Physico-mechanical Characterization and Evaluation of Directly Compressible Grades of Hypromellose

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ABSTRACT SUMMARY

A directly compressible type of HPMC, Benecel™ PH DC HPMC that enables robust, scaleable and directly compressible matrix tablet formulations has been developed. HPMC K100M DC shows significantly improved powder flow behavior as measured by Johanson Indicizer and Brookfield powder flow testing procedures. The improved flow was related to markedly reduced cohesion forces as compared to the standard controlled release grade of Benecel™ PH HPMC K100M CR. The reduced cohesivity was also manifested in improved powder flow for directly compressible metformin HCl and quetiapine fumarate formulations that contained HPMC at levels ranging from 25 to 60%. The formulations comprising HPMC K100M DC also demonstrated a 30% increase in tablet strength in typical metformin matrix tablet formulations when compressed at commercial tablet production rates. Content uniformity of tablets readily met the USP mandated threshold acceptance value of 15. Dissolution profiles and tablet strengths for quetiapine formulations prepared by wet granulation using standard HPMC K100M CR and by direct compression using HPMC K100M DC were similar, but the HPMC K100M DC powder blend exhibited significantly improved powder flow as compared to the wet granulated formulation.

INTRODUCTION

Hypromellose (HPMC) at levels exceeding 15% is frequently processed in controlled release formulations via wet granulation, roller compaction or direct compression. From the point of view of cost and manufacturing simplicity, direct compression is the most preferred option. However, roller compaction or wet granulation are still often used, as in many cases the inherent powder and mechanical properties of HPMC tend to result in limitations either in powder flow, compactibility or ability to ensure content uniformity for low doses. Directly compressible grade of hypromellose, Benecel™ PH DC HPMC obviates the above named shortcomings and meets pharmacopeial specifications. In this work, we report on the mechanical and powder properties of HPMC K100M DC and relate these to the improved functionality in typical controlled release matrix formulations.

EXPERIMENTAL METHODS

The flow properties of HPMC K100M DC, standard HPMC K100M CR and various formulated powder blends were compared by measuring the flow rate index on Johanson Indicizer. Additionally the Brookfield PFT powder flow tester was used to measure flow function in an annular shear cell as per ASTM D6128. The traditional compressibility index based on the ratio of bulk and tap density was also measured. Meformin HCl and quetiapine fumarate at levels ranging from 5% to 50% were used as model drugs. The standard grade HPMC K100M CR and directly compressible grade HPMC K100M DC were compared in directly compressible metformin HCl formulations at levels ranging from 25 to 60%. Additionally the feasibility to convert wet granulation formulations to direct compression using HPMC K100M DC was evaluated by preparing quetiapine fumarate matrix tablets by wet granulation using standard HPMC K100M CR and by direct compression using HPMC K100M DC. 600 mg flat faced round tablets (11.25 mm) were compressed on a Stylcam 200R compaction simulator which was configured to simulate a Fette 2090 rotary press with 30

stations at tablet production speeds of 60,000 to 160,000 tablets per hour. Additionally 12 kg batches of various formulations were run on a Cadmach CMD4 20 station tablet press using flat round beveled edge tooling (11.25mm) at 48 rpm.

RESULTS AND DISCUSSION

Pure Polymer Characterization:

When comparing HPMC K100M DC with the standard CR grade of HPMC K100M CR using the Johanson Indicizer, we observed a more than two fold increase in the flow rate index for HPMC K100M DC (250 vs. 100 lbs/ft^3). While bulk densities for the two grades were essentially similar (0.26-0.29g/ml), the cohesion forces measured for HPMC K100M DC were significantly lower in comparison to standard K100M CR (0.15 vs. 0.55 kPa respectively), thus indicating significantly lower inter-particle attraction and friction which accounts for improved flow behavior.

Direct Compression Metformin HCl Formulations:

Powder flow for metformin HCl formulations with drug levels varying from 5-50% and HPMC K100M varying from 50-60% consistently showed better flowability for HPMC K100M DC with compressibility indices lower than 15%. Content uniformity for these directly compressed tablets was universally acceptable with acceptance values ranging from 1-13, thus well below the USP mandated acceptance value threshold of 15. Formulations comprising HPMC K100M DC demonstrated significantly improved compactibility over standard HPMC K100M CR with hardness values ranging from 150-130N over the tablet production speed range of 60,000-160,000 tablets/ hr at compression force of 35KN. Formulations comprising standard HPMC K100M CR varied in hardness from a 110-90 N under the same conditions. Comparisons of dissolution profiles and erosion and swelling behavior of HPMC K100M DC and HPMC K100M CR showed no significant differences.

Comparison between wet granulated and directly compressed quetiapine fumarate formulations:

Quetiapine fumarate formulations, comprising 38.38% drug and 25% HPMC, processed by wet granulation using standard HPMC K100M CR and by direct compression using HPMC K100M DC showed no significant difference in dissolution profiles (f_2=60). Similarly, tablet hardness varied less than 10% (33kP vs. 30 kP) at a compaction force of 15 KN. However, flow behavior of the dry blended formulation comprising HPMC K100M DC was significantly better when compared with wet granulated powder blend comprising HPMC K100M CR as measured by the Brookfield flow function test.

CONCLUSION

The directly compressible grade of HPMC, shows significantly improved powder flow properties and improved compactibility. These properties enable the development of scaleable and robust directly compressible controlled release matrix tablet formulations with excellent content uniformity, compactibility and reliable dissolution behavior.