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The effect of particle size and viscosity grade on the compaction properties of hydroxypropylmethylcellulose 2208

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Abstract

The influence of particle size and viscosity grade of hydroxypropylmethylcellulose 2208 (HPMC) on the tensile strength, compressibility, energies involved during consolidation, mean yield pressure and elastic recovery of HPMC compacts have been determined. The relationship between particle size, tensile strength and the viscosity grade of HPMC was complex. At smaller particle sizes (< 45 and 45–125 μm), an increase in the viscosity grade of HPMC resulted in a reduction in the tensile strength of its compacts. However, at larger particle sizes (125–180, 180–250 or 250–350 μm), the tensile strength of HPMC compacts decreased with an increase in viscosity grade up to HPMC K15M, but for HPMC K100M there was a small increase in tensile strength. The compressibility indices of HPMC K100, HPMC K4M, HPMC K15M and HPMC K100M increased 58%, 74%, 49% and 70%, respectively, as the particle size was reduced from 250–350 μm to < 45 μm. This indicates that the interparticle frictional and cohesive forces increased with decreasing particle size. The tensile strength of compacts made of the smallest particle size (< 45 μm) fraction at each viscosity grade were at least three times more than the tensile strengths of compacts made of 250–350 μm. Particle size was the single most important factor in controlling the tensile strengths of HPMC tablets. The mean yield pressure to induce plastic deformation calculated from the slopes of Heckel plots was the lowest for HPMC K100. Increase in particle size resulted in an increase in elastic recovery, presumably due to a reduction in the number of particle-particle interaction points during compaction, and in a reduction of the plastic energy for all the samples. The viscosity grade of HPMC had no effect on the elastic energy. Particle size, however, did significantly affect the elastic energy of HPMC K4M and HPMC K100M.

Keywords: Hydroxypropylmethylcellulose; Viscosity grade; Tensile strength; Particle size; Compaction energy; Compressibility index

1. Introduction

The particle size of a material is one of the most important factors affecting tablet strength (Sheikh-Salem and Fell, 1982). It has been claimed that when the interparticulate bonds in a

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compact are weak (e.g. for lactose) the initial particle size is not expected to influence tablet strength (Shotton and Ganderton, 1961). However, Vromans et al. (1985) found that a decrease in particle size of lactose resulted in an increase in tensile strength of the tablets. When the interparticulate bonds are strong, however, fracture occurs across the grains of crystals and the strengths of the resultant tablets are a function of the initial particle size. Generally, smaller particles give stronger tablets (Hüttenrauch, 1977). Smaller particles tend to aggregate under compaction, whereas larger particles are fractured. A number of studies confirm that the fragmentation propensity of a substance under load increases with its particle size (Hersey et al., 1973; McKenna and McCafferty, 1982; Alderborn et al., 1985). For this reason a change in mean particle size may alter the predominant consolidation mechanism.

Alderborn et al. (1988) categorised the effects of particle size on the basis of the mechanisms involved during compaction. For materials with a high tendency to fragment, the original particle size is of less importance than for plastic materials and the tablet strength is generally independent of particle size. For materials with intermediate tendency to fragment, the tablet strength is increased with reducing particle size. For materials with a low tendency to fragment, the situation is complex. Reduction in particle size can give an increase in tablet strength, probably due to the increased number of points of contact between particles.

Compaction speed plays an important role in determining the effect of initial particle size on tensile strength. Differences in the strengths of tablets obtained from different sieve fractions of lactose became negligible as the compaction speed was increased (Alpar et al., 1970). This increase caused a greater fragmentation of the starting material which eliminated any differences between the initial sizes.

For the plastically deforming materials, sodium chloride and potassium chloride, Hersey et al. (1973) and Humbert-Droz et al. (1982) reported that yield pressures were independent of particle size. However, for materials which deform by particle fragmentation (lactose and calcium carbonate) Hersey et al. (1973) and York (1978) found that the yield pressure of compacts increased with a reduction in particle size.

The aims of this study were to determine the effect of different particle sizes of HPMC 2208 of different viscosity grades on compression properties. Malamataris et al. (1994) partly researched the effect of particle size of HPMC on its compression behaviour but only used the < 120, 120–320, and > 320 μm fractions of HPMC K4M, HPMC K15M and HPMC K100M. Similarly, Malamataris and Karidas (1994) examined the tensile strength of HPMC matrices but neither study fully examined the compaction behaviour of HPMC in the absence of adsorbed moisture.

2. Materials and methods

Different viscosity grades of hydroxypropylmethylcellulose 2208 (HPMC K100, HPMC K4M, HPMC K15M and HPMC K100M manufactured, respectively, as Methocel K100LV, Methocel K4M, Methocel K15M and Methocel K100M by Dow Chemicals, USA) were used. Particle size fractions (< 45, 45–125, 125–180, 180–250, and 250–350 μm) of each HPMC were obtained by sieving the materials through test sieves (Endecotts Ltd., London, UK) on a mechanical vibrator (Pascal Engineering, Sussex, UK). The sieved fractions were dried at 70°C for 5 days prior to use.

2.1. Determination of packing properties

The compressibility index (Carr, 1965) is a measure of the propensity of a powder to consolidate. The true density (ρ_g), bulk density (ρ_b) and tap density (ρ_t) of different particle size fractions of different viscosity grades of HPMC were determined. True densities were determined using a Beckman air comparison pycnometer model 930 (CA, USA). The bulk density was determined for each polymer from a weighed 10 g sample, carefully poured into a 50 ml cylinder. Then the samples were tapped 100 times to obtain constant volume. Changes occurring in packing arrangement during the tapping procedure are expressed as the compressibility index, Eq. 1.

$$\text{Compressibility index} = [(\rho_t - \rho_b)/\rho_t] \times 100 \quad (1)$$

2.2. Compression

Compressions were carried out using a High Speed Compaction Simulator (ESH Testing Ltd Brierley Hill, UK), as modified at the Liverpool School of Pharmacy, fitted with 12.5 mm flat-faced punches. The details of the compaction simulator have been published elsewhere (Nokhodchi et al., 1995a, b). Four tablets were produced for each particle size of each viscosity grade of HPMC. A constant weight of 400 mg was maintained for all the samples and each tablet was compressed by a compaction force of 10 kN. During compression, upper punch load and punch separation were monitored to an accuracy of ± 0.05 kN and ± 12 μm, respectively (Bateman, 1988). Before each compaction, the die wall was cleaned with acetone and prelubricated with 4% w/w magnesium stearate in acetone.

2.3. Measurement of plastic and elastic energies

The manipulation of compression data has been described previously (Nokhodchi et al., 1995b). For a system where both punches are mobile, the punch separation may be plotted against upper punch force. The area under this curve will be the work done or energy (joules). The plastic and elastic energy of compaction of the HPMC tablets were measured using energy analysis on the force-punch separation plot. Gross, plastic and elastic energies were determined for each compaction.

Fig. 1 illustrates a typical force-punch separation plot, where A is the punch separation at the first measurable force, B is the force at the minimum punch separation D, and C is the decompression force. The area under the curve ABD gives the gross energy, whilst that under curve CBD corresponds to the decompression energy or elastic energy. The net compaction energy or plastic energy was determined from the difference between area ABD and area CBD.

2.4. Heckel analysis

The data were also analysed using Eq. 2 (Heckel, 1961a, b):

$$\ln[1/(1 - D)] = KP + A \quad (2)$$

where D is the relative density of the tablet at pressure P and K denotes a material constant which is the slope of the straight line portion of the Heckel plot (for example, Fig. 2), the reciprocal of which is the mean yield pressure. A is the value of the intercept of the straight line and is a function of the initial bulk volume. Regression analyses were carried out on the Heckel plots for data between 20 and 75 MPa and the mean yield pressures from each set of data. All data were therefore the means of four determinations. The relative densities of the powders (D_o), at the point when a measurable force is applied, and the relative density, D_a, predicted from the intercept of the Heckel plot (Fig. 2), were also calculated.

2.5. Determination of elastic recovery

The percentage elastic recovery of each compact was determined using Eq. 3 (Armstrong and Haines-Nutt, 1972; Malamataris et al., 1984);

$$ER = [(H_t - H_m)/H_m] \times 100 \quad (3)$$

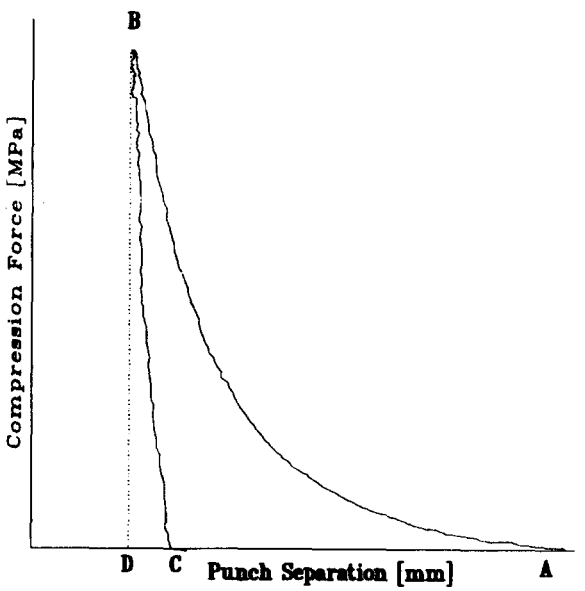

Fig. 1. Typical force-punch separation plot for HPMC K4M obtained at a compression speed of 15 mm/s.

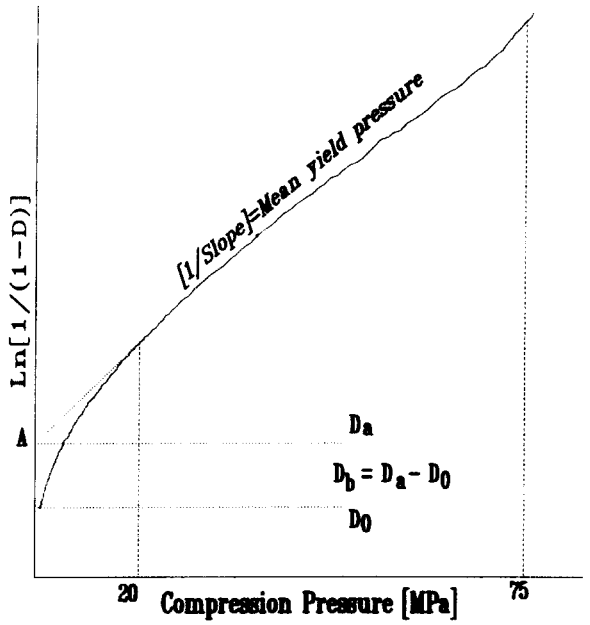

Fig. 2. Typical Heckel plot for HPMC K4M obtained at a compression speed of 15 mm/s.

where H_m is the height of the tablet at maximum compression force and H_t is the tablet height 24 h after ejection.

2.6. Tensile strength

Tensile strengths were determined from the force required to fracture tablets by diametral compression on a motorised tablet hardness tester (model 2E, Schleuniger, Zurich, Switzerland). The tensile strengths were calculated according to Eq. 4 (Fell and Newton, 1970):

$$T = 2P/\pi DH \quad (4)$$

where T is the tensile strength, P is the applied load, D and H are tablet diameter and thickness, respectively.

2.7. Statistical analysis

All data were statistically analysed by two-way analysis of variance and Tukey's multiple comparison test. Results are quoted as significant where $P < 0.05$.

3. Results and discussion

Table 1 gives data indicating the effects of viscosity grade and particle size of HPMC on the tensile strength of its compacts. Two-way analysis of variance confirmed that there were significant differences in tensile strength between the various viscosity grades. Tukey's test showed that tensile strength decreased as the viscosity grade increased from HPMC K100, through HPMC K4M to HPMC K15M for all particle sizes. However, with the exception of the 250–350 μm fractions, there were no statistical differences between the data for HPMC K15M and for HPMC K100M. Two-way analysis of variance also showed that there was interaction between particle size and viscosity grade of HPMC.

The tensile strengths of tablets containing the smaller particle sizes (<45 and 45–125 μm) of HPMC K100 or HPMC K4M were statistically similar (Tukey's test) but were significantly higher (Tukey's test) than for tablets containing the same size fraction of HPMC K15M or HPMC K100M which were also statistically indistinguishable from each other (Tukey's test). The tensile strengths of matrices containing 125–180 or 180–250 μm HPMC K100 were significantly higher (Tukey's test) than the tensile strengths of tablets containing similarly sized HPMC K4M, HPMC K15M or HPMC K100M which were also indistinguishable by Tukey's test from each other (Table 1). Paradoxically, the strengths of tablets containing 250–350 μm HPMC K100 or HPMC K100M were statistically higher than those of matrices containing similar sized fractions of HPMC K4M or HPMC K15M.

For each particle size, compacts made from the lowest viscosity grade (HPMC K100) had the highest tensile strengths and the lowest tensile strengths were found for compacts composed of either HPMC K15M or HPMC K100M (Table 1). These results indicate that densification of the polymer became less difficult as the viscosity grade of HPMC decreased. The subsequent increase in tensile strength at larger particle sizes was probably due to an increase in plastic flow, which would cause a resistance to fracture during the diametral compression.

Table 1
The effect of particle size on the tensile strengths (MPa) of HPMC compacts of different viscosity grades prepared at a compression speed of 15 mm/s and compression force of 10 kN (results are the means and standard deviations of four determinations)

Particle size (μm)	Tensile strength (MPa ± SD)			
	HPMC K100	HPMC K4M	HPMC K15M	HPMC K100M
<45	2.03 ± 0.10	2.02 ± 0.06	1.73 ± 0.41	1.67 ± 0.06
45–125	1.47 ± 0.23	1.33 ± 0.02	0.85 ± 0.06	0.88 ± 0.03
125–180	1.01 ± 0.04	0.70 ± 0.06	0.64 ± 0.07	0.74 ± 0.06
180–250	0.82 ± 0.07	0.64 ± 0.02	0.60 ± 0.04	0.64 ± 0.04
250–350	0.57 ± 0.04	0.48 ± 0.03	0.45 ± 0.01	0.57 ± 0.05

Particle size had a marked effect on the tensile strength of the HPMC compacts (Table 1). A decrease in the particle size resulted in an increase in tensile strength of compacts at all viscosity grades of HPMC. Particle size is one of the most important factors which controls the tensile strength of compressed tablets. Both the direction and magnitude of the effect of particle size on tablet strength vary between substances and are related to the fragmentation propensity of the materials. For a highly fragmenting material, such as dicalcium phosphate (De Boer et al., 1978) the original particle size is of less importance than for plastic materials and the tablet strength is generally independent of particle size. For materials which fragment to a lesser extent, e.g. lactose (Cole et al., 1975) significant changes in tablet strength due to changes in particle size or shape have been observed. In materials undergoing extensive fragmentation, new clean surfaces are created during the compression and therefore the particle size of the original material exerts a smaller effect compared with those materials which are less prone to fragmentation.

The dependence of tablet strength on particle size for each of the HPMCs suggests that extensive fragmentation did not occur during compression of HPMC. Generally, the particle size of HPMC had a significant effect (two-way analysis of variance) on tensile strength. The tensile strengths of each particle size fraction of HPMC K100 could clearly be differentiated from each other (Tukey's test). On the other hand, there were no significant differences between the 125–180 μm and 180–250 μm fractions of HPMC K4M and HPMC K15M (Tukey's test). For HPMC K100M the 180–250 and 250–350 μm fractions could not be differentiated by Tukey's test.

Table 2 shows the effect of particle size and viscosity grade of HPMC on the compressibility index (CI). Increase in particle size resulted in a decrease in compressibility index for each grade of HPMC. This indicates that there is an increase in both the interparticulate frictional and cohesive forces with decreasing particle size. These factors may explain the increase in tablet tensile strength with decreasing particle size of different viscosity grades of HPMC (Table 1) and the CI may indicate the ease with which particle rearrangement occurs. Two-way analysis of variance showed that both particle size and viscosity grade had a significant effect ($P < 0.05$) on the compressibility index of HPMC samples and there was interaction between particle size and viscosity grade of HPMC. Tukey's test showed that the compressibility indices of HPMC K100 and HPMC K100M were affected up to 125–180 μm. In other words, there was no significant difference between their 180–250 and 250–350 μm fractions. The compressibility index of each particle size fraction of HPMC K4M could clearly be differentiated from each other ($P < 0.05$) with the exception of 180–250 and 125–180 μm fractions. On the other hand, for K15M, there was no significant difference between the 250–350 and 180–250 and the 45–125 and <45 μm fractions. Tukey's test showed that the <45 μm fraction of HPMC K4M had significantly the highest compressibility index. At 45–125 μm the compress-

Table 2
The effect of viscosity grade and particle size of HPMC on the compressibility indices (results are the means and standard deviations of four determinations)

Particle size (μm)	Compressibility index (%$\pm$SD)			
	HPMC K100	HPMC K4M	HPMC K15M	HPMC K100M
<45	35.9$\pm$1.9	42.6$\pm$0.5	36.9$\pm$0.5	39.3$\pm$0.7
45–125	34.3$\pm$0.8	34.4$\pm$0.9	35.2$\pm$1.0	33.1$\pm$0.8
125–180	26.3$\pm$3.1	30.7$\pm$1.0	31.7$\pm$0.9	25.7$\pm$1.7
180–250	23.2$\pm$2.1	29.4$\pm$0.6	26.8$\pm$1.6	24.1$\pm$0.2
250–350	22.7$\pm$1.6	24.5$\pm$0.8	24.8$\pm$1.0	23.2$\pm$0.9

ibility index was not affected by viscosity grade of HPMC. The compressibility index appeared to be independent of the viscosity grade.

The effects of particle size on the mean yield pressures for the HPMCs are shown in Fig. 3. For each of the HPMCs, except HPMC K100M, the mean yield pressures were independent of the particle size. For HPMC K100M, the mean yield pressures decreased with increase in the particle size. This would be expected for a material that deforms by the combined mechanisms of particle fracture and plastic deformation. This conclusion is supported by the fact that the calculated mean yield pressures were unaffected by particle size for all the HPMCs except K100M (Fig. 3), indicating that the deformation properties were unchanged for HPMC K100, HPMC K4M and HPMC K15M by particle size. Thus HPMC K100M performs similarly to lactose, where the yield pressure increased as its particle size decreased (Roberts and Rowe, 1986) in contrast to the other grades of HPMC which performed similarly to microcrystalline cellulose (Roberts and Rowe, 1986). Two-way analysis of variance showed that there was interaction between particle size and viscosity grade of HPMC (Fig. 3).

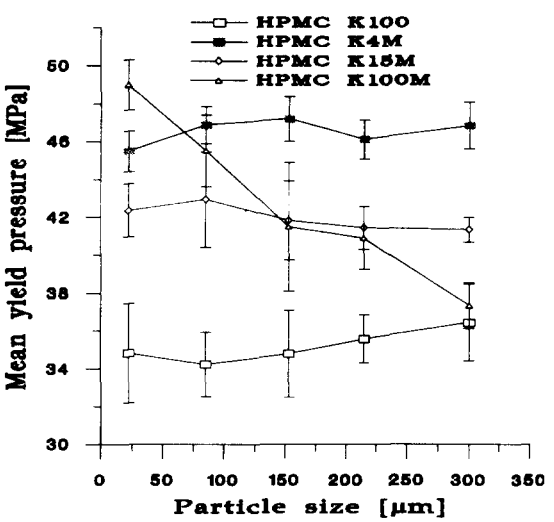

Fig. 3. The effects of particle size and viscosity grade of HPMC on the mean yield pressures of tablets compressed at a compression speed of 15 mm/s to a compression force of 10 kN (results are the means and standard deviations of four determinations).

The effects of particle size on the elastic recovery of the HPMCs are shown in Fig. 4. Elastic recovery, in the die, increased with increasing particle size and was generally independent of the grade of HPMC. Indeed, for the 250–350 μm fractions of HPMC, only HPMC K100M could be differentiated from the other HPMCs by Tukey's test. Two-way analysis of variance showed that there was interaction between particle size and viscosity grade of HPMC (Fig. 4). The effects of particle size on the plastic energy of different viscosity grades of HPMC are illustrated in Table 3. Generally the plastic energies decreased with increase in particle size but were independent of viscosity grade and this was confirmed by two-way analysis of variance. The smaller particle sizes of HPMC gave thinner tablets (Table 4) which would indicate that the top punch had travelled further during compression. The corresponding increase in plastic energy or net compaction energy should indicate a higher ability of the smaller sized material to deform plastically.

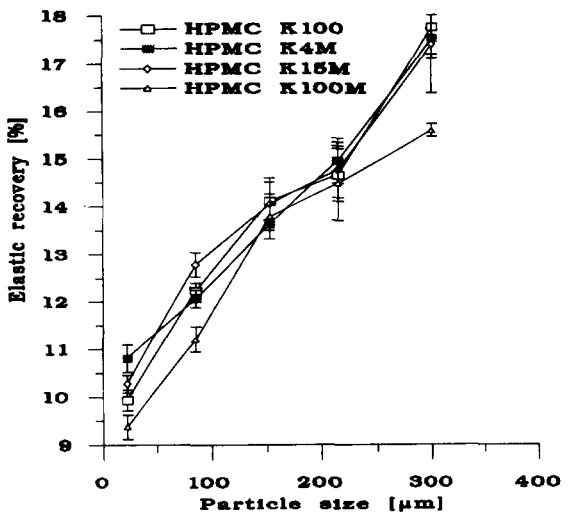

Fig. 4. The effect of particle size and viscosity grade of HPMC on the elastic recoveries of compacts compressed at a compression speed of 15 mm/s to a compression force of 10 kN (results are the means and standard deviations of four determinations).

Since particle size had no significant effect on the plasticity, i.e. mean yield pressure, of the HPMCs except HPMC K100M (Fig. 3), it may therefore be assumed that the effect of particle size on the plastic energy is not due to differences in the plasticity but is caused by differences in particle interactions, i.e. the number of contact points. This interaction may be due to interparticle friction or a different degree of bonding. This explanation will also apply to the effects of particle size on tensile strength (Table 1), and elastic recovery (Fig. 4).

The plastic energy of HPMC K100M was independent of the particle size. However, for HPMC K100, HPMC K4M and HPMC K15M, the plastic energies significantly decreased (Tukey's test) as the particle size was increased from <45 μm to 125–180 μm whereas the plastic energies could not be differentiated for particle size fractions of 125–180, 180–250 and 250–350 μm.

The effects of particle size on the elastic energy of different viscosity grades of HPMC are shown in Table 5. Two-way analysis of variance showed that an increase in particle size generally increased elastic energy for all K grades of HPMC. This was due to a decrease in the number of particle-particle interaction points. These trends were supported by the increase in elastic recovery of the compacts (Fig. 4) with increasing particle size. Two-way analysis of variance also showed that the viscosity grade of HPMC had no significant effect on the elastic energy.

Tukey's tests showed that the particle size had no significant effect on the elastic energies of HPMC K100 and HPMC K15M but had a significant effect on the elastic energies of HPMC K4M and HPMC K100M.

The compression studies showed that HPMC K100 is the easiest of four polymers to compress and it undergoes more plasticity during compression. This study also showed that not only viscosity grade but also the particle size of HPMC affected their compression and compaction properties. Since the compaction characteristics of polymers are dominant factors in choosing a polymer for sustained release, the selection of a definite particle size and viscosity grade of HPMC may be important in the formulation of a controlled release drug delivery system.

4. Conclusion

The results suggest that tensile strength, compressibility index, plastic and elastic energies and elastic recovery are significantly affected by particle size of HPMCs. It was found that the smallest particle size (<45 μm) and the lowest viscosity grade (HPMC K100) of HPMC have the best compaction properties compared with the other particle sizes and viscosity grades. HPMC K100 produced compacts of superior mechanical strength compared with the other grades. This study also showed that HPMC K100 and HPMC K4M can probably be chosen for sustained release drug delivery systems because of their high tensile strength. The plastic energy of HPMC K100M was independent of its particle size. Elastic energy was not affected by the viscosity grade of HPMC. The mean yield pressures of the different viscosity grades of HPMC were not affected by particle size except for the highest viscosity grade (HPMC K100M). This study, however, has not attempted to correlate compaction properties

Table 3
The effect of viscosity grade and particle size of HPMC on the plastic energies of tablets compressed at a speed of 15 mm/s to a compression force of 10 kN (results are the means and standard deviations of four tablets)

Particle size (μm)	Plastic energy (Joule ± SD)			
	HPMC K100	HPMC K4M	HPMC K15M	HPMC K100M
<45	6.83 ± 0.31	6.85 ± 0.20	6.80 ± 0.25	6.33 ± 0.15
45–125	6.64 ± 0.25	6.60 ± 0.22	6.58 ± 0.40	6.54 ± 0.06
125–180	6.09 ± 0.33	5.86 ± 0.12	6.16 ± 0.26	5.88 ± 0.22
180–250	6.08 ± 0.17	5.93 ± 0.14	5.98 ± 0.18	6.12 ± 0.56
250–350	5.97 ± 0.23	5.91 ± 0.07	6.13 ± 0.11	5.85 ± 0.43

Table 4
The effect of particle size of HPMC on the thicknesses of tablets in the die and obtained at a compression force of 10 kN and speed of 15 mm/s (results are the means and standard deviations of four tablets)

Particle size (μm)	Thickness of tablets (mm ± SD)			
	HPMC K100	HPMC K4M	HPMC K15M	HPMC K100M
<45	2.494 ± 0.020	2.473 ± 0.051	2.500 ± 0.023	2.501 ± 0.004
45–125	2.536 ± 0.029	2.526 ± 0.027	2.549 ± 0.021	2.551 ± 0.007
125–180	2.548 ± 0.023	2.555 ± 0.013	2.555 ± 0.006	2.556 ± 0.016
180–250	2.577 ± 0.032	2.552 ± 0.004	2.572 ± 0.008	2.575 ± 0.013
250–350	2.566 ± 0.007	2.575 ± 0.025	2.570 ± 0.009	2.580 ± 0.012

Table 5
The effect of viscosity grade and particle size on the elastic energies of HPMC compacts compressed at a compression speed of 15 mm/s to a compression force of 10 kN (results are the means and standard deviations of four tablets)

Particle size (μm)	Plastic energy (Joule ± SD)			
	HPMC K100	HPMC K4M	HPMC K15M	HPMC K100M
<45	1.30 ± 0.13	1.33 ± 0.15	1.22 ± 0.15	1.03 ± 0.05
45–125	1.38 ± 0.22	1.29 ± 0.14	1.32 ± 0.24	1.18 ± 0.13
125–180	1.45 ± 0.06	1.35 ± 0.11	1.35 ± 0.17	1.39 ± 0.15
180–250	1.43 ± 0.10	1.58 ± 0.08	1.40 ± 0.15	1.32 ± 0.19
250–350	1.52 ± 0.32	1.58 ± 0.06	1.50 ± 0.16	1.61 ± 0.22

with dissolution rate data and it is possible that the grades of HPMC most suited by their compression properties may not give the desired dissolution rate profiles.

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