Benefits of Continuous Granulation for Pharmaceutical Research, Development and Manufacture.

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Introduction

Continuous granulation offers opportunities for product and process development using small quantities of materials with minimized risks of scale-up. Characterisation of the granulation process using Design of Experiments techniques can be achieved using less API. In the development of new drugs/excipients, small scale continuous systems reduce time to market and employ processes comparable to production, with reliable scale-up.

Economic Small Scale Compounding

Using only small quantities of new ingredients during formulation and process development for proof-of-concept studies can deliver significant cost savings.

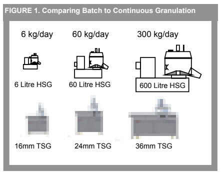
Compared with more traditional batch processes, using mixing vessels with volumes between 6 and 600 litres, continuous twin screw granulators with throughputs ranging from 1 to 50 kg/hr, can deliver similar production outputs. (Figure.1) Less obvious are the time savings due to the reduced material handling and smaller in-process inventory of expensive API and excipients. In addition reduced cleaning time and lower investments due to a smaller footprint are available.

Operation of Batch Granulators

In the batch process the dry materials are all introduced into the mixer and errors in any ingredient, be they in quantity or quality will render the full batch unusable. Moreover the addition of the liquid binder also represents a risk, as the quantity added and the exact time and method of addition, can critically affect the end product quality[1].

Because of the complex scale-up laws,[2] development work is often carried out on large units at great cost.

FIGURE 1. Comparing Batch to Continuous Granulation



Operation of Continuous Twin Screw Granulators

The individual components of a formulation made up of API (Active Pharmaceutical Ingredient), excipients and binders can be added separately as controlled continuous feed streams into different zones of the continuous granulator. This means that expensive ingredients and APIs can be held separately until the point they are introduced to the extruder, and the quantity of material "at-risk" is significantly reduced.

In a DoE investigation, changes in formulation can be easily made by adjustment to individual ingredient feeds, allowing the minimum sized samples to be prepared. The quantity of material within the continuous granulator is very small. Compared with dry blending, the requirements of ingredient particle size and distribution are less critical because the twin screw granulator handles the mixing and wetting.

Experimental costs

Because, when using a Batch mixer it is possible to produce only one sample per batch, the cost of making that sample, covers materials and the time of a mixing cycle includes charging and cleaning. In the case of a continuous granulator, where process parameters, and even formulation, can be easily changed during operation. This means that multiple samples can be collected from one batch of ingredients, and the sample cost is greatly reduced. As an example, if the ingredient bulk density is 0.5 g/ml, and the ingredient costs total € 1,000 / kg, it is easy to calculate the cost of preparing a "Sample" while experimenting with operating conditions.

To determine which are the Critical Processing Parameters, for any process, many different samples must be run. Figure 2 calculates the Sample Costs for different size mixers, and equivalent output twin screw

FIGURE 2. Material cost for experimental samples

	Sample Size	Sample Material Cost	Typical Daily Production
6 Litre HSG	1.5 kg	€ 1,500	9 kg
60 Litre HSG	15 kg	€ 15,000	60 kg
600 Litre HSG	150 kg	€ 150,000	450 kg
16 mm TSG	250g	€ 250	20-50 kg
24 mm TSG	1,000g	€ 1,000	100–400 kg
36 mm TSG	4,000 g	€ 4,000	200–1,000 kg

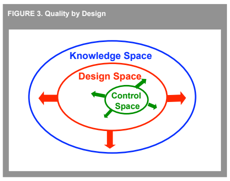
Quality by Design

An understanding of the manufacturing process, allows production equipment to be designed to deliver desired quality of product. Critical quality attributes are defined and controlled, and the impact of variables is analyzed (Raw materials, Process, Equipment, Personnel). Product specifications are tied to "fit for use" and not empirically derived from batch analysis[5]. This can be graphically displayed in Figure 3.

Knowledge Space, when applied to Process Equipment, is defined from our understanding of the limitations of the equipment and characteristics of the materials being processed.

Design Space is defined from an understanding of the Critical and Non-Critical parameters, and experimentation to define the relationship between different process parameters. Even using Design of Experiments techniques, a large number of experiments are required to define the design space based on the effects of different process parameters on product quality attributes.

FIGURE 3. Quality by Design



Control Space defines the operating window within which all critical process parameters can be reliably controlled to deliver the required product quality attributes.

The need for multiple batch experiments, in which each process parameters is varied in turn, places an enormous burden on the development engineers. In a batch method there is always a compromise between experimenting on a small mixer, using less material, and shorter cycles, or on a larger mixer where scale-up risks are minimized. In either case generating over 200 samples that are required for a full evaluation is a long and expensive process.

In comparison using a continuous process with individual feed streams allows formulation changes to be rapidly made and the minimum sample size produced. Material usage and experimental time can be significantly reduced.

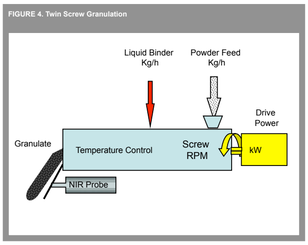
Twin Screw Granulation

Figure 4 is a schematic of the twin screw process.

A co-rotating twin screw extruder has excellent conveying capacity. For this reason it is normal to meter raw materials into the barrel, which allows several feed streams can be dosed, in a controlled way. But more importantly the screw speed of the extruder can be changed to achieve different mixing effects.

Use of co-rotating and intermeshing twin-screw extruders, provides an ideal method of continuous granulation. Firstly the screws are self-wiping which eliminates dead areas in the extruder barrel. Secondly twin screws have excellent product conveying properties, which makes them particularly useful for incorporating low bulk density ingredients. Thirdly the independence of screw speed and feed rate allows a far greater degree of control over the mixing process.

FIGURE 4. Twin Screw Granulation

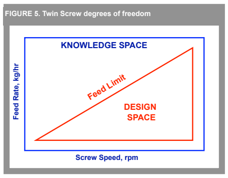


Twin screw degrees of freedom

With the independent control of Feed Rate and Screw Speed a "Knowledge Space" can be defined as shown in figure 5.

In a typical Granulation process, for a given screw configuration, throughput will be proportional to the conveying capacity of the screws, up to the maximum screw speed. The slope of the Feed Limit rate line will define the "Design Space" for a particular extruder. This slope will vary, depending on the screw configuration fitted in the extruder, and the bulk density of the feed materials.

FIGURE 5. Twin Screw degrees of freedom



Quality by Design

The following patterns outlined in figures 6, 7 and 8 are typical of a continuous granulation process. The shape and positioning of the boundaries are significantly influenced by the formulation and screw configuration. For each formulation a series of experiments must be performed to measure the critical process parameters. However once these are defined and mapped the process can be easily controlled and monitored to ensure a consistent, reliable product.

For example, degree of granulation has been seen to vary depending on the degree of fill in the extruder. Typically this follows the pattern shown in figure 6. Higher shear and increased degree of fill in the extruder can lead to over granulation

In a similar way,[6] average granule size, which is influenced more by residence time, is shown in Figure 7. However it has been observed that at high screw speeds, larger granules can be broken down to create a higher proportion of fines.

Another property, granule flow, measured from angle of repose[6], is dependent on granule shape and surface characteristics. This is influenced more by residence time as shown in Figure 8.

FIGURE 6. Effect on extent of Granulation

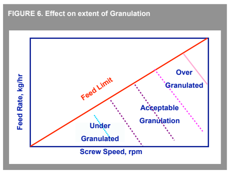
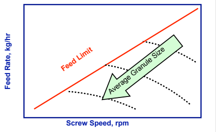


FIGURE 7 Effect on Granule Size



Control Space for Twin Screw Granulation

Combining these two product properties in figure 9 defines a "Control space" within which the desired granule strength and particle size can be guaranteed.

It must be stressed that the shapes of these curves come from one series of experiments, using a single formulation and only one screw configuration.

Application of PAT tools

Traditional methods of sampling and testing for quality control are being replaced by on-line instrumented techniques using for monitoring key Process Parameters[3].

The interesting conclusion from Figure 9 is that 90% of the defined tests can be accomplished using NIR Spectrometry. When NIR is linked to continuous granulation, it means that the actual granulation process can be continuously monitored. Savings in time and materials can be quickly realized since any deviation from the established parameters can be readily identified, so the process can be controlled or even halted. Here the benefit of continuous granulation from having only a small quantity of material in-process reduces product losses.!

FIGURE 8. Effect on Granule Flow

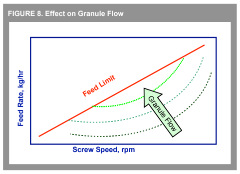
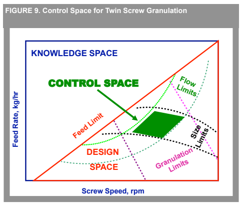


FIGURE 9. Comparing traditional and modern testing

Specification	Traditional Test	21st Century Testing
Dissolution	Dissolution Test	NIR
Disintegration	Physical Test	NIR
Assay	HPLC	NIR / Other
Hardness	Physical Test	NIR
Content uniformity	HPLC	NIR
Impurity	HPLC	On-line HPLC
Stability	Long term programme	NIR Accelerated programme
Appearance	Visual comparison	Colorimetry
Identification	IR / UV Spectroscopy	NIR
Moisture content	Karl-Fischer	NIR / NMR / Others

FIGURE 9. Control Space for Twin Screw Granulation



Twin Screw Continuous Granulators

The latest twin screw granulators (photograph 10) are equipped with sophisticated PLC control systems to continuously monitor critical process parameters, and can be programmed to alarm or abort if those parameters go outside the defined limits. In addition In-line monitoring such as NIR spectroscopy, can be used to measure product composition to reduce the levels of quality assurance checks.

The small footprint of this equipment reduces installation costs, and the flexibility of production allows small or large quantities to be manufactured on the same machine,

Photograph 10

Conclusions

From an understanding of the Critical Process Parameters in twin screw granulation the process can be mapped and a Control Space defined to ensure consistent product quality.

References

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