ASSESSING THE FEASIBILITY OF TWIN SCREW EXTRUSION PROCESSING IN THE DEVELOPMENT OF PHARMACEUTICAL PRODUCTS

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INTRODUCTION AND OBJECTIVE

Within the framework of the Horizon Europe project ETERNAL, Twin Screw Extrusion is being investigated as a key enabling technology for a greener pharmaceuticals production. This is due to its unit operation, small footprint, flexibility, solvent-free Continuous Manufacturing (CM) nature and suitability for real-time monitoring [1].

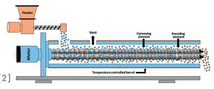
The case study consists in the feasibility assessment of producing a medicinal product using Twin Screw Granulation (TSG) to produce a granulate for an immediate-release tablet.

The aim is to evaluate the reduction of the environmental impact in terms of energy efficiency and resource use, by comparing it with the current batch manufacturing process.

Traditional manufacturing

- Batch process.
- Numerous phases and equipment.
- Multiple production rooms.

New investigated process



[2]

- Twin Screw Extruder.
- Suitable for Continuous Manufacturing.
- Smaller equipment train.

METHODOLOGY

Literature research — Selection of excipients in relation to technology and product characteristics

Preformulation studies

Current manufacturing energy and water Baseline — Energy consumption estimation and measurement of the current manufacturing:
- electrical and thermal kWh/batch for equipment
- kWh/batch for HVAC for rooms

Water consumption

Formulation trials
- **TSG**
- **Tableting**

Granules and tablets characterization — Best prototype selection by:
- evaluating the composition using a D-Optimal DOE design with 9 experimental trials
- defining process steps and parameters

Stress test — Thermal, hydrolytic and photolytic stress tests

Stability study — Preliminary 12M-stability study:
- timepoints 3-6-9-12 months
- long-term, intermediate, accelerate conditions
- 2 packaging types (blisters, glass bottles)

Microbiological-chemical-physical analyses to assess stability

Preliminary evaluation of Target energy consumption — Estimation of energy consumption of the new process hypothesizing the use of a production scale 40mm-extruder at two throughputs (kg/h) and considering smaller spaces to be air-conditioned.

DoE on TSG process useful for scale-up — Full factorial mixed design including 24 experiments

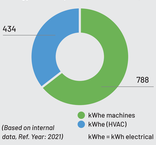
4 Factors:
- throughput 0.6-1.2kg/h (Thr)
- screw speed 150-500 rpm (Sti)
- temperature 55-65°C (Temp)
- screw configuration A-B-C (Scr)

Main Responses
- particle size (lumps, fines)
- Flowability
- Torque

RESULTS

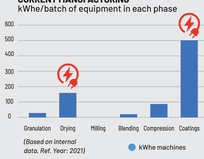
BASELINE Manufacturing process

CURRENT MANUFACTORING
Energy consumption (kWhe/batch)



(Based on internal data, Ref. Year: 2021)

CURRENT MANUFACTORING
kWhe/batch of equipment in each phase



(Based on internal data, Ref. Year: 2021)

TARGET Manufacturing process

MANUFACTURING STEPS:
- Mixing
- Twin Screw Melt Granulation (TSMG)
- Milling
- Blending
- Tableting

Removal of high energy consumption steps.
- DRYING
- COATING STEPS
- SOLUTIONS PREPARATION

No added water

No process steps involving thermal energy by natural gas

Prototype definition

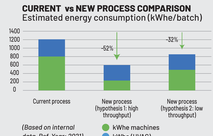
- Definition of QTPPs and identification of CQAs.
- Stable up to 12M, need of a storage limitation temperature (25°C).
- Tablet weight decreased (-18%).

QTPPs = Quality Target Product Profiles; CQAs = Critical Quality Attributes

BASELINE vs TARGET energy consumption

- The reduction in electrical energy consumption has been preliminarily estimated between 32% and 52%, depending on the throughput.

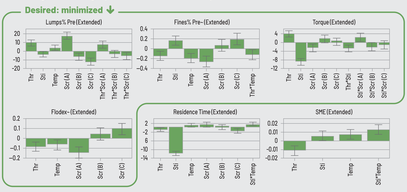
CURRENT vs NEW PROCESS COMPARISON
Estimated energy consumption (kWhe/batch)



(Based on internal data, Ref. Year: 2021)

DoE on TSG process

- Identification of key factors affecting the product quality and process performance.
  - Scr. B-C (2 kneading zones) reduce coarse particles.
  - Scr. A (1 kneading zone) decreases torque and leads to better flowability.
  - High throughputs increase lumps and decrease fines.



- Evaluation of Specific Mechanical Energy [kW/(kg/h)] and residence time in relation to granules quality, useful for scale-up phase.
- Prediction of the best trial: 1.2 kg/h, Screw speed 410 rpm, 65°C, Conf. C.

CONCLUSIONS

- A suitable prototype has been developed at R&D scale by using a CM technology, i.e. Twin Screw Granulation, followed by tableting. The new process might be carried out continuously
- New tablets show appropriate quality attributes
- The energy consumption is decreased by reducing the steps and due to the small equipment footprint, which allows for smaller rooms
- The use of resources, such as raw materials and water, are optimized since the new tablet has a lower weight and less/smaller machines need to be cleaned.
- As next step, the TSG process will be optimized and scaled-up using a pilot 18mm-extruder by an ETERNAL consortium partner and the related energy consumption will be measured

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Co-funded by the European Union

ETERNAL project has received funding from the European Union's Horizon Europe Framework Programme (HORIZON) under grant agreement No 101057688. The work of UK-based Associated Partners has been funded by UK Research and Innovation (UKRI) under the UK government's Horizon Europe funding guarantee.