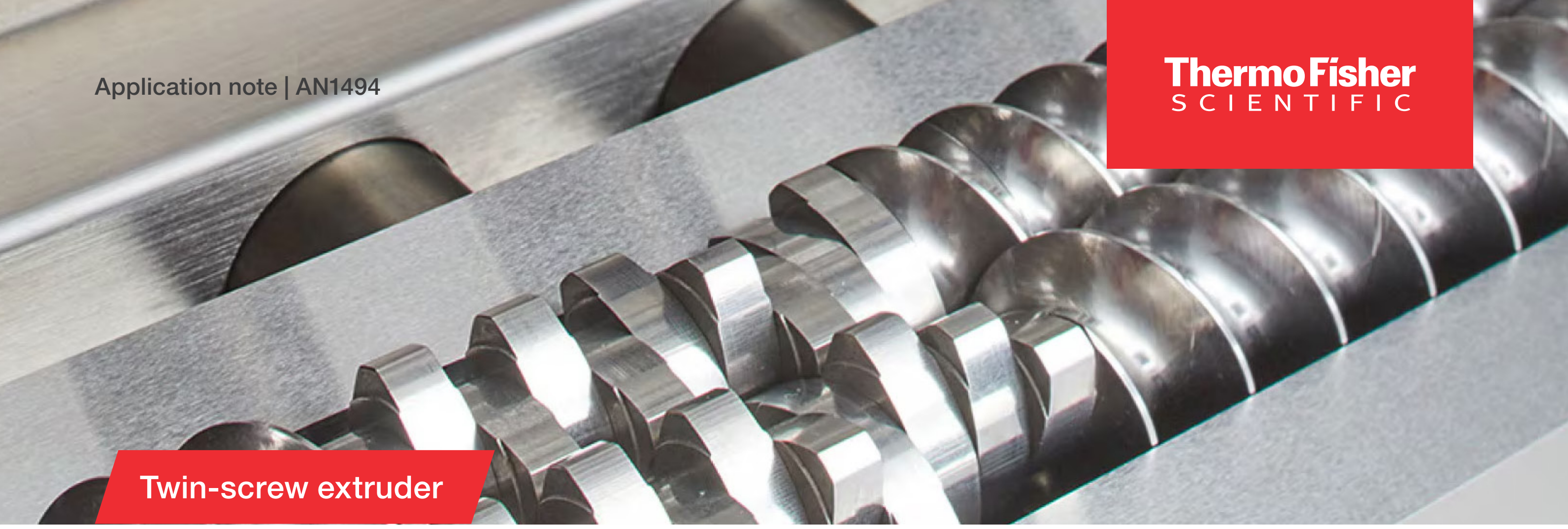
Application note | AN1494




# Reactive Extrusion

## Continuous organic synthesis performed on a Thermo Scientific™ twin-screw extruder

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### Introduction

The process of constructing complex molecules from simpler starting materials is a cornerstone of chemistry with broad applications in pharmaceuticals, agrochemicals, polymers and specialty chemicals. Traditionally, organic synthesis has been performed in batch reactors, which requires multiple steps, long reaction times and significant energy consumption. Recent developments in continuous manufacturing have opened new routes for performing organic synthesis using twin-screw extruders, as they offer a unique environment for organic reactions, combining mixing, heating and chemical transform in one continuous process.

### How it works

The Thermo Scientific™ Process 11 Twin-Screw Extruder consists of two co-rotating, intermeshing screws with a modular screw design, housed in a split barrel with multiple feed and venting ports. The screws transport and mix the reactants as they move through the barrel, where the heat generated by mechanical shear and external heaters initiates and sustains chemical reactions. The screws are modular, meaning their design can be customized from single screw elements to create specific reaction zones, control mixing intensity, and manage residence time. (See Figure 1.)

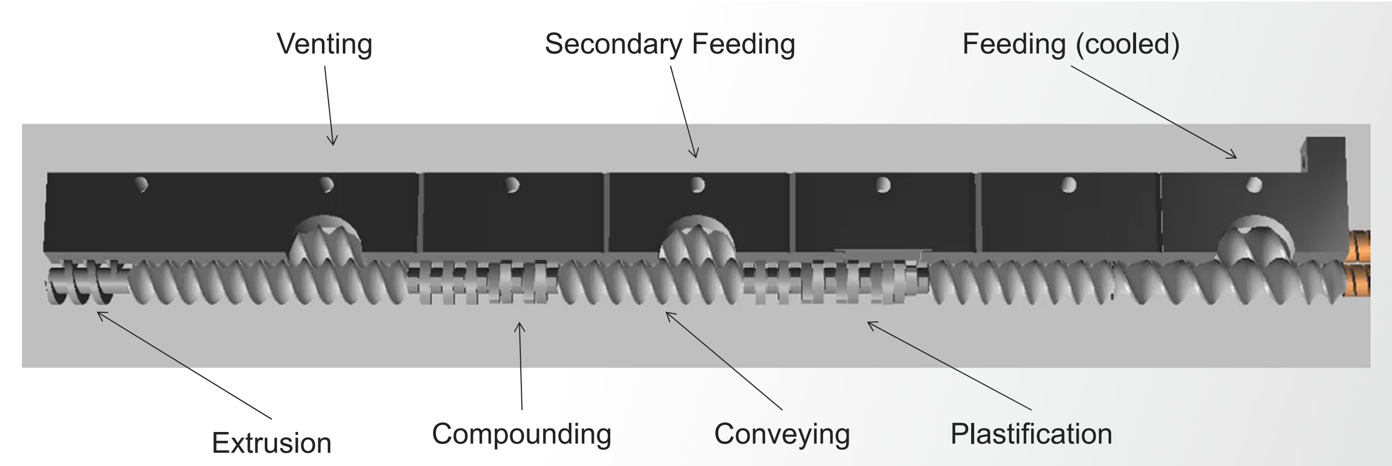


**Figure 1.** Schematic cross-section of a twin-screw barrel with its processing zones

This allows precise control over the conditions under which the reaction occurs. Once steady-state is reached, the reaction product is constantly formed and can be collected at the extruder´s exit, enabling continuous production.

## Examples of organic reactions in a twin-screw extruder[1]

Numerous chemical reactions have been successfully transformed into continuous reactive extrusion processes.

### Polymerization

Polycondensation reactions, such as the synthesis of polyesters and polyamides or radical polymerization, which are often used to make polymers like polystyrene or polyethylene, are commonly carried out in twin-screw extruders. The extruder's screw design and precise temperature control ensures the reaction progresses without unwanted side reactions.[2,3,4,5]

### Esterification and transesterification

These reactions are fundamental in the synthesis of biodiesel and specialty esters.[6,7]

### Oxidation and reduction reactions

Crucial in the production of fine chemicals and pharmaceuticals, these reactions require controlled temperatures and oxygen exposure that can be optimized in the extruder´s multiple zones.[8,9]

### Carbon-carbon bond forming reactions

Cross coupling reactions, like Suzuki or Heck reactions, are challenging to perform in a batch reactor. In twin-screw extruders, these reactions can be efficiently performed with continuous mixing, improving yields and selectivity.[10,11]

## Benefits and challenges of organic synthesis in twin-screw extruders

One of the primary advantages of using twin-screw extruders for organic synthesis is the ability to shift from batch to continuous processing. In batch reactors, organic synthesis often involves multiple steps for reactions, long processing times, solvents, and labor-intensive transfers between stages. In contrast, twin-screw extruders allows for continuous feeding of reactants and production of products. This leads to increased efficiency, scalability and environmental friendliness.

Monitoring and controlling reactions in a continuous system can also be challenging. Unlike batch reactors, where samples can be taken at different time points to monitor the progress of the reaction, twin-screw extruders require sophisticated in-line monitoring tools, such as an NIR or Raman spectrometer, to ensure product quality and consistency.

Some organic reagents or reaction intermediates can be corrosive or reactive towards the material used in the extruder, such as stainless steel. Special attention must be given to material selection, especially when handling reactive or corrosive chemicals.

## Case Study – Knoevenagel reaction

A Knoevenagel reaction between vanillin and barbituric acid was chosen as an example of reactive extrusion on the Process 11 twin-screw extruder. This example has become an archetypal study for ball milling reactions and has been published in a number of articles. A research group led by Deborah Crawford[12] has successfully transferred this example from the ball mill to the twin-screw reactor. A premix of vanillin and barbituric acid was dosed into the Process 11 twin-screw extruder using a gravimetric MiniTwin feeder. The premix had a 1:1 mol ratio and the feed rate into the extruder was set to 0.5 kg/h. The extruder, equipped with a screw setup using two kneading zones, was heated to 160°C over its entire length and the screw speed was kept constant at 50 rpm.


**Figure 2.** Process 11 twin-screw extruder equipped with a granulator kit

The end of the extruder was designed as a granulator for this test (see Figure 2) without a die attached. This pressure-less and open outlet enabled the material flow out of the extruder as a powder. The two starting materials are present as white powders, and the bright yellow color of the product at the extruder outlet indicates that a reaction has taken place.

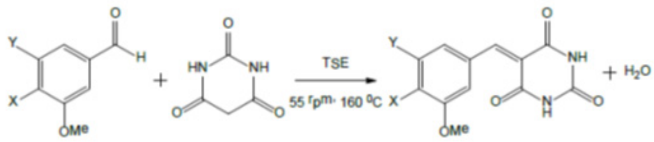


**Figure 3.** Knoevenagel reaction equation

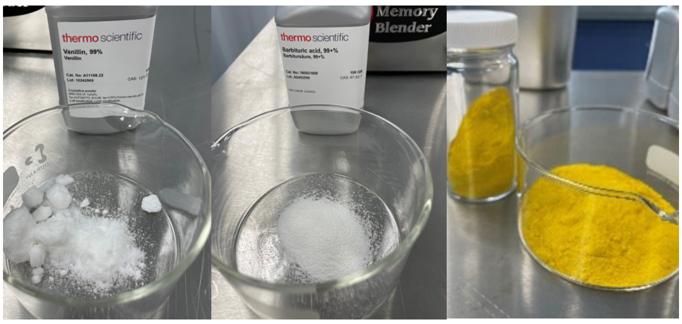


**Figure 4.** The white educts lead to a bright yellow product after reaction

The result of the reaction was analyzed using two different methods. Firstly, the starting substances were compared with the product using a Thermo Scientific™ MarqMetrix™ All-In-One Process Raman Analyzer. Secondly, we used a Thermo Scientific™ ARL™ EQUINOX 100 X-ray Diffractometer to assess the materials.

## RAMAN

The product and the two educts, vanillin and barbituric acid, were measured with the Thermo Scientific™ MarqMetrix™ All-In-One Process Raman Analyzer.

A before-and-after comparison of Raman patterns shows that the peaks from the educts that were present prior to the reaction are no longer present in the post-reaction Raman pattern, while new peaks from the product have become visible.


**Figure 5.** The Thermo Scientific MarqMetrix All-In-One Process Raman Analyzer

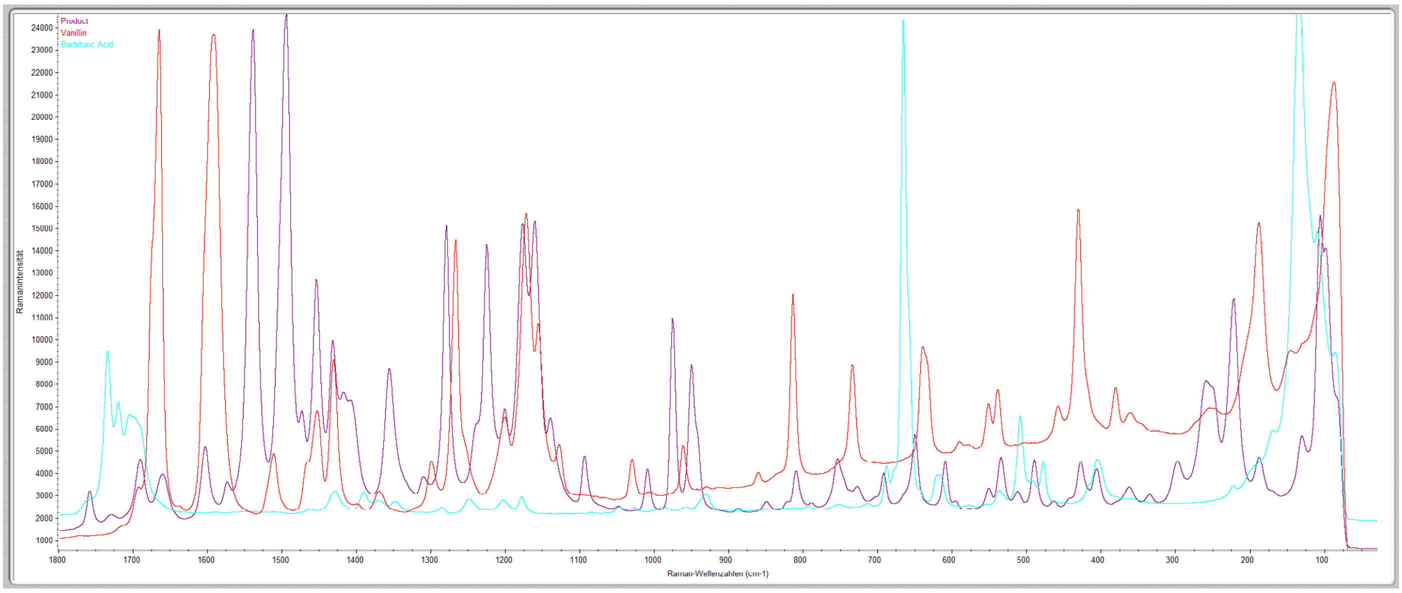


**Figure 6.** Raman pattern of the product (violet) and starting materials Vanillin (green) and Barbituric Acid (red)

## XRD

Comparing an XRD pattern of the product with peak positions of the educts shows that both educts disappeared. The pattern of the product resembles a new phase with reflections at low angles (d1=13.5 Å, d2=9.3 Å) which are typical for COF (covalent organic framework) structures. The exact type of the COF structure could not be identified.

## Experimental

X-Ray powder diffraction measurements (carried out using the Thermo Scientific™ ARL™ X'TRA Companion) were performed in Bragg-Brentano geometry using Cu Kα radiation (Ni filter). Powder samples (vanillin, barbituric acid, and the yellow product) were prepared in top-loading zero background cups and measured for 10 minutes. Phases analysis was performed using Profex13 and structure files from COD.


**Figure 7.** The Thermo Scientific™ ARL™ Equinox™ 100 X-Ray Diffractometer used in the experiment

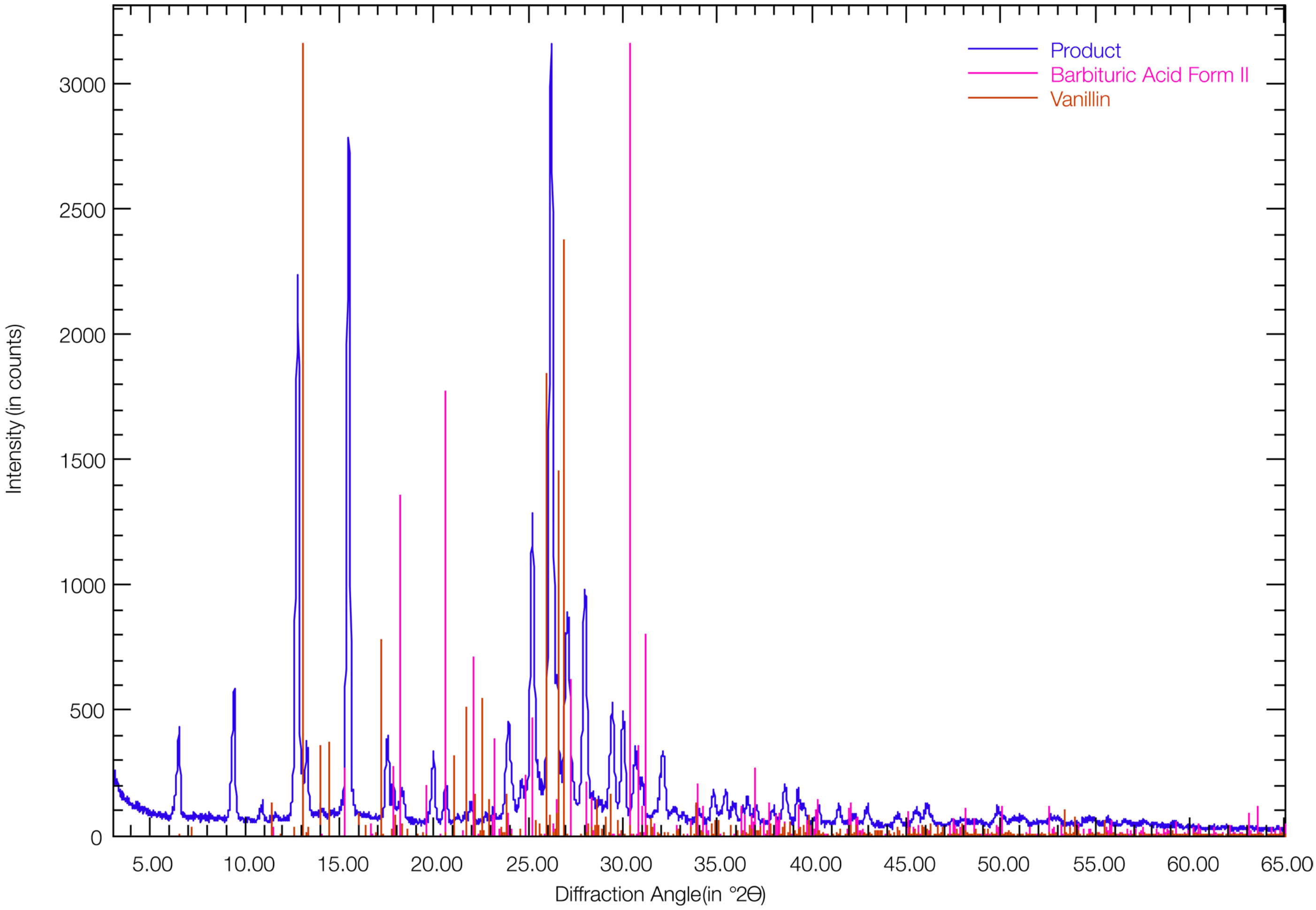


**Figure 8.** XRD pattern (10 minutes) of the product. Indicator lines (pink: Barbituric Acid Form II; brown: Vanillin) are added

## Conclusion

The use of Thermo Scientific twin-screw extruders for organic synthesis represents a revolutionary advance in chemical processing, offering significant benefits in terms of efficiency, scalability and sustainability. By integrating chemical reactions and material processing in a continuous system, twin-screw extruders open new possibilities for the synthesis of complex organic molecules, from pharmaceuticals and fine chemicals to specialty polymers.

While challenges such as residence time limitations and thermal sensitivity remain, ongoing research and optimization in screw design, monitoring technologies and material selection continue to expand the capabilities of twin-screw extruders. As industries increasingly adopt continuous manufacturing and green chemistry practices, twin-screw extrusion is poised to play a critical role in the future of organic synthesis, driving innovation in chemical processing across a wide range of sectors.

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