Effect of Processing Conditions on Hypromellose Matrix Formulations of Acetaminophen Prepared by a High Shear Wet Granulation Process

ABSTRACT SUMMARY

The effect of high shear wet granulation processing conditions on performance of hypromellose matrices containing acetaminophen (APAP) was evaluated. Results showed that the choice of processing parameters can influence the overall granulation time, properties of formulation blends and resulting matrix tablets. These findings provide processing guidelines for developing a hypromellose matrix formulation using a wet granulation process.

INTRODUCTION

Hypromellose (hydroxypropyl methylcellulose, HPMC) has been widely used in formulation of hydrophilic matrix systems for oral extended release (ER) drug delivery due to its key advantages, including versatility and suitability for various drugs and release profiles, global regulatory acceptance, stability and ease of manufacture. Drug release performance and physical properties of HPMC matrix tablets may be affected by several variables, including formulation components (polymer, drug, fillers) and manufacturing methods (direct compression, dry or wet granulation).[1-3] The objective of this study was to investigate the effect of various processing conditions on performance of HPMC formulations of APAP, a sparingly water soluble drug, at a low dose, using a high shear wet granulation process (WG). This includes evaluation of (i) the effect of spray (atomized) vs. poured (non-atomized) and rates of water addition; (ii) the effect of use of binder solution vs. deionized water(DIW); and (iii) the effect of intra- vs. extra-granular addition of polymer and filler. For comparative purposes, one parameter at a time was investigated while others were kept constant. The impact of process parameters during formulation development could be linked to QbD studies.

EXPERIMENTAL METHODS

The formulation composition of ER matrices of APAP is shown in Table 1.The wet granulation process was carried out in a high shear granulator (VG-25, Glatt Air Techniques, USA) (batch size, 2 kg). All ingredients, except magnesium stearate and silica, were added to the granulator and dry blended for 10 minutes. Where applicable, the extra-granular ingredients were blended together separately (twin shell blender, Patterson Kelly, USA) and further mixed with the intra-granular ingredients. The moisture content of the blends was measured and recorded. Granulation was performed using various processing conditions (Table 2). Granulation liquid was added into the dry blend via spray (atomizing pressure, 1 bar) or pour application. The impeller and chopper were operated at constant speeds of 300 rpm and 3000 rpm, respectively. The granulation end point was determined manually, using conventional snow-ball technique. The resulting

granules were dried using a fluid bed system at a product temperature of 38ºC-45ºC (Comil, Quadro Engineering, Canada), using a 1.18 mm grated screen, (GPCG-3, Glatt Air Techniques, USA) to achieve the moisture content value of the dry blend (~ 4% w/w). Dried granules were milled (Comil) followed by the addition of magnesium stearate and silica and blending for 3 minutes. The blends were examined for particle size distribution, bulk and tapped densities, Carr's Compressibility Index and powder flow (Sotax, USA). Tablets were manufactured on an instrumented Piccola rotary tablet press (Riva, Argentina), using standard round concave tooling (8 mm) at the target weight of 200 mg and compression force of 5-20 kN (compression pressure of 101-404 MPa). All tablets were examined for physical properties, including weight variation, thickness, breaking force and friability. Drug release from APAP matrices, compressed at 15 kN (303 MPa), was evaluated in DIW using USP Apparatus II (paddles) with sinkers at 100 rpm. The closeness of drug release profiles was measured using the similarity factor (f_2)[4].

Table 1. Extended Release Matrix Formulation of APAP

Ingredients	Supplier	Quantity (%w/w)
Acetaminophen (APAP)	Mallinckrodt, USA	10.0
HPMC (METHOCEL™ K4M PREM CR)	Dow Chemical Company, USA	30.0
Partially pregelatinized maize starch (Starch 1500®)	Colorcon, USA	59.0
Fumed silica (Cab-O-Sil M5P)	Cabot Corp., USA	0.5
Magnesium stearate	Mallinckrodt, USA	0.5
Total		100.0

Table 2. Wet Granulation Process Conditions

Batch	Granulating Liquid	Addition Method	Addition Rate (g/min)	Intra-/Extra-Granular
F1	DIW	spray	100	Intra
F2	DIW	spray	20	Intra
F3	DIW	spray	50	Intra
F4	DIW	spray	200	Intra
F5	DIW	pour	50	Intra
F6	Binder solution*	spray	100	Intra
F7	DIW	spray	100	Filler intra-HPMC (1:1 intra: extra)
F8	DIW	spray	100	Filler & HPMC (1:1 intra: extra)

*Binder Solution is METHOCEL E5 LV in DIW (DI water), 5% w/w

RESULTS AND DISCUSSION

The results showed that the water quantity required for granulation slightly increased with increasing spray rate in the range of 50-200g/min (F2 = F3 < F1 < F4) (Table 3). Faster spray rates led to faster granulation processes. Pouring required slightly more water than spray when applied at the same rate (F5 > F3). Application of a binder solution resulted in reduced quantity of granulating liquid required and shorter process time (F6 < F1) to achieve comparable granulation. No significant difference was observed in the wet granulation process for intra- and extra-granular additions. Comparison of blend properties showed that increasing the spray rate led to an increase in particle size and improved Sotax powder flow (F2 < F3 < F1 < F4). Bulk density was the highest for F1 and F5 and the lowest for F2 and F3. Comparison of spray vs. pour (F3 and F5) revealed higher bulk density and wider particle size distribution for pour application. The use of a binder solution in lieu of water at the same rate of application (F6 and F1) showed that the granules of the former possess lower bulk density and narrower particle size distribution. Comparison of the intra- and extra-granulation blends (F1, F7 and F8) showed that F1 has the highest values for particle size, bulk density and powder flow. This could be due to the presence of non-granulated polymer/filler within F7 and F8 (Table 3).

Table 3. Comparison of Granulation and Blend Properties

Batch	Granulating Liquid Added (%w/w)	d(15-85%) (µm)	Bulk density (g/cm^3)	Carr's Index (%)	Sotax flow (g/sec)
F1	26.4	65 - 790	0.54	19.7	7.9
F2	22.7	87 - 316	0.43	19.9	6.7
F3	22.7	98 - 432	0.42	21.2	7.3
F4	29.2	119 - 1,085	0.50	18.6	10.5
F5	25.2	55 - 897	0.55	22.2	9.5
F6	21.7	89 - 525	0.45	23.0	7.5
F7	23.9	96 - 518	0.45	20.6	6.9
F8	25.1	59 - 409	0.48	24.9	6.7

Comparison of tablet characteristics (Figure 1) showed that in general, F1, F2, F3, and F4 have similar hardness values. Thus, spray rate did not seem to have a significant effect on tablet hardness. Tablets of batch F5 (pour application) show the lowest hardness values. Friability data followed a similar pattern (data are not shown). Results showed that regardless of use of water or binder solution as granulation liquid, the mechanical properties of tablets were similar (F1 and F6). Comparison of tablets produced via intra- or extra-granular addition of polymer/filler showed that tablet hardness and thickness were lower when all ingredients were added intra-granularly. The average weight variation for matrix tablets was ≤1% RSD. Dissolution profiles for APAP matrix tablets are illustrated in Figure 2, indicating that varying wet granulation process conditions did not impact drug release rate. The calculated f_2 values showed similar drug release from all matrices (f_2 > 66) when compared to F1 tablets, as the reference. Among the matrix tablets, F4 showed slightly faster release rate. F8 demonstrated a slight decrease in release rate when both Starch 1500 and HPMC were added intra- and extra-granularly.

Figure 1. Comparison of Tablet Breaking Force as a Function of Compression Force (Tablet Hardness, kp, can be converted to MPa [1 kp/mm^2= 9.81 MPa], using tablet cross sectional surface area)

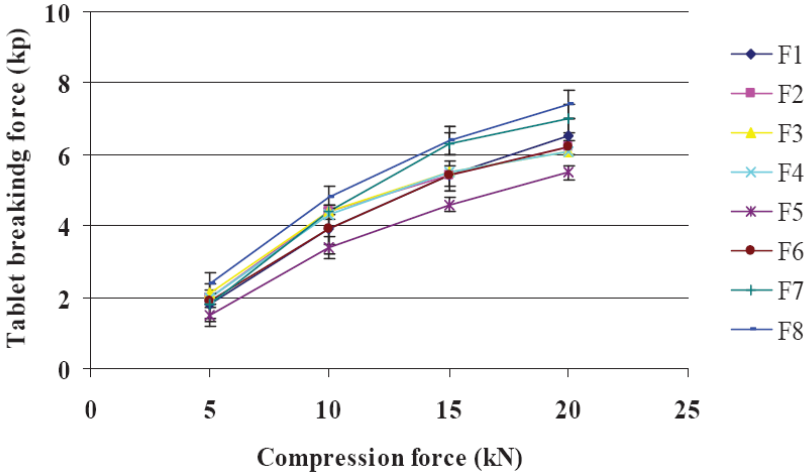
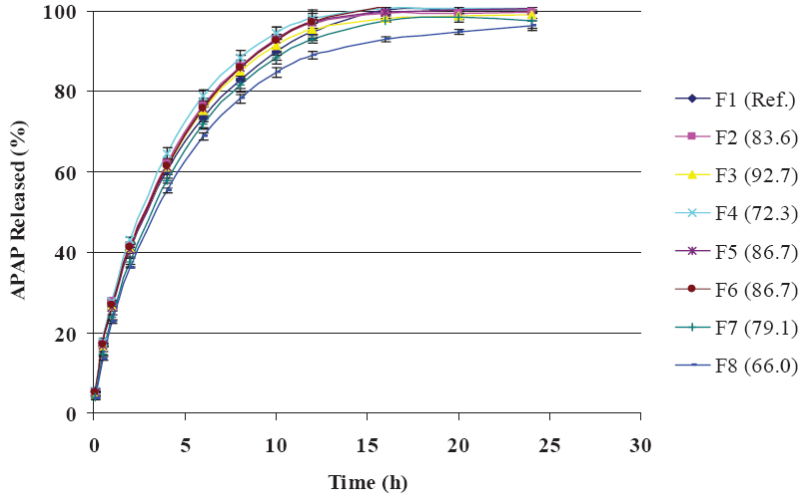


Figure 2. Drug Release Profiles for Matrix Tablets (n=6) (f_2 values are reported in brackets)



CONCLUSIONS

Various high shear granulation processing conditions were used to manufacture HPMC matrices in order to establish the best practice guidelines. The results indicated that increasing the spray rate led to increase in particle size and powder flow of the granules, while tablet properties were not significantly affected. The extra-granular addition of HPMC and Starch 1500 led to increase in tablet hardness. Drug release from the resulting matrices was not significantly influenced by changing the granulation processing conditions. This may indicate the robustness of the formulation and may provide guidance on designing QbD studies on process optimization for hydrophilic matrices.

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Authors: Shahrzad Missaghi, Piyush Patel, Sandip B. Tiwari, Thomas P. Farrell and Ali R. Rajabi-Siahboomi

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North America	Europe/Middle East/Africa	Asia Pacific	Latin America
+1-215-699-7733	**+44-(0)-1322-293000**	**+65-6438-0318**	**+54-11-5556-7700**

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