Use of Roller Compaction in the Preparation of Verapamil Hydrochloride Extended Release Matrix Tablets Containing Hydrophilic Polymers

ABSTRACT SUMMARY

Roller compacted hydrophilic polymer combinations were used to formulate verapamil hydrochloride (HCl) extended release hydrophilic matrix tablets. The effect of roller compaction (RC) parameters on the properties of blended polymers, tablets and drug release were investigated. RC granulation improved the powder properties without affecting the pharmacotechnical properties or the drug release profiles of the formulations.

INTRODUCTION

Hydroxypropyl methylcellulose or hypromellose (HPMC) has long been the polymer of choice in formulations of hydrophilic matrices for oral extended release (ER) drug delivery. Attention has been given to the use of polymer blends, particularly the combination of HPMC with one or more ionic, non ionic or insoluble polymers, to provide the formulator with greater flexibility in achieving desired drug release profiles.[1-3] Hydrophilic polymers used in the formulation of ER matrices are generally supplied in an ultra-fine particle size range 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% or more are typically recommended for obtaining a robust matrix formulation.[4] This fine particle size distribution coupled with high levels of polymer in the formulation may reduce powder flow and necessitate a granulation method to provide adequate flow for efficient high speed tablet manufacturing.[5] Aqueous wet granulation of hydrophilic polymers may be challenging and costly, therefore roller compaction, a dry process that results in improved powder flow, has been investigated.

The purpose of this study was to evaluate the effects of roller compaction on the flow and compressibility of blends of HPMC, polyvinyl acetate phthalate (PVAP) and carbomer [cross-linked poly (acrylic acid)]. Drug release of an ER verapamil HCl matrix formulation containing this blend was also evaluated.

EXPERIMENTAL METHODS

Verapamil HCl was purchased from Nicholas Piramal, India. Colloidal silicon dioxide (CAB-O-SIL) and magnesium stearate were purchased from Cabot Corporation (USA), and Mallinckrodt (USA), respectively. HPMC (METHOCEL™, premium cellulose ethers, K4M Premium, the Dow Chemical Company, USA) was blended with PVAP (Phthalavin, Colorcon, Inc., USA) and carbomer (Carbopol 974P NF, Lubrizol Advanced Materials, Inc., USA) at two ratios of 50:10:40 (Blend A) and 50:40:10 (Blend B) in an 8 quart, twin-shell blender (Patterson-Kelley, USA). In some compositions, lactose (Fast-Flo, Foremost Farms, USA) was blended with the polymers as a potential RC processing aid at a level of 10% w/w with respect to the total polymer content. No lubricant was added to the HPMC blends prior to roller compaction.

The HPMC blends were compacted using an instrumented single-screw feed roller compactor (WP 120 V Pharma, Alexanderwerk AG, Germany) using knurled compression rollers. Roller speed was maintained at 4 rpm and the gap between the rollers was maintained at 2.0 mm. Compaction pressure was varied from 20 to 80 bar. Compacted ribbons were milled with an oscillating granulator (Erweka, Germany) fitted with an 18 mesh (1.0 mm) screen. Particle size, density and Carr's index of the granules were determined. Powder flow was measured using a vibratory funnel-type flowability tester (FT300, Sotax, Switzerland).

Granules produced at 40 bar RC pressure were incorporated into verapamil HCl ER matrix formulations and tabletted using an instrumented rotary press (Piccola, Riva, Argentina). Formulations consisted of 33% w/w each of active, hydrophilic polymer blend and lactose, and 0.5% w/w of lubricant (magnesium stearate) and glidant (colloidal silicon dioxide). Tablet weight, hardness and thickness were measured with an automated tablet tester (Multicheck, Erweka, Germany). Tablet friability was measured according to USP <1216> with a friabilitor (Model 45-2000, VanKel, USA). 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 using sinkers at 37°C ± 0.5°C.

RESULTS AND DISCUSSION

Table 1 illustrates the effects of increasing compaction force on the powder properties of HPMC blends A and B. The roller compaction process increased the powder density of the polymer blends. Powder flow of each blend also improved as compaction force was increased which is reflected by the decreasing Carr's index values and the increase in measured flow (Table 1). For both formulations, the first 20 bar of roller compaction force yielded the greatest increase in powder density and flow; these properties continued to gradually improve as compaction force was increased further. Flow properties of the granulated polymer blends were not significantly enhanced by the inclusion of lactose as a processing aid during the RC process. Particle size distribution of the RC granulations was dependant on the compaction force and the blend composition. In general, RC of blend A resulted in larger particle size with increasing compaction force, while in case of blend B, the enhancement in particle size was greatest at a compaction force of 20 bar.

Table 1. Powder Properties of Roller Compacted Polymer Blends

Force (bar)	Polymer Blend	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carr's Index (%)	Flow (g/sec)
0	A*	0.30	0.50	41	0.3
	B**	0.33	0.51	37	2.1
20	A	0.38	0.53	29	5.0
	B	0.35	0.49	29	5.0
40	A	0.39	0.56	29	5.5
	B	0.40	0.56	28	7.2
60	A	0.42	0.55	25	5.6
	B	0.43	0.57	25	6.5
80	A	0.41	0.58	30	5.9
	B	0.45	0.61	26	6.9

*A: Blend ratios 50:10:40 HPMC: PVAP: Carbomer

** B: Blend ratios 50:40:10 HPMC: PVAP: Carbomer

The improved flow properties of the polymer blend granulations enabled compression of the formulations with a rotary tablet press. Tablet formulations with roller-compacted polymer granules required greater compression forces during tabletting to achieve hardness levels similar to the direct compression (DC) formulations (Figure 1). This may be due to prior deformation and a loss of compressibility of the polymers during the RC process. Despite this loss of compressibility, granules produced with 40 bar pressure yielded tablets with acceptable pharmacotechnical properties. Tablet weight uniformity (300 mg ± 1.5%) and thickness (4.3 ± 0.1 mm) were not significantly affected by the RC process. However, tablets using roller compacted granules exhibited lower friability (0.15%) than those using DC polymer blends (0.35%).

Figure 1. Verapamil HCl ER Tablet Hardness Versus Compression Force for DC and Roller Compacted Granules of Polymer Blend A

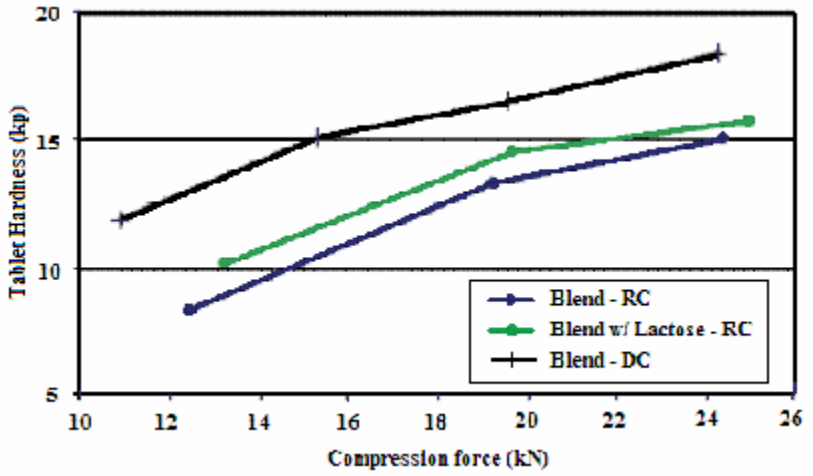
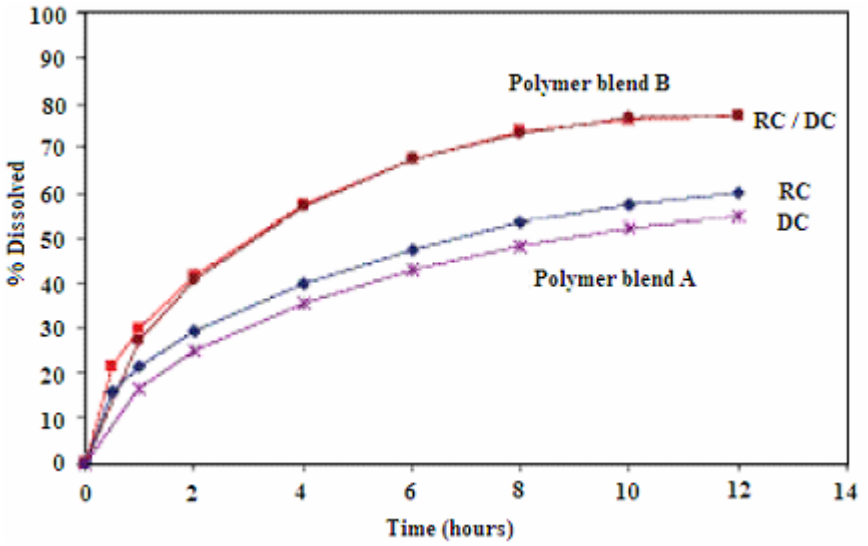


Figure 2 shows Verapamil HCl release profiles for ER formulations containing roller compacted and DC polymer blends. Roller compaction of the polymer blends did not significantly affect drug release from their matrices (f2 > 50). Moreover, the use of lactose as a processing aid in the RC of polymer blends did not significantly alter drug release compared to the formulations using polymer-only matrix granules (f2 > 50).

Figure 2. Drug Release Profiles of Verapamil HCl ER Tablets Formulated with Direct Compression (DC) or Roller Compacted Polymer Blends without Lactose



CONCLUSIONS

The roller compaction granulation process successfully increased the powder flow and density of hydrophilic polymer blends comprised of HPMC, PVAP and Carbomer. The roller compacted polymer granules were successfully incorporated into a verapamil HCl ER matrix formulation, resulting in tablets with good pharmacotechnical properties. Drug release profiles from these matrix tablets in water were similar to formulations using ungranulated direct compression polymer blends.

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