Journal of Pharma Creations (JPC)

JPC |Vol.11 | Issue 4 | Oct - Dec -2024

www.pharmacreations.com

DOI : https://doi.org/10.61096/jpc.v11.iss4.2024.279-285

ISSN: 2348-6295

Review

Trends In Granulation Techniques

K. Vinod kumar*[1], B. Rama Devi[2], B. Siva sai[3], B. Sai anil kumar Dora, G. Yeshwanth[5], SK. Ashik[6]

[1]Professor Department of pharmaceutics, SIMS college of Pharmacy, Guntur, India
[2-6]Scholar, SIMS College of Pharmacy, Guntur, India

*Author for Correspondence: Dr. K. Vinod kumar
Email: Kvinodkumar1@gmail.com

Published on: 11 Oct 2024

Published by:
DrSriram Publications

Abstract

Granulation is a crucial process in pharmaceutical production, specifically in the manufacturing of tablets and capsules. It involves enlarging particles through agglomeration to create free- flowing, dust-free granules that are easy to compress. However, granulation presents various challenges due to the high quality standards required for the granules in terms of uniformity, size, density, hardness, moisture content, compressibility, and stability. There are two main types of granulation processes: wet granulation, which involves the use of liquid, and dry granulation, which does not require liquid. Choosing the appropriate process depends on understanding the physicochemical properties of the drug, excipients, desired flow and release characteristics, among others. Various technologies such as spray drying, roller compaction, high shear mixing, and fluid bed granulation are commonly used in granulation. The field of pharmaceutical granulation technology is continuously evolving, with new and innovative technologies emerging. This review highlights recent advancements in granulation techniques and technologies, including pneumatic dry granulation, reverse wet granulation, steam granulation, moisture-activated dry granulation, thermal adhesion granulation, freeze granulation, and foamed binder or foam granulation, providing a brief description of each development along with its significance and limitations.

Keywords: Granulation technique and technology, Pneumatic dry granulation, Reverse wet granulation, Steam granulation, Moisture-activated dry granulation, Thermal adhesion granulation.

INTRODUCTION

Granulation is the process in which primary powder particles are made to adhere to form larger, multi particle entities called granules. Pharmaceutical granules typically have a size range between 0.2 and 4.0 mm,

depending on their subsequent use. In the majority of cases this will be in the production of tablets or capsules, when granules will be made as an intermediate product and have a typical size range between 0.2 and 0.5 mm, but larger granules are used as a dosage form in their own right.

After granulation the granules will either be packed (when used as a dosage form), or they may be mixed with other excipients prior to tablet compaction or capsule filling.

Need for Granulation

To prevent segregation of the constituents of the powder mix

Segregation is due primarily to differences in the size or density of the components of the mix. An ideal granulation will contain all the constituents of the mix in the correct proportion in each granule, and segregation of the ingredients will not occur.

To improve the flow properties of the mix

Many powders, because of their small size, irregular shape or surface characteristics, are cohesive and do not flow well. Poor flow will often result in a wide weight variation within the final product owing to variable fill of tablet dies etc.

To improve the compaction characteristics of the mix

Granules of the same formulation are often more easily compacted and produce stronger tablets, rather than powders. This is associated with the distribution of the adhesive within the granule and is a function of the method employed to produce the granule. Often solute migration occurring during the post granulation drying stage results in a binder-rich outer layer to the granules. This in turn leads to direct binder–binder bonding, which assists the consolidation of weakly bonding materials. Apart from the above primary reasons the secondary reasons include the following

- The granulation of toxic materials will reduce the hazard associated with the generation of toxic dust that may arise when handling powders. Suitable precautions must be taken to ensure that such dust is not a hazard during the granulation process. Thus granules should be non-friable and have a suitable mechanical strength.
- Materials, which are slightly hygroscopic, may adhere and form a cake if stored as a powder. Granulation may reduce this hazard, as the granules will be able to absorb some moisture and yet retain their flow ability because of their size.
- Granules, being denser than the parent powder mix, occupy less volume per unit weight. They are therefore more convenient for storage or shipment.

Methods of Granulation

Granulation methods can be divided into two types: wet method and dry method.

Dry granulation

In the dry methods of granulation the primary powder particles are aggregated under high pressure. There are two main processes. Either a large tablet (known as a '*slug*') is produced in a heavy-duty tableting press (a process known as '*slugging*') or the powder is squeezed between two rollers to produce a sheet of material ('*roller compaction*'). In both cases these intermediate products are broken using a suitable milling technique to produce granular material, which is usually sieved to separate the desired size fraction. The unused fine material may be reworked to avoid waste. This dry method may be used for drugs that do not compress well after wet granulation, or those, which are sensitive to moisture.

Wet granulation

Wet granulation involves the massing of a mix of dry primary powder particles using a granulating fluid. The granulation liquid may be used alone or, more usually, as a solvent containing a dissolved adhesive (also referred to as a binder or binding agent), which is used to ensure particle adhesion once the granule, is dry. Organic solvents are used when water-sensitive drugs are processed, as an alternative to dry granulation, or when a rapid drying time is required. In the traditional wet granulation method the wet mass is forced through a sieve to produce wet granules, which are then dried. A subsequent screening stage breaks agglomerates of granules and removes the fine material, which can than be recycled.

Mechanisms of Granule Formation

The proposed granulation mechanism can be divided into three stages.

- Nucleation
- Transition
- Ball growth

Nucleation

Granulation starts with particle–particle contact and adhesion due to liquid bridges. Further agitation densifies the pendular bodies to form the capillary state, and these bodies act as nuclei for further granule grow.

Transition

Nuclei can grow in two possible ways: either single particle can be added to the nuclei by pendular bridges, or two or more nuclei may combine. The combined nuclei will be reshaped by the agitation of the bed. This stage is characterized by the presence of a large number of small granules with a fairly wide size distribution. Providing that this distribution is not excessively large, this is a suitable end-point for granules used in capsule and tablet manufacture, as relatively small granules will produce a uniform tablet die or capsule fill.

Ball growth

Further granule growth produces large, spherical granules and the mean particle size of the granulating system will increase with time. If agitation is continued, granule coalescence will continue and produce an unusable, over massed system, although this is dependent upon the amount of liquid added and the properties of the material being granulated. Although ball growth produces granules that may be too large for pharmaceutical purposes, some degree of ball growth will occur in planetary mixers and it is an essential feature of some Spheronizing equipment.

An Overview of Fluid Bed Coating Process

Batch-type fluid bed processes for pharmaceutical manufacturing have been in use for more than 40 years. Originating in Europe, this technology gradually found its way into U.S. manufacturing facilities, beginning with the use of fluid bed driers. The introduction of an expansion space between the product container and the filter chamber, and the inclusion of a liquid-spray nozzle in that space, gave rise to fluid bed agglomeration (more commonly referred to as fluid bed granulation) – an effective alternative to conventional low-shear mixing and tray drying (Olsen, 1989). The fluid bed coaters are mainly classified into 3 categories. They are

Top Spray Coating

This process is used for general coatings right up to enteric coating. With top spray coating in the fluid bed (batch and continuous), particles are fluidized in the flow of heated air, which is introduced into the product container via a base plate. The coating liquid is sprayed into the fluid bed from above against the air flow (countercurrent) by means of a nozzle. Drying takes place as the particles continue to move upwards in the air flow. Small droplets and a low viscosity of the spray medium ensure that the distribution is uniform.

Coating in the continuous fluid bed is particularly suitable for protective coatings/color coatings where the product throughput rates are high. The product is continuously fed into one side of the machine and is transported onwards via the sieve bottom by means of the air flow. Depending on the application, the system is sub-divided into pre-heating zones, spray zones and drying zones. The dry, coated particles are continuously extracted (Glatt-Technology, Fluid Bed Coating).

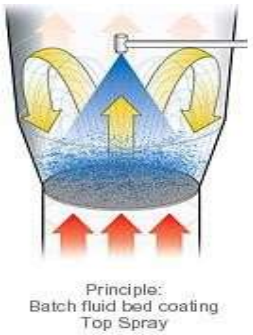

Fig 1: Top Spray fluid bed coating

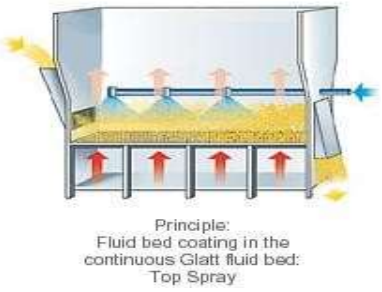

Fig 2: Top Spray continuous fluid bed coating

This type of coating is widely used for the granulation process for the manufacture of tablets. The principle involved in the granulation process is as followed. During fluid bed granulation the granules are usually not formed by the binder itself, as often anticipated; but by the spray liquid, whereas the binder consolidates the originally formed agglomeration. Granulate growth is controlled by moisture control of the product bed when a certain quantity of liquid has been sprayed onto the substrate a first agglomeration can be observed.

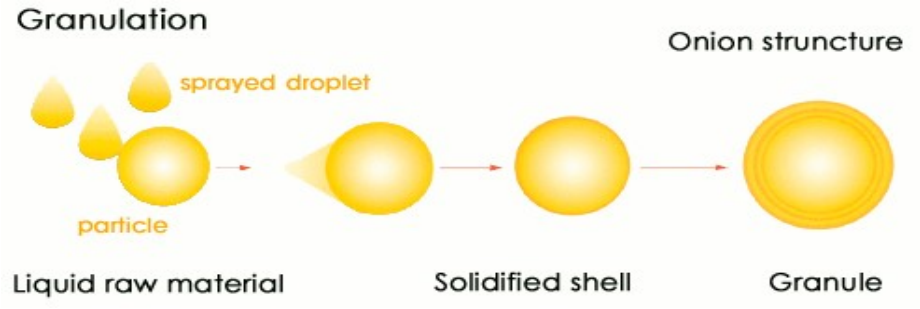

Fig 3: Principle involved in Top spray granulation

Bottom Spray Coating (Wurster coating)

This process is particularly suitable for a controlled release of active ingredients. In the Wurster process, a complete sealing of the surface can be achieved with a low usage of coating substance. The spray nozzle is fitted in the base plate resulting in a spray pattern that is concurrent with the air feed. By using a Wurster cylinder and a base plate with different perforations, the particles to be coated are accelerated inside the Wurster tube and fed through the spray cone concurrently. As the particles continue traveling upwards, they dry and fall outside the Wurster tube back towards the base plate. They are guided from the outside back to the inside of the tube where they are once again accelerated by the spray. This produces an extremely even film. Particles of different sizes are evenly coated.

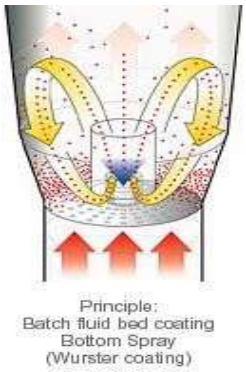

Fig 4: Bottom spray fluid bed coating

Bottom Spray Coating (Continuous fluid bed)

Particularly suitable for protective coatings/color coatings where the product throughput rates are high. The product is continuously fed into one side of the machine and is transported onwards via the sieve bottom by means of the air flow. Depending on the application, the system is sub-divided into pre-heating zones, spray zones and drying zones whereby spraying can take place from below in the form of a bottom spray. The dry, coated particles are continuously extracted.

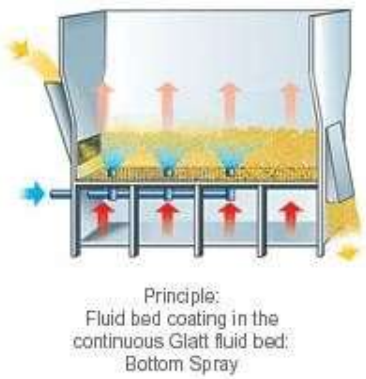

Fig 5: Bottom spray continuous fluid bed coating

Tangential Spray Coating (Rotor pellet coating)

This process is ideal for coatings with high solid content. The product is set into a spiral motion by means of a rotating base plate, which has air fed into the powder bed at its edge. The spray nozzle is arranged tangentially to the rotor disc and also sprays concurrently into the powder bed. Very thick film layers can be applied by means of the rotor method.

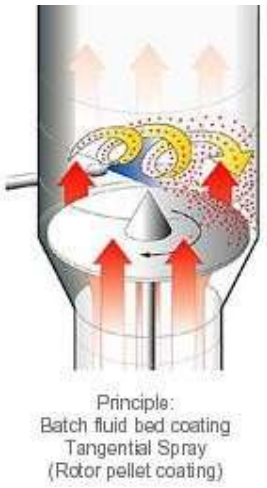

Fig 6: Tangential spray fluid bed coating

When an organic system is used, the success of the process will depend on the selection of the appropriate fluid-bed drier. The bottom-spray and tangential spray fluid-bed coaters appear to perform satisfactorily. However, the top-spray fluid-bed coater does not appear to be the optimal choice because of the distance and direction the coating solution must travel before coming in contact with the substrate and because the heat of vaporization tends to be lower for an organic solvent than for water.

Pneumatic Dry Granulation (PDG)

The PDG Technology:

- Is based on a pneumatic dry granulation process, a novel dry method for automatic or semi-automatic production of granules,
- Enables flexible modification of drug load, disintegration time and tablet hardness

Can achieve:

- High drug loading, even with 'difficult' APIs and combinations
- Taste masking

Excellent stability,

- Is compatible with other technologies, such as sustained release, fast release, coating,
- Is suitable for heat labile and moisture sensitive drugs, and
- Is the subject of a number of patent applications.

The PDG Technology produces porous granules with excellent compressibility and flowability characteristics.

Granulate Any API

The pneumatic dry granulation process can granulate virtually any pharmaceutical solid dosage ingredient. The granulated material has exceptionally good flowability and compressibility properties. PDG Technology has been used with superior results in developing fast-release, controlled-release, fixed-dose, and orally disintegrating tablets. The technology is applicable to practically any solid dosage pharmaceutical product.

Pneumatic Dry Granulation Replaces Wet Granulation

Today, wet granulation is the most commonly used granulation method. Formulation teams will usually target a direct compression or dry granulation formulation where possible but in approximately 80% of the cases they end up with a wet granulation formulation due to processing issues.

Wet granulation is also unsuitable for moisture sensitive and heat sensitive drugs, it is more expensive than dry granulation, it is relatively labour intensive and can take a long time. There are a large number of process steps and each step requires qualification, cleaning, and cleaning validation, high material losses can be incurred because of the transfer between stages, there is the need for long drying times. Scale up is usually an issue, and there are considerable capital requirements. PDG Technology solves the above problems. PDG Technology granules have excellent properties compared to wet granulation, dry granulation and direct compression.

At the same time, the granules show both high compressibility and flowability. The results can be archived without using exotic and expensive excipients.

Advantages of PDG Technology

The PDG Technology has a number of advantages to support the above claims including the following:

- Good granulation results even at high drug loading have been achieved even with materials known to be historically difficult to handle,
- Faster speed of manufacturing compared with wet granulation,
- Lower cost of manufacturing compared with wet granulation,
- The system is closed offering safety advantages due to low dust levels and potential for sterile production or handling of toxic materials,
- The end products are very stable - shelf life may be enhanced,
- Little or no waste of material,
- Scale-up is straightforward,
- The granules and tablets produced show fast disintegration properties, offering the potential for fast release dosage forms,
- Release time can be tailored to requirements.

Benefits to Pharmaceutical Companies

PDG Technology is the key solution to challenges faced by pharmaceutical companies in development of solid oral dosage forms. The technology replaces existing solid dosage form development and manufacturing technologies, offering more rapid development and better quality. The unique capabilities of the technology have been demonstrated in number of evaluation studies with top-tier pharmaceutical companies.

REFERENCES

1. Hilton AK, Deasy PB. In vitro and in vivo evaluation of an oral sustained-release floating dosage form of amoxycillin trihydrate. International Journal of pharmaceutics. 1992 Oct 10;86(1):79-88.
2. Sheth PR, Tossounian J. The hydrodynamically balanced system (HBS™): a novel drug delivery system for oral use. Drug development and industrial pharmacy. 1984 Jan 1;10(2):313-39.
3. Harrigan RM, inventor. Drug delivery device for preventing contact of undissolved drug with the stomach

lining. United States patent US 4,055,178. 1977 Oct 25.
4. Whitehead L, Fell JT, Collett JH. Development of gastroretentive dosage form. European Journal of Pharmaceutical Sciences. 1996(4):S182.
5. Kawashima Y, Niwa T, Takeuchi H, Hino T, Itoh Y. Hollow microspheres for use as a floating controlled drug delivery system in the stomach. Journal of pharmaceutical sciences. 1992 Feb 1;81(2):135-40.
7. Stockwell AF, Davis SS, Walker SE. In vitro evaluation of alginate gel systems as sustained release drug delivery systems. Journal of controlled release. 1986 Jan 1;3(1-4):167-75.
8. Moës AJ. Gastroretentive dosage forms. Critical reviews in therapeutic drug carrier systems. 1993 Jan 1;10(2):143-95.
9. Bechgaard H, Ladefoged K. Distribution of pellets in the gastrointestinal tract. The influence on transit time exerted by the density or diameter of pellets. Journal of Pharmacy and Pharmacology. 1978 Sep;30(1):690-2.
10. Gruber P, Rubinstein A, Li VH, Bass P, Robinson JR. Gastric emptying of nondigestible solids in the fasted dog. Journal of pharmaceutical sciences. 1987 Feb;76(2):117-22.
11. Kavimandan NJ, Lakshman JP, Matharu AS, Ogorka J, Royce AE, Teelucksingh NR, inventors; Novartis AG, assignee. Extended release gastro-retentive oral drug delivery system for valsartan. United States patent application US 12/377,949. 2010 Sep 16.
12. Hwang SJ, Park H, Park K. Gastric retentive drug-delivery systems. Critical Reviews™ in Therapeutic Drug Carrier Systems. 1998;15(3):243–284.
13. Kinloch AJ. The science of adhesion: part 1 surface and interfacial aspects. Journal of materials science. 1980 Sep;15:2141-66.
14. Henriksen I, Green KL, Smart JD, Smistad G, Karlsen J. Bioadhesion of hydrated chitosans: an in vitro and in vivo study. International journal of pharmaceutics. 1996 Dec 6;145(1-2):231-40.
15. Moës AJ. Gastroretentive dosage forms. Critical reviews in therapeutic drug carrier systems. 1993 Jan 1;10(2):143-95.
16. Whitehead L, Fell JT, Collett JH, Sharma HL, Smith AM. Floating dosage forms: an in vivo study demonstrating prolonged gastric retention. Journal of controlled release. 1998 Oct 30;55(1):3-12.
17. Andrews GP, Laverty TP, Jones DS. Mucoadhesive polymeric platforms for controlled drug delivery. European journal of pharmaceutics and biopharmaceutics. 2009 Mar 1;71(3):505-18. doi: 10.101016/j.ejpb.2008.09.028
18. Fiebrig I, Harding SE, Rowe AJ, Hyman SC, Davis SS. Transmission electron microscopy studies on pig gastric mucin and its interactions with chitosan. Carbohydrate polymers. 1995 Nov 1;28(3):239-44.