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Effect of drug, formulation and process variables on granulation and compaction characteristics of heterogeneous matrices. Part 1: HPMC and HPC systems

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Abstract

The purpose of this study was to investigate the effects of hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC) ratios, total polymer loading and the use of pseudoephedrine as a co-active on the physical properties of acetaminophen granulation as well as that of the compressed tablets. The incorporation of pseudoephedrine to the acetaminophen–polymer formulations resulted in a decreased amount of water required for the wet granulation process. Moreover, the particle size of the granules decreased and the tablet hardness increased. Increasing the HPMC-to-HPC ratio increased both the particle size of granules and the tablet hardness. No clear trend in the particle size of granules and the tablet hardness was seen when the total polymer loading was varied at a given HPMC-to-HPC ratio. The tablet disintegration time was not influenced by the presence of pseudoephedrine; however, it decreased for the formulations containing a lower total polymer content. All the matrix systems investigated showed good compressibility. The effect of pseudoephedrine on the physical properties of wet granulated or compressed acetaminophen tablets was attributed to interference in the hydration characteristics of the matrix polymers. © 1997 Elsevier Science B.V.

Keywords: Acetaminophen; Co-active; Compaction characteristics; Heterogeneous matrix; Pseudoephedrine

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1. Introduction

Several long-acting commercial dosage forms for respiratory ailments contain acetaminophen in combination with a decongestant such as pseudoephedrine or phenylpropanolamine (Anon., 1997). These actives have been formulated with the appropriate amounts of polymeric excipients in order to confer desirable properties on the granules and on the final product (Esezobo, 1985). Alderman has reported that some of these sustained release respiratory products show tendency to disaggregate initially following ingestion, before a protective gel barrier is formed around the matrix tablet to retard drug release (Alderman, 1984). Therefore, current research efforts have been centered around identifying polymeric excipients and blends which would hydrate rapidly and form a gel barrier around the tablet to regulate the release of the drug. However, little attention has been focused on the effects of drugs and additives present in these multicomponent formulations on the physical properties of such matrices and how they affect the drug release (Touitou and Donbrow, 1982).

Acetaminophen powder has a low bulk density and poor compressibility due to lack of cohesiveness (Patel et al., 1989). The powder acquires static charges while flowing through the hopper and during milling operations (Gold and Palermo, 1965). Acetaminophen tablets also undergo elastic deformation during compression, often resulting in capping problems (Obiora and Shotten, 1976). Improvement of powder properties has always been a major concern for the tablet formulator (Rubio and Ghali, 1994). The wet and dry granulation are processes for the densification of powders that will produce a formulation with better compression characteristics. Agglomeration during the wet granulation process is caused by a complex interaction of several variables (Phadke and Anderson, 1990). In discussing these variables, Aulton and Banks (1981) distinguished between apparatus, process and product variables. The product variables are related to the starting materials, the applied binder and the binder solvent (Phadke and Anderson, 1990).

The potential of cellulose ether polymers such as HPMC and HPC as matrix ingredients to regulate the release of drug substances has long been reported (Alderman, 1984; Rao et al., 1988). They have broad FDA acceptance, are considered cost effective, non-toxic, can accommodate high levels of drug loading, and can also be blended in different proportions to tailor a desired drug release profile producing a release profile approximating zero order (Rao et al., 1988).

In this investigation, the HPMC and HPC polymers were utilized as matrix excipients (Rao et al., 1988). The objective of this study was to identify some of the underlying physicochemical factors that will assist to explain the mechanism by which pseudoephedrine influences the characteristics of wet granulated acetaminophen, and through this, the compressed tablets. To examine these factors, the effects of polymer ratio, total polymer content and amount of the granulating fluid on the granulation and compaction characteristics of such heterogeneous matrices were examined.

2. Materials and methods

2.1. Materials

Acetaminophen (Rhone-Poulenc, NJ, USA) and pseudoephedrine sulfate (Knoll Pharmaceutical, NJ, USA) were chosen as the model drugs. Other materials used in this study were as follows: hydroxypropyl methylcellulose (HPMC: Methocel® E4M, Dow Chemical, MI, USA), hydroxypropyl cellulose (HPC: Klucel® LF, Aqualon, DE, USA), magnesium stearate, NF (Mallinckrodt, MO, USA) and Cab-O-Sil M5 (Cabot Corporation, IL, USA). All materials were used as received without further purification.

3. Methods

3.1. Preparation of granules

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) Cab-O-sil and various HPMC and HPC blends were

Table 1
Composition of matrix formulations

Matrix formulation	Polymer ratio[a]	Model drug	Total polymer (%)
A	2:1		
B	4:1.5	APAP	6.3
C	5:1.3		
D			3.5
B			6.3
E	4:1.5	APAP	9.6
F			19.2
G	2:1	APAP	
H	4:1.5	+	6.3
I	5:1.3	PE	

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

prepared. The HPMC-to-HPC ratios used were 2:1, 4:1.5 or 5:1.3, while the total polymer content varied from 3.5 to 19.2% (w/w). The composition of the powder blends and the amount of water used as the granulating liquid are shown in Tables 1 and 2, respectively. The quantity of granulating liquid indicated in the above tables represents the amount needed to form a coherent mass, and this was determined from preliminary experiments.

Previously determined amounts of the drug(s), HPMC and HPC were placed in a plastic bag. The Cab-O-sil was premixed with an equal portion of acetaminophen in a small jar. The mixture was passed through a # 30 mesh hand-screen and added to the remainder of the ingredients in a plastic bag. The contents of the bag were further mixed by hand for 2 min to uniformly disperse the polymer in the formulation. The mixture was then transferred to a Collette Gral 10 granulator (Machines Collette, USA). The chopper and mixer speeds were set at 2 for high shear and the matrix ingredients in the stainless steel bowl were further blended for 1 min. The blending was continued and deionized water was passed through an inlet rubber tubing into the bowl at the rate of 20 g/min for 5–10 min. The remainder of the deionized water was added at the rate of 10 g/min and the granulation was further blended for 1 min. The granulated matrix was dried in a fluid bed drier (Model WSG 3-2V, Glatt Air Techniques,

Table 2
Formulation requirements and physical characteristics of matrix base granulations for various designated matrix formulations containing HPMC and HPC as polymeric excipients

Matrix formulation[a]	Amount of water used (g)	Moisture content (% MC)	Percent yield (% Y)	Micromeritic properties[e]			Density[f] (g/ml)		Carr's index (I)
				d_g	σ_g	d_{vs}	V_B	V_T	
A[b]	269.8	1.5	94.0	230	1.60	206	0.47	0.55	14.0
B[b]	307.0	1.1	95.3	231	1.65	204	0.46	0.54	14.0
C[b]	332.3	1.5	91.6	284	1.73	227	0.50	0.56	12.1
D[c]	263.4	1.1	85.0	242	1.58	218	0.52	0.60	14.0
E[c]	332.3	0.9	90.4	283	1.79	239	0.49	0.56	13.1
F[c]	332.7	1.1	92.4	264	1.61	236	0.51	0.58	12.1
G[d]	193.9	1.1	84.9	226	1.60	203	0.53	0.60	11.4
H[d]	160.8	1.1	92.5	228	1.63	202	0.49	0.55	11.0
I[d]	160.6	1.1	91.6	204	1.70	177	0.51	0.58	12.7

[a] Formulas for the specified formulations are contained in Table 1.
[b] Matrix formulation contains APAP as a model drug. The HPMC-to-HPC ratios were 2:1 (A), 4:1.5 (B), or 5:1.3 (C). 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-HPC ratio was kept constant at 4:1.5. The total polymer contents were 3.5% (D), 9.6% (E), or 19.2% (F) (w/w).
[d] Same composition as in footnote b, except that 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).

USA) with inlet air temperature at 60°C. During the drying process, the flap was initially set at 100 to pulse the bed and finally at 25–30. The drying was continued for approximately 11 min and the end point was determined when the bed temperature reached 35°C or when the percent loss on drying (LOD) was 1–1.5%, whichever occurred first. The dried granulation was passed through a # 14 mesh oscillator screen and the percentage yield recorded.

3.2. Characterization of the granules

Loss on drying for the granules was performed by Cenco Moisture Balance (Fisher Scientific, USA). Particle size distribution of each batch of the base granulation was determined by sieve analysis using 100 g of the test material and a series of US standard sieves ranging in size from mesh # 20 to # 140. The test material was placed on the top sieve and mechanically shaken for 10 min on a shaker. The fraction retained on each screen was determined and the average particle size assigned to each isolate was computed by average sieve sizes (in μm) for the 20/40 (637.5 μm), 40/60 (337.5 μm), 60/80 (215 μm), 80/100 (165 μm) and 100/140 (128 μm) sieve fractions. The geometric mean diameter of the granulation was calculated from the sieve analysis data (Phadke and Anderson, 1990).

The bulk density of the granulation was determined by filling the granulation into a tarred graduated cylinder to the 100 ml mark. The graduated cylinder was weighed and the bulk density (V_B) calculated as the ratio of the sample weight to sample volume (Phadke and Anderson, 1990). The graduate was then tapped on a flat surface. The tap density (V_T) was calculated as the ratio of the sample weight to the final sample volume after 100 taps. No further volume reduction occurred after 100 taps. The changes occurring in packing arrangement during the tapping procedure are expressed as the Carr's index (I) as shown by the following equation (Malamataris et al., 1994):

$$I = \left[1 - \frac{V_B}{V_T}\right] \times 100$$

3.3. Compression of matrix tablets

A quantity of the base granulation for each formulation, enough to make 2000 tablets, was weighed and placed in an 8 quart plastic container. The lubricant, 1% (w/w) magnesium stearate, was premixed with an equal portion of the granulation and passed through a # 20 mesh hand-screen. The mixture was blended with the remainder of the granulation for 3 min using a PK blender (Patterson-Kelly, USA). The blend was compressed into tablets on a Manesty B3B instrumented tablet press using a 9/16 inch flat-face tooling, at a compression speed of 203 tpm. Tablets were compressed at varying compression forces ranging from 2000 to 5000 lb.

3.4. Tablet thickness testing

The thickness of the matrix tablets was determined using a Mitutoyo Caliper and the results were expressed as mean values of 10 determinations.

3.5. Tablet weight variation testing

In order to determine batch to batch variations, 10 matrix tablets were selected from a given batch and weighed using a Mettler balance. The results were expressed as mean values of 10 determinations.

3.6. Hardness determination

The hardness of the tablet were determined using the KEY HT 300 hardness tester and the mean of 10 determinations calculated (Esezobo, 1985).

3.7. Friability studies

Tablet friability test was performed on 10 tablets at 25 rpm for 4 min using a Roche friabilator (Sjokvist and Nystrom, 1991). Three replicate determinations of each formulation were averaged.

Table 3
Particle size distribution data for matrix base granulation containing HPMC and HPC as polymeric excipients

Matrix formulation[a]	Average particle size retained (%)							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	
A[b]	5.8	25.5	30.9	16.4	5.4	8.1	7.9	230
B[b]	5.3	26.9	29.6	15.9	5.2	8.3	8.9	231
C[b]	15.3	38.7	22.7	8.8	2.7	4.7	6.7	284
D[c]	6.5	42.8	20.8	11.8	3.8	6.1	8.3	242
E[c]	11.7	37.3	26.3	11.0	3.3	5.1	6.8	283
F[c]	10.0	35.8	28.5	11.7	3.5	5.1	5.3	264
G[d]	3.7	23.0	30.7	19.5	6.8	10.1	6.3	226
H[d]	4.5	24.4	27.8	19.6	6.8	10.1	7.0	228
I[d]	4.1	17.9	22.3	21.3	9.0	15.1	10.3	204

[a] Formulas for the specified formulations are contained in Table 1.
[b] Matrix formulation contains APAP as model drug and 2:1 (A), 4:1.5 (B), or 5:1.3 (C) of 6.3% HPMC/HPC blend.
[c] Matrix formulation contains APAP as model drug and 3.5% (D), 9.6% (E), or 19.2% (F) total polymer comprising 4:1.5 HPMC/HPC blend.
[d] Same composition as footnote b, but contains APAP and pseudoephedrine as model drugs.
[e] Average particle size in μm.
[f] Retained on US standard sieve of mesh size # 20.

3.8. Disintegration testing

The tablet disintegration test was performed according to the USP 23 disintegration test, basket rack assembly method in deionized water at 37 ± 0.5°C. The results were presented as mean values for three tablets (Touitou and Donbrow, 1982).

4. Results and discussion

Table 2 lists the amount of water used to granulate, final moisture contents and the physical characteristics of the granules. The moisture content of the granules ranged from 0.9 to 1.5% (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 Carr's index values for the different matrix systems studied were below the acceptable value of 15% (Marshall, 1989). These results indicate that the matrix granulations formulated with various compositions of HPMC and HPC showed good flow characteristics and hence good compressibility. The small variations in the Carr's index values observed may be attributed to differences in solubilities and molecular weights of acetaminophen and pseudoephedrine present as active ingredients (Dow Chemical Company, 1984).

The sieve analysis data for the granulations are shown in Tables 2 and 3. Formulations (G, H and I) containing pseudoephedrine showed a shift in particle size distribution from the coarser fraction (> 637.5 μm) of the dried granulation to the fines (< 165 μm). The relatively lower values of the mean volume-surface diameter obtained (Table 2) for granules containing pseudoephedrine indicate an increase in their specific surface areas since the volume-surface diameter (d_{vs}) is inversely related to the specific surface area according to the following equation:

$$S_W = \frac{6}{\rho d_{vs}}$$

where S_W is the specific surface area and is the true density of the particle.

Carstensen and Zoglio (1985) have proposed a model for the wet granulation process of a bolus-

type granulation. A schematic diagram of the model is shown in Fig. 1 (Carstensen and Zoglio, 1985). According to this model, "as the granulation fluid is added, two parts exist in the mixer: a bolus wetted part (shown as circles in rectangle) and the unwetted primary particles (shown as random circle). The next step involves shredding off of the nuclei (gray particles) which combine with the primary particle and results in granule growth. This process continues during mixing and eventually all the wet materials get distributed as equilibrium granules".

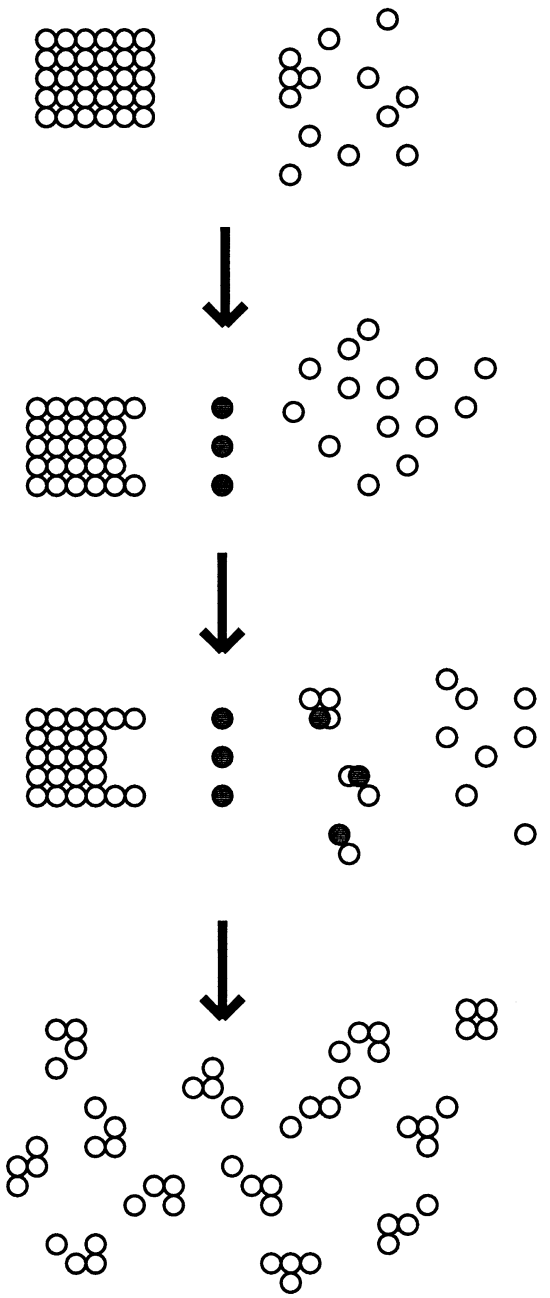

Fig. 1. Model for bolus-type granulation showing bolus wetted part (circle in rectangle), unwetted primary particles (random circle), and nuclei undergoing shredding (gray particles) (Carstensen and Zoglio, 1985).

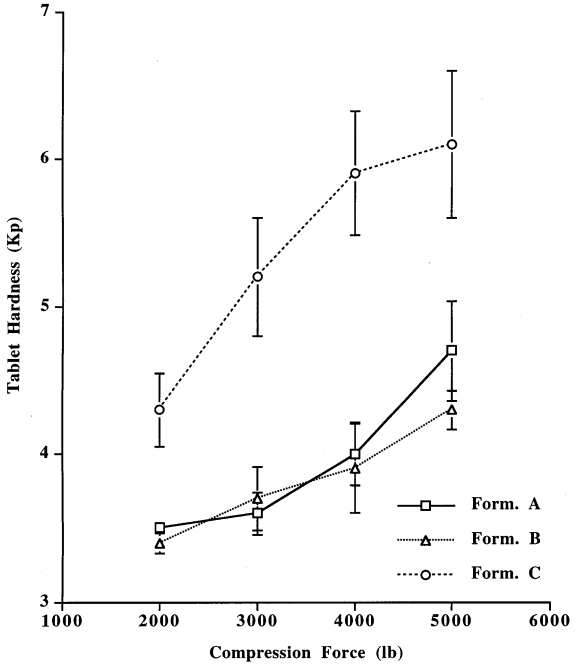

Fig. 2. Tablet hardness as a function of compression force for matrix formulations containing acetaminophen and 2:1 (A), 4:1.5 (B) or 5:1.3 (C) HPMC and HPC as polymeric excipients. Error bars represent the standard deviation.

In the present investigation, formulations containing both acetaminophen and pseudoephedrine (G, H and I) required relatively less water for granulation than similar formulations containing only acetaminophen (A, B and C). This could be because pseudoephedrine has a very high aqueous solubility and hence a small bolus wetted part is formed rather quickly during the wet granulation process. The fewer number of nuclei that are formed compared to the primary particles hinder

granule growth (Phadke and Anderson, 1990). Moreover, the drug may be deposited on the surface of the granules because of the fine particle size (approximately 62 μm) of pseudoephedrine and its high aqueous solubility, thus preventing further granule growth due to electrostatic interactions between particles. It is also possible that the presence of pseudoephedrine particles on the surface of the granules interferes with the hydration process of the polymeric excipients, thus diminishing their wetting capacity. This leads to formation of a small fraction of the wetted bolus and a limited granule growth (Phadke and Anderson, 1990). These results are consistent with the sieve analysis data showing comparatively smaller values of geometric mean diameter obtained for the formulations containing pseudoephedrine as one of the active drugs (Table 2).

Increasing the concentration of HPC in formulations C, B and A from 20, 27 and 30%, respectively, decreased the coarser fraction (>637.5 μm) of the dried granulation and increased the amount of fines (<165 μm) (Tables 2 and 3). Phadke and Anderson (1990) have observed similar results for granulations consisting of HPMC, acetaminophen and increasing levels of polyplasdone X-10. They reported that the effect of crosspovidone (polyplasdone X-10) was attributed to the interference of the hydration of HPMC and an increase in the total surface area of the powder blend. Furthermore, it has been reported that water-soluble polymers compete for available water during the wet granulation process, resulting in an increased amount of the unwetted primary particles that lack cohesiveness and, thus, producing a larger percentage of fines in the granulation (Alderman, 1984). The present data indicated that no particular trend in the size distribution of the granulation was observed when the total polymer content was varied from 3.5 to 19.2% (w/w). Very small changes were observed in the values of the bulk density and tap density for the various HPMC/HPC systems (Table 2).

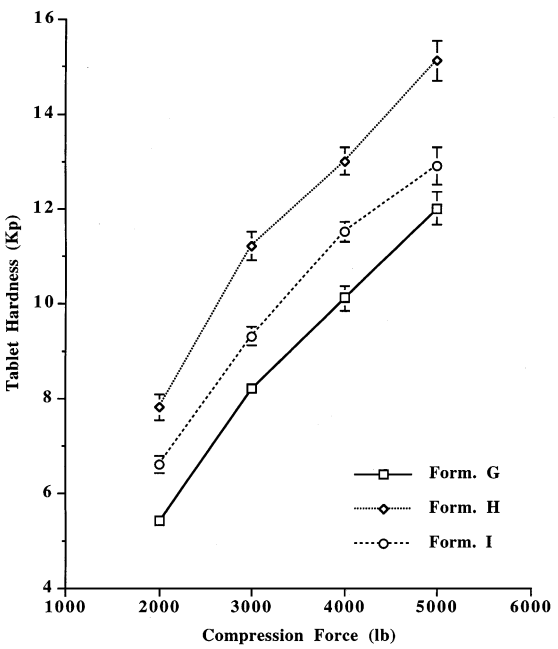

Fig. 3. Tablet hardness as a function of compression force for matrix formulations containing both acetaminophen and pseudoephedrine, and 2:1 (G), 4:1.5 (H) or 5:1.3 (I) HPMC and HPC as polymeric excipients. Error bars represent the standard deviation.

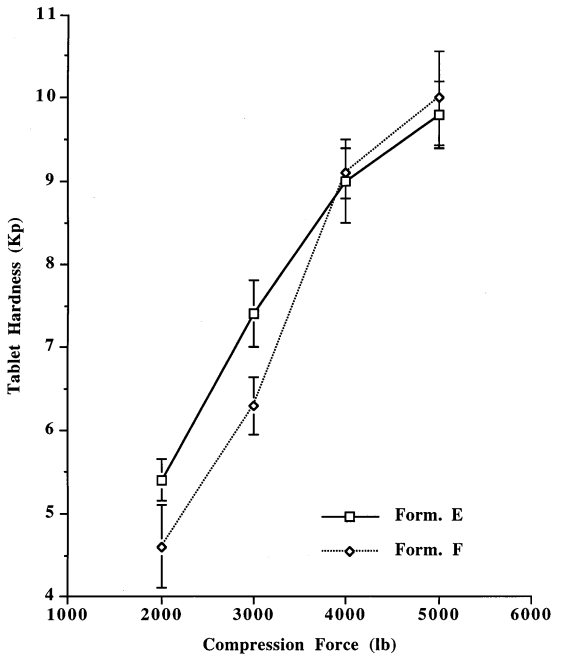

Fig. 4. Tablet hardness as a function of compression force for matrix formulations containing acetaminophen and 9.6% (E) or 19.2% (F) total polymer content comprising 4:1.5 HPMC and HPC. Error bars represent the standard deviation.

Table 4
Comparison of the physical properties of the matrix tablets containing HPMC and HPC and compressed at a compression force of 3000 lb

Matrix formulation[a]	Physical characteristics[b]				
	Hardness (kp), $n = 10$	Thickness (inches), $n = 10$	Weight (g), $n = 10$	Friability (%), $n = 3$	Disintegration time (h), $n = 3$
A[c]	3.63 (0.14)	0.185 (0.001)	0.828 (0.002)	0.52 (0.07)	6.00 (0.14)
B[c]	3.72 (0.22)	0.178 (0.001)	0.800 (0.004)	0.99 (0.01)	5.94 (0.10)
C[c]	5.24 (0.40)	0.178 (0.001)	0.802 (0.007)	0.45 (0.00)	6.25 (0.00)
D[d]	4.95 (0.32)	0.175 (0.001)	0.773 (0.003)	1.81 (0.14)	4.19 (0.03)
E[d]	7.36 (0.40)	0.184 (0.001)	0.832 (0.006)	0.68 (0.01)	>9.00
F[d]	6.26 (0.35)	0.212 (0.001)	0.933 (0.003)	0.66 (0.02)	>10.00
G[e]	8.16 (0.17)	0.191 (0.001)	0.866 (0.004)	1.16 (0.13)	6.27 (0.02)
H[e]	11.23 (0.31)	0.193 (0.001)	0.876 (0.004)	0.62 (0.01)	6.39 (0.19)
I[e]	9.31 (0.19)	0.191 (0.001)	0.869 (0.003)	0.80 (0.08)	7.00 (0.00)

[a] Formulas for the specified formulations are contained in Table 1.
[b] Results represent means of replicate determinations with the standard deviation in parenthesis.
[c] Matrix formulation contains APAP as a model drug. The HPMC-to-HPC ratios were 2:1 (A), 4:1.5 (B), or 5:1.3 (C). 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% (D), 9.6% (E), or 19.2% (F) (w/w).
[e] Same composition as in footnote c, except that it contains APAP and pseudoephedrine as model drugs.

The effect of compression force on tablet hardness for the matrix formulations are shown in Figs. 2–4. As expected, the tablet hardness increased as compression force increased. However, the matrix tablets showed tendency to cap above the compression force of 3000 lb. Tablet hardness increased considerably in formulations containing pseudoephedrine, as shown in Fig. 3. This could be because formulations containing both acetaminophen and pseudoephedrine produced granulation with smaller particle size than those containing only acetaminophen. It is possible that during the tabletting process, the fines filled the interstitial spaces between the coarse particles, which resulted in enhanced interparticular bonding between the particles.

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 7.0 h. 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 a more viscous barrier between the granules and the water, thus resulting in a longer disintegration time (Esezobo, 1985). Except for very few instances, the friability values decreased as the tablet hardness increased for the different matrix formulations. The friability values obtained for formulations containing pseudoephedrine and acetaminophen decreased as the fraction of HPMC in the formulations increased.

5. Conclusions

Pseudoephedrine present as a co-active in a multicomponent formulation has significant effect on the particle size distribution of acetaminophen granulation, tablet hardness and friability. The mechanism of its influence appears to be related to its small particle size and high water absorption capacity. For heterogeneous matrices comprising more than one polymeric component, the granulation and compaction properties of the system can be altered when the hydration characteristics of

one or more of the polymers is affected. A good understanding of the effect of drug(s) and to lesser extent, polymer–polymer ratio and total polymer loading on the overall behavior of the matrix is desirable. The importance of these physicochemical changes on drug release from these heterogeneous matrices has been investigated and the results will be presented in a separate report.

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