Macedonian Pharmaceutical Bulletin, 72 (Suppl 1) 141 - 142 (2026)
Online ISSN: 1857-8969
DOI: 10.33320/maced.pharm.bull.2026.72.03.068
Short communication

Influence of diluent type and grade on blend properties and capsule filling performance in high dosage formulations

Isidora Nuneva*, Frosina Jovanovikj, Packa Antovska, Ana Atanasova

Research and development, Alkaloid AD, Aleksandar Makedonski 12,1000, Skopje, Republic of North Macedonia

Introduction

The selection of excipients is a critical aspect in the development of solid oral dosage forms, particularly in hard gelatin capsule formulations containing a high percentage of active pharmaceutical ingredient (API). In such formulations, diluents play an important role in ensuring adequate powder flow, blend uniformity, manufacturability, and consistent drug product performance (Shah et al., 2008; Freeman et al., 2011). Among commonly used diluents, microcrystalline cellulose (MCC) and lactose, are widely employed due to their distinct physicochemical and functional properties. Different grades of these diluents exhibit variations in particle size distribution, surface morphology, density, compressibility, and moisture content, which can significantly influence both the manufacturing process and the critical quality attributes (CQAs) of the final drug product (Aulton et al., 2018). In high-dose capsule formulations, where the proportion of excipients is limited, these differences become even more pronounced and can determine the success or failure of the formulation.

The present study aims to compare different grades of MCC and lactose in high dosage API hard gelatin capsule formulation and to evaluate their influence on blend properties and capsule filling performance.

Materials and methods

Eight experimental formulations (Exp. 1–8) were prepared, differing in the type and grade of diluent used. Exp. 1–6 contained different grades of microcrystalline cellulose (MCC 101, 102, 103, 105, 113, and 301, respectively), while Exp. 7 and 8 contained lactose monohydrate (grades 200 and 100, respectively).

In addition, Exp. 6–8 included a small amount of sodium stearyl fumarate (<0.5%) as a lubricant.

The blends were prepared by dry-mixing the API and diluent in a plough-share mixer for predefined time. The obtained blends were filled into hard gelatin capsules using an automatic capsule filling machine.

All experimental formulations were evaluated by determination of flow rate and angle of repose according to European Pharmacopoeia Chapter 2.9.36, and bulk and tapped density according to Chapter 2.9.34, with subsequent calculation of Carr index and Hausner ratio of the mixture. The influence of diluent type and diluent grade on capsule filling process was assessed through evaluation of blend characteristics, process performance, and capsule filling consistency.

*inuneva@alkaloid.com.mk

Results and discussion

Across the observed formulations, a clear relationship emerged between blend physical properties and capsule filling performance. In addition to excipient characteristics, the API itself contributed significantly to the overall behavior of the blends, as it is characterized by relatively high density and very good intrinsic flowability. This API behavior influenced the bulk properties of the mixtures, often compensating partially for less optimal excipient characteristics, while still requiring careful balance with the other formulation components.

Formulations containing diluents with balanced particle size distribution and moderate density (Exp. 1–6) exhibited optimal flowability and compressibility, reflected by low angles of repose, acceptable Carr index, and stable Hausner ratios. When it comes to diluents associated with higher bulk density and fine, sharp-edged particles (Exp. 7) resulted in poorer flow characteristics, higher compressibility indexes, and greater variability in flow rate. In contrast, when it comes to high-density system with optimal particle morphology and size (Exp. 8) good flow properties were observed, highlighting that particle surface and shape alongside density are equally critical determinants of powder behavior.

From a process performance perspective, achieving an optimal flow profile is critical for consistent capsule filling. The results show that neither very high nor very poor flow ensures robust processing; instead, a balanced flow behavior is required.

Although several blends initially appeared acceptable based on flow properties alone, this was not sufficient to guarantee consistent processing.

This was most evident in the case of Exp. 1, 3, and 5, where fill weight variability indicated unstable and inconsistent dosing due to difference in powder packing and transfer behavior under dynamic conditions.

A contrast was observed for Exp. 4 and 8, which exhibited the best overall process performance due to the moderate flow rate and compressibility resulting in consistent capsule fill weight. This confirms that slightly cohesive but still free-flowing blends are often preferable in capsule manufacturing.

Furthermore, particle adhesion and cohesion played a significant role, evident in Exp. 1,2,7 where, the particle size and morphology likely promoted sticking of the blend to the dosing units, negatively affecting process performance.

Conclusion

This study demonstrated that optimal capsule filling performance depends on achieving a balance between bulk properties such as flow, packing behavior, particle interactions as well as the API properties. The high density and good intrinsic flowability of the API can enhance overall blend performance, but only when complemented by appropriately selected excipients that ensure balanced flow, minimal segregation, and consistent dosing under manufacturing conditions.

Overall, these findings underline the importance of a systematic approach to excipient selection, where both API and excipient material attributes are carefully considered to achieve optimal powder properties, which are essential for obtaining consistent, high-quality capsules.

References

Aulton, M.E. et al., 2018. Aulton's Pharmaceutics: The Design and Manufacture of Medicines, fifth ed. Elsevier, London.

European Pharmacopoeia Commission, 2025. European Pharmacopoeia, 12th ed. Council of Europe, Strasbourg.

Freeman, T. et al., 2011. Capsule filling performance of powdered formulations in relation to flow characteristics. Royal Society of Chemistry, pp. 131–144. https://doi.org/10.1039/9781849735148-00131

Shah, R.B. et al., 2008. Comparative evaluation of flow for pharmaceutical powders and granules. AAPS PharmSciTech 9, 250–258. https://doi.org/10.1208/s12249-008-9046-8