Investigation of Moisture-Activated Granulation of Hydrophilic Polymer Blends in Verapamil HCl Extended Release Matrices

ABSTRACT SUMMARY

Hydrophilic polymer blends processed by moisture-activated granulation (MAG) were used to formulate verapamil hydrochloride (HCl) extended release hydrophilic matrix tablets. The effects of MAG processing on the properties of the polymer blend, tablets and drug release were investigated. MAG processing improved the powder properties and provided extended drug release for all formulations studied.

INTRODUCTION

Hypromellose (Hydroxypropyl methylcellulose, HPMC) has long been the polymer of choice in the formulation of hydrophilic matrices for oral extended release (ER) drug delivery. Recently, the combination of HPMC with one or more ionic, nonionic or insoluble polymers, has been shown to provide the formulator greater flexibility in achieving desired drug release profiles.[1-3] Hydrophilic polymers with ultrafine particle size are used in extended release matrix formulations to increase the rate of polymer hydration and promote rapid formation of the gel layer around the tablet. In addition, minimum polymer levels of 30% w/w or more are recommended for obtaining a robust matrix formulation.[4] The high levels of polymers, coupled with their fine particle size, can reduce formulation flowability and may necessitate the use of a granulation method to provide adequate flow for efficient high speed tablet manufacturing. Aqueous wet granulation of such hydrophilic polymer formulations typically requires relatively high quantities of water and can be a challenging process. The purpose of this study was to evaluate the effect of MAG, a low-moisture process, on the properties of matrix formulations using blends of HPMC, polyvinyl acetate phthalate (PVAP) and carbomer [cross-linked poly (acrylic acid)]. Verapamil HCl was used as a soluble model drug.

EXPERIMENTAL METHODS

Powder blends of three ratios of HPMC (METHOCEL™, premium cellulose ethers, K4M Premium CR, IFF, USA), PVAP (Phthalavin®, enteric coating polymer, Colorcon, USA), and Carbomer (Carbopol 974P NF, Lubrizol Advanced Materials, Inc., USA) were mixed in a twin-shell V-blender (50:10:40, blend A; 50:20:30, blend B; 50:40:10, blend C). MAG was conducted by exposing the polymer blends to two environmental conditions (20°C/78% RH maintained using a saturated salt solution and a 40°C/75% RH stability chamber) for a period of 0-72 hours. Granulation end point was determined by physically observing the homogenous granule distribution. The resulting polymer cakes were dried in a convection oven at 40°C to moisture contents ranging from 2.3% - 2.6%. The granulations were milled with an oscillating granulator (Erweka, Germany). The particle size distribution and density of the resulting granulations were measured.

Granule flow was characterized by Carr's Index[5] and the use of a vibratory funnel-type flowability tester (FT300, Sotax, Switzerland). Powder moisture content was determined by measuring loss on drying (LOD) (Denver Instruments IR-200, USA) at 105 °C. To investigate the possible change in matrix pH due to MAG processing, the micro-environmental pH of the hydrated polymer granulations was measured.[6] The polymer blend granulations produced at 40°C/75% RH were incorporated into verapamil HCl 99 mg ER matrix formulations by blending 33% w/w each of verapamil HCl (Nicholas Piramal, India), directly compressible lactose (Fast-Flo, Foremost Farms, USA), and granulated polymer blend. Colloidal silicon dioxide (CAB-O-Sil, Cabot Corporation, USA) and magnesium stearate (Mallinckrodt, USA) were used as glidant and lubricant respectively at 0.5% w/w levels. The simple physical blend of the polymers served as a control formulation. Bulk density (BD) and tapped density (TD) of the powders were measured using a tapped density apparatus (Model 10705, VanKel, USA). Tablets were compressed using an instrumented rotary tablet press (Piccola, Riva, Argentina) at a tablet weight of 300 mg. Tablet properties were measured using an automated tablet tester (Multicheck, Erweka, Germany). Drug release profiles were measured spectrophotometrically at a wavelength of 273 nm in 900 ml of deionized water using USP Apparatus II at 100 RPM and 37 °C ± 0.5 °C.

RESULTS AND DISCUSSION

The MAG process resulted in decreased bulk and tapped density while increasing the flow of the polymer blends. Granulations produced using two environmental conditions (20°C/ 78% RH for 72 hours and 40°C/ 75% RH for 24 hours) resulted in similar powder properties (bulk density, tapped density, particle size distribution). However, MAG processing at the lower temperature (20 °C) required a significantly longer conditioning time (72 hours) to achieve complete granulation. The moisture content achieved during the MAG process ranged from 11% to 15%. The MAG process yielded large reductions in Carr's Index values for all three blend ratios, indicating improvements in powder flowability. The increase in powder flow was also confirmed by the Sotax flowability values (Table 2). The improvement in the flowability of blends A and B was especially noticeable because both blends were practically non-flowing in the ungranulated state. Granulations produced at 20 °C achieved moderately greater Sotax flowability values than those produced at 40°C. Granulating at the higher temperature favored the reduction of fines and growth of larger particles in the blends (Table 2).

Table 1. Powder Properties of Granulations

Blend	MAG Condition (°C/%RH)	BD (g/ml)	TD (g/ml)	Carr's Index (%)	pH[a]	Flow (g/sec)
A	CF[b]	0.30	0.50	41	3.2	0.3
	20/78	0.26	0.33	22	3.4	6.0
	40/75	0.27	0.32	15	3.3	5.3
B	CF	0.31	0.53	42	3.0	0.3
	20/78	0.28	0.35	19	3.6	5.8
	40/75	0.25	0.32	20	3.5	4.9
C	CF	0.33	0.51	37	3.6	2.1
	20/78	0.27	0.37	28	4.2	5.4
	40/75	0.26	0.35	27	4.0	4.6

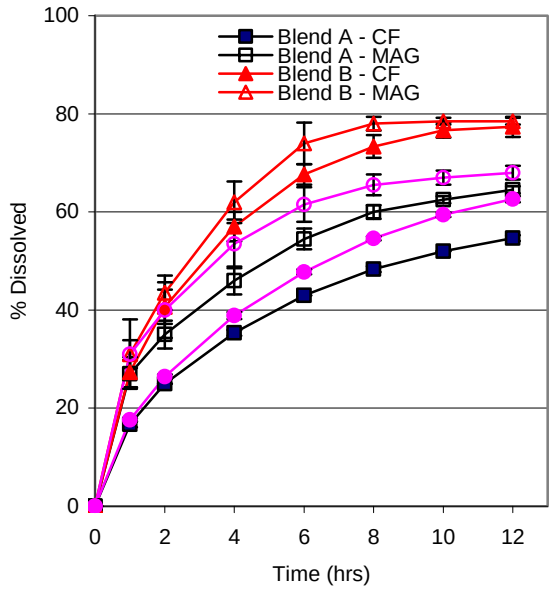
[a] *pH* is the micro-environmental pH of the hydrated polymer matrix.
[b] *CF* is the unconditioned control formulation (simple blend of polymers).

Table 2. Particle Size Distribution of Granulations

Blend	MAG Condition (°C/%RH)	% Retained on Screen				
		18 Mesh	30 Mesh	50 Mesh	100 Mesh	Pan
A	CF	0	1	19	63	17
	20/78	8	24	28	23	18
	40/75	15	27	24	19	14
B	CF	0	0	16	60	24
	20/78	7	21	28	25	19
	40/75	N/A	N/A	N/A	N/A	N/A
C	CF	0	0	8	31	61
	20/78	1	9	19	33	37
	40/75	5	14	21	30	30

The improved flow properties of the polymer blend granulations enabled compression of the formulations using a rotary tablet press. Breaking forces for the verapamil HCl tablets incorporating polymer blends ranged from 10-15 kp and tablet weight variations were below 2.5%. All polymer blend granulations provided extended release of verapamil HCl, and the drug release was slower compared to HPMC-only formulations (data not shown). The slower release with polymer blend formulations may be attributed to the synergistic interaction of HPMC, PVAP and Carbomer.[7] The MAG blends resulted in faster drug release compared to the control formulations, which can be explained by the partial hydration of the polymers during MAG, leading to loss of some degree of secondary hydration during dissolution.

Figure 1. Dissolution Profiles of Verapamil HCl ER Tablets



CONCLUSIONS

A moisture-activated granulation process successfully enhanced the flow and powder properties of hydrophilic polymer blends comprised of HPMC, PVAP and Carbomer. The MAG processed granulations were successfully incorporated into ER matrix tablets that possessed good pharmacotechnical properties. Drug release profiles from the matrix tablets exhibited extended release characteristics.

REFERENCES

1. Tiwari SB, Martin L, Rajabi-Siahboomi AR. The influence of anionic polymers on hydrochlorothiazide extended release hypromellose matrices. AAPS annual meeting and exposition. 2007.
2. Tiwari SB and Rajabi-Siahboomi AR. Modulation of drug release from hydrophilic matrices. Pharm. Technol.Europe. September 2008.
3. Dabbagh MA Ford JL, Rubinstein MH, et al. Release of propranolol hydrochloride from matrix tablets containing sodium carboxymethylcellulose and hydroxypropylmethylcellulose. Pharm. Dev. Technol.1999; 4(3):313-324.
4. Ford JL, Rubinstein MH, Changela A, et al. Influence of pH on the dissolution of promethazine HCl from HPMC controlled release tablets. J Pharm Pharmacol. 1985;37:115P
5. Carr R.L. Evaluating flow properties of solids. Chem Eng.1965;72:163–168.
6. Tatavarti AS, Mehta KA, Augsburger LL, et al. Influence of methacrylic and acrylic acid polymers on the release performance of weakly basic drugs from sustained release hydrophilic matrices. J Pharm Sci. 2004;93(9):2319-2331.
7. Martin LM, Tiwari SB, Rajabi-Siahboomi AR. The influence of hydrodynamic conditions on verapamil hydrochloride release from hydrophilic matrices using ionic and non-ionic polymers. AAPS annual meeting and exposition. 2008.

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North America	Europe/Middle East/Africa	Asia Pacific	Latin America
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