Dissolution Behavior of Extended Release Tablets Manufactured Using Continuous Mixing and Direct Compression
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Purpose
The benefits of continuous pharmaceutical manufacturing of oral solid dosage forms (OSD) have been well established. Manufacturing of extended release (ER) matrix tablets can be a challenging task in both batch and continuous processing. The performance of tablets based on this formulation type relies not only on assuring the right drug content and proper distribution of the drug substance but also on the ability to provide extended and robust drug release in vivo. In this study the viability of integrated continuous mixing and compression processes for manufacturing of ER tablets was investigated in terms of dissolution behavior. The continuous process was provoked by a challenging formulation design, including variable powder characteristics and compositions of high and low amount of the drug substance (ibuprofen). Additionally a relatively low amount (32%, w/w) of the ER matrix former (HPMC) was used to challenge the system. At these low amounts of matrix former there is a known risk that formulations may show poor release robustness. The present work aimed to evaluate the combined effect of processing variables and compositional variables on the release robustness.

Methods
Two different grades of hydroxypropyl methylcellulose (HPMC) were used as matrix formers, i.e. standard granulation grade CR and direct compression grade DC2.
Two different particle sizes of poorly soluble and poorly flowing model drug substance (ibuprofen) were used. Mannitol was added as a soluble filler and sodium stearyl fumarate as a lubricant. Design of experiments was a full factorial with 19 runs. The continuous mixing and direct compression manufacturing set-up was used in the study. The feeding, mixing, and compressing parts are all integrated into a complete continuous tablet manufacturing line. Raw materials were fed from the feeders directly into the continuous mixer (Modulomix, Hosokawa Micron). After mixing, the powder mixture was guided into the tablet press. Tablet weight was 150 mg.

Results
Robust and sustained ibuprofen release was obtained faster when HPMC CR was used (Figure 1A: N2, N5, N10). However, robust release was also obtained when using HPMC DC2 at high ibuprofen content, even though it took slightly longer time to reach the steady state of the process. Tablets collected at early processing times released ibuprofen markedly faster than tablets collected at later time points. This effect was more pronounced when HPMC DC2 was used (Figure 1B). The tendency for faster release from tablets containing DC2 was most probably related to a less effective ability to form a homogeneous gel layer at the tablet/dissolution media interface. For the low dose compositions this effect was aggravated by the relatively high amount of easily soluble mannitol and hence “burst” release was observed. The results also showed that by using continuous processing it is possible to manufacture and achieve robust performance of many compositions that would not be possible with traditional batch processing.

Conclusion
The present work shows significant benefit of continuous mixing followed by direct compression compared to traditional batch processes: It enables manufacturing of extended release tablets from poorly flowing materials with a high potential for robust release performance.

Figure 1. A. Typical ibuprofen release profiles of individual ER tablets. B. The affect of time on ibuprofen release when using DC2 (run N11).