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Effect of Drug, Formulation, and Process Variables on Granulation and Compaction Characteristics of Heterogeneous Matrices: Part II. HPMC and PVP Systems

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ABSTRACT

A heterogeneous matrix comprising hydroxypropyl methylcellulose (HPMC) and polyvinylpyrrolidone (PVP) at various ratios was granulated using acetaminophen and pseudoephedrine as model drugs. The effect of drug, polymer ratio, total polymer loading, and volume of the granulating fluid on granule growth, granule size distribution, compaction, and tablet properties of the matrix was studied. Formulations containing both acetaminophen and pseudoephedrine required less water to granulate than those containing only acetaminophen. Moreover, the particle sizes of granules prepared with acetaminophen and pseudoephedrine were smaller than those containing only acetaminophen. Tablet hardness increased and friability decreased considerably in all formulations containing pseudoephedrine. In general, the tablet hardness and tablet disintegration time varied with changes in total polymer loading, fraction of HPMC in the matrix, and composition of the model drug(s). All the matrix systems studied showed good flow characteristics at

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different polymer loadings or HPMC–PVP ratio for matrices formulated with either acetaminophen or both acetaminophen and pseudoephedrine. The results of this study indicate that the presence of drug and/or other excipient(s) in the formulation affects the hydration characteristics of the matrix polymer(s) and compression properties of the granules.

INTRODUCTION

Hydroxypropyl methylcellulose (HPMC) is a nonionic cellulose ether polymer and it is compatible with a variety of pharmaceutical excipients (1). It has been blended with various polymers to modify drug release characteristics from the matrix. The polymer forms a gel upon hydration in an aqueous medium and thus controls the release of a drug (2). Heterogeneous matrices comprising a mixture of hydrophilic polymers such as HPMC and polyvinylpyrrolidone (PVP) have been developed for oral use to regulate the release of acetaminophen (3). HPMC polymers have also been extensively used in formulating various slow-disintegrating tablets due to their ability to form a gel upon hydration with water (4). In the presence of little moisture, HPMC provides van der Waals forces to poorly cohesive masses, such as acetaminophen, to form granules for tableting (5). For efficient results, moist granulation of HPMC has been often recommended (5).

Cross-linked PVP has been reported to show superior disintegrating action because of its tremendous swelling property in the presence of water (6). Moreover, it has been reported by Phadke et al. (3) to influence the characteristics of wet-granulated acetaminophen through interference in the hydration characteristics of HPMC, thus increasing the total surface area of the powder blend.

In our previous study, we investigated the effect of process and formulation variables on the physical properties of granules and tablets formulated with HPMC and hydroxypropyl cellulose (HPC) polymers and acetaminophen and pseudoephedrine as coactive agents (7). The intention of the present study, however, was to investigate the effect of HPMC–PVP blends on the physical characteristics of granules and tablets prepared with acetaminophen and pseudoephedrine as coactives. PVP is more hygroscopic compared to HPC, and the former has been reported to affect the characteristic of wet-granulated acetaminophen.

MATERIALS AND METHODS

Materials

Acetaminophen (Rhone-Poulenc, New Jersey, USA) and pseudoephedrine sulfate (Knoll Pharmaceutical Co., New Jersey, USA) were chosen as model drugs for this investigation. Other materials used in this study were as follows: hydroxypropyl methylcellulose (HPMC: Methocel® E4M, DOW Chemical Co., Michigan, USA), polyvinylpyrrolidone (PVP: K 29–32, International Specialty Products, New Jersey, USA), magnesium stearate, NF (Mallinckrodt, Inc., Missouri, USA) and Cabosil® M5 (Cabot Corporation, Illinois, USA). All materials were used as received without further purification.

Methods

Preparation and Characterization of Granules

The method for preparing and characterizing the granules has been previously described by Ebube et al. (7). The granules were formulated such that each tablet contained either 750 mg of acetaminophen or 750 mg of acetaminophen and 60 mg of pseudoephedrine. Batches of the formulations ranging from 787 to 942 g containing 0.25% w/w Cabosil® and various HPMC and PVP blends were prepared. The ratios of HPMC to PVP used were 2:1, 4:1, or 5:1, while the total polymer content varied from 3.5 to 19.2% w/w. The composition of the powder blends and the optimum amount of water used as the granulating liquid are shown in Tables 1 and 2, respectively.

Table 1

Composition of Matrix Formulations

Matrix Formulation	Polymer Ratio[a]	Model Drug	Total Polymer (%)
519H	2:1		
521H	4:1	APAP	6.3
523H	5:1		
531H			3.5
321H			6.3
533H	4:1	APAP	9.6
535H			19.2
525H	2:1	APAP	
527H	4:1	+	6.3
529H	5:1	PE	

[a]HPMC:PVP; APAP—acetaminophen, PE—pseudoephedrine.

Table 2

Formulation Requirements and Physical Characteristics of Matrix Base Granulations for Various Designated Matrix Formulations Containing HPMC and PVP as Polymeric Excipients

Matrix Formulation[a]	Amount of Water Used (g)	Moisture Content (% MC)	Percent Yield (% Y)	Micromeritic Properties[e]			Density[f] (g/cm^3)		Carr's Index (I)
				d_g	s_g	d_{vs}	V_b	V_T	
519H[b(1)]	264.0	1.2	88.4	280	1.65	247	0.546	0.622	12.2
521H[b(2)]	332.4	1.1	89.0	252	1.59	226	0.494	0.579	14.7
523H[b(3)]	332.7	0.9	90.9	255	1.59	228	0.490	0.577	15.1
531H[c(4)]	332.3	0.9	90.4	265	1.72	229	0.477	0.561	15.0
533H[c(5)]	332.6	1.2	90.0	254	1.70	220	0.512	0.575	11.0
535H[c(6)]	220.5	1.1	95.0	211	1.29	204	0.476	0.563	15.5
525H[d(1)]	169.4	1.1	95.9	234	1.71	202	0.475	0.540	12.0
527H[d(2)]	151.5	1.1	92.6	195	1.74	167	0.496	0.570	13.0
529H[d(3)]	175.2	1.1	89.1	230	1.60	205	0.512	0.584	12.3

[a]Formulas for the specified formulations are given in Table 1.
[b]Matrix formulation contains APAP as a model drug. The HPMC to PVP ratios were 2:1 (1), 4:1.5 (2), or 5:1.3 (3). The total polymer concentration in the formulations was kept constant at 6.3% w/w.
[c]Matrix formulation contains APAP as a model drug. The HPMC-to-PVP ratio was kept constant at 4:1.5. The total polymer contents were 3.5 (4), 9.6 (5), or 19.2 (6)% w/w.
[d]Same composition as *b* except it contains APAP and pseudoephedrine as model drugs.
[e]Micromeritic properties: d_g—geometric mean diameter (μm), σ_g—geometric standard deviation, and d_{vs}—volume-surface diameter (μm).
[f]Density: V_b—bulk density and V_T—tap density.

The properties of the granules for each formulation were evaluated by determining the particle size distribution, moisture content, bulk density, tap density, and Carr's index (7).

Compaction to Tablets

A quantity of the base granulation for each formulation, enough to make 1000 tablets, was weighed and placed in an 8-quart plastic container. Magnesium stearate (1% w/w as lubricant) was premixed with an equal portion of the granulation and passed through a #20 (850 μm) mesh sieve by hand. The mixture was blended with the remainder of the granulation for 3 min using a PK blender (Patterson-Kelly Co., USA) and compressed into matrix tablets on a Manesty B3B instrumented tablet press using 9/16-in. flat-face punches and dies at a compression speed of 203 tablets per min. Tablets were compressed at varying compression forces ranging from 2000 to 6000 lb.

Tablet Properties

The properties of the compressed matrix tablets such as hardness, friability, disintegration time, weight variation, and thickness were determined as previously described by Ebube et al. (7).

RESULTS AND DISCUSSION

Table 2 lists the amount of water used to granulate, final moisture contents, and physical properties of the granules formulated with HPMC and PVP as matrix polymers. The final moisture content of the granules ranged from 0.9 to 1.2% w/w, and at this moisture content, the formulations showed good compressibility. Formulations containing acetaminophen and pseudoephedrine generally required less water to granulate than similar formulations containing only acetaminophen as the model drug. The results of this study are consistent with the results of the previous investigation by Ebube et al. (7) for similar matrices formulated with HPMC and HPC. The amount of water required to granulate formulation 535H containing a total polymer (HPMC-PVP) loading of 19.2% and acetaminophen as a model drug, was less than the amount of water required to granulate formulations 531H and 533H containing a total polymer (HPMC-PVP) loading of 3.5% and 9.6%, respectively. This may be because formulation 535H contained more PVP than formulations 531H and 533H, and PVP has a high aqueous solubility and thus facilitates initial wetting of the powders. Moreover, at high total polymer loading, it promotes rapid granule nucleus formation. Increasing the volume of water (i.e., >220

g for formulation 535H) resulted in overwetting and caking of powders.

The bulk and tap density values of the granules ranged from 0.475 to 0.546 and from 0.540 to 0.622 g per cm^3, respectively. These values represent very small changes. The Carr's index values for the different matrix systems investigated in this study were below the acceptable value of 15%. These results indicate that the matrix granulations formulated with various compositions of HPMC and PVP showed good flow characteristics and hence good compressibility. Moreover, formulations 525H, 527H, and 529H, which contained pseudoephedrine as a coactive, produced granules with lower values of Carr's index than similar formulations (519H, 521H, and 523H) containing only acetaminophen.

Tables 2 and 3 show the particle size distribution of the granules. Increasing the polymer concentration from 3.5% (in formulation 531H) to 19.2% (in formulation 535H) decreased the particle size of the granules. This result is contrary to the observation of Bank et al. (8) and Schaefer and Worts (9), who reported that granule size increased with increasing binder content of the granules. However, Aulton and Banks (10) have reported that larger granules are produced by a more dilute binder solution due to greater wetting of the powders. This may be because of the formation of a large number of liquid bridges between the powder particles. Similarly, in the present study, granules with larger mean particle size were produced in the formulation where total polymer content was 3.5% w/w. This may be attributed to the relatively higher quantity of water used for granulation. Thus, at low total polymer loading and high solvent volume, greater wetting of the powder occurred, with the formation of large number of liquid bridges between powder particles. As a result, granules with larger mean particle size were produced.

Formulations 525H, 527H, and 529H containing acetaminophen and pseudoephedrine showed small mean particle size of the granules. Moreover, particle size distribution of these granules showed a shift from the coarser fraction (>637.5 μm) of the dried granulation to the fines (<165 μm). Similar results were obtained in our previous study when HPMC and HPC were used as matrix polymer (7). Formulations containing pseudoephedrine and acetaminophen (525H, 527H, and 529H) required relatively less water to granulate than similar formulations containing only acetaminophen (519H, 521H, and 523H). This could be because pseudoephedrine and PVP have very high aqueous solubility, thus resulting in rapid initial wetting of the powders and promoting faster formation of the granule nucleus. During the granulation process, the shredded nuclei combine with primary particles, resulting in granule growth (11). This process continues during mixing, and eventually all the wetted materials are distributed as

Table 3

Particle Size Distribution Data for Matrix Base Granulation Containing HPMC and PVP as Polymeric Excipients

Matrix Formulation[a]	Average Particle Size Retained: Size and (%)							Geometric Mean Diameter (μm)
	>850[e] (20)[f]	637.5 (20/40)	337.5 (40/60)	215 (60/80)	165 (80/100)	128 (100/140)	<106 Pan	
519H[b(1)]	6.5	46.7	23.1	9.6	3.7	5.2	4.3	280
521H[b(2)]	8.5	37.3	25.7	12.3	3.8	6.3	6.1	252
523H[b(3)]	13.0	36.4	22.3	12.2	3.8	6.1	6.2	255
531H[c(4)]	12.1	35.2	22.9	11.9	4.1	6.6	7.0	265
533H[c(5)]	13.3	36.2	18.8	11.8	4.2	7.5	8.3	254
535H[c(6)]	7.6	30.8	30.5	15.9	5.1	5.9	4.2	211
525H[d(1)]	8.6	30.5	21.3	14.0	6.2	10.1	9.3	234
527H[d(2)]	4.1	16.8	21.1	19.0	9.9	16.6	12.7	195
529H[d(3)]	6.2	25.1	28.5	18.2	5.9	8.7	7.5	230

[a]Formulas for the specified formulations are given in Table 1.
[b]Matrix formulation contains APAP as a model drug and 2:1 (1), 4:1.5 (2), or 5:1.3 (3) of 6.3% HPMC/PVP blend.
[c]Matrix formulation contains APAP as a model drug and 3.5% (4), 9.6% (5), or 19.2% (6) total polymer comprising 4:1.5 HPMC/PVP blend.
[d]Same composition as *b* except it contains APAP and pseudoephedrine as model drugs.
[e]Average particle size in micron (μm).
[f]Retained on US standard sieve of mesh size #20.

equilibrium granules. Therefore, for the formulations containing pseudoephedrine, the equilibrium granules are formed quickly and further granule growth is inhibited due to depletion of the nuclei required to combine with the primary particles for continued granule growth. Moreover, further addition of the granulation fluid may lead to overwetting and the powders may form cake. The mechanism of the pseudoephedrine effect has been described in detail in our previous report (7).

The effects of compression force on tablet hardness for the matrix formulations are presented in Figs. 1–3. As expected, the tablet hardness increased as compression force increased. The tablets showed a tendency to cap above the compression force of 3000 lb. Formulations containing only acetaminophen (519H, 521H, and 523H) did not show any differences in tablet hardness as the ratio of HPMC to PVP was varied, and maximum hardness was reached at compression force of 4000 lb (Fig. 1). As shown in Fig. 2, tablet hardness increased considerably in formulations containing pseudoephedrine. This could be because formulations containing both acetaminophen and pseudoephedrine produced granules with smaller mean particle size than those containing acetaminophen. It is possible that during the tableting process, the fines filled the interstitial spaces between the coarse particles, which resulted in enhanced interparticular bonding between the particles. These results are similar to those reported by Ebube et al. (7) for similar tablets formulated with HPMC and

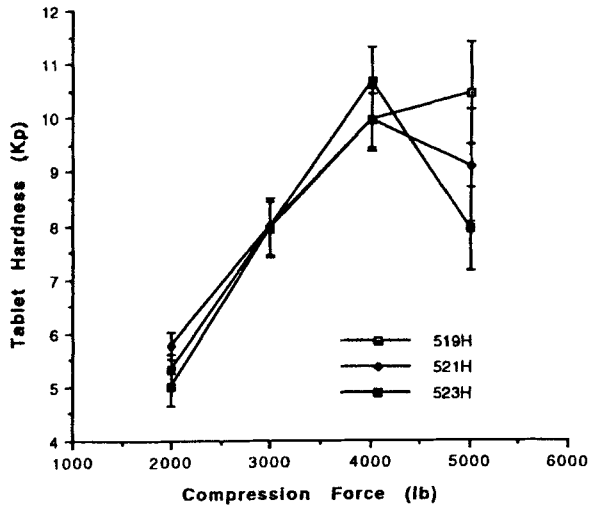

Figure 1. Tablet hardness as a function of compression force for matrix formulations containing acetaminophen and 2:1 (519H), 4:1 (521H) or 5:1 (523H) HPMC and PVP as polymeric excipients. Error bars represent the standard deviation.

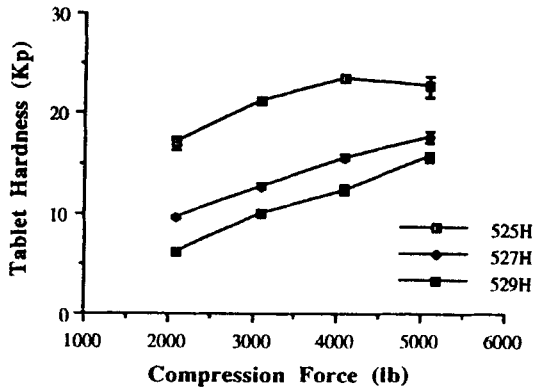

Figure 2. Tablet hardness as a function of compression force for matrix formulations containing both acetaminophen and pseudoephedrine and comprising 2:1 (525H), 4:1 (527H), or 5:1 (529H) HPMC and PVP as polymeric excipients. Error bars represent the standard deviation.

HPC, except that matrix systems containing PVP were harder than those containing HPC. This difference in tablet hardness may be attributed to the fact that PVP is a better binder than HPC and the former may produce greater interparticular bonding of the powders than the latter. This is further explained by the fact that tablet hardness increased as the proportion of PVP in the formulation increased, as shown in Fig. 2. The changes in tablet hardness for matrices formulated with different total polymer loadings did not follow any particular trend. However, at low total polymer content, softer tablets were produced (Fig. 3).

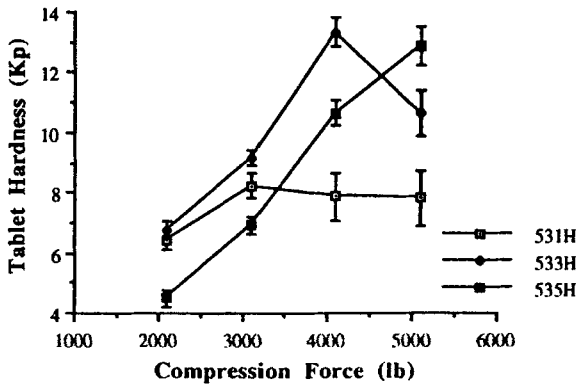

Figure 3. Tablet hardness as a function of compression force for matrix formulations containing acetaminophen and 3.5% (531H), 9.6% (533H), or 19.2% (535H) total polymer content comprising 4:1 HPMC and PVP. Error bars represent the standard deviation.

Table 4

Comparison of the Physical Properties of the Matrix Tablets Containing HPMC and PVP and Compressed at a Compression Force of 3000 lb

Matrix Formulation[b]	Physical Characteristics[a] Hardness (kp), $n = 10$	Thickness (in.), $n = 10$	Weight (g), $n = 10$	Friability (%), $n = 3$	Disintegration Time (hr), $n = 3$
519H[c(1)]	7.91 (0.51)	0.176 (0.001)	0.787 (0.004)	1.24 (0.05)	4.69 (0.39)
521H[c(2)]	7.97 (0.52)	0.177 (0.001)	0.787 (0.002)	0.92 (0.00)	4.19 (0.10)
523H[c(3)]	8.59 (0.34)	0.179 (0.001)	0.784 (0.004)	2.01 (0.05)	6.22 (0.05)
531H[d(4)]	7.97 (0.42)	0.174 (0.001)	0.777 (0.002)	1.35 (0.02)	3.50 (0.00)
533H[d(5)]	8.89 (0.25)	0.184 (0.001)	0.824 (0.002)	0.66 (0.01)	8.73 (0.24)
535H[d(6)]	6.67 (0.29)	0.216 (0.001)	0.943 (0.004)	1.00 (0.06)	>9.5
525H[e(1)]	20.42 (0.40)	0.186 (0.001)	0.869 (0.005)	0.33 (0.01)	5.72 (0.13)
527H[e(2)]	11.91 (0.35)	0.196 (0.001)	0.883 (0.004)	0.79 (0.07)	5.27 (0.06)
529H[e(3)]	9.10 (0.33)	0.199 (0.001)	0.887 (0.003)	1.83 (0.14)	6.50 (0.00)

[a]Results represent means of replicate determinations with the standard deviation in parentheses.
[b]Formulas for the specified formulations are given in Table 1.
[c]Matrix formulation contains APAP as a model drug. The HPMC-to-HPC ratios were 2:1 (1), 4:1.5 (2), or 5:1.3 (3). The total polymer concentration in the formulations was kept constant at 6.3% w/w.
[d]Matrix formulation contains APAP as a model drug. The HPMC-to-HPC ratio was kept constant at 4:1.5. The total polymer contents were 3.5 (4), 9.6 (5), or 19.2 (6)% w/w.
[e]Same composition as *c* except it contains APAP and pseudoephedrine as model drugs.

The comparison of the tablet hardness, friability, and disintegration time at a compression force of 3000 lb for the different matrix formulations is shown in Table 4. The disintegration time for the matrix tablets ranged from 3.5 to 6.5 hr. Higher values were obtained for formulations containing 9.6% and 19.2% w/w total polymer (Table 4). At high total polymer content, a thicker gel formation around the granules may have created more viscous barrier between the granules and water, thus resulting in longer disintegration time (12). Except for formulation 523H, the friability values decreased as the tablet hardness increased for the different matrix formulations. The friability values obtained for formulations containing acetaminophen and pseudoephedrine increased as the fraction of HPMC in the formulation increased. This shows an opposite trend compared to the values reported for HPMC and HPC matrices in our previous study (7).

CONCLUSION

From the results of this and previous studies, it is evident that pseudoephedrine significantly affects the particle size distribution of acetaminophen granules, tablet hardness, and friability. Moreover, the mechanism of its influence appears to be related to a cumulative effect of its small particle size and higher wetting capacity. At high total polymer loading, PVP appears to produce an effect that is similar to those of pseudoephedrine, and this may be due to the high water solubility of PVP. The presence of drug(s) and/or other excipients in the formulation that influence the hydration characteristics of the matrix polymers may affect the compression properties of the granules. However, it is worth mentioning that the differences in particle size distribution and solubility of both drug(s) and excipients should be considered when selecting components of a sustained release matrix system.

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