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Short communication

The impact of the active pharmaceutical ingredient's particle size distribution on the product quality of third-generation cephalosporin film coated tablets

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Introduction

Cephalosporins are an important class of β-lactam antibiotics widely used to treat bacterial infections.

To ensure consistent manufacturing performance and drug product quality, a complete understanding of Critical Material Attributes (CMAs) and their influence on manufacturing processability is essential. Among these attributes, particle size distribution (PSD) is recognized as a key factor affecting granulation behavior, powder flow, compressibility and content uniformity (Fichtner et al., 2005; Yohannes et al., 2015).

The objective of this study was to evaluate the effect of API's particle size distribution variability on the drug product quality of third-generation cephalosporin film-coated tablets. Hence, APIs obtained from three suppliers have been considered to evaluate whether supplier-related differences in API particle size distributions could affect the critical quality attributes of the final drug product.

Materials and methods

The BCS class IV API was obtained from two different alternative suppliers, designated as supplier "Q" and supplier A", and from the previously validated supplier "O". The quantitative and qualitative composition of the drug formulations remained unchanged when API from each supplier was used. The same manufacturing process, equipment and established process parameters were also applied throughout the study.

The Certificates of Analysis (CoAs) of the three suppliers were compared regarding differences in API particle size distribution. Moreover, prospective process validation studies were performed using three consecutive validation batches manufactured with API from each supplier.

The PSD of the final blends was determined by analytical sieving using a Retsch AS 200 Control sieve shaker, according to the Ph. Eur. Method 2.9.38. A representative sample of approximately 50 g was analyzed for each batch, and the cumulative PSD of the final blends was evaluated.

Results and discussion

The comparative CoAs assessment confirmed differences in API - PSDs among the three API suppliers. Thus, supplier "O" provides particles

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characterized by D50 and D90 values of 105 µm and 147 µm, whereas suppliers "Q" and "A" demonstrate particle size distribution with D50 values of 107.9 µm and 119 µm and D90 values of 173.8 µm and 187 µm, respectively.

The conducted validation studies showed that the differences observed at the API level have been partially reflected in the PSD of the final blends. The final blend manufactured using API from supplier "Q" contained the highest average proportion of particles below 80 µm (37.3%), followed by supplier "A" (31.5%), whereas the final blend prepared with already validated supplier "O" contained only 9.3% of particles below 80 µm. Similarly, the proportion of particles below 150 µm was 59.2% for "Q", 52.2% for "A" and 51.0% for "O". However, the PSD profiles became increasingly similar at larger particle size fractions, with more than 89% of particles below 500 µm and more than 96% below 630 µm for all evaluated suppliers, indicating that the wet granulation process notably modified the API's original particle size characteristics.

The influence of the PSD on the blend uniformity was monitored by analyzing the assay of the final blends. All validation batches complied with the predefined acceptance criterion of 90.0–110.0%. For "Q" batches, average assay values ranged from 97.4% to 99.9% with RSDs of between 1.9% and 3.8%. The "A" batches showed average assay values between 99.0% and 102.3% with RSD values ranging from 0.9% to 1.9%, while, the "O" batches showed average values between 97.6% and 102.8% with RSD values between 1.5% and 2.2%.

Compression performance was comparable for all evaluated formulations. The average tablet core mass remained close to the target value of 750 mg for all validation batches, with average values ranging from 749.7 mg for the "A" batches to 750.6 and 750.7 mg for the "Q" and "O" batches. These results show stable filling and uniform granule flow properties regardless of the API supplier.

Tablet hardness values were likewise comparable, ranging from 15.6 to 20.2 kP. All tablet cores remained within the predefined specification limits. The results showed that the differences in API-PSD did not adversely affect granule compressibility or tablet mechanical strength.

All batches demonstrated rapid tablet core disintegration. The "O" batches showed the fastest disintegration with a maximum disintegration time of 1 minute and 32 seconds. "Q" batches had a maximum disintegration time of 2 minutes and 23 seconds while "A" batches had a maximum disintegration time of 3 minutes and 50 seconds. The observed differences are well below the acceptance criterion of 15 minutes for disintegration time.

The assay results obtained from tablet cores were likewise comparable. Supplier "O" showed average assay values from 100.58% with RSD values below 0.9%, while the suppliers "Q" and "A" showed average assay values of 98.6 % and 99.6%, respectively, with RSD values below 1.5 and 1.9%. No evidence of assay variability was observed Finally, the results from dissolution testing on film-coated tablets confirmed that differences in API particle size did not have a significant effect on dissolution behavior.

Conclusion

The results of this study confirmed that supplier-related differences in API particle size distribution did not adversely affect the manufacturing performance or final drug product quality of third-generation cephalosporin film-coated tablets. Although some variability in API-PSD was observed among the suppliers, all validation batches met the predefined acceptance for blend uniformity, tablet mass, hardness, disintegration, assay and dissolution. Additionally, introducing alternative API suppliers did not require any modification to the established critical process parameters. The results confirm that the manufacturing process is sufficiently robust to accommodate supplier-related PSD variability while consistently producing cephalosporin film-coated tablets that meet the required quality standards.

References

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