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RECENT ADVANCEMENT IN TABLET TECHNOLOGY: A REVIEW

Hemant Rathod*[1],
M.P. Khinchi[1], Dilip Agrawal[1], M.K. Gupta[1]

[1]Kota College of Pharmacy, Kota, Rajasthan

ABSTRACT

Tablets and Capsules are the most commonly used dosage forms all over the world, due to patient compliance, flexibility in dosage regimen and designing of the dosage form. Besides the oral mode of administration, the other tablets may possess more or less the same features which are attributed to conventional oral tablets .A bulk of the research scientist are involved industry, academic liaison to propose an implement newer heights in tablet technology. Granulation is one of the most important unit operations in the production of pharmaceutical oral dosage forms. Granulation process will improve flow and compression characteristics, reduce segregation, improve content uniformity, and eliminate excessive amounts of fine particles. The results will be improved yields, reduced tablet defects, increased productivity, and reduced down time. Pharmaceutical products are processed all over the world using the direct-compressing, wet-granulation, or dry granulation methods. Which method is chosen depends on the ingredients individual characteristics and ability to properly flow, compresses, eject, and disintegrate. Choosing a method requires thorough investigation of each ingredient in the formula, the combination of ingredients, and how they work with each other. Then the proper granulation process can be applied. The objective of present article was to focus on the novel granulation technology.

Key words: *Foam Binder Granulation, Melt Granulation, Moisture Activated Dry Granulation, Spheronizer, All in one Granulation, GELCAP.*

Correspondence to Author

Hemant Rathod

Kota College of Pharmacy, Kota, Rajasthan

Email: hemant2787@gmail.com

INTRODUCTION

Tablets are oral solid dosage forms of medicinal substances usually prepared with the aid of suitable pharmaceutical adjuvants. Although the recent trends in tablet technology reduce the manual input and performing the process validation of each unit operation thus ensuring enhance product quality and process reliability. Objectives of the research also include meeting the changing regulatory compliances, increasing product output and decreasing product through-put time, reducing labor and energy cost. Material technology has also been revolutionized with direct compressible ingredients, avoiding wet and dry granulation.

Granulation is the process in which primary powder particles are made to adhere to form larger, multiparticle entities called granules. Pharmaceutical granules typically have a size range between 0.2 and 4.0 mm, depending on their subsequent use. 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.

Granulation method can be broadly classified into two types: Wet granulation and Dry granulation. Great significance is still attached to wet granulation, because direct compressing is not the most suitable technology for many active substances that are in high dosages or in fine powder form. Even if the active substance is sensitive to hydrolysis, modern equipment, e.g. in a fluidized bed, eliminates all problems in wet granulation. Granulation is used mainly to improve flow and compressibility of powders, and to prevent segregation of the blend components. Particle size of the granulate is mainly affected by the quantity and feeding rate of granulating liquid. [1, 2]

ADVANCEMENT IN THE MATERIAL HANDLING TECHNOLOGY:

Traditional manual handling of the materials is expensive and unsafe process which also suffers from disadvantages like production delays and loss of material ultimately affecting product output. Advances in this area have benefits like reducing handling costs, improved working conditions, improved raw material distribution systems and hence facilitated manufacturing capacity. Advancement in the material handling can be explained by the case of MERCK SHARP & DOHME CO. which employs 3 storey building and 3 operational columns. Material is transferred to the top by vacuum transfer systems and it is allow to flow under gravity through operational columns during which materials are processed for various unit operations. ELLI-LILLY & Co. utilizes driveless trains to convey raw materials and vacuum powder transfer mechanism. Mechanical devices are used to deaerate light and bulky materials with force flow feeders, increasing the powder density and cohesivety. [3]

ADVANCEMENT IN RAW MATERIALS:

Recent trends in technology direct the material science to affect the flow properties & compressibility in order to get a directly compressible vehicle or multiple use excipients. So as to avoid multiple steps involved in the tablet manufacturing & subsequently to have one or two step technology. Ready to use co-processed blends for direct compression are available. Ex;-Indipress cellatose, Pharmatose DCL 40**.** [4, 5]

Commercially available ready-to-use co-processed blends are listed in the below table. [6, 7, 8]

Table 1: Raw Materials with their Trade names and general Composition

Table Excipients	Trade Name	Composition
Filler/disintegrant	Avicel	Microcrystalline cellulose
Filler/disintegrant	Elcema	Micro fine cellulose
Filler/disintegrant	Sta-Rx 1500	Directly compressible starch
Filler/binder	Dipac	97% sucrose + 3% modified dextrins
Filler/binder	Emdex/cellutab	90-92% dextrose + 3-5% maltose

Filler	Di-tab	Dicalcium phosphate dehydrate
Filler	Terra-alba	Calcium sulphate
Glidant	Ac-di-sol	Colloidal silica
Glidant	Cab-o-sil	Colloidal silicon dioxide

ADVANCEMENT IN GRANULATION TECHNOLOGY:

1. Pneumatic Dry Granulation (PDG)

The PDG Technology: [9, 10]

- 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.

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 labor 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. [11, 12]

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, and
- Release time can be tailored to requirements.

2. Freeze granulation Technology

Swedish Ceramic Institute (SCI) has adopted and developed an alternative technique – freeze granulation (FG) – which enables preservation of the homogeneity from suspension to dry granules. By spraying a powder suspension into liquid nitrogen, the drops (granules) are instantaneously frozen. In a subsequent freeze-drying the granules are dried by sublimation of the ice without any segregation effects as in the case of conventional

drying in air. The result will be spherical, free flowing granules, with optimal homogeneity.

FG provides optimized condition for the subsequent processing of the granules, for example easy crushing to homogeneous and dense powder compacts in a pressing operation. High degree of compact homogeneity will then support the following sintering with minimal risks for granule defects. [13, 14]

Advantages of Freeze Granulation [15, 16]

- Control of granule density by the solids content of the suspension.
- Mild drying prevents serious oxidation of non-oxides and metals.
- No cavities in the granules.
- Low material waste (high yield).
- Small (50–100 ml suspension) as well as large granule quantities can be produced to equal quality.
- Easy clean of the equipment (latex binder can be used).
- Possibility to recycle organic solvents.

3. Foamed Binder Technologies (FBT)

Foamed binder technology from The Dow Chemical Company can help you achieve faster, simpler, and safer wet granulation processing. Using familiar, proven METHOCEL polymers, this technology greatly improves binder distribution in the formulation mix and yields a remarkable array of processing advantages. Compared to conventional spray processing, foamed binder technology can shorten processing times by reducing water requirements. It can improve reproducibility through more uniform binder distribution. Moreover, it eliminates spray nozzles and their many variables in granulation processing equipment. Foam processing also offers better end point determinations and reduced equipment clean-up time. While foamed binder processing offers many advantages, this technology doesn't demand new equipment or radical changes in processing techniques. You can very easily use it with familiar high shear, low shear, or fluid bed granulation equipment, in both laboratory- and production-scale settings. Our evaluations also show it yields familiar metrics for particle size distributions, solid dose physical properties, and dissolution profiles. [17, 18, 19]

Working of Foam Binder

Foam granulation takes advantage of the tremendous increase in the liquid surface area and volume of polymeric binder foams to improve the distribution of the water/binder system throughout the powder bed of a solid dose pharmaceutical formulation. A simple foam generation apparatus is used to incorporate air into a conventional water-soluble polymeric excipients binder such as METHOCEL hypromellose (hydroxypropyl methylcellulose). The resulting foam has a consistency like shaving cream. Hypromellose polymers are ideal candidates for this technology because they are excellent film formers and create exceptionally stable foams. In a small-scale laboratory setting or in a full-scale production setting, the foam generator can be connected directly to high-shear, low-shear, or fluid bed granulation equipment. [20]

4. Melt Granulation Technology

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. [21, 22, 23, 24]

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-swellable 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 form. The melt granulation process uses substances that melt at relatively low temperature (i.e., 50-80 C). 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.When water insoluble binders are needed, Stearic acid, cetyl or stearyl alcohol, various waxes and mono-, di-, & triglycerides are used as melting binders.

5. Steam Granulation

• It is modification of wet granulation. Here steam is used as a binder instead of water.

• In this method of granulating particles involves the injection of the required amount of liquid in the form of steam.

• This steam injection method, which employs steam at a temperature of about 150° C., tends to produce local overheating and excessive wetting of the particles in the vicinity of the steam nozzles, thereby causing the formation of lumps in the granulated product. [25]

Advantage

- Higher distribution uniformity,
- Higher diffusion rate into powders,
- Steam granules are more spherical,
- Have large surface area hence increased dissolution rate of the drug from granules,
- Processing time is shorter therefore more number of tablets are produced per batch,

6. Moisture Activated Dry Granulation (MADG)

• In this method moisture is used to activate the granules formation but the granules drying step is not necessary due to moisture absorbing material such as MCC.

• The moisture-activated dry granulation process consists of two steps, wet agglomeration of the powder mixture followed by moisture absorption stages.

• A small amount of water (1–4%) is added first to agglomerate the mixture of the API, a binder, and excipients. Moisture absorbing material such as MCC and potato starch is then added to absorb any excessive moisture.

• After mixing with a lubricant, the resulting mixture can then be compressed directly into tablets. Hence, this process offers the advantage of wet granulation is that eliminates the need for a drying step.

• MCC, potato starch, or a mixture of 50% of each was used as moisture absorbing material. [26, 27]

Advantage:

- It utilizes very little granulating fluid.
- It decreases drying time and produces granules with excellent flow ability.
- Single production equipment (high shear granulator)
- No equipment change
- Lower tablet capping
- No over and under granulation

7. Thermal Adhesion Granulation Process (TAGP)

It is applicable for preparing direct tabletting formulations. TAGP is performed under low moisture content or low content of pharmaceutically acceptable solvent by subjecting a mixture containing one or more diluents and/or active ingredients; a binder; and optionally a disintegrant to heating at a temperature in the range from about 30ºC to about 130ºC in a closed system under mixing by tumble rotation until the formation of granules. This method utilizes less water or solvent than traditional wet granulation method. It provides granules with good flow properties and binding capacity to form tablets of low friability, adequate hardness and have a high uptake capacity for active substances whose tabletting is poor. In thermal adhesion granulation, granules are formed during mixing of the moist powder under continuous tumble rotation, as the heated powder mass flows within the container and agglomerates with the aid of the binder. Drying and milling to form the desired granules are unnecessary in the present invention due to the low amount of moisture introduced to the tabletting mixture. Another major advantage of granulating pharmaceutical products in a closed system is that it helps to minimize the generation of dust during powder processing. This technique serves to contain fine-powder active ingredients whose spread or loss from the system is not desirable due to their cost or biological activity. [28, 29, 30, 31]

ADVANCEMENT IN EQUIPMENT TECHNOLOGY:

Semiautomatic or fully automatic instrumentation system has been held in last decade to optimize each unit operation from granulation, slugging, compaction, and compression or otherwise combine all or most of the unit operation in one system. Ex.-Rotary fluidized bed granulator/dryers (glatt rotor granulator, vector spir-a-flow granulator), Mixer-processor & mixer-granulator with vacuum drying mechanism (day nauta, topo & cf granulator), Mixer-processor & mixer-granulator with fluidized bed drying mechanism (diosna, little ford, gral mixer processor).[32]

A. SPHERONIZERS:

- Spheronization is a technology of pellatization which refers to the formation of spherical particals from wet granulation.
- Spheronization equipment generally operates by extruding wetted/blended tableting material into the cylindrical material of uniform size and narrower size distribution, breaking the segments and then rolling them into the solid spheres/granules.
- Spheronization equipment merumerizer is the latest innovation in the market evolved with a combination of roller compaction and spheronization mechanism.
- Recently, new equipment, Roto Coil has become available for continuous processing. [33]

B. MIXER-PROCESSOR &MIXER-GRANULATOR:

- It has the potential for sequencing the unit operations of powder mixing/blending, wet massing, agglomeration and specialized granulation drying capabilities.
- Day Nauta, Gral, Diosna, Little ford MGT mixer-granulator and CF granulator are the latest technologies employed for the granulation with fluidized bed drying or vacuum drying facilities.
- Topo mixer-processor reduces the proportion of excipients and granulating fluid with resultant increase in the granulation forces and hence intensified compaction.
- Diosna, Little ford and Gral contains a high speed mixer blade for mixing and wet granulation and a high speed chopper blade system as a lump and agglomerate broker with a compatible fluid bed drying unit to facilitate material transfer. [33]

C. ALL-IN-ONE GRANULATION TECHNOLOGY:

Recent technological advances have allowed the mixing, wetting, agglomeration and drying of tableting materials in a continuous process, all within a single instrument.

Examples are:

I. Fluidized bed processor performs a combination of operation within a single piece of instrument like preblending the tablet powder including excipients in a bed by fluidized air, granulating by spraying adhesive/binder onto the fluidized powder bed and dries the granulated product to the desired moisture level for final tableting compression.

II. The microwave processor also employs a mechanism to mix, wet, agglomerate and dry the powder to be tableted within one piece of equipment. It involves the techniques of gentle mixing, vacuum and microwave for drying with micro processing control of operation which reduces the drying time considerably. [34]

ADVANCEMENT IN COMPRESSION TECHNOLOGY:-

- It has been improved by replacing old single fill station gravity fed compression mechanics with newer high speed rotary tablet presses having induced die fed and automated weight control.
- The rotary tablet presses has evolved into models capable of compressing tablets at high production rates installed with either single or dual compression points.
- The single or double rotary machine may be equipped with special cams to precompress the material before the final compression at the pressure rolls.
- The rotary tablet machines also have been developed into models capable of producing one, two or three layered tablets.

  Ex.:-Rota press=10,000 tablets/minute, Korsch pharmapress=6, 00, 000 to 8, 00,000

tablets/hour, Magna vector=14,000 tablets/minute. [34, 35,]

ADVANCEMENT IN TABLET COATING MATERIALS:

- Aqueous based coating materials like colloidal dispersion(30%) of polymer Ethyl Cellulose(Aqua coat and Aquateric) are now replacing organic solvent based coating materials to meet EPA & OSHA regulations and to reduce the cost & hazards associated with it, paving the way to produce totally water based enteric and sustained release coatings.
- Water based controlled release tablet coatings by Latex and Pseudo latex of acrylate polymers and ethyl cellulose have been reported.
- Cross-linked product of hydroxyl-end blocked polydimethyl-siloxane and an alkoxysilane has been developed as water based controlled release tablet coating system.
- The most common colorants used are FD&C or D&C colourants, but recently a variety of colour concentrates like Opalux, Opaspray and Opadry have been introduced to achieve less lot-to-lot variation.[36, 37, 38]

ADVANCEMENT IN THE TABLET COATING TECHNIQUES:

A. FLUID BED OR AIR SUSPENSION COATING:

- It involves the spray coating of pellets, beds, granules, powders or tablets held in the suspension by a column of air.
- The fluid bed processing equipment is multifunctional and may be used in preparing tablet granulation as well.
- Depending upon the mode of applying solutions the system could be top spray, bottom spray or tangential fluidized bed system.
- The top spray coating method is recommended for taste masking, coating of enteric release and barrier films on particles or tablets. The method is of special significance when coatings are being applied from aqueous solutions, latexes or hot melts. The bottom spray coating is recommended for sustained release and enteric release products. The tangential spray technique is recommended for layering coatings and also for sustained release and enteric release products. [34, 39]

B. COMPRESSION COATING:

- It is an anhydrous process and the tablet prepared by it has an inner core and an outer shell of drug material and thus the technique is safely employed in the coating of tablets having a solvent sensitive or moisture sensitive drug or may provide delayed or enteric release product. [3, 32]

C. ELECTROSTATIC COATING:

- It is an efficient technique of applying coating to tablets having conductive substrates.
- Vacuum fill coating is a new coating technology that employs a specially designed baffled pan coating system with a hot water jacket. This enables a reduction in the high velocity of the heated air thus minimizing the energy requirement and maximizing the coating efficiency. [40]

D. GELCAP (GELATIN COATED CAPSULE SHAPED TABLETS):

- It provides reduction in product size and gelatin coating facilitates ease of swallowing.
- GELCAPS are more temper evident and resistant.[34]

ADVANCEMENT IN COATING EQUIPMENT TECHNOLOGY:

- Most coating processes use one of the three general coating systems like standard coating pan, perforated coating pan and the fluidized bed coater.
- A significant landmark in the performance of standard coating pan systems have been introduced with the development of Pelligrini pan, Immersion sword and immersion tube systems as in these systems coating solutions are applied by an atomized spray system directed to the surface of the rotating tablet bed.

- Similarly, tablet coating technology has been improved with the advent of perforated pan coaters (Dria-coater, Hi-coater and Accela-coater). The Glatt-coater (cap. 25-1000 kg) is the latest perforated pan coater to be introduced in the market.
- Auto coaters (Granscoater) are available with software programmes and parameter setting profiles like temperature maintenance, spray pattern or spray rate, compressed air pressure etc.
- NeoCota is the recent introduction of fully automated sugar and film coating system of tablets and pellets. [6 ,41]

CONCLUSION:

To Summarize, recent innovations have been made and directed towards process validation and quality assurance of each unit operation starting from the raw material specification to storage and packaging of tablets to make tabletting technology a complete automated system. In addition to this, efforts have been made to meet the various regulatory requirements, to reduce the cost for input and to ensure safety of the workers.

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