

Pseudo-continuous Wet Granulation with a micro-scale Granulator Dryer

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Unlike food and chemical production, pharmaceutical manufacturing relies almost exclusively on batch processing. Whilst reduced profit margins and price competition, which is typical of food and chemical industrial sectors, led to the development of low-cost/highly efficient manufacturing procedures based on continuous processing, pharmaceutical companies have competed solely on innovation through development of new drugs leaving manufacturing methodologies, dominated by batch processing, almost unchanged for decades. Some of the reasons frequently reported to justify the use of batch rather than continuous processing in pharmaceutical production are the following:

1. continuous processing is suitable only for high volume products;
2. continuous processing is not applicable when product changeover is frequent;
3. products manufactured by continuous processing do not comply with the stringent quality requirements of pharmaceutical regulations;
4. given the current regulatory framework which envisages batch processing as the cornerstone of any pharmaceutical manufacturing procedure, a product developed using continuous processing could face obstacles and delays on its approval pathway.

Many, if not all, of those beliefs have been denied. Over the past 10 years, world health authorities created a regulatory environment supportive of manufacturing modernization, considering continuous processing/control as one of the most effective means through which the objective of having both pharmaceutical development and manufacturing firmly grounded on a risk- and science-based foundation can be achieved. The FDA "PAT" initiative, aimed at fostering improvements in manufacturing efficiency and product quality, and the QbD approach along with ICH Q8, Q9 and Q10, are good examples of this new "vision" characterizing the current position of regulatory authorities.

Efficiency, productivity, effectiveness and quality are the four conceptual pillars of the new manufacturing paradigm and the use continuous or semi-continuous processing machines the way to put it in practice.

The prototype machine we are presenting provides a technical solution for wet granulation which is compromise between continuous processing and a traditional batch approach (semi or pseudo-continuous wet granulation). It consists of a small high-shear granulator connected, or better, integrated with a drying unit. It's a single machine capable of producing a limited amount of dried product (60 – 100g) in a very short

processing time (1.5–2 min at the maximum) thus achieving a daily productivity, calculated on three shifts per day, of 52 – 90 kg. To increase production a number of mini-units can be arranged and run in parallel. The single mini-unit operates discontinuously thus resembling a miniaturized large scale unit. The pseudo-continuous operation mode does not require any steady-state attainment. This feature is quite important since it avoids any off-specs conditions as they may happen in continuous processes. Under the assumption of introducing an "on-line" quality control at the end of each minibatch, it is possible to move from conventional "off-line" sampled control to total quality control. In any case, if a single minibatch does not respect the quality standards, the amount of rejected product is negligible. The most important fallout of mini-units arrangement is having the same basic unit for Phase I, II, III and industrial production. This allows shortening the time-to-market by reducing scale-up activities and validation burden with an evident and significant return on investment and an increased income. It has been said that the equipment has to operate 24hours a day producing hundreds of minibatches. A consequent risk connected to such a high number of batches is wear of mechanical parts, the most exposed being the moving elements such as drive shaft, dry seals and impeller. A micro-unit, or parts of the micro-unit, could fail also due to the excessive work, i.e. filters, (e.g. obstruction), load and unload valves (e.g. sticking) and auxiliary ducts (i.e. fouling of feeding and discharging ducts).