Application Note
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Pharma MiniLab – a small scale compounder for pharmaceutical research

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Abstract
Hot melt extrusion and continuous process leads to cost efficient production. In development of new drug/ excipients small scale extrusion systems reduce time to market and use comparable processes to production. Applications and products for development with the Thermo Scientific micro compounder HAAKE Pharma Minilab are described.

Introduction

The pharmaceutical industry uses numerous batch processes. Recently a trend to continuous processes is visible because continuous processing has a couple of advantages. Especially the hot melt extrusion can produce more efficiently and with higher output. Furthermore it allows monitoring of processing parameters the extrusion process, which is particularly important in PAT.
As compounding takes place directly in the molten stage, aqueous solutions are avoided. Reducing or removing drying steps help to save energy.
Extrusion is a predominant technique in polymer processing. Profiles, sheets and bags are produced as end products, compounds as intermediate products. Even in the huge installation of a petrochemical plant we see extruders producing LDPE, PP resins with an output of 40 t per hour. In pharmaceutical technology the extrusion is known for more than 35 years[1]. Developed in industries for products far less expensive on a kilogram basis extrusion gives a key to survival under growing cost constraints.

Thermo Scientific HAAKE Pharma MiniLab

The following article is focused on smallest scale of extrusion with an output of several grams to 150 grams per hour. With the transfer of knowledge from polymer processing and a proven track record with customers the HAAKE Pharma MiniLab (Fig.1) for small scale / clinical sample development requiring GMP.

Figure 1: HAAKE Pharma MiniLab: closed barrel, with force feeder and pressure transducer

Figure 2: Opened barrel for cleaning

Economic Small Scale Compounding

Using only small quantity of new ingredients during formulation development for proof-of-concept studies lead to cost reduction.

For expensive APIs or if only smallest amounts of material are available from synthesis, the benefit of the small scale is obvious. Compared to more traditional pharmaceutical twin screw compounders with throughputs starting from 1 to 10 kg/hr, the HAAKE Pharma MiniLab requires as little as 5 grams for a discontinuous trials and up to only 150 grams for a continuous extrusion. This allows evaluation of an extrusion process in a very early phase.
Less obvious is the time saving due to the easier handling of the small instrument, reduced cleaning time and lower investments due to a small footprint (e.g. clean room, glove box).

Function of Micro Compounders

A pre blend of API (active pharmaceutical ingredient) and excipients is added in the feed zone. Compared to dry blending the requirements of particle size and distribution are less critical. Powders, granules and small pellets can be fed. By the force feeder they are continuously pressed to the dosing section and transported by the co rotating screws of the compounder.
The screw are conical design to reduce total volume and gain an extra pressure build up at the screw tips. Transportation, melting, pressure build up and mixing are simultaneous unit operations taking place in the barrel of the HAAKE Pharma MiniLab.

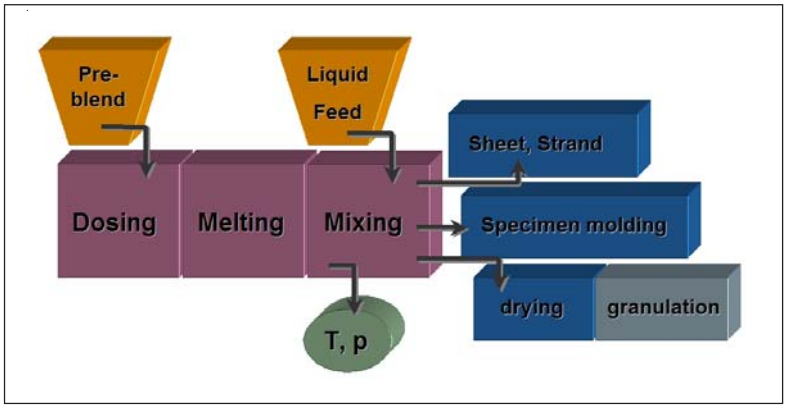

Figure 3: Scheme of the Pharma MiniLab, unit operations, data and Products (Data: temperature (T), pressure (p))

Liquids can be added via an optional feeding port. Process data is displayed and stored in the log file.
The material is extruded as tape or rod, depending on the shape of the die, or injection moulded to specimens for evaluation studies by the HAAKE MiniJet (Fig. 6).
The Thermo Scientific micro compounder HAAKE MiniLab is either available in a standard version (HAAKE MiniLab) or in a GMP compliant version (HAAKE Pharma MiniLab). The Pharma MiniLab version allows preparation for instance of first clinical samples in low quantity & small scale production.

Specific features and Specifications of the Pharma MiniLab

Dosing system
- Force Feeder Stainless steel No. 1.4404 (316 L), 1.4112 (440 B)
- < 0.8 µm surface roughness

Extruder barrel
- Stainless steel No. 1.4112 (440B)
- Hardened to 55 Rockwell C
- Roughness of wetted surface 0.4 µm
- Modified outlet section

Software
- Password protected Software
- Data log includes time and date including all critical control parameters

Housing
- No painted parts
- All sheet metal is made of stainless steel 1.4301 (304)

Drug development applications

A recent report suggests that the successful development of one or two new drugs requires approximately 100 discovery projects and initial in-vitro screening of approximately 7 million compounds[2]. After in-vitro screening, pharmacological and preclinical safety studies are performed followed by clinical studies to confirm the efficacy and safety of the drugs in humans before being marketed.
The largest potential for extrusion in the pharmaceutical industry resides with the processing of active or excipient materials to produce products such as:
- thermal binders
- extrusion spheronization process
- controlled drug delivery systems
- medical grade film products
- transdermal drug delivery systems
- drug – excipients compatibility
- implants[3]
- granule and capsule preparation[4]
- immediate release dosage forms
- hot melt mixed solid dosage forms

The extrusion process in the pharmaceutical technology is described in detail[5], including rheological measurement techniques and co rotating twin screw compounders. Promising results were found not only with large scale production equipment but also with microcompounders as the HAAKE MiniLab. Various studies proof the benefit of hot melt extrusion and creating dispersions of poorly soluble drugs in an amorphous carrier. The hot melt extrusion can compare to other formulation techniques, like capsules film coated beads[6].
Hot melt extrusion offers added value: Known physical instabilities for solid dispersed drugs as aging recrystallization or phase separation are reduced by selecting a polymer with a high glass transition temperature Tg (150 to 200°C). The increased Tg of the system leads to low molecular mobility resulting in acceptable physical storage properties[7].

How can the HAAKE Pharma MiniLab can help to improve results? A short summery with examples gives an ide of which tests now can be done in a much smaller scale.
- thermal stability of API in a excipient matrix (e.g. Polylactide)
- dissolution testing of specimens (e.g. excipients testing Eudragit, MCC)
- bioavailability studies
- processing parameter studies
- gas absorption and permeability
- Stability (storage conditions, re crystallization)
- hardness tests of films
- scale up studies

Comparison to a parallel twin screw compounder, PRISM PharmaLab

A better understanding of the process early in R&D will lead to a smoother scale up for manufacturing. For a few application the output of the Microcompounders, typically in a range 50 to 150 g/h is the direct production output. Usually a scale up to parallel co rotating twin screw compounder is necessary to reach outputs of 1 to 10 kg/h.
The Thermo Scientific PRISM PharmaLab (Fig. 5) is the GMP version of a 16 mm extruder with high flexibility. Similar to the micro compounder the split barrel concept ensures easier cleaning. Data from previous tests on the 5 g sample – as thermal stability or compatibility – can directly used on the 16 mm twin screw.

Figure 4: Material characterization solutions in drug development

Figure 5: The Thermo Scientific PRISM PharmaLab

Thermo Scientific HAAKE MiniJet

In the development of new materials it is an important advantage over competition to shorten the time to market. So it is critical not only to check the formulation with the HAAKE Pharma MiniLab, but also to measure rheological and mechanical properties of the end product. The Thermo Scientific HAAKE MiniJet (Fig. 6) is developed as an instrument handling the small amounts produced with the MiniLab. Using the HAAKE MiniJet specimens can be produced very efficiently, even when a minimum of sample material is available.

Figure 6: HAAKE MiniJet, Injection moulding with few grams

The instrument is build as a piston injection machine. The amount of required sample material is minimized to less than 5 g as the sample material is almost completely transformed into the mould. The waste material of conventional screw driven injection moulding machines can be avoided by this principle.
Disks, plates or even more sophisticated geometries as capsule shapes and tensile bars are useful to test hardness, breaking strength and dissolution. In the initial stage of the screening process for the candidate compounds reproducible results are obtained in a shorter time.

Conclusion

By using knowledge base from polymer processing especially in small scale, Thermo Fisher Scientific was able to build up a line of dedicated instruments for the pharmaceutical industry. Focus is to cover the range from lead optimization to the production and QC with extrusion technology (Fig.4). This means in terms of output, a range of 5 g to 20 kg/h and beyond especially requested for pharmaceutical production. Future developments are yet to come focussing on the shapes moulded specimens, the take off systems for more complex geometries or higher outputs by scale up of the twin screw extruders[8].

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