

## Single Pot Processing



*Collette Technologies*



# Product know-how



## Process expertise

Collette has supplied granulation and drying systems to various industries for more than a century, and to the pharmaceutical industry in particular for more than 50 years. Based on this experience, Collette supplies advanced solids processing systems for mixing, granulating and drying in the pharmaceutical industry. This includes small capacity systems designed for R&D as well as industrial size plants for batch and continuous production of pharmaceutical compounds under cGMP conditions.

Collette's plant and process expertise is based on experience and R&D. With more than 1000 plants installed around the world and literally thousands of tests performed, it has established a solid base of expertise related to the needs of the pharmaceutical manufacturing industry.

### **Delivering the right solutions**

Every Collette project begins with the customer's desire to create a product that will succeed in the market. In Collette, the customer finds a partner who will assist in meeting that goal. Collette's expertise lies in the processing of Active Pharmaceutical Ingredients into secondary pharmaceuticals using technologies such as blending, granulation, drying, pelletising and crystallization.

### **Plants customized for success**

Every pharmaceutical plant and system from Collette is a unique union of proven technology and individual solutions. The company supplies plants for cGMP production configured to meet the customer's specific requirements.

### **Safety and the environment**

Collette offers a range of solutions, fully compliant with national, local and in-house regulations, to control product containment, explosion safety and solvent emission, including solvent recovery systems and full containment plants. Equipment can be supplied to meet explosion proof and pressure shock resistant standards as required.

### **A partnership in every perspective**

Working with Collette means entering into a partnership every step of the way. From process testing and design, to specification of the software controlling the customer's plant. Collette's comprehensive after sales program ensures that the customer's return on investment is optimised throughout the lifetime of the plant.

- Mixing • Granulating
- Pelletizing • Drying

## Process technologies

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Whether the customer's requirement is for mixing, granulation or drying, Collette has a solution for every processing challenge. Collette's Single Pot Technology offers a choice of mixing, granulation and drying options integrated into one processing vessel. With Collette's help, this allows the customer to choose the most appropriate technique for the product.

### Dry mixing

Whatever the subsequent production steps, the formulation of an active compound and other excipients needs to be mixed homogeneously. Single Pot Processing, like high shear mixing, relies on the use of a high intensity mixing blade resulting in a homogeneous blend.



### Wet granulation

During granulation, the active compound and other excipients are combined with a binder solution to form granules with a fixed composition. The Single Pot granulation process uses a high speed mixing blade and chopper to achieve this. During the granulation process, density and compressibility of the product is modified to achieve the optimal tableting properties.



### Melt granulation

In a melt granulation process, the binder solution of a standard wet granulation process is replaced with a meltable binder. This binder can be added in molten form, but the Single Pot Process offers the benefit of allowing the binder to be added in its solid state. Melting is achieved by the energy added through the mixer friction, the heated jacket of the bowl and/or microwave energy. Rapid solidification of the granules can be achieved using liquid nitrogen.



### Pelletizing

The formation of pellets can be considered as granulation taken one step further, to achieve spherical granules. For Single Pot pelletisation, a special mixing tool is available to optimize the process and maximize the output. Drying of the pellets can be achieved in the same processing vessel, eliminating the need for transfer of the product.

# Built-in versatility



## Effervescent production

Producing effervescent granules can be achieved in many different ways. Single Pot Processing is suitable for both 2-step and 1-step granulation techniques. Water as well as solvents can be used for granulation. When water is used, the reaction can be stopped immediately by activating the integrated drying system. No time is lost in transferring the product from one vessel to another and the whole process is kept under contained and controlled conditions.

## Vacuum drying

After wet granulation, the granulation liquid needs to be eliminated to achieve stable, dry granules that can be further processed.

Single Pot Processing relies on the application of a vacuum within the bowl to dry the wet mass. This technique allows drying of pharmaceutical compounds at low temperature, and for minimal environmental exhaust through a very efficient solvent recovery, even if organic solvents are used for granulation.

## Gas assisted vacuum drying (Transflo™)

The vacuum drying process can be enhanced by the addition of a small amount of gas, passing through the product during the drying phase.

The gas-assisted vacuum drying (Transflo™) technique results in shorter drying times and lower residual moisture content of the final product.

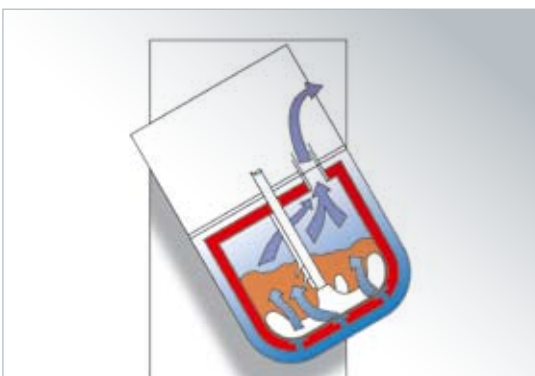


## Microwave drying

To really enhance the drying process, microwaves can be added as an additional energy source. Because of the additional energy added to the process, microwave drying is the fastest drying technique available in Single Pot processing. Through careful control of product temperature and forwarded and reflected microwave power, this technique is ideal for fast processing of pharmaceutical products.

## Crystallization

Using a combination of drying techniques it is possible to carefully control the speed of drying, allowing crystallization processes to be executed in a Single Pot Processor. A major benefit of this technique is the option to granulate the crystallized product immediately without having to transfer it to a different equipment, greatly improving product containment & yield.



*More than a century of mixing experience*



## History

Collette was founded in Antwerp in 1892 as a manufacturer of mixers and kneaders for the baking industry. Over the years, the equipment range expanded and diversified to cover equipment for other industries and, from the early fifties, the pharmaceutical industry.

The major breakthrough in the pharmaceutical industry came with the introduction of the first High Shear Mixer Granulator (GRAL) in 1975. In 1980 the Single Pot concept was introduced with the TOPO-design and the GRAL-processor, and shortly afterwards, the Process Development Center opened, a test lab for the customers to explore this new technology.

With the introduction of the Vactron in 1990, Collette was one of the first machine manufacturers to promote microwave drying for pharmaceutical applications, emphasising its focus on this industry.

Within the pharmaceutical industry, Collette stands for innovation, new technologies, reliability, service and know-how. As part of the GEA Pharma Systems Group within GEA, Collette is able to offer many advantages in support and synergy including full process line design and turnkey project management.

The test laboratories within the GEA Pharma Systems Group, the PDC in Belgium and the GPS Technology Centre in Switzerland, play a very important role in Collette's customer relationships by providing process development and process understanding within Collette's equipment range.



# Compact, flexible, contained

## Single Pot Processing

Single Pot Technology, with its various processing options is ideal for many different applications and processing issues. Collette, within GEA Pharma Systems, is able to assist in the selection of the processing requirements.



### Containment

Because of its very nature, a Single Pot process is a contained process. No transfers are required between process steps, except for loading the raw materials and unloading the dry granules. This is not only beneficial for protecting the operators from potent products, but also for protecting the products from external influences such as heat, light or moisture. Specific solutions are available for product loading and discharging to achieve the desired level of containment for the whole process.

### Compact technology

Overall investment cost for a certain technology including installation cost and required cGMP space is becoming more and more important in the pharmaceutical industry. cGMP production area is expensive and is minimised wherever possible. Single Pot technology is a very compact technology achieved by incorporating several processing steps into one machine. This reduces the capital cost of the equipment as well as the cGMP & technical space required for granule production and therefore the overall project cost.

### Flexibility and utilisation

Single Pot processing is an extremely flexible technology. Whether for standard wet granulation, melt granulation, pelletizing or effervescent production, combined with drying, a Single Pot Processor can achieve the required result. With easy and efficient cleaning, using a CIP system, quick product changeover is achievable.



# Drying Technology

As Single Pot Processing builds upon the well established high shear technology, all process options available for the UltimaGral™ range are also available for the UltimaPro™ range.

## Through-the-wall configuration

Through the wall offers the best option in terms of cleanliness, maintenance and explosion protection. The Through-the-wall configuration provides a sealed separation between technical and GMP space by the machine itself. This offers a clear containment concept including explosion area separation that fulfills the latest requirements like ATEX. By keeping technical components out of the process room, the equipment is much easier to clean. Maintenance is carried out from the technical area, reducing the need for the maintenance engineer to work in a GMP area. This reduces downtime and the risk of contamination. For ATEX, the design allows the technical area to be classified as safe.

## Loading

Depending on the layout of the production area, several options for loading the powders are available. When the processing room is sufficiently high, gravity loading is applicable, using post hoists to lift the IBC on top of the UltimaPro™. Alternatively gravity loading with the IBC located on a docking station on the floor above the machine is possible if a multiple floor installation is preferred.

In height-restricted areas however, vacuum loading can be used. In this case the product is sucked into the processing vessel from an IBC located close to the machine on the floor.

## Binder solution addition

A range of binder addition systems is available to give the optimum binder liquid droplet size for an even distribution throughout the powder mass, for different viscosities.

The liquid is transferred to the mixing bowl using a peristaltic pump or pressure vessel, while the rate and amount is controlled by a loss in weight system or a mass flow meter.

## Moveable head

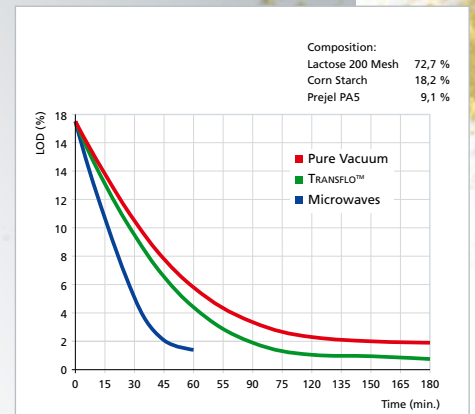
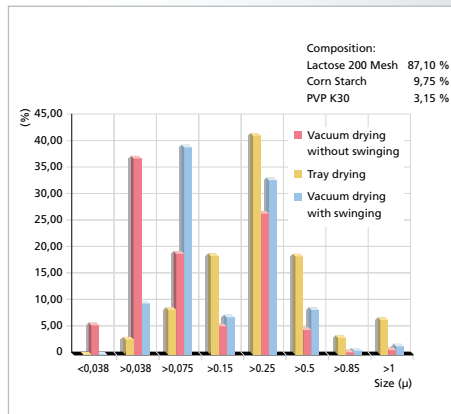
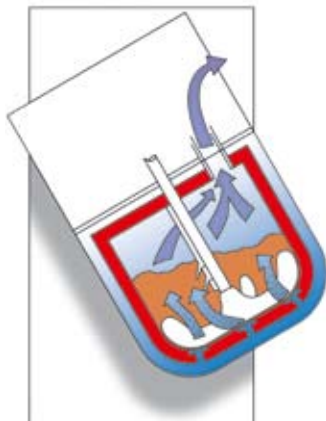
The UltimaPro™ can be equipped with a 'Movable Head' to enhance flexibility. This feature allows operators to lower the closed bowl to enable better accessibility and easy loading. The closed bowl can also be raised for dust free discharging. This option is extremely useful in height-constrained processing areas.





# UltimaPro™

Using proven standard components, Collette can supply both simplicity and flexibility in plant design. User-selected process options, control systems and liquid recovery units combine in a system to meet process requirements exactly. This approach ensures that qualification and validation work can be kept to a minimum and secures successful results.



## Drying options

The vacuum system of the UltimaPro™ range has been designed to yield optimal drying efficiency. By incorporating condenser systems and selecting the right pumps, excellent solvent recovery and a competitive drying rate can be achieved. Different configurations are available to suit any process requirements.

The Transflo™ system for gas-assisted vacuum drying has been designed for optimal distribution of the stripping gas through the product, without compromising on inspection, validation or cleanability.

Microwave drying is without a doubt the fastest drying method available in Single Pot systems. Our system is equipped with control and safety features to ensure excellent process control and complete safety for product, operator and equipment.

## Swinging bowl

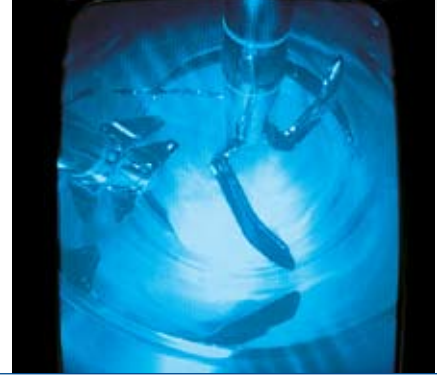
The use of the swinging bowl during vacuum drying results in an improvement of the granule characteristics and a reduction in drying time. It is a very gentle method to agitate the product during drying, producing less fines and therefore allows processing of formulations that were not explicitly developed for vacuum drying in a Single Pot Processor.

## From R&D to large scale production

Collette is your partner for your granulation process from process development up to full-scale production.

With capacities from 10-L to 1500-L, the UltimaPro™ range can cover all requirements starting with the process development stage and clinical batch production to scale-up trials and large-scale production for marketed products.

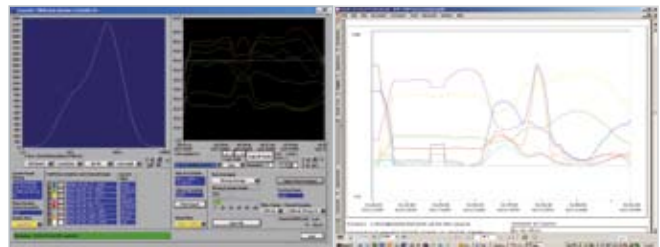
# Understanding and controlling your process



Built-in into the control system, Collette has integrated its process knowledge and experience to help operators monitor and control the process easily. Depending on the automation and reporting requirements, Collette can offer two different control systems both of which provide the operator with all necessary process information in a clear and easy to understand way.

## OP/ PLC control system

This control system provides basic functionality and process visualisation with data recording via a separate paperless recorder. It is designed to be FDA 21 CFR Part 11 compliant and provides a basic level of process automation with recipe control.



## Procoll pro control system

This SCADA based control system provides a maximum level of flexibility and functionality in terms of process visualisation, automation and data recording. It is designed for integration with customer MES systems for receiving and reporting GMP relevant data. The system is very much process orientated and guides using in-built intelligence the creation of recipes and automatic processing. All process data is stored in a relational database. The system is fully FDA 21 CFR Part 11 compliant and provides features like audit trail including reporting and configurable graphs for process values. This batch control system is designed according to the S88.01 batch control standards.

## Process monitoring

A video camera installed in the head of the machine provides a complete view into the process vessel. This is the ideal tool for state of the art processing and gives the operator a clear indication of the product behaviour and flow while the vessel is closed. Not only for product development but also for production this feature provides a huge advantage for modern integrated and contained processing.

## PAT integration

As well as the classical tools for monitoring and controlling process like torque measurement for granulation control, or temperature, pressure and energy input for the drying process. Collette has developed innovative solutions for the integration of NIR (near infrared) and FBRM (focused beam reflectance measurement) sensors into its processes and the controls. These advanced measurement tools are used for the direct measurement of product quality parameters such as moisture content, homogeneity of the mix, and particle size distribution, providing control parameters for direct release of the product.



# Design for cleanability & maintenance

Manufacturing compliance depends on efficient, effective cleaning. Automation of the cleaning process ensures repeatability, allows validation and minimises down-time.

In recognition of the fundamental role played in today's advanced powder processing industry by automated clean-in-place procedures, Collette has developed a unique approach to CIP.



## Concealed services

The design of the UltimaPro™ ensures that lines and hoses for the utilities on the machine (water, electricity, hydraulics, etc.) are concealed in the machine encasement. This creates an uncluttered working space without hoses being run to the machine in the process area.

## CIP and WIP

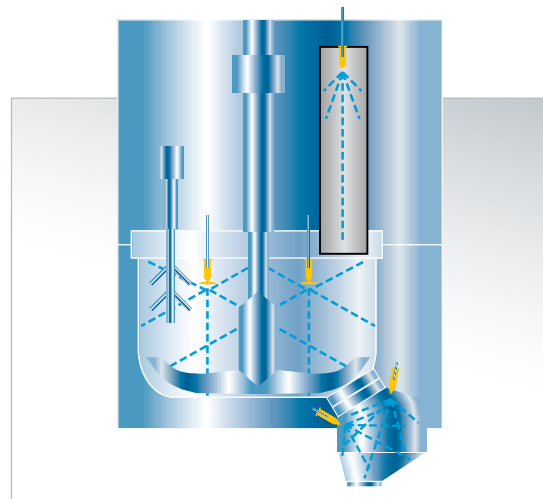
The UltimaPro™ can be supplied with a wide range of washing-in-place and fully automated cleaning-in-place options. These include spray nozzles adapted for most effective cleaning of product feed, product filter, bowl, lid and discharge valve (for example retractable spray nozzles for the lid).

Even downstream equipment, such as a mill, can be incorporated in the cleaning system.

## Easy maintenance

The through-the-wall design of the UltimaPro™ ensures that technical interventions can be easily carried out without having to access the processing area and disturbing the clean environment.

Even the concealed service lines can be easily accessed via sealed doors in the machine encasement.



## High containment

# Optimum process efficiency

Current good manufacturing practices increasingly require that product is fully contained during processing to protect operators and environment.



The concept of a Single Pot Processor in itself already ensures contained processing by avoiding product transfers. Additionally, the UltimaPro™ can be equipped with several features to optimise the containment of toxic products.

A product feed and discharge valve can be equipped with Buck high containment split butterfly valves and upon customer request, even with isolator boxes.

A sampling valve that allows the operator to take samples during the process without having to stop the machine, open the bowl, or even open a port in the lid, can be integrated into the processing vessel and adapted to different containment levels. The sample container is completely contained allowing the sample to be transported to the QC lab without exposure to the atmosphere.

The concept of containment not only applies to the production area. When working with organic solvents, recovery and containment of these solvents is as important as containment of the product itself.

The UltimaPro™ is equipped with a very efficient recovery system that can recover up to more than 99% of the used solvents.



# Continuous improvement

## Safety



### Explosion safety

When using solvents during granulation or certain dry products with a low MIE, there is a risk of explosion. By eliminating one of the sources necessary to create an explosion, this risk can be effectively mitigated. The Single Pot system by Collette relies on an inertization procedure for this end. The oxygen in the bowl is replaced by nitrogen in a automatic cycle. Oxygen sensors can be provided to ensure the level is below the explosion limits.

### Operator safety

Apart from the containment measures to protect the operator from exposure to possible harmful active ingredients, the UltimaPro™ is also equipped with many safety features to eliminate any risk to the operator while working with the equipment. Examples are 2 hand trip control for closing the bowl, safety grids with proximity switches, interlocks in the software, etc.

### Risk analysis

Collette is open to assist its customers with extensive in house experience in establishing a risk based approach for validation and for HAZOP studies.



# The complete partnership

Entering a partnership with Collette means entering a partnership that does not end until the customer is completely satisfied. From the moment requirements are specified until the plant has been put into service and has been qualified, Collette's trained staff work closely with the customer during every step of the process to create the components that will result in a finished plant.

## Project management

The expertise of the Collette engineering team is available to help customers find the optimum solution for their individual processing needs. The company assists with single phases of a project, or takes full responsibility for design and installation of a complete turnkey plant.

In case of joint GEA Pharma Systems projects, one project manager is appointed to oversee the whole project and co-ordinate the project between the customer and the GEA Pharma System companies.

## After sales

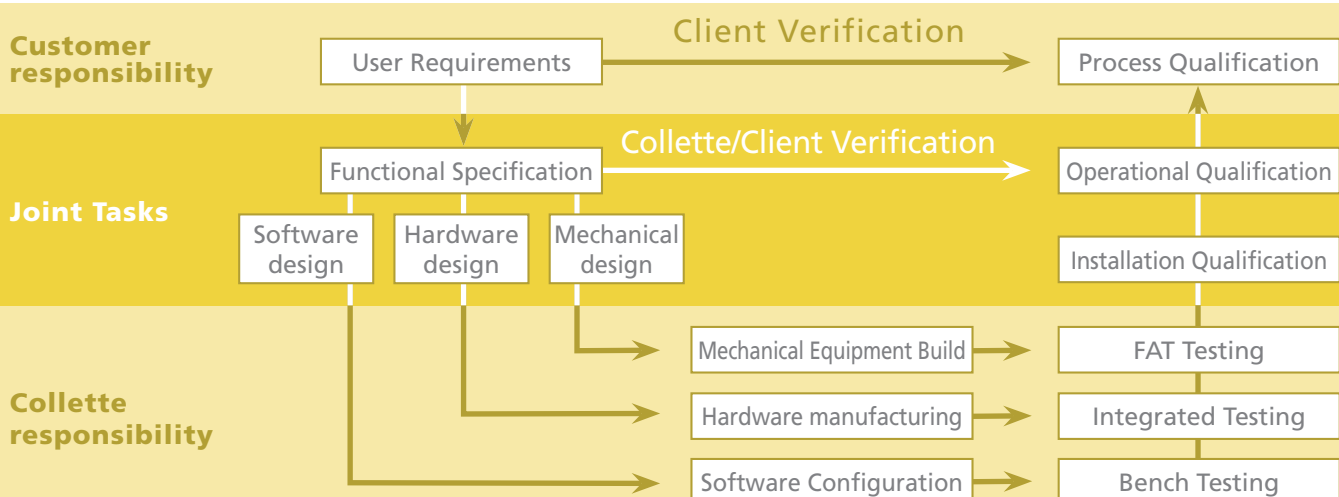
Regular maintenance is essential to ensure equipment operates to maximum efficiency. Fully trained engineers can carry out on-site servicing and calibration of equipment, either as part of a planned maintenance programme or in response to customer need. Replacement parts can be supplied from stock or manufactured to order. To avoid the expense of equipment replacement, Collette can upgrade existing systems and plant to meet different operational parameters, to comply with changing regulations, or to modify for use at another location.

## Training

Finally, operators of Collette equipment can undergo training to help them maximise efficiency, either at the time of installation or periodically as required.

## ...Every step of the way

Based on years of experience, equipment qualification will be carried out according to an agreed plan based on documents prepared by Collette. Collette's engineers will contribute to a successful qualification of the equipment in close co-operation with the customer's validation staff.



# The Process Development Center

## Proven process

The Process Development Center (PDC) plays a major role in the partnership between the customer and Collette. This fully equipped laboratory offers the opportunity to benefit from Collette's years of experience in wet granulation, pelletising and drying processes in High Shear Mixers and Single Pot Processors.

The staff of the PDC consists of very experienced and dedicated people with a background in engineering, chemistry and pharmacy. They will assist customers with all questions concerning processes in Collette equipment.

A fixed, through-the-wall installation of an UltimaPro™ 75 High Shear Processor is at the disposal of Collette's customers to test the equipment with their own products. Also, 2 mobile units, an UltimaPro™ 10 and 25 High Shear Processors are available to rent, for customers who prefer to perform tests in their own facilities. Finally, the PDC also has one or more MicroGrals™ available for testing small-scale batches or for rent. This enables processing batches between 100 g and 30 kg in the Collette PDC.



Next to the high-shear mixer/processors, a wide range of analytical equipment is available for characteristics of granulate and tablets.

Small scale trials can furthermore be executed in the GPS laboratories in Switzerland, Singapore and the US.





### Central know-how on a global scale

Based on a strong commitment to research and development, pharmaceutical technology centres in Belgium, Denmark, Switzerland, the UK, Singapore, and USA provide global technical support and know-how to the pharmaceutical industry.

These centres of excellence give customers

access to a range of test facilities and expert teams with technical and process know-how. Our teams work closely with our customers to optimise processes and evaluate their products, enabling them to achieve their process and production goals.



### Contracting profitable experience

A world leader in supplying pharmaceutical equipment, GEA Pharma Systems offers manufacturers all over the world the opportunity to enter into a profitable partnership for development and contract. GPS combine advanced in-house technology with a thorough

understanding of the pharmaceutical industry to help customers maximize their development results.



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