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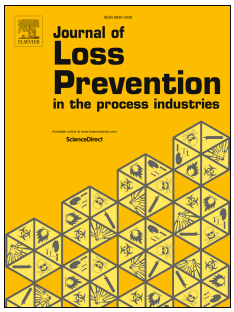

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Resilience and risk analysis of fault-tolerant process control design in continuous pharmaceutical manufacturing

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Abstract:

The shift from batch to continuous manufacturing, which is occurring in the pharmaceutical manufacturing industry has implications on process safety and product quality. It is now understood that fault-tolerant process control of critical process parameters (CPPs) and critical quality attributes (CQAs) is of paramount importance to the realization of safe operations and quality products. In this study, a systematic framework for fault-tolerant process control system design, analysis, and evaluation of pharmaceutical continuous oral solid dosage manufacturing is proposed. The framework encompasses system identification, controller design and analysis (controllability, stability, resilience, *etc*.), hierarchical three-level control structures (model predictive control, state estimation, data reconciliation, *etc*.), risk mapping, assessment and planning (Risk MAP) strategies, and control performance evaluation. The key idea of the proposed framework is to identify the potential risks associated with the control system design itself, the material property variations, and other process uncertainties, under which the control strategies must be evaluated. The framework is applied to a continuous direct compaction process, specifically the feeding-blending subsystem, wherein the major source of variance in the process operation and product quality arises. It is demonstrated, using simulations and experimentally, that the process operation failures and product quality variations in the feeding-