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Initial studies of water granulation of eight grades of hypromellose (HPMC)

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Abstract

The purpose of this study is to investigate the water granulation mechanism of the hydrophilic matrix polymer HPMC in a high shear mixer and to relate the properties of the granules and tablets to the molecular weight and the degree of substitution for eight HPMC grades. Although the hydrophilic matrix system is a well known drug delivery one, there is a difficulty in that the desirable water granulation technique often causes problems in the presence of relatively large amounts of HPMC due to its hydrophilicity. The results of this study show that the properties of the granules and the tablets fall into two groups according to whether the molecular weight of the polymer is high or low. The granules of low molecular weight were smaller and more compact, with better flow properties but with less tensile strength of the compacts, whereas the opposite was valid for granules of high molecular weight. The explanation for these differences is linked to the proposed granulation mechanism of HPMC, in which the properties of the gel layer are important. The dominant factors governing the properties are the molecular weight and, to lesser extent, the degree of substitution.

Keywords: Hydroxypropyl methylcellulose; Water granulation; Molecular weight; Degree of substitution; High shear granulation

1. Introduction

Hypromellose (HPMC) is widely used as a drug release rate controlling excipient in hydrophilic matrix tablets, since it is odorless, tasteless, non-toxic and easy to handle (Huber et al., 1966; Lapidus and Lordi, 1968). The HPMC is available in several pharmaceutically approved grades with various viscosities and different degrees of substitution of the hydroxypropoxyl and methoxyl groups. Since all of these parameters regulate the drug release rate (Nellore et al., 1998), there is an opportunity during the development of hydrophilic matrix tablets to obtain a specific drug release profile simply by changing the grade of the HPMC. However, this requires that it be possible to process the HPMC powders to obtain well defined tablets.

It is well known that the commercially available HPMC grades consist of irregularly shaped particles of small sizes (Bonferoni et al., 1996). This gives poor powder flow and may cause problems, for example in high rotary speed tablet presses (Sheskey and Williams, 1996; Nellore et al., 1998). Therefore, a size enlargement step is usually required to improve the flow properties of the HPMC primary particles and to obtain a robust production method for the hydrophilic matrix tablets. Several particle size enlargement methods, such as roller compaction (Sheskey et al., 1994, 2000; Sheskey and Hendren, 1999), wet granulation (Timmins et al., 1991, 1992; Liu et al., 1993; Sheskey and Williams, 1996; Xu et al., 1997; Nellore et al., 1998), which includes fluid-bed granulation (Dahl and Bormeth, 1990; Nellore et al., 1998; Rekhi et al., 1999), have been evaluated for hydrophilic polymers. The roller compaction technique generally offers low production costs; from environmental point of view it is a good alternative since it does not use organic solvents (Miller, 1994). However, the main disadvantage of this technique is the partial production of non-compacted (and thus non-granulated) material, which may lead to segregation and low flowability of the powder (Inghelbrecht and Remon, 1998). Wet granulation techniques that require an organic solvent or a mixture of organic solvent and water are undesirable for environmental and health care reasons, whereas the use of pure water

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as the granulation liquid for hydrophilic matrix compositions may give lump formation (Shah et al., 1996). On the other hand, Timmins et al. (1992) have pointed out that water can be used as the granulation liquid for hydrophilic based matrix tablets.

The present paper investigates the influence of different degrees of HPMC on the lump formation, characterized as agglomerates >1 mm, when water granulation is the chosen particle enlargement method. Furthermore, the literature lacks studies that connect the properties of the HPMC to those obtained for granules and compacts, when water is used as the granulation liquid. This investigation deals specifically with this connection. To strengthen the effect of the polymer properties on the characteristics of the granules and tablets, pure polymer compositions, without other excipients and drugs, are investigated. The desirable properties of granules, such as high bulk densities and good flowability, are generally promoted by adding standard excipients or drugs, like diclofenac, to the formulation (Liu et al., 1993).

2. Materials and methods

2.1. Materials

Hypermellose (HPMC) obtained from two suppliers, Metolose from Shin Etsu Chemical Co., Tokyo, Japan, and Methocel from Dow Chemical Company, Midland, MI, USA, was studied. The qualities of the HPMC used are presented in Table 1. Purified water was used as the granulation liquid and sodium stearyl fumarate (MOEHS, Barcelona, Spain) was chosen as the lubricant for the tablets when the release was investigated.

2.2. Characterization of polymers

The molecular weights of HPMC samples were determined using size exclusion chromatography equipped with a multi-angle laser light scattering detector and a refractive index detector. The system consisted of a TSK-GEL GMPW$_{XL}$, 7.8 mm × 300 mm size exclusion column (TosoHaas, Montgomeryville, PA), with a particle size of 13 μm and a linear mixed bed. The column was connected online to a multi-angle laser light scattering detector (DAWN DSP, Wyatt Technology, Santa Barbara, CA) and a refractive index detector (Optilab DSP, Wyatt Technology). The ASTRA 4.73 software (Wyatt Technology) was used to analyze the RI and MALLS chromatograms obtained. The analyses were made at room temperature. The flow rate of the mobile phase (0.01 M NaCl and 0.02% NaN_3) was 0.5 ml/min, and the sample concentrations ranged from 0.3 to 0.5 mg/ml. For further information about the molecular weight determination, see Körner et al. (2005). The apparent particle density (B.S. 2955, 1958) on primary particles and granules was measured with a helium pycnometer (AccuPycc 1330, Micromeretics, USA) and the reported results are based on 10 repeated runs for each sample.

The cloud point was defined as the temperature where the transmission of white light was reduced to 96% of the original transmission upon heating of a 1% water solution of the polymers. The measurements were performed in triplicate in a MettlerToledo FP 90 with a Mettler FP 81C MBC cell (Mettler-Toledo GmbH, Switzerland).

Particle size analysis of the starting material was carried out with a laser diffraction analyzer (Coulter LS, Coulter, USA) equipped with a dry powder module and by using the Fraunhofer model for data analysis. The particle diameters were measured as an average of two runs for each batch; this refers to the calculated average sizes based on volume distributions.

2.3. Granulation and characterization of granules

The powder (200 g) was placed in a high-shear mixer (Braun Combimax 750), equipped with a specially designed impeller that has four blades but no chopper. The ratio of water to dry

Table 1
Information about the starting materials, Metolose and Methocel

Manufacturer	Polymer[a]	USP[b]	Molecular weight[c] (g/mol) ($\times 10^3$)	Polydispersity index[d]	Apparent particle density[e] (g/cm^3)	Average particle size[f] (μm)	Cloud point data[g] (°C)
Shin Etsu Chemical Co., Ltd.	60SH50	2910	96	2.4	1.282	90	50.8
	60SH10000	2910	443	4.2	1.282	89	49.6
	65SH50	2906	88	2.1	1.293	102	54.4
	65SH4000	2906	341	3.6	1.307	94	53.3
	90SH100	2208	103	2.2	1.327	97	65.1
	90SH15000	2208	435	3.7	1.326	136	60.1
Dow Chemical Company	K100LV	2208	134	2.8	1.323	112	64.7
	K4M	2208	312	3.0	1.319	100	61.7

[a] The trade designations.
[b] Degree of substitution according to the US Pharmacopeia Classification.
[c] The average weight molecular weight and the relative standard deviation, based on three injections, was less than 3%.
[d] Polydispersity index was defined as the ratio between the average weight and number molecular weights.
[e] Standard deviation based on 10 determinations was less than 0.008.
[f] Average based on two measurements that differed less than 1 μm.
[g] Average based on three determinations, standard deviation less than 0.8.

polymer content was chosen after making some preliminary tests. These tests covered water to polymer ratios (0.67–0.82), water addition times (3–7 min), wet massing times (1–3.5 min) and drying times in a fluid bed (15–30 min). From these preliminary experiments a set of process parameters was selected to facilitate evaluation of the properties of the granules and the tablets for all HPMC grades using the same process parameters. The parameters were: 145 g of water was sprayed into a mixing bowl at an approximate rate of 40 g/min; after the water addition the wet mass was further agitated for 1 min and the granules obtained were dried for 30 min at 60 °C in a fluid bed (Uni-Glatt, Glatt, Germany).

A halogen moisture analyzer (HR37 Halogen Moisture Analyzer, MettlerToledo) was used for measurement of the moisture content of the granules by heating 3 g of the sample at 110 °C for 10 min. This time interval was long enough for a stable plateau to be reached when no further loss of weight was observed. The percentage loss of weight, corresponding to water evaporation, was then calculated and set equal to the moisture content. The moisture content was measured directly after the granulation, and again after drying and equilibrating at 45% relative humidity and room temperature.

The flow properties of the granules were examined with an Erweka GT Granule tester (Erweka, Germany). The granules were poured into a funnel and then allowed to pass through a nozzle onto a balance-plate. A force feeder at level 3 and a nozzle size of 11.3 mm were used to ensure good reproducibility of the tests. The angle of repose was determined with a laser beam that scanned the heap of granules formed on the balance-plate. The mass flow rate was measured as the mass of granules flowing through the nozzle onto the balance during a period of 10 s. Nine runs were made for each batch. The average values and the standard deviation were recorded for these measurements. The standard deviation was below 3.5 g/s for the mass flow rate and below 3° for the angle of repose for all HPMC batches. The bulk and tapped densities were determined using a tap volumeter (J. Engelsmann Apparatenbau, Germany). The bulk densities, σ_b, were established by pouring the granules into a 100 ml cylinder and weighing it; the tapped densities, σ_t, were determined after tapping the cylinder 1250 times. The Hausner ratio was calculated as the ratio of the bulk and tapped densities, while the Carr index, CI, was calculated as:

$$\mathrm{CI} = \frac{\sigma_t - \sigma_b}{\sigma_t} \times 100 \qquad (1)$$

The size distribution of the granules was determined by sieve analysis (Sonic sifter, Allen Bradley, USA). Approximately 6 g of granules were sieved for 10 min. The granules were analyzed qualitatively with scanning electron microscopy, SEM (Leo Ultra 55 FEG SEM, Leo, Germany), and microphotographs of unsputtered granules were taken.

2.4. Preparation and characterization of the tablets

The granules were equilibrated at 45% relative humidity and room temperature before compaction using a Korsch EK-0 (Korsch, Germany) instrumented single punch press. The mass of the compacts was calculated for each individual batch to correspond to a tablet height of 35% of the punch diameter at zero tablet porosity. Each sample was weighed on an analytical balance and poured manually into the die. The tablets were compacted at a compaction speed of 30 rpm; the punch and the die were wiped clean with ethanol (99.5% pure) between each tablet compaction. To investigate the mechanical strength, unlubricated granules were compacted using 10 mm flat-faced punches and a compaction pressure of 200 MPa (±7%). The masses of the eight batches were between 430 and 450 mg, depending on the apparent density. For the dissolution study, lubricated granules (lubricated with 0.5%, w/w, sodium stearyl fumarate) were compacted using 8 mm flat-faced punches and a compaction pressure of 100 MPa. The masses of these tablets were 170–185 mg, depending on the apparent density.

The tablets were stored for at least 6 days, in 45% relative humidity and at room temperature, before characterization. The height and diameter of the tablets were determined using a micrometer gauge (Mitutoyo, Japan). The total porosity of the compacts was calculated from the apparent particle density of the granules, and the weight and volume of the compacts.

The tablets were loaded diametrically using a tablet hardness tester (Holland C50, UK) at a loading rate of 2 mm/min until they fractured in tension. The radial tensile strength was calculated from the force needed to fracture the tablets ($n = 5$) according to:

$$\sigma_x = \frac{2P_x}{\pi D H} \qquad (2)$$

where P_x is the breaking load (N), D and H (m) are the diameter and thickness of the tablets, respectively, measured as described above and σ_x is the radial tensile strength ($\mathrm{N\,m^{-1}}$) (Fell and Newton, 1970).

The release of polymers from the tablets was studied by using a USP II paddle apparatus at 100 rpm (Prolabo, France). Preweighted tablets were placed in baskets with mesh sizes of about 3 mm, and the baskets were placed 1 cm above the paddle tip. The release medium was phosphate buffer (pH 6.8, $I = 0.1$). At predetermined times the tablets were taken out, dried in an oven at 60 °C overnight (HORO, Germany) and weighed again. The material released was assumed to be equal to the decrease in mass of the tablet before exposure to water and after drying.

3. Results and discussion

3.1. Properties of the original powder

The characteristics of the granulation process, as well as the properties of the granules, depend on the properties of the starting material. Therefore, the molecular weights, particle sizes, particle size distributions and apparent densities of the starting material were characterized and the averaged data are presented in Table 1.

The molecular weights for HPMC batches with low viscosity grade range from 88 to 134×10^3 g/mol, which is about one-third of the molecular weight for the HPMC batches with high viscosity. The polydispersity index, defined as the ratio

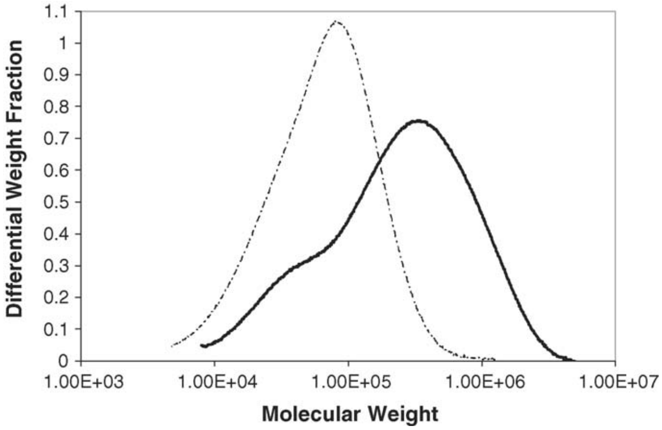

Fig. 1. The molecular weight distributions for HPMC 60SH50 (broken line) and HPMC SH10000 (solid line).

between the average weight molecular weight and the average number molecular weight, is shown in Table 1. The polydispersity index is between 2.1 and 4.2 for all polymer batches, with a tendency of increasing polydispersity index with increasing molecular weight. In Fig. 1 the molecular weight distributions for 60SH10000, the batch with the highest polydispersity index, and 60SH50 showed, where the later is displayed as a reference with a considerable lower polydispersity index but with the same degree of substitution. As can be seen in the figure, 60SH10000 has a tendency of being a mixture of one low and one high molecular weight samples, which is a common procedure of the suppliers to do then they want gain a correct viscosity. It is well known that the molecular weight of the polymers is related to the viscosity, independently of the polydispersity of the samples. Thus, an increased average molecular weight will increase the viscosity. Furthermore, for hydrophilic matrix systems the molecular weight also affects the drug release rate and the degree of swelling (Gao et al., 1996). In this study, the molecular weight of the starting material is related to properties of the granules and the tablets made with it.

The average particle sizes were determined to be 85–140 μm. These particle sizes are similar to those found by others, for example Heng et al. (2001) presented a sieved median particle size of 112 μm for HPMC K15M, and Gustafsson et al. (1999) reported average particle sizes (determined by laser diffraction) between 90 and 116 μm for the three degrees of substitution (USP 2208, 2906 and 2910). The results in Table 1 show that no trends due to the degree of substitution or to the molecular weight were observed for the particle size or the apparent particle densities. This observation is not obvious, since slightly differing production parameters must be used to obtain the different degrees of substitutions and molecular weights, and these differences in process parameters could have influenced the particle sizes. According to the suppliers, the raw materials in commercially available HPMC are: cellulose fibers from wood pulp as the starting material for the Metolose (Shin Etsu); cotton for the Methocel (Dow). However, these differences in the starting material had no major influence on the particle sizes determined or the molecular weights.

3.2. *Properties of the granules*

The properties of the granules made from eight polymer grades were investigated and are presented in Tables 2 and 3. The moisture content after drying was 1.6–3.6%, see Table 2; it was higher for the granules made of the USP2208 batches than for the other batches. This is in agreement with what Malamataris and Karidas (1994) found for HPMC powder with same viscosity (thus approximately the same molecular weight), but with differing degrees of substitution. They even stored the powder in a variety of environments and relative humidities before determining the moisture content, however in all of the environments the USP2208 batches had a higher capacity to bind water than the other batches (Rajabi-Siahboomi et al., 1996).

By comparing the moisture content (Table 2) as a function of the molecular weight, an interesting trend can be observed. The moisture content is higher for the batches containing low molecular weight polymers than for batches with high molecular weight polymers, which is not shown by the moisture content before drying (data not shown). This trend is not observed in the data presented by Malamataris et al. (1994) where no significant differences in moisture content for ungranualted USP 2208 batches with different molecular weights was found. The fraction passing through a 1 mm sieve screen was determined (Table 2) and this fraction was 83–93% for all batches.

The granules were sieved and evaluated by assuming a model for a normal or a logarithmic normal particle size distribution. The best fits of the experimental data to the models, judged by comparing the R^2 values, were obtained for the logarithmic

Table 2
Moisture content and size of the granules for eight grades of HPMC

USP	Polymer	Moisture after drying (%)	Fraction particles < 1 mm	Normal distribution		log normal distribution	
				Median (μm)	R^2	Median (μm)	R^2
2910	60SH50	2.4	0.88	489	0.94	418	0.998
2910	60SH10000	1.6	0.91	476	0.94	401	0.999
2906	65SH50	1.7	0.93	429	0.91	344	0.998
2906	65SH4000	1.6	0.91	479	0.95	406	0.997
2208	90SH100	3.6	0.91	413	0.92	327	0.999
2208	90SH15000	2.3	0.84	502	0.94	444	0.997
2208	K100LV	3.4	0.94	420	0.92	335	1.000
2208	K4M	2.1	0.85	492	0.90	417	0.994

Table 3
Flow properties of granules in eight grades of HPMC

Granules	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner ratio	Carr index (%)	Mass flow rate (g/s)	Angle of repose
60SH50	0.38	0.46	1.22	18	8.6	40
60SH10000	0.30	0.38	1.25	20	5.4	42
65SH50	0.38	0.45	1.19	16	6.9	38
65SH4000	0.27	0.32	1.21	18	4.9	44
90SH100	0.35	0.44	1.27	21	8.0	40
90SH15000	0.33	0.39	1.20	16	4.9	42
K100LV	0.37	0.45	1.21	17	8.5	38
K4M	0.31	0.37	1.17	15	6.3	42

normal particle size distribution (Table 2); the median values determined by this model are used hereafter. The median sizes of the granules ranged from 330 to 440 μm. The median particle sizes of granules of the low molecular weight polymers 65SH50, 90SH100 and K100LV were smaller than for the corresponding high molecular weight polymers with same degree of substitution. The granules of 60SH had approximately the same size regardless of molecular weight. The particle size distributions, as expected, are shifted to low sizes for batches with low median particle size, see Fig. 2. The fact that the median particle sizes and the distributions depend on the molecular weight indicates that the mechanism for the agglomeration process during the granulation step is also linked to the molecular weight. Another point, shown by the figure, is that the particle size distributions contain a substantial fraction of small particles (<250 μm), which may facilitate producing of tablets with high mechanical strength.

The bulk and tapped densities (Table 3) show that the granules made of polymers with low molecular weights exhibit higher bulk and tapped densities than granules made of the other polymers. The Hausner ratio and the Carr index were calculated to be approximately 1.2 and 18%, respectively, for all batches, indicating fairly good flow properties for all granules (Staniforth, 1988). The mass flow rates (4.9–8.6 g/s) and angle of repose (38–44) indicate better flow properties for granules of low molecular weight polymers than those of high molecular weight.

The scanning electron micrographs of randomly chosen granules (Fig. 3) show agglomerates in which the individual primary particles can be identified. Some of the primary particles protrude out from the surface of the granules. There is a limited tendency for more primary particles to protrude from the granules of high molecular weight polymers, as indicating by a more irregular surface. The particle shape is also somewhat elongated depending on the molecular weight, where the granules of high molecular weight have a small tendency to be more irregularly shaped. This somewhat rougher surface may be the reason why the flow properties are not as good for the high molecular weight granules as for those of low molecular weight.

3.3. Properties of the tablets

The tensile strength of the HPMC tablets was determined 6 days after compaction, see Table 4. As can be seen in the table, the tensile strength for all eight kinds of tablets is below 1.5 MPa. The same as for the properties of the granules, the tensile strengths and the porosities can be divided into two groups: the granules of polymers of high molecular weight belong to the group of tablets that have higher tensile strength than the second group. Gustafsson et al. (1999) have measured the tensile strength of tablets made from different sieving fractions of primary particles of HPMC batches of different viscosities

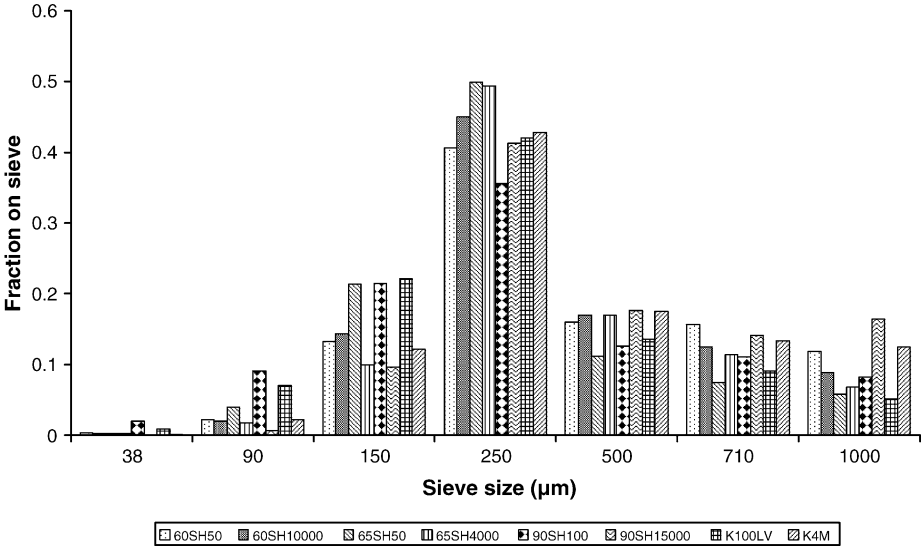

Fig. 2. Size distribution of granules made of eight HPMC grades, as identified in the legend.

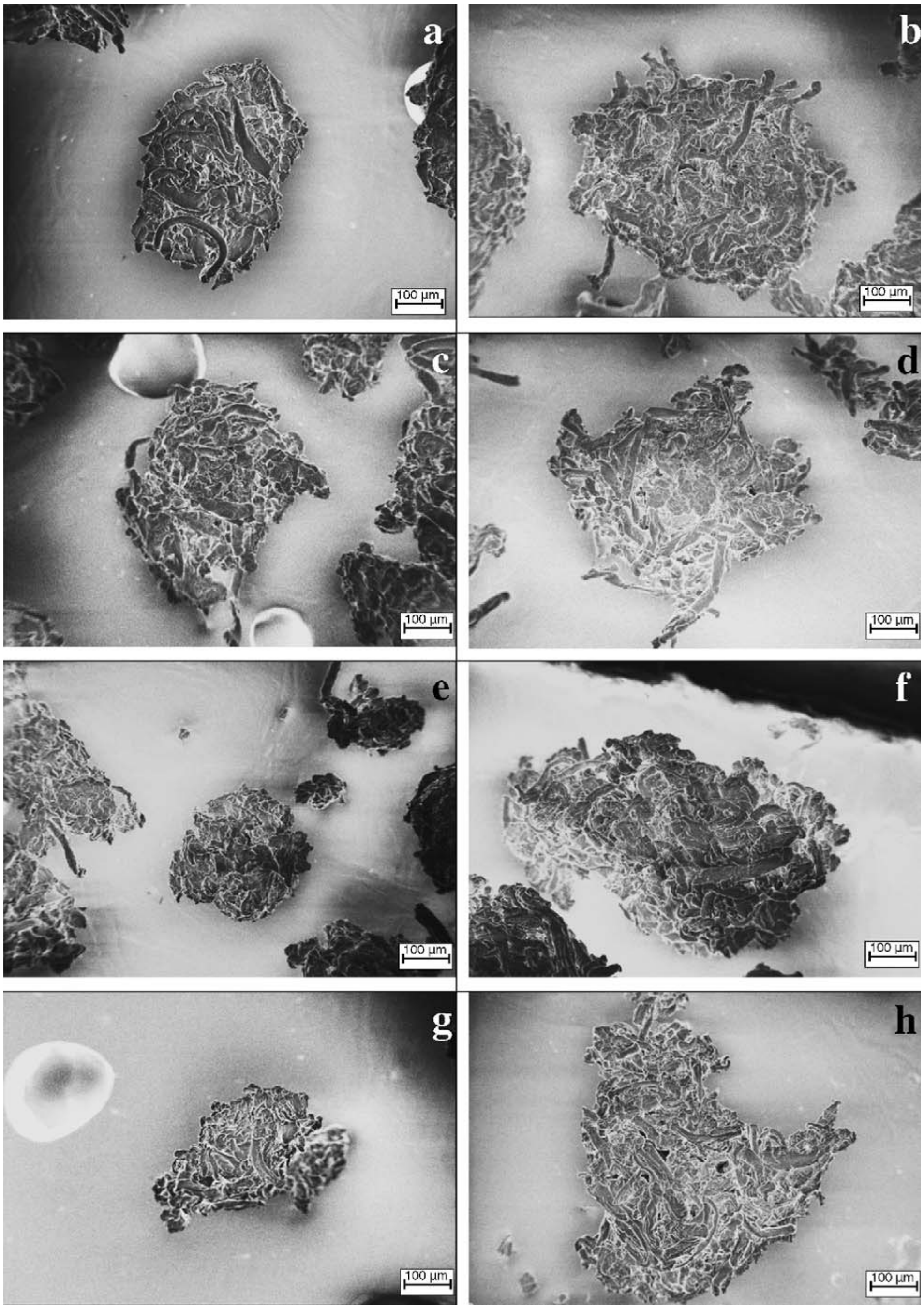

Fig. 3. Scanning electron micrographs of the HPMC granules: (a) 60SH50, (b) 60SH10000, (c) 65SH50, (d) 65SH4000, (e) 90SH100, (f) 90SH15000, (g) K100LV and (h) K4M. Scale bar is 100 μm.

(USP2208). In their study, no clear dependence of the tensile strength on the viscosity, and thus the molecular weight, could be observed. Similar observations have been made by Malamataris and Karidas (1994), and they found no correlation between the viscosity and the tensile strength. That our study is in contradiction to their studies on primary particles of HPMC may indicate that the HPMC granules and primary particles behave differently during compaction.

It has been found that the tensile strength of compacts of primary HPMC particles normally increases with decreasing particle sizes, see Malamataris and Karidas (1994). In contrast, the tensile strength in our study decreases with decreasing size of the granules. An explanation for the deviation may be that the small compact granules, obtained for the low molecular weight batches, are more difficult to deform, which means that fewer new bonding surfaces are generated during the compaction, and thus the tensile strength is lower. The tensile strength is also reduced by an increase in the total porosity of the compacts, as reported in several other studies (Nokhodchi et al., 1996; Gustafsson et al., 2003).

The HPMC 60SH (USP2910) batches show a tendency to form tablets with lower radial tensile strength, and higher poros-

Table 4
Properties of the tablets ($n = 5$)

Polymer	Tensile strength (MPa)[a]	Porosity[a]
60SH50	0.39 (±0.048)	0.28 (±0.014)
60SH10000	0.99 (±0.048)	0.23 (±0.011)
65SH50	0.53 (±0.069)	0.27 (±0.0031)
65SH4000	1.47 (±0.148)	0.23 (±0.0044)
90SH100	1.21 (±0.066)	0.22 (±0.0033)
90SH15000	1.16 (±0.094)	0.24 (±0.0043)
K100LV	0.99 (±0.048)	0.23 (±0.0030)
K4M	1.31 (±0.054)	0.24 (±0.0038)

[a] Data given in the table as average (±standard deviation).

ity than the batches with other degrees of substitution. These observations agree with the findings of Malamataris and Karidas (1994), Bonferoni et al. (1995) and Gustafsson et al. (1999). The explanation suggested by Dahl and Bormeth (1990) was that the higher content of hydrophobic methoxy groups in USP2910 can prevent from hydrogen bonding between the particles, thereby lowering the tensile strength. This explanation may also be valid for our work.

3.4. Proposed granulation mechanism

All of the properties of the granules and tablets investigated in this study show a tendency to divide into two groups, one for granules of low molecular weight HPMC and the other for granules of high molecular weight HPMC. The granules of low molecular weight HPMC had, in general, smaller sizes, higher bulk and tapped densities, good mass flow rates and lower angles of repose. This gives a picture of granules that are smaller, more compact, and with smoother surfaces, which was confirmed in the SEM study.

A reasonable explanation of why the properties of the granules separate into two groups, suggested below, is related to the mechanism for the formation of the granules. When water comes in contact with the HPMC particles, the water starts to dissolve the polymer chains. The dissolving process of polymers is not the same as the dissolving process for low molecular weight substances, e.g. lactose, since polymers dissolving in a desirable solvent form a highly viscous and entangled polymer layer around the particles, often called a gel layer (Körner et al., 2005). The properties of this gel layer, e.g. the thickness of the layer and capacity to adhere, are related to the molecular weight and the degree of substitution. When the HPMC particles are exposed to water during the granulation, a gel layer forms around them; they can then, during the movement in the granulation bowl, strike other particles, with or without gel layers, and when in close contact with each other they can agglutinate. The formation of a thick gel layer raises the capacity of the particles to cluster together, which generates larger agglomerates. The resistance of the gelled HPMC agglomerates to breakage is also linked to the gel layer, where a decrease in the viscosity would probably lead to breakage of the agglomerates. Another aspect of the formation and the deformation of the agglomerates is that a stronger affinity between the particles (higher viscosity in the gel layer) would probably make it more difficult to deform the agglomerates when trying to form regularly shaped round granules: instead some primary particles may be fixed in a position where they protrude from the surface of the granules.

The results of this study correlate the molecular weight of a polymer to the shape and flow properties of the granules. Since HPMC can act as its own binder by forming a gel layer in contact with water, it might be interesting to compare our results with those of other studies in which HPMC of varying molecular weights was dissolved in the granulation liquid and used as a wet binder. Danjo et al. (1994) found that the mean granule sizes increased with increasing molecular weight of the HPMC in the binder solution. The suggested explanation was that the affinity between the particles became greater with increasing viscosity of the binder solution, which supports the explanations and results obtained in this investigation.

Interestingly, the degree of substitution had relatively little influence on the properties of the granules and the tablets in comparison with the molecular weight which was a more dominant factor. This is not obvious, since the degree of substitution is related to the hydrophobicity of the polymers; it determined the water–polymer interactions. Two experimental techniques to show the interactions between the polymer and water are the release of polymers from hydrophilic tablets and the cloud point temperature, i.e. the temperature when the UV transmission of a polymer solution has decreased, due to precipitation, to a predefined value (in this study 96% in transmission was used). The cloud point temperature for 1% solutions of 60SH10000 and 90SH15000, with approximately the same molecular weight, in a phosphate buffer (pH 6.8, ionic strength equal to 0.1) varies by more than 10 °C, see Table 1. This indicates a strong dependency of the precipitation of the polymers, and thus of the polymer–water interaction, on the degree of substitution. The fractions of polymer released from tablets were determined, and both the effect of the molecular weight and the degree of substitution are shown, see Fig. 4. By comparing the release curves of HPMC 60SH50 and 60SH10000, the effect of the molecular weight is shown, and as expected the tablets of high molecular weight released more slowly than the others. By comparing the release curves for 60SH10000 and 90SH15000, two batches with different degrees of substitution but with similar molecular weight (Table 1), the effect of the degree of substitution can be clearly seen. Therefore, both the cloud point temperature and the

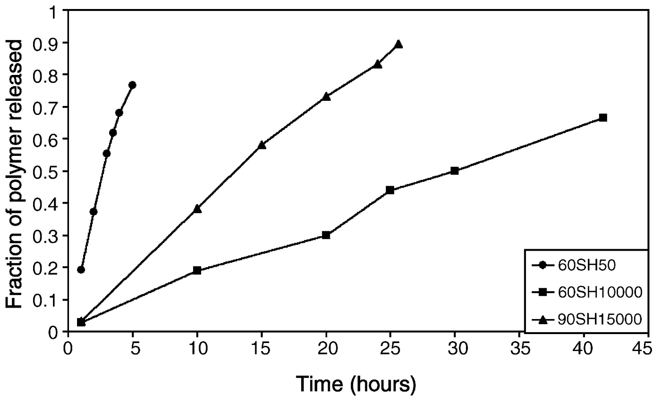

Fig. 4. Release of polymers from pure HPMC tablets.

polymer release curves indicate a large difference in the way the water and the different degrees of substitutions interact. Then the questions arise: Why is the degree of substitution so important for many water–polymer properties, but not for the formation of the granules? Why does the degree of substitution seem to be much less important than the molecular weight? Although the answers are not clear, it may be that the adhesiveness during the granulation is related to the viscosity, and that the viscosity variation for batches of high or low molecular weight is larger than the differences caused by the degrees of substitution. Support for the idea that the viscosity is significant important for the formation of the granules can be seen by comparing the 60SH50 and 65SH50 batches, for which, according to the supplier, the viscosity should be equal. Almost every property of the granules coincides for these batches (Table 3), except the size of the agglomerates (Table 2), where 60SH50 (relative 60SH10000) appears to deviate from the other batches.

4. Conclusions

This study shows that the molecular weight is a key parameter for the properties of the granules and the tablets obtained, whereas the degree of substitution has less influence. The granules made from low average molecular weight polymers are, in general, smaller, more compact with better flow properties (higher flow rate, lower Hausner ratio and Carr index), and higher bulk densities, however the tensile strength of the tablets is lower. The opposite was found for batches made from high molecular weight polymers. This may be explained by the mechanism proposed for the agglomeration process: high molecular weight polymers have higher viscosities and a thicker gel layer, which facilitates better adhesion of the particles, although it is more difficult to consolidate the agglomerates into a spherical shape. Although the granules from high molecular polymers have less desirable flow properties, during compaction they are easier to deform, which yields larger bonding surfaces and, thus, tablets with higher tensile strengths. The opposite is valid for granules made from low molecular weight HPMC.

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