A Mechanistic Approach for Analyzing the Pellet Coat Damage Caused by Compaction in a Rotary Tablet Press
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Purpose
Development of tablets containing coated pellets or commonly referred to as multiple unit pellet system (MUPS) tablets, has seen growing interest in the pharmaceutical industry. However, the compaction force exerted on the coated pellets could damage their functional polymer coat and often lead to catastrophic failure of their sustained drug release function. As many studies on pellet coat damage caused by compaction were conducted using a single punch tablet press, studies in a rotary press would be closer to actual production. There are considerable differences in force application mechanisms between single and rotary tableting processes and the latter is commonly employed in commercial tablet production. This study employed a mechanistic approach to understand the pellet coat damage seen during compaction of coated pellets in a rotary tablet press.

Methods
Sugar pellets were layer-coated with metformin and subsequently overcoated with ethylcellulose for sustained release. Coated pellets were then characterized for their size and size distribution, shape and tensile strength. The pellets and co-spray dried micronized lactose with mannitol were then blended and compacted into MUPS tablets at various pellet volume fractions using a rotary tablet press. Three levels of compaction pressures (20, 30 and 40 MPa) and dwell times (10, 25 and 40 ms) were chosen to evaluate the effect of process parameters on the properties of MUPS tablets and extent of pellet coat damage. The resultant MUPS tablets were examined for their overall tablet thickness, tensile strength and drug release behavior. The extent of pellet coat damage was measured by comparing drug release rates of the coated pellets before compaction and the resultant MUPS tablets. Coated pellets were carefully excavated from various locations at the surface, interior and periphery area of the MUPS tablets for examination of their coat damage individually by dissolution testing and scanning electron microscope (SEM) image examination.

Results
For a MUPS tablet formulation which consolidated by plastic deformation, an extended dwell time improved the mechanical strength of the resultant tablets without accelerating the drug release rate. However, increase in compaction pressure led to faster drug release rate, suggesting greater pellet coat damage. From the SEM photomicrographs, it was observed that when compacted using pressure higher than the pellet tensile strength (14.7 MPa), the ethylcellulose coat was ruptured, whereas the coat only deformed when the compaction pressure was slightly lower than 14.7 MPa. The position of coated pellets in a MUPS tablet also affected the extent of coat damage, likely due to the unequal pressure distribution on the materials in the die during compaction. The formation of a continuous network of cushioning agents was necessary to prevent the direct contact between pellets and punch/die-wall surfaces as well as inter-pellet contact. The critical pellet volume fraction to minimize the pellet coat damage was 0.374 in this study.

Conclusion
For compaction of sustained release pellets coated with a brittle polymer using a rotary tablet press, the formation of a continuous network of cushioning agents during compaction and employment of compaction pressure lower than the pellet tensile strength were found to be essential to ensure pellet coat integrity. The tensile strength of the MUPS tablets could be enhanced without exacerbating pellet coat damage by extending the dwell time during compaction in the rotary tablet press. The mechanistic understanding of pellet coat damage caused by compaction in a rotary tablet press would contribute to a more rational design of the formulation and process strategies for commercial manufacturing of MUPS tablets.