophilic Meltable binders
2) Hydrophobic Meltable binder

Advantage of melt granulation:

- Neither solvent nor water used.
- Fewer processing steps needed thus time consuming drying steps eliminated.
- Uniform dispersion of fine particle occurs.
- Good stability at varying pH and moisture levels.
- Safe application in humans due to their non-swell able and water insoluble nature

The melt granulation process carries several advantages over conventional pharmaceutical granulation methods, as the process does not require the use of solvents. A further significant advantage of melt granulation is that judicious choice of the granulation excipient may enable the formulator to manipulate the drug dissolution rate from the corresponding dosage form20

The melt granulation process uses a substances that melt at relatively low temperature (i.e., 50-800 These substances can be added to the molten form over the substrate or to a solid form, which is then heated above its melting points by hot air or by a heating

jacket. In both cases, the substance acts like a liquid binder after it melts. Thus melt granulation does not require the organic or aqueous solvents. Moreover the drying step is not necessary in melt granulation, thus the process is less time consuming and more energy efficient than wet granulation.

After selecting a suitable binder, one can use melt granulation to prepare controlled release or improved release granules. Polyoxyl stearates may be considered as potentially useful hydrophilic binders in melt granulation. When water soluble binders are needed, Polyethylene Glycol (PEG) is used as melting binders. 23 When water insoluble binders are needed, Stearic acid, cetyl or stearyl alcohol, various waxes and mono-, di-, & triglycerides are used as melting binders.

3. TYPES OF GRANULATIONS TECHNIQUES[11-15]

High-Shear Wet Granulation
Fluid-Bed Granulation
Low-Shear Wet Granulation
Dry Granulation (Roller Compaction →Milling)
Spray Drying
Melt Granulation/Spray Congealing

ADVANTAGES

- Able to control the granule density through the solid content of the suspension, preparation of granules with no cavities
- Useful for the preparation of granules that needs to be prepared from suspensions whose particle size and homogeneity need to be preserved.
- Minimize damage of organic compounds and improve stability and/or solubility.
- High product yield due to low waste of material
- Possibility of recycling organic solvents.
- Good granulation results even at high drug loading have been achieved with materials known to be historically difficult to handle.
- Faster speed of manufacturing compare with wet granulation.
- Lower cost of manufacturing compare with wet granulation.
- The system is closed offering safety advantage due to low dust levels and potential for sterile production or handling of toxic material.
- The end products are very stable- shelf life may be enhanced.
- The granules and tablet produced show fast disintegration properties, offering the potential for fast release dosage forms

DISADVANTAGES

- Heat sensitive materials are poor candidates.
- Lower melting point binder may melt/ soften during handling or storage.
- Long processing time, a relatively high capital investment on heavy duty presses or compactors.
- Process is expansive because of labour, space, time. Loss of material during various stages of processing.
- Moisture sensitive and thermolabile drugs are poor candidates. Multiple processing steps involved in the process and complexity

MERITS

- No water or solvent
- No drying process
- Energy input
- Cost and process time
- water sensitive drugs.

LIMITATIONS

- Tehermolabile drugs.
- Limited binders

4. APPLICATIONS OF MELT GRANULATION TECHNIQUE[16-23]

- The technology also uses less water per granulation which means less drying time 4and less impact on the environment.
- Foam technology has been proven to scale very easily for both immediate release and matrix controlled release tablets.
- This technology appears to help solve the issues that people have been having with wet granulation of highly water soluble and even very poor water soluble drugs.
- Foam granulation does a good job of solving issues with distributing a very low concentration drug level i.e. milligram (or) micro gram per tablet in a powder bed because it is a good carrier of compounds, not just the liquid itself and the polymer, but it also can carry active ingredients at very low concentrations.
- The technology seems to provide a better and a wider end point in which to granulate to each with some very difficult activities that we work with, including natural ingredients in the nutritional supplements.

5. CONCLUSION:

In the melt granulation process, cooling takes the place of drying to remove the water from wet granulation. With the molten granulation process,

both heating and chilling can be done concurrently in the same piece of equipment. Power consumption can be used to identify the granulation end point, further automating the process. The achievement of reproducible product characteristics has demonstrated the success of melt granulation process scale-up. Both immediate-release dosage forms and sustained-release dosage forms can benefit from the melt granulation technique, which has been proven to be effective**.**

6. REFERENCES:

1. A. Royce and J. Suryawanshi, 1992 AAPS Eastern Regional Meeting, Poster No. 48, Alternative granulation techniques: Wax granulation, 1992.
2. J. Suryawanshi, R. Sandry, A. Royce, and U. Shah, 1994 AAPS Eastern Regional Meeting, Poster No. 117, Process characterization of a wax granulation technique in a high shear mixer, 1994.
3. B. Lippold, in Oral Controlled Release Products, Therapeutic and Biopharmaceutic Assessment (U. GundertRerny and H. Moller, eds.), Wissenschaftliche Verlagsgesellschaft, Stuttgart, 1990, p. 39.
4. R. Gordon and D. Former, in Pharmaceutical Dosage Forms: Tablets, Vol. 2 (H. Lieberrnan, L. Lachman, and J. Schwartz, eds.), Marcel Dekker, New York, 1989, p. 245.
5. H. P. Bier, H. Leuenberger, and H. Sucker, Die Pharmazeutische Industrie, 41(4), 375-380 (1979).
6. T. Schaefer, P. Holm, and H. G. Kristensen, Drug Dev. Ind. Pharm., 16, 1249 (1990). H. Leuenberger and G. Imanidis, Pharrn. Tech., 10(3), 56 (1986).
7. T. Schaefer, P. Holm, and H. G. Kristensen, Acta Pharm. Nord., 4(4), 245 (1992).
8. P. Flanders, G. A. Dyer, and D. Jordan, Drug Dev. Ind. Pharm., 13(6), 1001 (1987).
9 .C. M. McTaggart, J. A. Ganley, A. Sickmueller, and S. E. Walker, Int. J. Pharm., 19, 139 (1984).
10. Brahmaiah Bonthagarala ,Varun Dasari,, Vijay Kotra, Suryakanta Swain, Sarwar Beg, Qualityby-Design based development and characterization of Pioglitazone loaded liquisolid compact tablets with improved biopharmaceutical attributes, Journal of Drug Delivery Science and Technology, 51 (2019), 345-355
11. Brahmaiah Bonthagarala, Varun Dasari, Vijay Kotra, Solubility enhancement effect at absorption site on bioavailability of Ritonavir using liquisolid technique, Therapeutic Delivery, 2019, Vol. 10, No. 05, 295-310.
12. Brahmaiah Bonthagarala , Prasanth Pasumarthi, Katta Vamshi Kiran, Sathram Nataraja, Sudarshan Donthiboina, Formulation and evaluation of orodispersable Atenolol Maleate Tablets: A comparative Study on Natural Super disintegrents and Synthetic Super disintegrents, International Journal of Research in Ayrveda and Pharmacy, ISSN(Online)-2299-3566, ISSN (Print)-2277-4343, 5(2), Mar-Apr 2014, 185-192.
13. Brahmaiah. B , Madhu Gudipati, GP Bhagath, Formulation and Evaluation of Gastro retentive Floating Drug Delivery System of Metoprolol Tartarate, International Journal of Life Sciences Biotechnology and Pharma Research, ISSN:2250-3137, Vol-2(1), 184-201, January 2013.
14. Brahmaiah Bonthagarala , Sreekanth Nama, Prasanna Kumar Desu, Formulation and Evaluation of Fast Dissolving Films of Sumatriptan, International Journal of Advanced Pharmaceutics, e-ISSN-2249-7706, Print-ISSN-2249-7714, Vol-3 (2), 2013, 102-109.
15. A thesis submitted in fulfillment of the requirement for the degree of Doctor of Philosophy by Melvin X. L. Tan. Bachelor of Engineering (Hons) Department of Chemical Engineering Monas University Clayton Victoria 3800 Australia, November, 2010, 1- 2621.
16. Anas Bhanassi, Dianazidon. Formulation and Evaluation of Aceclofenac fast Dissolving Tablet using Foam Granulation Technique. Indoglobal journal of Pharmaceutical sciences, 2(4), 2012, 342 – 347.
17. Himanshu. K. solanki, Tarashankar Basuri, Recent Advances In Granulation Technology. International Journal of Pharmaceutical Sciences Review and Research, 5(3), 2010, 48-54.
18. Lachman L, Lieberman H. A, Kanig JL, Third edition Granulation, The theory and practice of industrial pharmacy, Verghese Publishing House, Bombay, 1991, 58-59.
19. Mahammed Athar A. Saikh, A Technical Note on Granulation Technology: A Way to Optimize Granules. International Journal of Pharmaceutical Sciences and Research, 4 (1), 2012, 55 – 67. 20.Michael D. Tousey, The granulation process 101 Basic Technologies for Tablet Making Pharmaceutical Technology Tabletting and Granulation, 2002, 8-13.
21. Saikh Mahammed Athar Alli, Updated insight on Foamed Binder Granulation. International research journal of pharmacy, 4 (9), 2013, 35-40.
22. Shethvijay P. Ranpuravicky D. Steam Granulation: Novel Aspects In Granulation Techniques. International Journal of

Pharmaceutical Sciences, 3(3), 2012, 2170 – 2184.
23. Yaswanth Allamneni, Navya Allamneni, Foam Granulation technology as a New Innovation in Granulation of Pharmaceutical drugs: An Over view. International journal of Pharmaceutical frontier research, 2 (2), 2012, 68-79