Effect of Filler Type on Low Dose Acetaminophen Hydrophilic Matrix Formulations Prepared by a High Shear Wet Granulation Process

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Purpose

Hypromellose (hydroxypropyl methylcellulose, HPMC) has been widely used in the 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, availability, stability and ease of manufacture. Drug release from HPMC matrix tablets may be affected by several variables including: polymer type and level, drug dose and solubility, ratio of polymer to drug, filler type and level, ratio of polymer to filler, tablet size and particle size, to name a few.[1-3] The objective of this study was to investigate the effect of four commonly used fillers in formulation and processing of HPMC matrices utilizing a high shear wet granulation process. For this purpose, acetaminophen (APAP) was used as a sparingly water soluble model drug at a low dose (10% w/w). For comparative purposes, the amount of fillers and the process parameters for wet granulation were kept constant for all matrix formulations.

Methods

Formulation and Preparation of APAP Hypromellose Matrices

The compositions of extended release matrix formulations of APAP are shown in **Table 1**. The wet granulation process was carried out in a high shear granulator (VG-25, Glatt Air Techniques, USA) using a batch size of 1.7-2.5 kg. All ingredients, except for magnesium stearate and silica, were added to the granulator and dry blended for 10 minutes at an impeller speed of 300 rpm without using the chopper. The moisture content of the dry blends was determined using a moisture analyzer (IR-200, Denver Instrument Company, USA). Granulation was performed by spraying deionized water (100 g/minute) and using an impeller speed of 300 rpm and a chopper speed of 3000 rpm. The granulation end point was determined manually based on the quality of the formed granules, which was similar for all formulations. Wet screening of granules was performed through a 7.92 mm mesh followed by fluid bed drying at the product temperature of 38ºC-45ºC (GPCG-3, Glatt Air Techniques, USA) to achieve the moisture content values of the respective dry blends. Dried granules were milled using a 1.18 mm grated screen. Magnesium stearate and silica were then added to the dried granules and blended for 3 minutes using a twin shell blender (Patterson Kelly, USA).

Methods (cont'd)

Table 1. Extended Release Matrix Formulations of APAP

Ingredients	Supplier	Composition (%w/w)			
		F1	F2	F3	F4
APAP	Mallinckrodt, USA	10.0	10.0	10.0	10.0
HPMC (METHOCEL™ K4M Premium CR)	Dow Chemical Company, USA	30.0	30.0	30.0	30.0
Partially pregelatinized starch (Starch 1500®)	Colorcon, USA	59.0	-	-	-
Lactose monohydrate (Lactochem)	Friesland Foods Domo, Netherlands	-	59.0	-	-
Microcrystalline cellulose (MCC) (Emcocel 50M)	JRS Pharma, Germany	-	-	59.0	-
Dibasic calcium phosphate dihydrate (DCP)	Spectrum Chemical Co., USA	-	-	-	59.0
Fumed silica (Cab-O-Sil M5P)	Cabot Corp., USA	0.5	0.5	0.5	0.5
Magnesium stearate	Mallinckrodt, USA	0.5	0.5	0.5	0.5
Total		100.0	100.0	100.0	100.0

Characterization of Granules

The blends were examined for particle size distribution using sieve analysis, powder flow using a vibratory funnel-type powder flowability tester (Sotax, USA), and bulk and tapped density. The latter values were used to calculate Carr's compressibility indices.

Compression and Characterization of Matrix Tablets

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, at the compression force range of 5, 10, 15, and 20 kN (compression pressure of 101, 202, 303, 404 MPa). All tablets were examined for physical properties including weight variation, thickness, hardness, and friability. Drug release from APAP matrices, compressed at 15 kN (303 MPa), was examined in DI water using USP apparatus II (paddles), with sinkers, at 100 rpm. Drug release profiles among various formulations were compared using similarity factors (f_2 values).[4]

Results

Comparison of Granulation Process

The time taken to wet granulate and dry different APAP ER formulations was in the range of 14-32 minutes. The wet granulation parameters showed that F3 (MCC formulation) consumed the most amount of water and hence required longer processing time. F4 (DCP formulation) required the least water quantity and processing time. The process time was dependent on the initial batch size and the amount of the granulating liquid (**Table 2**).

Results (cont'd)

Table 2. Comparison of Granulation Process for APAP Formulations

Formulation	Batch Size (kg)*	Moisture Content of Dry Blend (%w/w)	Granulating Liquid Added** (%w/w)	Granulation Time (min)	Drying Time (min)
F1 (Starch 1500)	2.5	5.4	26.7	6.5	25
F2 (Lactose)	2.5	1.8	22.9	5.5	19
F3 (MCC)	1.7	3.9	36.4	6	21
F4 (DCP)	2.5	2.2	16.4	4	10

* Batch size for F3 was smaller than other compositions to account for higher water uptake by MCC and batch growth in the bowl of the granulator.
** Granulating liquid was water.

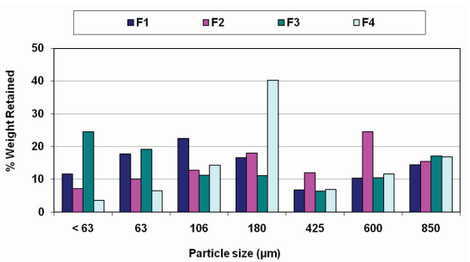
Granule Characterization

F4 (DCP) and F3 (MCC) showed the highest and lowest Sotax powder flow, respectively (**Table 3**), which could be associated with the properties of the plain fillers. Particle size distribution for the granules is displayed in **Figure 1**. MCC (F3) granules had the lowest geometric mean particle size and the largest percentage of fines.

Table 3. Physical Properties of APAP Granules

Formulation	Particle size, Geometric mean (µm)	Bulk Density (g/cm³)	Carr's Index (%)	Sotax Powder Flow (g/sec)
F1	226	0.54	19.7	7.9
F2	354	0.58	14.2	10.5
F3	175	0.43	21.1	6.4
F4	339	0.60	16.3	15.0

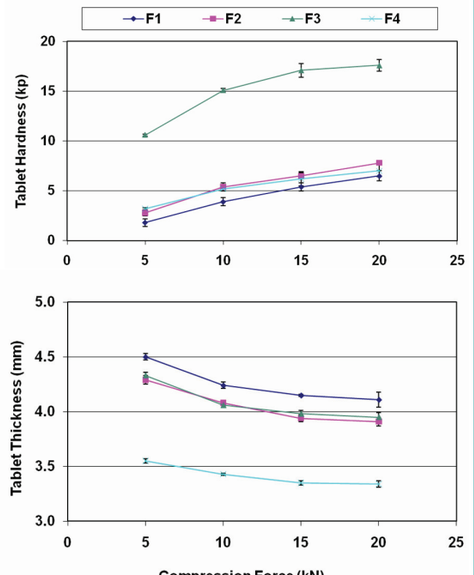
Figure 1. Particle Size Distribution of Granulated APAP Formulations



Physical Properties of Matrix Tablets

Mean tablet hardness followed the rank order of MCC (F3) > Lactose (F2) and DCP (F4) > Starch 1500 (F1) (**Figure 2**). All matrix tablets exhibited low friability values (<0.5%) at the compression forces of 10 kN-20 kN. The weight variation of the tablets was ≤1.5%. Tablet thickness was the highest for Starch 1500 (F1) and the lowest for DCP matrix tablets (F4) (**Figure 2**). The ejection force values were below 120 N for all tablets.

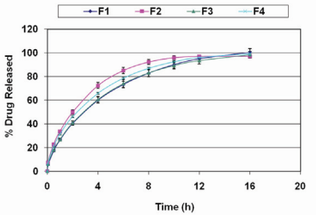
Figure 2. Physical Properties of APAP Tablets as a Function of Compression Force



* To normalize tablet hardness to surface area, hardness (kp) is divided by cross sectional surface area (mm²) of the tablet, followed by conversion to MPa (1 kp/mm²=9.81 MPa)

Dissolution profiles showed slightly faster drug release for Lactose (F2) tablets; however, f_2 values showed similarity among all matrices using the drug release profiles of MCC tablets (F3) as reference ($f_2 > 60$).

Figure 3. Drug Release Profiles for APAP Matrix Tablets (n=6)



Formulation	f_2 Value
Starch 1500 (F1)	98.1
Lactose (F2)	60.6
MCC (F3)	Ref.
DCP (F4)	72.4

Conclusions

In high shear granulation of hypromellose-APAP matrix formulations, filler type affected the amount of granulating liquid required for the wet granulation process, as well as the properties of the corresponding granules and matrix tablets. However, drug release from all formulations was unaffected by the choice of filler. These results provide start-up guidelines for wet granulation process applications when designing hypromellose matrix formulations for a low dose, sparingly soluble drug.

References

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