Macedonian pharmaceutical bulletin, 69 (Suppl 1) 139 - 140 (2023)
Online ISSN 1857 - 8969
DOI: 10.33320/maced.pharm.bull.2023.69.03.068
Short communication

From co-processing by melt granulation towards direct compression of high ibuprofen loaded formulations

Ivana Aleksić*, Slobodanka Ćirin-Varađan, Teodora Glišić, Nađa Petrović, Jelena Đuriš, Jelena Parojčić

Department of Pharmaceutical Technology and Cosmetology, University of Belgrade – Faculty of Pharmacy, Vojvode Stepe 450, 11221, Belgrade, Serbia

Introduction

Direct compression, as the simplest and therefore preferable method of tableting, is often hindered by poor flow and compaction properties of the active pharmaceutical ingredient (API). Tableting by direct compression is particularly challenging when high API loading is required. The use of co-processed excipients can result in a robust directly compressible formulation, while melt granulation has emerged as an environmentally friendly co-processing method that can result in highly functional co-processed excipients (Ćirin-Varađan et al, 2022).

The aim of the present study was to investigate the suitability of lactose co-processed with glyceryl palmitostearate for the preparation of a directly compressible formulation of ibuprofen, a challenging high-dose API. The influence of initial particle size of glyceryl palmitostearate, ibuprofen content and compression parameters on compaction behavior of tableting mixtures was investigated.

Materials and methods

Glyceryl palmitostearate (Precirol® ATO 5 Gattefossé S.A.S, France) was used as a meltable binder and lactose monohydrate (Carlo Erba Reagents, Italy) as a filler. Ibuprofen (Fagron, Netherlands) was selected as the model drug.

Co-processing was performed in a Mycrolab fluid bed processor (OYSTAR Hüttlin, Germany) using the in situ melt granulation. Lactose (85%) was granulated using Precirol® particles (15%) with a sieve fraction of 125-180 μm (≈ 150 μm) or 600-710 μm (≈ 655 μm) at an inlet air flow rate of 30 m^3/h. The temperature of the product during agglomeration was 65 °C.

The bulk density and the tapped density (1250 taps) of the mixtures of co-processed excipients and ibuprofen (30 to 70%) were determined using the STAV 2003 tap density tester (J. Engelsmann AG, Germany). Carr index values were then calculated.

Dynamic compaction analysis was performed on an instrumented single punch tablet press (GTP D-Series, Gamlen Tableting Ltd, UK) with 6 mm flat punches. From the obtained force-displacement curves, the detachment stress (DS), the ejection stress (ES) and the net work of compression (NW) were calculated. Elastic recovery was calculated using the tablet thickness in-die and after 24 hours. Tensile strength (TS) was calculated from tablet crushing force values obtained with the Erweka TBH 125D tablet hardness tester (Erweka GmbH, Germany).

Two level full factorial design was used to investigate the effect of binder particle size, ibuprofen content, compression load (CL), and compression speed (CS) on compaction properties (Table 1).

Table 1. The investigated variables.

Independent variable	Lower level	Higher level
Binder PS (μm)	150	655
Ibuprofen content (%)	30	70
Compression load (kg)	200	500
Compression speed (mm/min)	60	120

*ivana.aleksic@pharmacy.bg.ac.rs

Results and discussion

Higher ibuprofen contents in the mixtures with co-processed excipients resulted in higher Carr index values (Fig. 1). However, even at very high ibuprofen load (70%) fair to passable flow was observed. Regardless of the ibuprofen content, considerably better flow properties were observed with the co-processed excipient P655, which can be attributed to the larger and more spherical particles of this excipient.

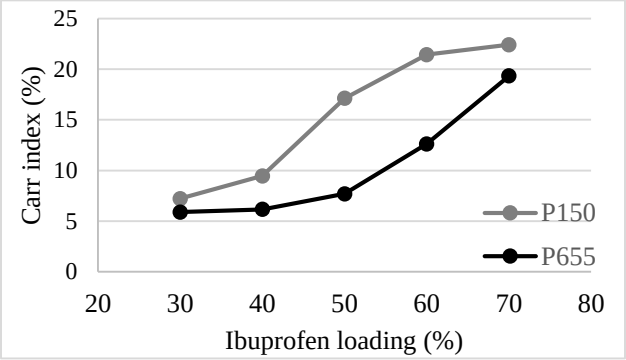

Fig. 1. Flowability of co-processed excipients at different ibuprofen loadings.

Ibuprofen is known for its poor compactibility, but interestingly, compression of its mixtures with the co-processed excipients studied resulted in tensile strength values greater than 1 MPa at ibuprofen loading up to 70%. Binder particle size, ibuprofen content, compression load and the interaction of these variables showed a statistically significant effect on tensile strength values. In general, higher ibuprofen content led to lower TS in the case of both excipients. At higher compression load, tablets prepared with 70% ibuprofen showed TS > 1MPa in the case of both excipients, but tablets with co-processed excipient P155 showed higher TS.

NW was significantly affected by all variables studied and their two-factor interactions. NW ranged from 0.4 to 0.7 J, with higher compression load and faster compression contributing to higher NW. The influence of ibuprofen content was more pronounced in the case of excipient P155, with higher NW observed for tablet mixtures with lower ibuprofen content.

In addition to poor flowability and poor compactibility, ibuprofen is characterized by a high tendency to stick to punch surfaces during tableting. Therefore, the influence of the investigated variables on detachment and ejection stress as indicators of adhesion problems was investigated. The obtained results revealed low values of these parameters (DS < 1.7 MPa, ES < 1.3 MPa). It was found that the ibuprofen content, the compaction parameters and the interactions between the investigated factors have a significant influence on DS and ES. In general, higher compression load and speed, as well as higher ibuprofen content, led to higher values of these parameters.

The values obtained for elastic recovery ranged from 11 to 28% and were mainly influenced by the compression load and speed. A higher ER was observed at higher values of the compression parameters. The interaction between ibuprofen content and compression speed also had a significant effect on ER, with more pronounced influence of compression speed at higher ibuprofen content.

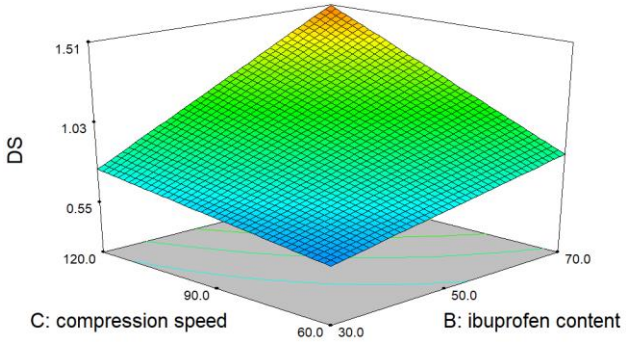

Fig. 2. The influence of CS and ibuprofen content on DS (CL 500 kg, binder PS 150 µm).

Conclusion

The novel lipid-based co-processed excipients showed significant potential for direct compression of formulations containing ibuprofen, a highly challenging API. Apart from good flowability and acceptable mechanical properties at high ibuprofen content, these excipients could be a suitable choice to overcome the adhesion problems typical for ibuprofen.

Acknowledgements: This research was funded by the Ministry of Science, Technological Development and Innovation, Republic of Serbia through Grant Agreement with University of Belgrade-Faculty of Pharmacy No:451-03-47/2023-01/ 200161.

References

Ćirin-Varađan, S., Đuriš, J., Mirković, M., Ivanović, M., Parojčić, J., Aleksić, I., 2022. Comparative evaluation of mechanical properties of lactose-based excipients co-processed with lipophilic glycerides as meltable binders. J. Drug Deliv. Sci. Technol. 67: 102981. https://doi.org/10.1016/j.jddst.2021.102981