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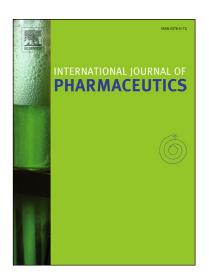
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### ACCEPTED MANUSCRIPT

# Control of Three Different Continuous Pharmaceutical Manufacturing Processes: Use of Soft Sensors

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#### **Abstract**

One major advantage of continuous pharmaceutical manufacturing over traditional batch manufacturing is the possibility of enhanced in-process control, reducing out-of-specification and waste material by appropriate discharge strategies. The decision on material discharge can be based on the measurement of active pharmaceutical ingredient (API) concentration at specific locations in the production line via process analytic technology (PAT), e.g. near-infrared (NIR) spectrometers. The implementation of the PAT instruments is associated with monetary investment and the long term operation requires techniques avoiding sensor drifts. Therefore, our paper proposes a soft sensor approach for predicting the API concentration from the feeder data. In addition, this information can be used to detect sensor drift, or serve as a replacement/supplement of specific PAT equipment. The paper presents the experimental determination of the residence time distribution of selected unit operations in three different continuous processing lines (hot melt extrusion, direct compaction, wet granulation). The mathematical models describing the soft sensor are developed and parameterized. Finally, the suggested soft sensor approach is validated on the three mentioned, different continuous processing lines, demonstrating its versatility.

Key words: Continuous manufacturing, soft sensor, process analytical technologies, near infrared spectroscopy, residence time distribution, control strategy

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