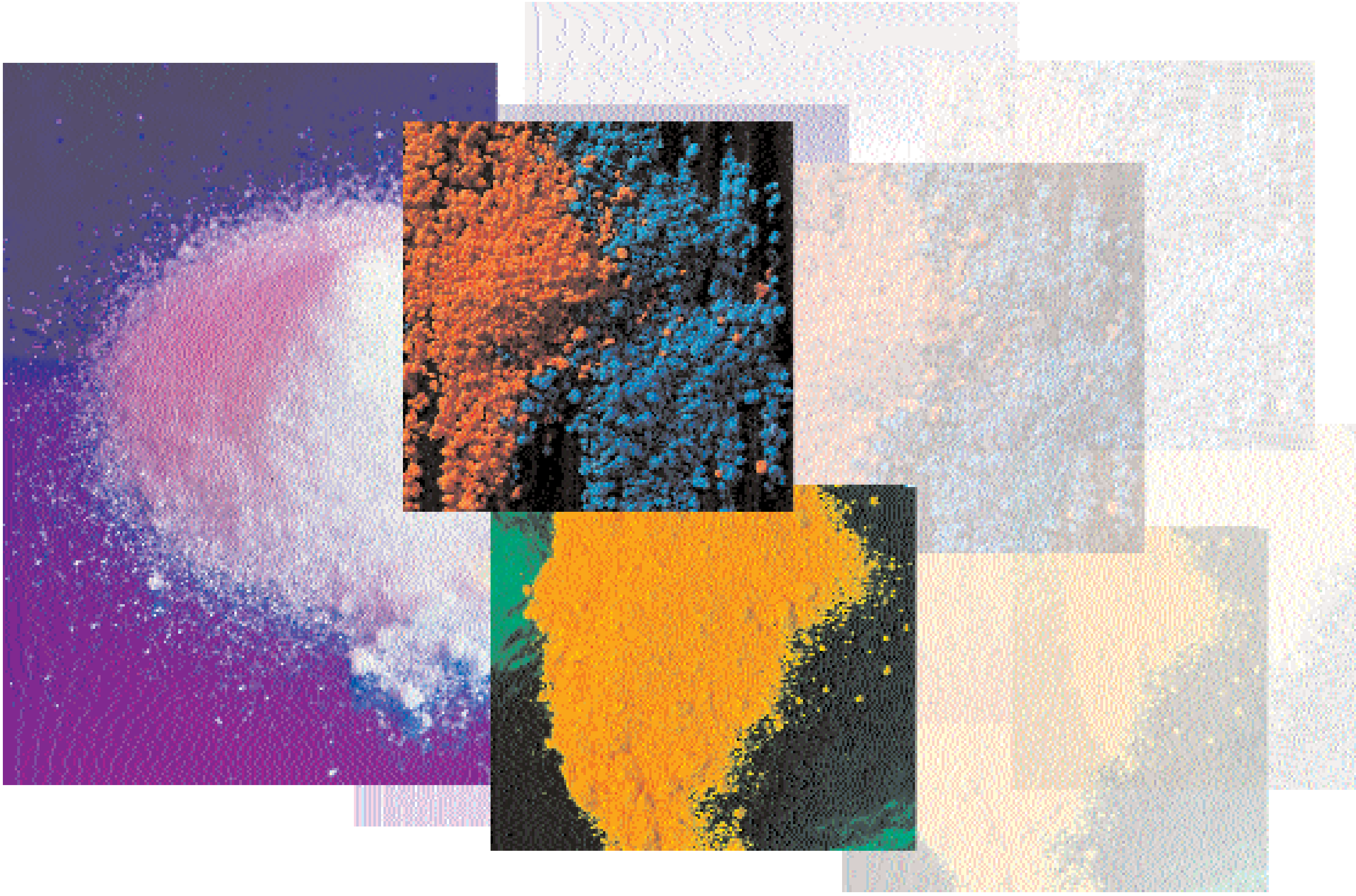


Comparing Different Granulation Techniques

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 process and looks at the implications of two different applications.

Harald Stahl
is the senior pharmaceutical technologist at Niro Pharma Systems, Mauchener Strasse 14, D-79379 Müllheim, Germany.
Tel. +49 7631 701 614
Fax +49 7631 701 669
hstahl@niro-pharma-systems.com

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 and offers unbiased advice on the merits of each system. It then looks at the implications of selection on two different applications.

Granulation methods

Single pot. A mixer/granulator that dries granules in the same equipment without discharging is commonly called a single pot (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 traditional heat source comes from the dryer walls, which are heated; the boiling temperature and vacuum are used to reduce and remove vapours. 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 only effective for small scale use.

Introducing stripping gas into the pot allows large scale operation. A small quantity of gas is introduced in the bottom of the equipment, which passes through the product bed, improving the heat flow from the wall into the product. The gas also improves 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 high boiling temperature under vacuum and a high heat of evaporation); 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 top spray granulation. Granulation can be performed using fluid beds fitted with spray nozzles. During the last 10 years, fluid beds have improved dramatically in response to single pot technology competition. It is possible to have completely closed material handling by a closed linking with upstream and downstream equipment (Figure 2). Also, fully automatic cleaning (clean-in-place [CIP] and wash-in-place [WIP]) in fluid beds using stainless steel filters now compares favourably with what is possible in a single pot.

High shear granulation/fluid bed drying combination

This is the most common configuration used at an industrial scale for the production of pharmaceutical granules (Figure 3). 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 CIP in a single automatic process.Whereas a single shaker might be acceptable for drying applications, a twin shaker or blow-back filter design should be used for granulation processes.

Continuous fluid bed granulation

A configuration enabling this process is shown in Figure 4. For start-up, the equipment is filled with raw material similar to a batch unit. After the material has been granulated, the process is switched to the continuous mode allowing material to be introduced via the rotary inlet valve and discharged as granules by a second outlet valve. The process can be controlled by monitoring the pressure drop over the product bed. The inlet air is segmented, which allows the product in different areas to be treated with different temperatures. Although the process is essentially plug flow, a significant amount of back mixing occurs during processing.

FSD. Fluidized spray drying (FSD) produces granules from a liquid in a one-step process (Figure 5). 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

Table I Comparison of processes — general aspects.

	Option 1 Single pot (1)	Option 2 High shear force mixer and FBD (1)	Option 3 Top spray granulation (2)	Option 4 Continuous top spray process (2)	Option 5 Spray drying (3)	Option 6 Pelletizing (4)
Scales available Laboratory scale (LS) Technical scale (TS) Production scale (PS)	LS TS PS	LS TS PS	LS TS PS	(TS) PS	TS PS	(TS) PS
Definition of batch	++	++	++	Material container	Material container	Material container
Scalability	+	+	+	++ (down?)	++ (down?)	++ (down?)
Need for special building	Weight	Height	Height	Integration into building	Height	Intergration into building
Energy/kg (5)	>0.25 kW/kg	>0.25 kW/kg	>0.37 kW/kg	>0.37 kW/kg	>7.5 kW/kg	>0.5 kW/kg
Yield	>99.5%	>99%	>99%	>99%	>99%	>98%

(1) Granulation with 10% granulation liquid (TS15%)
(2) Granulation with 15% granulation liquid (TS15%)
(3) Mix all components of formulation in liquid form (TS20%); drying step at the end of primary production can be saved
(4) Granulation with 20% granulation liquid (TS15%)
(5) Only drying energy

Key: ++ very good; + good; +- fair; - poor; -- very poor 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. A principle drawing of an FSD set-up is shown in Figure 5.

During the FSD process, the liquid feed is atomized at the top of the tower in a cocurrent 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 pipework, when changing to another product. Systems have, therefore, been developed where the external pipework does not come into contact with the product (Figure 6).

Pellet production line

To form granules from powders, granulation liquid and mechanical energy are needed. Alternatively, an extruder may be used similar to that used for pellet manufacture. In a typical set-up, all ingredients are preblended in a container after dispensing. Depending on the extruder design, the liquid can be added in the extruder or mixed separately to the correct consistency. The material produced is transferred directly into a continuous fluid bed where it is dried to the desired moisture level rather than rounded in a spheronizer (as it would be for pellet manufacture). An example of such a system is shown in Figure 7.

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.

General aspects

Scales. Option 1 is available in a range of 3–1200 L. Option 2 can handle up to 1800 L. In fluid beds, batches between 30 g and 2 tonnes can be granulated. For the continuous granulation technologies presented as Options 4–6, the situation is different. Whereas there exists 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 preblending; for example, out of large tanks or silos. The most straightforward 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.

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. 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.

Table II Comparison of processes — formulation aspects.

	Option 1 Single pot	Option 2 High shear force mixer and FBD	Option 3 Top spray granulation	Option 4 Continuous top spray process	Option 5 Spray drying	Option 6 Pelletizing
Containment	++	+	++	+	+	-
Handle organic solvents	++	+	+	+	+	+
Heat sensitive materials	++	+	+	(+)	(+)+(-)	(+)
Limitations by different formulations	None (behaviour of material if exposed to microwaves)	None	PSD of raw materials	PSD and flow properties of raw materials	Fine grades of raw materials required if worked from suspensions	Limited
Amount of granulation liquid required	8–15%	8–15%	15–30%	15–30%	>100%	15–50%

Building requirements. Production-scale singe 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. Because the transfer of wet granules is a critical step, the high shear granulator being in an elevated position makes this easier and safer. Therefore, additional height (a platform or separate floor) is required.

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. Because of the complex material handling requirements of continuous production (Options 4–6), these systems must be integrated into the building or, better still, the building must be tailored around the installation.

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 1 kg of water, 0.66 kWh of energy are 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 1 reflect typical scenarios.

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.

Figure 1 A typical single pot set-up.

Figure 2 Bed top spray granulation.

Table III Comparison of granule characteristics.

	Option 1 Single pot	Option 2 High shear force mixer and FBD	Option 3 Top spray granulation	Option 4 Continuous top spray process	Option 5 Spray drying	Option 6 Pelletizing
Dust/fine particles	<12%	<8%	<5%	<3%	<1%	None
D_{50}: PSD	100–800 µm	120–800 µm	150–600 µm	120–400 µm	150–300 µm	800–2000 µm
Span (6):	2.5–3	2.5	2	2.5	1.5	<1
Homogeneity	+	+	+	(+)	++	+
Flow properties	+	+(+)	+	+	+	++
Bulk density	0.7 g/cm^3	0.8 g/cm^3	0.7 g/cm^3	0.7 g/cm^3	0.6 g/cm^3	Near physical density
Dissolution	+	+	++	++	++	-

(6) Span = $(D_{90} - D_{10})/D_{50}$

Although the first five process options can be supplied in a gastight design, this is not possible for the pelletizing line (Option 6). There are also automatic cleaning problems. 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.

Organic solvents. If processing with organic solvents, the equipment must be gastight. 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.

Figure 4 Continuous fluid bed granulation.

Figure 3 A typical set-up installation at an industrial scale for the production of pharmaceutical granules.

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.

Figure 5 Principle of an FSD set-up.

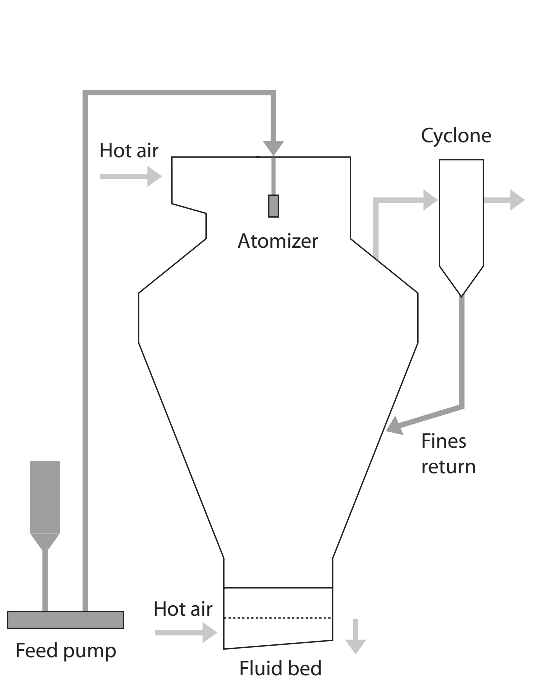
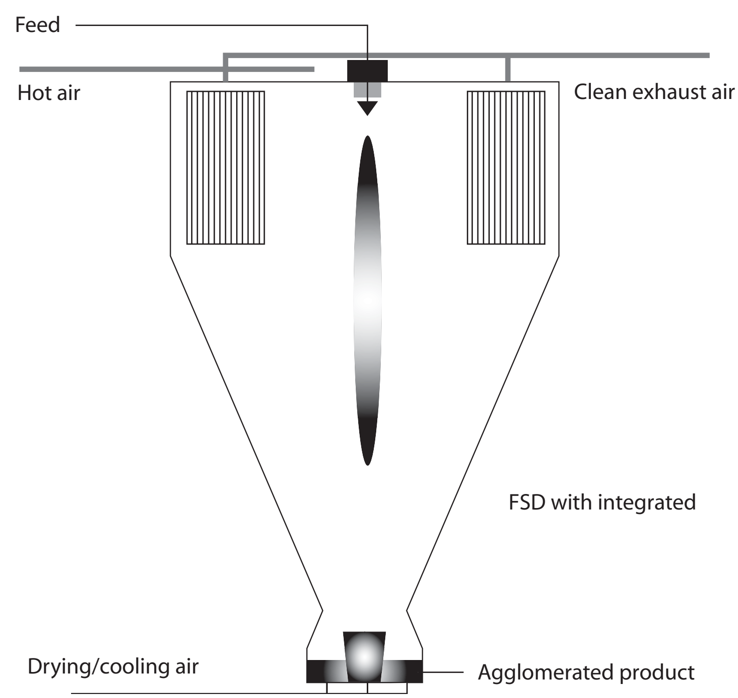


Figure 6 An FSD spray dryer with internal filters.



The nature of the product dictates which is the more 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. Tailor-made formulations containing, for example, a high amount of microcrystalline cellulose are needed to run an extrusion process. For poorly soluble actives in particular, the maximum drug load that can be achieved is limited. From a processing point of view, very soluble drugs can also cause many problems.

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.

Fine particle amount. If the percentage of fine particles (<63 µm) is too large, flow problems, segregation and poor tablet formation become common issues. The numbers shown in Table III are a reflection of the formulation and process parameters, and show a clear pattern. If Option 6 is taken, no fine particles in the final product occur as all material is incorporated into the extrudate. For Options 4 and 5, fine particles cannot be discharged (because of the way in which the equipment operates), but are blown back into the operation zone where they are likely to be bound into granules. The relatively high amount of fines for the single pot process is typical of all types of vacuum drying. If seen as problematic, this can be reduced by adjusting the formulation.

Mean particle size. All processes allow the mean particle size to be controlled by varying some process

Table IV Key figures of production scenario 1.

	Option 1 Single pot	Option 2 High shear force mixer and FBD	Option 3 Top spray granulation	Option 4 Continuous top spray process	Option 5 Spray drying	Option 6 Pelletizing
Equipment scale	1200 L (3 plants)	High shear 2000 L; fluid bed of adequate scale	Product container size: 3200 L	250 kg/h	250 kg/h	250 kg/h
Batch size	417 kg	715 kg	1000 kg	-	-	-
Batch time	5 h	2 h 50 min	4 h	-	-	-
Throughput				250 kg/h	250 kg/h	250 kg/h

Table V Key figures of production scenario 2.

	Option 1 Single pot	Option 2 High shear force mixer and FBD	Option 3 Top spray granulation	Option 4 Continuous top spray process	Option 5 Spray drying	Option 6 Pelletizing
Equipment scale	400 L	High shear 600 L; fluid bed of adequate scale	Product container size: 600 L	50 kg/h	50 kg/h	50 kg/h
Batch size	160 kg	240 kg	200 kg	-	-	-
Batch time	5 h	3 h	4 h	-	-	-
Throughput				50 kg/h	50 kg/h	50 kg/h

parameters. The given limits can, in some cases, be extended for bespoke equipment.

Span. The span describes how narrow a PSD is. All results shown are not 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. The material produced in the continuous fluid bed granulator might, in rare cases, show some homogeneity problems, particularly if the material produced just after start-up and just before close down is examined separately and is not blended with the material produced in between.

Flow properties. Achieving free flowing materials is a major reason for including granulation. Therefore, 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.

Production scenario 1

A dedicated plant for the production of 1000 tonnes of granules of a water-based formulation. The amounts of granulation liquid are estimated as shown in Table I. Further, it is assumed that cleaning is required once a week for only a few hours because it is a dedicated installation; the plant is operated in three shifts for 5 days each week; and the plant achieves 20 productive hours per day and 200 productive days per year.

Working on these assumptions, 5 tonnes of granules must be produced per day. Table IV shows the results for the different production scenarios. To complete this table (for the batch machines), the batch times were evaluated. These are based on customers' experiences and calculations regarding the drying capacity of the different equipment. Some materials with special granulation/drying properties may achieve entirely different batch times. By calculating the number of batches per day, the required batch size of 5 tonnes of granules per day was determined. For the single pot option it was not possible to achieve the requested throughput using only one machine. For all continuous processes, equipment with the requested throughput is available. To include the necessary investment costs in the table is extremely complicated as this depends on many other factors in addition to the granulation equipment and needs, and must, therefore, be evaluated carefully, case by case.

Production scenario 2

Installation for the production of four different water-based granulated products, each with a capacity of 32 tonnes per year. The amounts of granulation liquid are estimated as shown in Table I. The process length for each product should be 1 week. It is also assumed that cleaning must be done only at the end of each process, which means that Friday is not a productive day. Further assumptions are that the plant is operated in two shifts for 5 days each week and that the plant achieves 16 productive hours per day and 200 productive days per year. ■