

QbD ‘designed in’, Gerteis® Dry Granulation Technology Could be the Key to Your Future Pharma Solid Dosage Success.

Preface

The Pharmaceutical industry is undergoing change. Under fire by political pressures to drive down the cost per tablet, compounded by new drug discovery becoming more challenging escalating research costs, therefore, the industry is looking to unleash its efficiency shackles of the past. With both the regulators, such as the FDA, recognising change is needed and an increase in demand for low cost essential drugs from new growth markets and developing nations provides an opportunity to capitalise on efficiency gains with the right technologies.

The industry is steeped in a history of batch based manufacturing unlike other sectors such as food and bulk chemicals. This is to give the accountability and traceability required to ensure drug safety to the public. After several years of focus on establishing new ways of analysing drug variability and quality in the various manufacturing process stages, under the Process Analytical Technology (PAT) initiative, the industry is now able to move to advanced techniques to analyse consistency on a time based approach (RTRT) rather than conventional batch sampling and analysis. The challenge is now for the industry to take this QbD concept and look at its manufacturing processes in ‘lean’ terms to start to adapt for a more efficient future.

Some existing process technologies are ideally suited to the new era of solid dose pharmaceutical efficiency.

Is the Pharmaceutical Industry Poised for the Paradigm Shift to Continuous Manufacturing or has Dry Granulation Been Waiting for the Opportunity to do it for Years?

Historically, tablet manufacturing has been substantially a batch based wet granulation process requiring various quality critical stages; materials quarantined, sampled and analysed prior to release. Therefore, equipment asset utilisation is inherently low, cleaning time and costs are substantial, in-train material, capital equipment cost, building costs and energy consumption costs are all high.

Direct compression tableting offers benefits over traditional wet granulation, however, as a process it is often costly and variable due to the extensive range of expensive raw materials used to enable the product to be processed or to be effective e.g. often leading to problems with solubility or bioavailability due to the influence of the necessary additives.

We believe the industry will evolve over the next 5 to 10 years into continuous processing for many products and in many plants. Some existing technologies are already well suited to the change and in fact they present real opportunities to aide in the transition.

In particular, Gerteis[®] dry granulation offers an ideal interim solution, as a semi-batch process, but is also likely to be one of the main final continuous solutions due to its process simplicity. In the next few paragraphs we will outline some of the significant benefits of selecting Gerteis technology.

Roller compaction is a continuous technology by design, but has been developed significantly further over recent years. A number of important changes have been made differentiating Gerteis[®] technologies from the 'run of the mill' conventional roller compactors.

Some of the key advantages of Gerteis are:

- ✓ **The advance feed system ensuring consistent and controllable feed from the infeed hopper through to the compacting rollers**
- ✓ **Special close loop control of compaction and the feed system to give consistent controllable product density**
- ✓ **Advanced roller design ensuring negligible process run up and run down, and no fines recirculation**
- ✓ **High tolerance granulator (milling and size reduction) integrated in the machine for consistent output of granules**
- ✓ **Low energy process input giving a negligible product heat gain of 2-3°C**
- ✓ **Predictive processing software for rapid processing results**

The details of some of these benefits are explained in more detail below. Furthermore, in appendix 1 we demonstrate an example of the on-going evolution of advanced measuring PAT technologies. We have given an example of PAT analysis data based on the measurement of terahertz wave forms. These are reflected from pharmaceutical roller compaction compacts of various densities. It demonstrates the potential for the technique as an in-line technology to analyse critical material attributes of compacted ribbons prior to milling to establish increased process understanding.

How does the Business Case stack up for a Gerteis® Roller Compactor?

Dry granulation offers some significant benefits both in process and lean terms compared to existing wet granulation processes. These benefits are summarised below (also see table 1):

1. **Capital investment costs are substantially reduced**
2. **Utility costs are substantially reduced, as is the GMP foot print**
3. **Substantially simpler and shorter process and increased yield**
4. **Reduced QA and validation costs**
5. **Zero scale up risk and cost**
6. **Reduced processing times and increased flexibility**
7. **Reduced labour costs**

1. Capital Investment Comparison

We would estimate that a conventional wet granulation line would typically require the following capital equipment and technology; this is *in addition* to a dry granulation roller compaction line, (also see the later cost comparison table 1):

You don't require this additional equipment with Gerteis Roller Compaction:

- Liquid dispensary
- Wet granulator high shear mixer (fixed batch capacity)
- Wet mill and transfer system
- Fluid bed dryer (fixed batch capacity)
- Dry mill and transfer system
- IBC handling system
- Automated IBC cleaning
- Complex integrated computer control system

Commissioning complexity and its associated high costs for a wet granulation system offer more opportunities for substantial savings. Typically a wet granulation suite will take anything from 3 to 6 months to commission, validate and qualify, it is complex and has to be tested on site to a large degree, where as a roller compactor system will go into an existing standard process room, as a self-contained machine with a test standard control system and can be operational in less than a week, validated and easily qualified within 3 weeks, ***saving substantial time, cost and project risk.***

2. Utility Costs are Substantially Reduced, as are the GMP Footprint Requirements

As sustainability is now a key focus of the industry, it is also important for the operational and environmental benefits to be highlighted. Much focus can be put on energy saving and reducing carbon footprints for a new facility rather than what happens to the internal manufacturing process in detail. It is possible to reduce the required processing areas quite easily by at least 50% by adopting dry granulation for future manufacturing expansion and new building designs over wet granulation. This reduction is substantial in terms of comparative sustainability costs; typically up to 70% of the cost of a pharmaceutical site energy consumption is due to HVAC, therefore, process design footprint requirements have a direct impact on energy consumption, **reducing this requirement by greater than 50% is therefore substantial in sustainability terms.**

Significantly reducing the amount of process equipment required, product transfers, process steps and product contact surfaces, will also significantly reduce the cleaning burden, e.g. water supply requirements; water supply capacity, purified water demand both in capital and consumption terms. **Thus, reducing expensive and hazardous use of detergents, surfactants and substantially reducing contaminated waste water.**

The Gerteis® roller compactors incorporate high efficiency cleaning design (CIP) and an optimised process using high pressure low flow water, negating the need for detergents in most cases and minimising water effluent disposal. Moreover, with machines being capable of achieving **high levels of containment** this minimises external cleaning requirements for the process room, cross contamination risks and costs, whilst additionally benefiting operator safety.

The GMP processing area and plant area requirements are also substantially smaller by comparison typically;

- GMP area of approximately 80m² compared to Gerteis needing 10 m², **potentially saving 70 m²**
- Technical area of approximately 50 m² compared to Gerteis needing 5 m², **potentially saving 45 m²**

3. Substantially Simpler and Shorter Process, and an Increased Yield

Dispensing of raw materials and dry blending of powders prior to compaction for batch based processing essentially remains unchanged for campaign based dry granulation. Should true continuous processing be adopted then **further efficiency improvements** can be achieved, subject to developing a validation strategy to monitor the feeding system and pre-blending technology to ensure blend uniformity or large batch sizes.

Assuming the dry blending process remains unchanged, e.g. an IBC dry blend is performed, the main process of feeding the roller compactor takes a few minutes from powders arriving at the infeed hopper until discharged as a finished granule ready for tableting, capsule filling or for sachets. This essentially reduces the wet granulation method process steps from 5 or more typically, taking a nominal 60-80 minutes of processing time in total, to a single step of roller compression and milling combined, all in a few minutes. Furthermore, this will reduce yield losses that can be significant, e.g. high shear granulation residues, fluid bed filter and bowl product retention and vacuum transfer **losses typically of 10-15% of accumulated batch losses.** With the controlled slow start technology available from Gerteis®, a stable process 'steady state' is achieved in a few seconds avoiding product

loss during process start up and close down, **losses of less than 1% by comparison**. Traditionally this is an area of inefficiency in continuous technologies.

Establishing a stable and repeatable process with conventional wet granulation is deemed more of an art than a science. Although this is achieved every day in production, it requires a high degree of quality control, highly skilled and experienced operators and a good control system due to the variability that can be observed working with large volumes of materials; e.g. variable air flow patterns, moisture content, particle sizes, agglomeration and compacting of some elements of the processed batch. With Gerteis[®] dry granulation by comparison, the volume of product being 'acted on' at any moment of time is constant and is in grams rather than 100's kg, a significant QbD difference. Also, again with certain manufacturers **the process can be stopped and restarted at any point, immediately establishing a steady state**, this is always problematic, if possible, for a wet granulation and fluid bed drying process.

4. Reduced Quality Assurance and Validation

By nature, the process steps being shorter for Gerteis[®] roller compaction, then also the intermediate and process transfer steps are either reduced or eliminated, and the in-train product is significantly reduced. This enables Quality Assurance to focus on a single process (in this comparison), that is controllable with significantly less variable parameters and set points, also potentially enabling real time release testing for future continuous processing. **By processing larger batches by processing continuously this substantially reduces sampling and lab analysis costs.**

A wet granulation line will typically have 15 to 20 variable critical control parameters, including temperatures, air volumes, humidity and so on, creating a substantial amount of validation and critical control activities and therefore risk. **Gerteis[®] have a small number of control parameters that are process critical and with the right equipment they are tightly defined and stable, this includes a patented linear force control system.** By calibrating this control function, a long term stable and a repeatable process is achieved consistently.

There is also a significant benefit to this tight repeatable control in terms of scale up and rapid process stabilisation. The latest Gerteis[®] innovative technology incorporates optimised process algorithms that can predict product characteristics. With minimal product process characteristics the machine software can adjust and anticipate the right start up parameters **allowing process developers to achieve immediate results, saving valuable material costs and development time.**

By achieving this tight and stable control of the process, developers are able to predict and establish the correct parameters for scale up from R&D, Pilot scale and manufacturing. Roller compactors are able to offer a substantial cost and time saving for the transition from development to production. The process conditions that act on the product are exactly the same on both large production and small scale development machines with a range of a few grams to 20kg/hour, up to 100kg/hour, and up to 400kg/hour depending on equipment size, **in effect no scale up is required with Gerteis[®] technology.**



Figure 1. Gerteis® Macro-Pactor®

This means that conventional scale up of wet granulation parameters that are not linear or easily predictable have to be developed and establish leading to extensive validation time and cost. **With a Gerteis® roller compactor the product process parameters are established very efficiently at lab scale and can be applied to large production machines more or less the following day, representing a huge saving in time and cost and almost eliminating scale up risk.**

There are a number of ways that PAT techniques can contribute to a QbD development and manufacturing strategy that will eventually be key to continuous processing. Depending on the objectives and site PAT strategy, measurements prior to the process can be taken to establish raw material consistency and final blend uniformity, as these are key to any continuous granulation process. This variability can be able to influence compacting set points, but essentially this will allow a consistent processing window, the boundary limits, to be established. This development of a typical processing window could then be tracked in a manufacturing environment, thus keeping data and instrumentation costs reasonable and as low as possible for this level of control.

5. Reduced Processing Times and Increased Flexibility

Process plant designs and configurations for both roller compaction and wet granulation will depend on the process need, e.g. larger dedicated campaigns or multi product small flexible campaigns. A Gerteis® roller compactor can be simply picked up and relocated, so is flexible for the future changes in demands. A wet granulation line is invariably fixed as an integral part of the building, requiring significant safety considerations and almost always requiring multi-level structural integration, therefore inflexible.

Batch size flexibility is also challenging to achieve with a high shear mixer or a fluid bed dryer and associated large IBC configuration. The working volumes are relatively fixed at the time of design and purchase leaving the only flexibility to be the number of batches that can be produced. Typically a wet granulation line will produce 1-2 batches per shift and typically requiring cleaning after 6 batches depending on the product. The Gerteis® roller compaction system does not have filter cleaning requirements as a wet granulation system and has the capability of running 24/7, potentially for weeks on end, for larger campaigns. More realistically, running the Gerteis® roller

compactor for an extra hour or 30 mins gives the ultimate product output flexibility, essentially time based to meet any variable production requirements.

As indicated earlier, for example, up to 400kg of product could be processed in an hour with a Gerteis® Macro-Pactor®(Figure 1) , the machine can be cleaned and operational with a new product in little over an hour later if required (or 2.5hours if a full CIP is needed), **then producing a batch of as little as 1kg or up to 800kg in the same shift potentially**. The Gerteis® Mini-Pactor® will process up to 100kg/hr, **with no scale up requirements between the Mini-Pactor® and the Macro-Pactor®**.

6. Further Considerations

There are some further points to be considered when selecting roller compaction technology. The technology has been used for many years, yet more process understanding and user familiarity are key to successful process development. Essentially, with the right Gerteis® equipment; if a product can be tableted it can be dry granulated, therefore, for versatility of R&D or more complex formulations and challenging API's Gerteis® have the solution and knowhow to succeed.

7. Financial benefits

Your particular cost savings comparing wet granulation to Gerteis® dry granulation can easily be calculated simply by evaluating the table below:

Table 1. Cost comparison indication in Euro

1. Direct Capital Benefits	Unit Cost	Wet Granulation	Dry Granulation	Saving €
<i>Capital Costs</i>				
Capital Equipment Cost		€2,000k	€800k	€1,200k
Building GMP Area*	€11,000/m ²	80 m ²	10 m ²	€770k
Building Technical Area*	€2,000/m ²	50 m ²	4m ²	€72k
Plant Utilities (capital)				TBI
Installation and Commissioning*		€500k	€50k	€450k
Scale Up		2 months	5 days	TBI
Process Start Up		3 months	10 days	TBI
Total (to be completed for your application)				
2. Indirect Cost Benefits	Operational Costs	Indicative saving %		To be identified
<i>(add your cost values)</i>				
Yield savings**	€	>60%		
QA savings	€	50%		
Operator Labor	€	50%		
Power (per €/KW)	€	70%		
Compressed Air	€	80%		
Towns Water	€	80%		
Purified Water	€	80%		
Total (to be completed for your application)				

* Nominal market values have been used in table 1 based on 200Kg batch processed in 2 hours. Figures will vary depending on the application and configuration. Where the € symbol is inserted in the table the writers was unable to realistically estimate the rate due to variation from site to site, although the cost differences are to be considered in the evaluation. To be identified (TBI).

**Compared to accumulative yield losses in a high shear granulator, fluid bed dryer and transfer system.

Conclusion

In conclusion, there is a very powerful business case to reduce the 'cost per table' for pharmaceutical and healthcare granulated products in capital, operational, strategic and environmental terms to consider Gerteis® roller compaction technology for development and use in a modern pharmaceutical solid dose manufacturing facility.

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