Novel Co-processed Excipient for Directly Compressed Controlled Release Formulations

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ABSTRACT SUMMARY

A novel excipient comprising 50% lactose monohydrate and 50% hypromellose K4M was prepared via co-processing, integrating the parent materials into a monoparticulate structure offering superior functional performance and simplified processing compared to simple physical admixtures of the same composition. Powder flow, tablet compaction, and wettability showed enhanced performance as a result of excipient co-processing. API dissolution studies with slight compositional modifications and simplified manufacturing method demonstrated flexibility in tablet performance without altering the API release profile.

INTRODUCTION

Hypromellose K4M and lactose monohydrate are often used in combination for the formulation development and manufacture of matrix forming controlled release tablets¹. A co-processed excipient (RetaLac®), comprising 50% hypromellose K4M and 50% lactose monohydrate was prepared. As a result of the manufacturing process, the parent ingredients are integrated into particles comprising each component and rendering the components mechanically inseparable. RetaLac® can be used to develop and manufacture controlled release tablets using direct compression, expediting formulation development, simplifying tablet production, and reducing overall costs.

The study’s objective was to investigate the HPMC/lactose-based matrix tablet preparation method effects on the functional properties: powder/granule flow, compactibility, wettability, and API release.

EXPERIMENTAL METHODS

Using a Hanson Research Flodex™, placebo powder flow of three RetaLac® lots and three prepared admixtures was assessed to determine volume flow rate as a function of aperture size and minimum aperture through which the co-processed powder and admixtures would flow. Using propranolol HCl as a model compound, three formulation sets were prepared with varying API levels. Propranolol HCl and RetaLac® were combined in a dry powder blends. Hypromellose, lactose monohydrate, and propranolol HCl mixtures were prepared by dry powder blend or wet granulation. Flow was assessed using equipment and methods described in the Ph.Eur.

A Korsch EK-0 tablet press was used to examine placebo compaction of three RetaLac® lots compared to three admixtures comprising equivalent compositions. Tablet tensile strength was plotted as a function of compression pressure.

To assess material wettability, 5 g hypromellose (K4M) or 10 g RetaLac® was added to 800 ml water (~22°C) and allowed to hydrate without agitation while timed.

Using metformin HCl as a model, tablets were prepared comprising directly compressed RetaLac® or traditional wet granulations of hypromellose and lactose monohydrate. API release was measured on a Type II apparatus using paddles. Percent metformin HCl released was plotted as a function of time to study tablet preparation method effect on release rate.

RESULTS AND DISCUSSION

Figure 1: Placebo powder flow showing the advantage of co-processed materials compared to simple blends of the individual ingredients.

Placebo powder flow assessment showed co-processing significantly improved material performance compared to simply blending the individual components (Figure 1).

Assessing preparation method on formulation flow, it was observed that the co-processed excipient demonstrated excellent flow overall relative to either...
the physical blends or wet granulated preparations (Figure 2).

![Figure 2: Assessment of formulation preparation method on powder flow.](image)

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The co-processed excipient compaction profiles also exhibited superior performance compared to the admixtures (Figure 3). The co-processed excipient showed a reduction in lot-to-lot variability as well compared to the simple physical mixture.

Wettability studies demonstrated that the co-processed excipient hydrated exceptionally well compared to traditional hypromellose K4M (Figure 4). The integrated hypromellose/lactose particles allowed more rapid hydration of the individual particles. The traditional hypromellose did not hydrate as quickly, possibly due to the diffusion barrier created by the initial wetting and swelling of the particles in immediate contact with the water. With the co-processed excipient, the lactose might have served to increase water permeability of this diffusion barrier.

![Figure 3: Placebo compaction profile comparing the co-processed excipient with admixtures in direct compression.](image)

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![Figure 4: Traditional hypromellose K4M (left) hydrates less rapidly compared to the co-processed excipient (right).](image)

Figure 4: Traditional hypromellose K4M (left) hydrates less rapidly compared to the co-processed excipient (right).

<table>
<thead>
<tr>
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<th>Direct Compression 1</th>
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<th>Direct Compression 2</th>
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<tr>
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Table 1: Formulation composition and preparation method for tablets used in assessing API release.

Again, an advantage was clearly demonstrated using the co-processed excipient since the formulations prepared using RetaLac® in direct compression showed equivalent dissolution compared to the wet granulated formulation (Figure 4).

![Figure 4: API release profiles comparing the co-processed excipient in two directly compressed formulations versus a traditional wet granulated formulation.](image)

CONCLUSION

The co-processed excipient, RetaLac®, demonstrated superior performance compared to the physical admixture of the individual components, lactose monohydrate and hypromellose K4M. Powder flow, compaction, and wettability were enhanced as a result of co-processing while API release was unaffected. Given the direct powder blend and direct compression functional performance, simplified formulations can be developed, shortening R&D timelines and eliminating complex manufacturing methods, improving overall cost and efficiency.

REFERENCES