

# Comparing Granulation Methods

There are a number of granulation technologies available to pharmaceutical manufacturers. Given the importance of granulation in the production of oral dosage forms, this paper offers advice on various processes.

Granulation is one of the most important unit operations in the production of pharmaceutical oral dosage forms. However, there are many different technologies each having different strengths and weaknesses. Most companies choose which one to use simply based on their own experience. This article introduces different processes, compares them objectively, offers unbiased advice on the merits of each system and then looks at the implications of selection a particular granulation process.

**UPDATE 2010: Originally written and published in 2004 by Dr. Harald Stahl, this document has now been updated to include the latest process advancements and innovations in Granulation technology.**

# Comparing Granulation Methods

## Granulation methods

**Single Pot** - A mixer/granulator that dries granules in the same equipment without discharging is commonly called a Single Pot Processor (or One-Pot Processor) (Figure 1). The granulation is done in a normal high shear processor; however, care must be taken to avoid the formation of lumps as they cannot be broken down before drying. There are various options for drying in Single Pots. The basic drying principle relies on the application of a vacuum in the bowl thus lowering the evaporation temperature of the used granulation liquid drastically. The traditional heat source comes from the heated dryer walls. The heat transfer is related to the surface area of the dryer walls and the volume of product treated. Therefore, this direct heating method is most effective for small scale, organic solvents or low quantities of binder fluids.

Introducing stripping gas into the pot allows lower final moisture content to be achieved. This very low moisture content is only required in some particular applications. A small quantity of gas is introduced in the bottom of the equipment, which passes through the product bed, improving the efficiency of vapour removal. However, as the heated wall is the only source of drying energy, linear scale-up is not possible. This problem is exacerbated if the material to be processed is heat sensitive (as this limits the wall temperature); if water is used as a granulation liquid (it has a relatively high boiling temperature under vacuum and a high heat of evaporation compared to organic solvents); and if used for larger-scale production (the surface/volume ratio deteriorates as the volume increases).

Microwave energy can be used to overcome these limitations. This provides a further source of energy and has the additional advantage, with organic solvents, that only pure organic vapours must be treated on the exhaust side, and not a mixture of solvent and large volumes of process gas, as would be required in most other wet granulation technologies.

**Fluid bed spray granulation** - Granulation can be performed using fluid beds fitted with spray nozzles. While for many years the top spray position was preferred, now the advantages of tangential spray systems have become obvious. The main advantage is the location of the spray nozzle, in an area with significantly higher shear forces, so allowing the processing of formulations that could before be granulated only in high shear processors. Additionally the introduction of the new FlexStream™ range of fluid beds (Figure 2) also eliminates the difficulty of scale up. Over recent years fluid beds have improved dramatically in response to competition from Single Pot technology. As can be seen for example in (Figure 3), it is possible to have completely closed material handling by a closed link with up- and downstream equipment. Also fully automatic cleaning (CIP) in fluid beds using stainless steel filters has now reached a level that compares favourably with what is possible in a single pot.



Figure 1: A typical Single Pot set-up



Figure 2: FlexStream™ fluid bed processor



Figure 3: Fluid bed top spray granulator

## Comparing Granulation Methods

### Integrated high shear granulation & fluid bed drying

This is the most common configuration used on an industrial scale for the production of pharmaceutical granules (Figure 4). Again, this system allows full integration with upstream and downstream equipment, and even includes a wet mill between the granulator and dryer. With modern control systems it is easy to load, mix and granulate a second batch in the high shear granulator whilst drying the previous batch in the fluid bed prior to discharge. All equipment can be cleaned in place in a single automatic process.

**Continuous granulation** - As a result of various FDA initiatives to improve product quality and to reduce the risk of product failure there is a huge interest in continuous processing. A typical installation is shown in (Figure 5).

The system has three modules: a wet high shear granulation module, a segmented dryer module, and a granule conditioning module.

In the granulation module, dry ingredients are dosed individually or premixed into the continuous high shear granulator. After a small dry mix section, the granulation liquid is added, so each particle receives the same amount of liquid. The particles follow a granulation track, which mimics the granulation in a batch process. Narrow tolerances between granulation screws and the barrel minimize back-mixing. The whole wet granulation process takes place in a few seconds with only a few grams of product in process at a given time, resulting in faster start-up and no losses. The particle size can be adjusted by changing the working level in the granulator; this results in a continuous flow of wet granules with a constant quality and density that is transferred to the dryer. There are no oversized agglomerates and thus no wet milling.

The dryer module, based on the fluid bed drying principle, splits the continuous flow of granules in packages of 1,5 kg, drying them each in a separate segment of the dryer. When the content of a segment has reached the desired moisture level, it is emptied and transferred to the granule conditioning module and refilled with a new package of wet granules. The drying curve of each package is monitored. In the granule conditioning module, the dried granules can be measured for critical quality attributes such as particle size distribution, humidity and content uniformity. At any time, there are only 6 to 9 kg in process, which minimizes the amount at risk in case of an incident (e.g. a power failure). The system can handle capacities from 500 g to tons, so there is no need for scale up. The unit's small size and modular construction allows for a fast deployment and makes it easy to install with existing equipment.

GEA Pharma Systems also has developed a continuous blender, which can be used for premixing or mixing the external phase into the granules on a continuous basis; GEA Courtoy's tablet presses are ideally suited to complete the system to create a fully continuous tablet manufacturing line. The ability of the Courtoy™ presses to produce a consistent tablet quality independent of the press speed is key to a successful integration.



Figure 4: A typical integrated production line for pharmaceutical granules

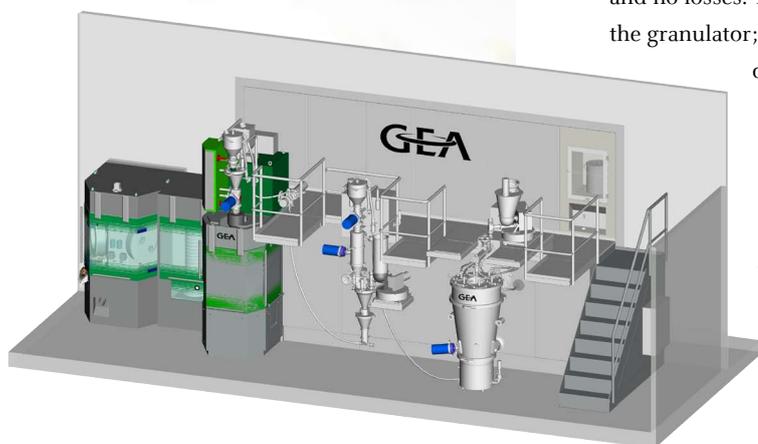


Figure 5: A continuous tableting line

## Comparing Granulation Methods

**Fluidized spray drying (FSD)** - Produces granules from a liquid in a one-step process (Figure 6). One option is to produce the active in the primary production as granules, so that it only requires blending with excipients suitable for direct compression for secondary processing. This can only be done with actives that are tacky (in a wet state) otherwise the addition of a binder is necessary. Another possible use of FSD technology is to mix all the ingredients into a solution or suspension and to produce granules in a one-step operation. During the FSD process, the liquid feed is atomized at the top of the tower in a co-current mode. After the liquid is evaporated, the particles generated leave the drying chamber together with the exhaust air. These particles are then separated in a cyclone or filter and reintroduced into the drying chamber where they come into contact with wet droplets and form agglomerates. After these agglomerates have reached a certain weight they cannot leave via the top of the tower with the exhaust air, but fall down into the integrated fluid bed at the bottom of the drying chamber. Here they are dried and cooled before being discharged. However, this type of equipment is difficult to clean, particularly the external pipe work, when changing to another product. Systems have, therefore, been developed where the external pipe work does not come into contact with the product.

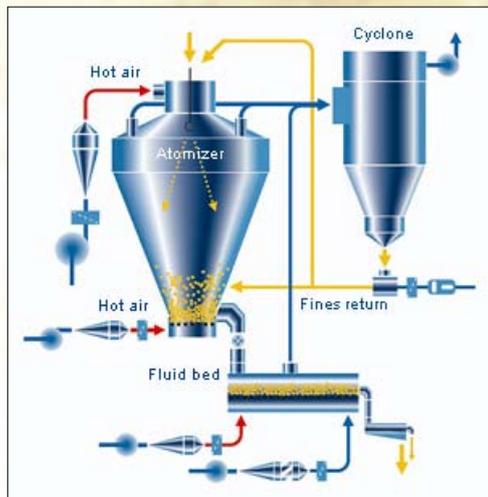


Figure 6: Fluidized spray drying (FSD)

### Comparison of granulation processes

Tables I - III provide a brief overview of the implications of particular granulation methods. All information shown assumes 'normal' products. Some special products may behave differently.

Table I - Comparison of processes - general aspects

	Option 1 Single-Pot (1)	Option 2 High Shear force mixer and FBD (1)	Option 3 Fluid Bed granulation (2)	Option 4 Continuous granulation process (1)	Option 5 Spray Drying (3)
Scale					
Lab. scale (LS)	LS	LS	LS	LS (granulator only)	
Technical scale (TS)	TS	TS	TS	TS	TS
Production (PS)	PS	PS	PS	PS	PS
Definition of batch	++	++	++	material container	material container
Scalability	+	+	+	++	++
Need special building	weight	height	height	no	height
Energy / kg (4)	<0.25kW/kg	<0.25kW/kg	<0.37kW/kg	<0.25kW/kg	<7.5kW/kg
Yield	>99.5%	>99%	>99%	>99.5%	>99%

(1) Granulation with 10% granulation liquid (TS 15%)

(2) Granulation with 15% granulation liquid (TS 15%)

(3) Mix all components of formulation in liquid form (TS 20%); drying step at the end of primary prod. can be saved

(4) Only drying energy

Key: ++ very good, + good, +-fair, - poor, -- very poor

## Comparing Granulation Methods

**Scales** - Option 1 is available in a range of 1–1200 litres. Option 2 can handle up to 1800 litres. Batches between 30 grams and 2 tonnes can be granulated in fluid beds. For the continuous granulation technologies presented as Options 4 and 5, the situation is different. There is no upper limit (milk powder granules are produced by spray drying at a rate of up to 10 tonnes/h), these technologies are not appropriate for very small scale production, even at the laboratory trial level, as some processing time is needed to reach equilibrium conditions.

**Batch definition** - This is irrelevant to batch technologies presented in Options 1–3, but requires some discussion for the continuous technologies, particularly if the raw materials are fed in continuously without dispensing and pre-blending: for example, out of large tanks or silos. The most straight forward approach is to collect the dry granulates in containers and define the load of each container as one batch. This method is used when operating a tablet press. Often, the size of such a container is selected to meet the batch size of a tablet coater. Moheb Nasr of the FDA states the following on fully continuous manufacturing. “A point of confusion is the word ‘batch’, which can mean either the mode of manufacturing or the quantity of material being processed,” says Nasr. The regulations specify: A batch is a specific quantity of a drug or material that is intended to have uniform character and quality, within specific acceptance limits, and is produced according to a single manufacturing order or during the same cycle of manufacture. [CFR, 21 Part 210.3(b)] “The definition of batch here refers to the quantity of material and does not specify the mode of manufacture,” says Nasr. [Continuous Processing: Moving with or against the manufacturing flow; Alex Pellek et al; PharmTech.com, Sept. 2008]

**Scalability** - As developments are usually started in a laboratory, up-scaling must be considered. For Options 1–3, users will only face ‘normal’ up-scaling problems. Often, processes run better when scaled-up. Linear up-scaling for the Single Pot is only possible if microwaves are used, otherwise drying time will be increased. With the introduction of the FlexStream™ fluid bed, scale-up has become much easier. For continuous processes, up-scaling is easy because operation time is the only parameter to be changed. The situation becomes more complicated if it cannot be done by just running the final production plant for short periods.

**Building requirements** - Production-scale Single Pots can weigh up to 10 tonnes, therefore a floor of appropriate strength must be prepared and the logistics of getting the equipment into the building considered, particularly if the equipment is not to be installed on the ground floor. For the high shear granulator/fluid bed dryer combination, both a vertical and horizontal product flow are possible. Production-scale fluid beds can be several metres high; however, it is not necessary to install the whole unit in the production room. If it is built as a ‘through the wall’ design, all necessary technical installations can be positioned in a technical area. The upper part of the fluid bed tower can also be in a technical area above the production room. Owing to the minimal required footprint and the built in flexibility, the continuous system (option 4) can be run in any existing GMP room. The complex material handling requirements of spray drying require this system (option 5) to be integrated into the building or, even better, the building needs to be tailored around the installation.

## Comparing Granulation Methods

**Energy** - As energy consumption for drying is significantly higher than that generated by motors or vents, only the required drying energy amount is discussed. To evaporate 1kg of water, 0.66kWh of energy is required. The total amount of energy is both a function of the amount of liquid to be evaporated and the grade in which the equipment utilizes the energy supplied. The figures in Table I assume average cases.

**Yield** - The yield of a process is particularly influenced by the time the process takes and formulation. Longer processes increase yield. The wetter the granulation process, the greater the material loss (as it sticks to the walls). A third important factor is the total surface area in contact with the product. These factors are not independent from each other. They are also influenced by product characteristics. It is, therefore, not possible to provide exact figures however the data shown in Table I reflect typical scenarios.

Table II Comparison of processes - formulation aspects

	Option 1 Single-Pot (1)	Option 2 High Shear force mixer and FBD (1)	Option 3 Fluid Bed granulation (2)	Option 4 Continuous granulation process (1)	Option 5 Spray Drying (3)
Containment	++	+	++	+	+
Organic solvents	++	+	+	+	+
Heat sensitive materials	++	+	+	+	(+)- (-)
Limitation of different formulations	None (when exposed to microwaves)	None	PSD of raw materials	None	Fine grades of raw materials required if worked from suspensions
Amount of granulation liquid required)	8-15%	8-15%	15-30%	5-12%	>100%

**Containment** - This is essential if processing toxic or very potent substances. In this case it is important to know if it is possible to achieve a closed material flow into and out of the equipment; if the equipment is tight; and if it can be cleaned automatically (including upstream and downstream connections), at least to a level where it can be opened without any danger. Closed material flow is possible for all processes shown. Even the very sensitive process of transferring wet granules via a wet mill from a high shear granulator into a fluid bed can be done closed. This is achieved by using modern split valve technology for contained docking to intermediate bulk containers. Whereas individual machines such as fluid beds, high shear granulators, single pots or spray dryers can be cleaned using very efficient automatic cleaning systems (WIP/CIP depending on the product), fully automatic cleaning becomes increasingly complicated as more upstream and downstream equipment are integrated. Other important factors affecting containment are how easily exhaust air filters can be changed without the risk of contamination; whether the equipment is operated continuously under negative pressure; and to what extent a sample can be contained.

## Comparing Granulation Methods

**Organic solvents** - If processing with organic solvents, the equipment must be gas tight. To eliminate the risk of an explosion it is necessary to either ensure that the mixture of organic vapours and oxygen is outside the explosion limits (which can sometimes be achieved in a spray granulation process) or that nitrogen is used as a process gas. If such processes are to rely entirely on the elimination of all potential spark sources, they must be carefully checked, case by case. Additionally, passive measures, such as a pressure shock design, suppression or venting, are always required except when using a Single Pot. This is because the risk of explosion exists only during the drying step, which is done under vacuum conditions. If the exhaust gas contains organic vapours it must be cleaned. This can be done in a closed cycle by cooling, adsorption or catalytic burning. Again, the Single Pot, particularly if used without stripping gas, has an advantage: only the pure organic vapours must be treated.

**Heat sensitive materials** - To treat heat sensitive materials successfully, the temperatures and exposure time must be carefully controlled, as should the presence of moisture and oxygen. Single Pot technology provides safe drying under vacuum, particularly if the granulation is done with organic solvents because the corresponding temperature is even lower. In a spray dryer, however, relatively high temperatures are involved, but only for a very short time. A batch fluid bed granulator can operate at higher air inlet temperatures while spraying and during the beginning of drying, reducing the inlet temperature afterwards to maintain a low product temperature. The nature of the product dictates which is the most appropriate treatment.

**Formulation limitations** - High shear granulators are able to granulate all types of formulations. For Single Pot use, the behaviour of all components exposed to microwave energy must be considered. Although this is not critical for most materials, it should be tested for new materials because of the small risk of an unexpected thermal runaway - the (microwave) absorption behaviour relies on the moisture content or on the actual temperature. Fluid beds inherently act as a classifier: that is, the particle size distribution (PSD) of all raw materials should be similar. Processing very fine powders can also be problematic because these particles tend to stay in the filter area. Sometimes this can be solved by introducing the spray liquid. If a suspension is used to feed the spray dryer the suspended particles need to be smaller than 30 µm to allow a proper atomization.

**Granulation liquid** - For the production of oral dosage forms, high shear granulators have almost replaced medium and low shear versions because their increased mechanical energy requires less granulation liquid to produce granules of similar properties. Also, smaller amounts of liquid added during granulation requires less evaporation during drying, resulting in a higher throughput and lower thermal stress for the active. The numbers provided in Table I largely depend on the nature of the formulation; whether the binder is added in a liquid or a solid form; and the granule characteristic required.

## Comparing Granulation Methods

**Fine particle amount** - If the percentage of fine particles (size < 63 µm) is too large, flow problems, segregation and poor tablet formation are the most common problems to be expected. The numbers shown in table III depend heavily on the formulation and the process parameters but show a clear tendency. In option 5 the process does not allow fine particles to be discharged but ensures they are blown back into the operation zone where they are most likely to be bound into granules. The relatively high amount of fines for the Single Pot process is a typical result of all types of vacuum drying. If seen as problematic this can be reduced by adjusting the formulation.

**Table III Comparison of granule characteristics**

	Option 1 Single-Pot (1)	Option 2 High Shear force mixer and FBD (1)	Option 3 Fluid Bed granulation (2)	Option 4 Continuous granulation process (1)	Option 5 Spray Drying (3)
Dust / fine particles	<12%	<8%	<5%	<3%	<1%
D <sub>50</sub> : PSD	100 - 800 µm	120 - 800 µm	150 - 600 µm	120 - 600 µm	150 - 300 µm
Span (5): particle size distribution	2.5 - 3	2.5	2	2.5	1.5
Homogeneity	+	+	+	+	++
Flow properties	+	+(+)	+	++	+
Bulk density	0.7 g/cm <sup>3</sup>	0.8 g/cm <sup>3</sup>	0.7 g/cm <sup>3</sup>	0.8 g/cm <sup>3</sup>	0.6 g/cm <sup>3</sup>
Dissolution	+	+	++	+	++

$$(5) \text{ Span} = (D_{50} - D_{10}) / D_{50}$$

**Mean particle size** - All processes allow the mean particle size to be controlled by varying some process parameters. The given limits can, in some cases, be extended for bespoke equipment.

**Span** - The span describes how narrow a PSD is. Not all results shown are critical for tablet compression but may be of some interest if the granules are sold as a final product.

**Homogeneity** - All technologies presented generally show no problems with product homogeneity. Mixing all components in a liquid stage followed by granule production in a one-step operation will give the best homogeneity level.

**Flow properties** - Achieving free flowing materials is a major reason for performing granulation so only processes able to fulfil this requirement are of interest. The slight differences shown in Table III result from the fact that high shear granulation in general produces more dense and mechanically more stable granules. During vacuum drying, some of these granules are destroyed and a larger amount of fines is generated.

**Bulk density** - The bulk density required depends on the physical densities of the materials used, from the amount and type of binder liquid, the process parameters selected and the process by which the granulation is done. The numbers shown in Table III may, therefore, vary for different materials or process conditions, but a clear pattern is shown illustrating which process will drive the bulk density in a particular direction.

**Dissolution** - How easily granules dissolve (instant properties) depends on their surface energy and structure. Granules produced with lower shear forces, such as in Options 3-5, show a more open porous structure, therefore, they have better instant properties, but are mechanically less stable.

# Comparing Granulation Methods

## Selection of Granulation Process

The most significant strengths and weaknesses of each technology:

### 1. Single Pot

- + High containment
- + One-pot operation
- + Small footprint
- + Granulation process can compensate fluctuations in raw material specification
- + Very fast changeover
- + Easy and safe handling of organic solvents
- + High Yield
- + Limited need of operators
- + Unique solution for effervescent production
  
- Limited throughput
- No possibility for additional unit operations
- Scale up

### 2. Fluid Bed Granulation

- + One-pot operation
- + Limited number of operators
- + Small footprint
- + Possibility of additional unit operations
- + Excellent compression behaviour of granules produced
- + Easy scale up (FlexStream™ range)
  
- Handling of organic solvents
- Height requirement
- Handling of organic solvents more complex

### 3. Integrated High Shear Granulator & Fluid Bed Dryer

- + Established technology
- + Very high throughput
- + Granulation process can compensate fluctuations in raw material specification
- + Possibility of additional unit operations
  
- Limitation in yield
- Large footprint
- Large height
- Long time for changeover
- Large number of operators
- Handling of organic solvents requires complex set-up
- Difficult scale up

### 4. Continuous granulation process

- + Small footprint and height requirement (especially if directly integrated with tablet press)
- + Minimal need operators (especially if directly integrated with tablet press)
- + Granulation process can compensate fluctuations in raw material specification
- + Fast changeover
- + No process scale-up (time is the only relevant factor)
- + High Yield
- + In line with latest FDA requirements
  
- No possibility for additional unit operations
- No possibility to work in gram scale
- Handling of organic solvents requires complex setup

As mentioned at the beginning of this article in most cases the granulation process / equipment is selected based on company experience / equipment present in the company. But there are good reasons to do this selection process in a more objective way.

The following factors should be considered:

- Volume of production
- Multi-purpose or dedicated plant
- Product mix / volumes and campaign lengths (resulting in the required number of changeovers)
- Existing products / processes (process already registered for a particular product)
- Need to process organic solvents
- Tradition (know how/policies)
- Other applications to be done in the same equipment (coating, etc.)
- Potency of API (environmental / personnel)
- Space / height available
- Capital / operating costs

### 5. FSD Spray Drying

This is a totally different concept that requires the combination of primary and secondary production. This can create materials with tailor-made characteristics (enhanced bioavailability, incorporated taste masking, suitable for direct compression ...) in a one-step operation.

## Comparing Granulation Methods

TCO (Total Cost of Ownership) - As the total cost of a manufacturing operation is a key decision criterion, GEA Pharma Systems offers its customers a TCO calculation on a case-by-case basis.

Required input parameters are:

### Characteristics of production pattern

Average batch size	kg
Time per batch	h
Average number of tablets per batch	tablets / batch
Average number of batches per campaign	batches / campaign
Available working hours per day	hours / day
Available working days per year	days
Total available working hours per year	hours
Time for cleaning between batches	hours
Time for campaign change-over	hours
Number of operators for production	
Number of operators for cleaning	
Cost per operator	€/h
Yield of process	%
Price of material	€/kg

### Characteristics of Investment

Price for granulation equipment	€
Depreciation time for equipment	years
Space requirement:	
GMP floor	m <sup>2</sup>
GMP room	m <sup>3</sup>
Technical floor	m <sup>2</sup>
Technical room	m <sup>3</sup>
Cost for GMP space	€/m <sup>3</sup>
Cost for technical space	€/m <sup>3</sup>

With the above information it's possible to do TCO calculations to compare different production scenarios.

by Dr. Harald Stahl  
Senior pharmaceutical technologist  
GEA Pharma Systems  
Kalscheurener Strasse 92,  
D-50354 Hürth, Germany  
Tel. +49 6349 927 706  
Fax +49 6349 9639 898  
harald.stahl@geagroup.com



[www.geapharmasystems.com](http://www.geapharmasystems.com)  
[pharma@geagroup.com](mailto:pharma@geagroup.com)