

## APPLICATION OF SOLVENTLESS GRANULATION METHOD FOR DEVELOPMENT OF NOVEL CO-PROCESSED EXCIPIENTS

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The lack of directly compressible excipients and the introduction of the high-speed manufacturing machines have further increased the interest in the development of co-processed excipients. In the present study, *in situ* fluidized bed melt granulation (FBMG) as an environmental friendly and cost-effective method, was applied to co-process the most common filler, lactose monohydrate, with lipid excipients glyceryl dibehenate (Compritol® 888 ATO) or glyceryl palmitostearate (Precirol® ATO 5) known for their antiadhesive, lubricant and flowing aid properties (1, 2). The goal of this study was to develop the lipid-based co-processed excipients and to investigate their flowability and tableting properties using a solvent-free and eco-friendly, FBMG method.

The flow properties of the tested samples (the single-component excipients, their physical mixtures, lactose (85% (w/w)) co-processed with Precirol® or Compritol® (15% (w/w)), and commercially available lactose-based co-processed excipients (Retalac® and Ludipress®) were evaluated by Carr index and Hausner ratio. Dynamic compaction analysis of the investigated excipients was performed on a single punch instrumented tablet press (GTP D series, Gamlen Tableting Ltd, UK).

Comparable or even better flowability of co-processed excipients obtained via *in situ* FBMG, in comparison to commercial co-processed excipients indicate their suitability for direct compression. Co-processed excipients with Precirol® and Compritol®, as well as the corresponding physical mixtures, showed two to almost three times lower values of total work of compression than those obtained for commercial lactose-based excipients. Furthermore, co-processed excipients prepared with lipid excipients showed up to 50-fold lower detachment work and up to 20-fold lower ejection work than those obtained for Retalac® and Ludipress®. Superior antiadhesive and lubricating properties of the excipients prepared by *in situ* FBMG can be attributed to the properties of lipid excipients. Both commercially available and the investigated co-processed excipients, prepared with lipid excipients, showed relatively high tensile strength values (>1.7 MPa).

The results presented in this study indicate that *in situ* fluidized bed melt granulation can be used as suitable co-processing technique, as a time and energy less consuming method in comparison with commonly applied techniques such as spray drying and wet granulation. According to the results obtained, by co-processing lactose with selected lipid excipients excellent flowability, as well as improved tableting properties can be achieved. Novel co-processed excipients were even found to be highly superior regarding their antiadhesive and lubricating properties in comparison to commercial lactose-based co-processed excipients.

### References

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# PRIMENA METODE GRANULACIJE BEZ UPOTREBE RASTVARAČA U RAZVOJU NOVIH KOPROCESOVANIH EKSCIPIJENASA

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Nedostatak direktno kompresibilnih ekscipijenasa i uvođenje proizvodne opreme velike brzine rada dodatno su povećali interesovanje za razvoj koprocesovanih ekscipijenasa. U ovoj studiji, *in situ* granulacija topljenjem u uređaju tipa fluidizirajućeg sistema (eng. *fluidized bed melt granulation, FBMG*), kao ekološki prihvatljiva i ekonomična metoda, primenjena je za koprocesovanje najčešće korišćenog sredstva za dopunjavanje, laktoze, monohidrata, sa lipidnim ekscipijensima, glicerildibehenatom (Compritol® 888 ATO) ili glicerilpalmitostearatom (Precirol® ATO 5), koji su poznati po svojim antiadhezivnim, lubrikatnim i protočnim osobinama (1, 2). Cilj ovog ispitivanja je bio razvoj novih koprocesovanih ekscipijenasa na bazi lipida primenom ekološki prihvatljive metode, koja ne zahteva upotrebu rastvarača, i ispitivanje njihove protočnosti i tabletabilnosti.

Protočne karakteristike ispitivanih uzoraka (pojedinačni ekscipijensi, njihove fizičke smeše, laktoza ((85% (m/m)) koprocesovana sa Precirol®-om ili Compritol®-om (15% (m/m)), i komercijalno dostupni koprocesovani ekscipijensi na bazi laktoze (Retalac® i Ludipress®)) procenjene su na osnovu vrednosti *Carr*-ovog indeksa i *Hausner*-ovog odnosa. Laboratorijski simulator kompakcije (GTP D serija, Gamlen Tableting Ltd, UK) korišćen je za dinamičku analizu kompakcije.

Uporedive ili čak bolje protočne karakteristike koprocesovanih ekscipijensa dobijenih metodom *in situ* FBMG, u poređenju sa komercijalno dostupnim koprocesovanim ekscipijensima, ukazuju na njihovu podobnost za direktnu kompresiju. Koprocesovani ekscipijensi sa Precirol®-om i Compritol®-om, kao i odgovarajuće fizičke smeše, pokazale su dva do skoro tri puta niže vrednosti ukupnog rada kompresije od komercijalno dostupnih ekscipijenasa na bazi laktoze. Dodatno, koprocesovani ekscipijensi na bazi lipida pokazali su do 50 puta manji rad odvajanja i do 20 puta manji rad izbacivanja od Retalac®-a i Ludipress®-a. Superiorna antiadhezivna i lubrikatna svojstva koprocesovanih ekscipijenasa pripremljenih *in situ* FBMG mogu se pripisati lipidnim ekscipijensima. Komercijalno dostupni kao i ispitivani koprocesovani ekscipijensi, na bazi lipidnih ekscipijenasa, pokazali su relativno visoke vrednosti zatezne čvrstine (> 1,7 MPa).

Predstavljeni rezultati ukazuju na to da se granulacija topljenjem u uređaju tipa fluidizirajućeg sistema može koristiti kao pogodna metoda za koprocesovanje, koja zahteva manji utrošak energije i vremena u poređenju sa uobičajenim tehnikama, poput sušenja raspršivanjem ili vlažne granulacije. Dobijeni rezultati pokazuju da se koprocesovanjem laktoze sa odabranim lipidnim ekscipijensima može postići odlična protočnost, kao i poboljšana tabletabilnost. Novi koprocesovani ekscipijensi su čak pokazali superiornije karakteristike u pogledu svojih antiadhezivnih i lubrikatnih karakteristika u poređenju sa komercijalno dostupnim koprocesovanim ekscipijensima na bazi laktoze.

## Literatura

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