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Online Monitoring and Control of Continuous Mechanosynthesis by UV-Vis Spectrophotometry

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Abstract : Traditional mechanosynthesis has been performed by either ball milling or manual grinding. However, neither of these techniques allow the easy application of process control. The temperature may change unpredictably due to friction in the process. Hence the amount of energy transferred to the reactants is intrinsically non-uniform. Recently, it has been shown that the use of Twin-Screw extrusion (TSE) can overcome these limitations. Additionally, TSE enables a platform for continuous synthesis or manufacturing as it is an open-ended process, with feedstocks at one end and product at the other. Several materials including metal-organic frameworks (MOFs), co-crystals and small organic molecules have been produced mechanochemically using TSE. The described advantages of TSE are offset by drawbacks such as increased process complexity (a large number of process parameters) and variation in feedstock flow impacting on product quality. To handle the above-mentioned drawbacks, this study utilizes UV-Vis spectrophotometry (InSpectroX, ColVisTec) as an online tool to gain real-time information about the quality of the product. Additionally, this is combined with real-time process information in an Advanced Process Control system (PharmaMV, Perceptive Engineering) allowing full supervision and control of the TSE process. Further, by characterizing the dynamic behavior of the TSE, a model predictive controller (MPC) can be employed to ensure the process remains under control when perturbed by external disturbances. Two reactions were studied; a Knoevenagel condensation reaction of barbituric acid and vanillin and, the direct amidation of hydroquinone by ammonium acetate to form N-Acetyl-para-aminophenol (APAP) commonly known as paracetamol. Both reactions could be carried out continuously using TSE, nuclear magnetic resonance (NMR) spectroscopy was used to confirm the percentage conversion of starting materials to product. This information was used to construct partial least squares (PLS) calibration models within the PharmaMV development system, which relates the percent conversion to product to the acquired UV-Vis spectrum. Once this was complete, the model was deployed within the PharmaMV Real-Time System to carry out automated optimization experiments to maximize the percentage conversion based on a set of process parameters in a design of experiments (DoE) style methodology. With the optimum set of process parameters established, a series of PRBS process response tests (i.e. Pseudo-Random Binary Sequences) around the optimum were conducted. The resultant dataset was used to build a statistical model and associated MPC. The controller maximizes product quality whilst ensuring the process remains at the optimum even as disturbances such as raw material variability are introduced into the system. To summarize, a combination of online spectral monitoring and advanced process control was used to develop a robust system for optimization and control of two TSE based mechanosynthetic processes.

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