

## Physical characterization of HPMC and HEC and investigation of their use as pelletization aids

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### Abstract

Pelletization of drugs with suitable excipients by extrusion/spheronization is one of the popular approaches in the development of solid dosage forms, especially for extended-release formulations. However, the choice of pelletization aids is limited to the use of microcrystalline cellulose (MCC), which is generally wet massed using water. In the formulation of water-sensitive drugs, however, pelletization excipients which may be wet massed using an organic liquid are desired. In the present study therefore, two cellulose ethers, hydroxypropyl methylcellulose (HPMC) and hydroxyethyl cellulose (HEC), were characterized for their physical properties, such as moisture content, bulk and tapped densities, median particle size and size distribution, surface area and surface morphology, in an attempt to evaluate the feasibility of their use as pelletization aids. Since HPMC and HEC are water-soluble, but insoluble in isopropyl alcohol, the latter was used as the wet massing liquid for pelletization. Microcrystalline cellulose, because of its established uniqueness as a pellet former, was used as the reference material and was also wet massed using isopropyl alcohol for consistency and comparison. Placebo pellets of the three cellulosic excipients, HPMC, HEC and MCC, were prepared by extrusion/spheronization. The placebo pellets were evaluated for their size and size distribution, hardness, friability, bulk and tapped densities and sphericity. Of the three cellulosic excipients, HPMC and MCC produced pellets with the most desirable attributes. In water as the dissolution medium, the HPMC pellets absorbed water and formed a single viscous gel matrix that slowly dissolved. HEC pellets were swollen but intact and slowly eroded, whereas MCC pellets stayed intact without dissolution or erosion. These findings indicate that HPMC will find application in pellet formulations of water-sensitive drugs, as well as in those formulations where water may not be used as wet massing liquid and an organic liquid must be used. It will also be a good choice as a pelletization excipient when complete water-solubility of all the formulation excipients is desired. It may be anticipated that modification of drug release from pelletized formulations may also be achieved by using cellulose ethers of varying viscosity grades and hydration rates. © 1998 Elsevier Science B.V.

**Keywords:** Physical characterization; Extrusion; Spheronization; Pellets; Pelletization; Hydroxypropyl methylcellulose; Hydroxyethyl cellulose; Microcrystalline cellulose

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## 1. Introduction

Pelletization is an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free-flowing, spherical or semi-spherical units, referred to as pellets. This may be performed by extrusion/spheronization, solid/suspension layering and powder layering. The extrusion/spheronization process was developed in the early 1960's and was first introduced in the US by Reynolds (1970) and Conine and Hadley (1970). Since then, it has generated much interest in the pharmaceutical industry due to its specialized applications in the field of solid dosage form technology, especially in the development of extended-release dosage forms.

The formulation aids available for pelletization by extrusion/spheronization are very limited due to the characteristics desired from their wet masses. The wet mass must meet the requirements for both extrusion, as well as spheronization. The main requirement for the extrusion process is the ability of the powder material to form a cohesive plastic mass upon wetting, that remains homogeneous throughout the extrusion process. For spheronization, a balance between plasticity and brittleness of the wet mass is needed to successfully obtain the product. Since rheological behavior of the wet powder mass, which is very important for both extrusion and spheronization processes, is dependent on the physical properties of the powders, such as particle size, size distribution, density, surface area and morphology, the physical properties of the powder materials play a critical role in obtaining a pellet product with desired attributes.

Microcrystalline cellulose has the ideal physical properties, including moisture retaining and distributing ability, for extrusion/spheronization and it is widely used as a pelletization aid by this technique. This is most likely due to the favorable rheological properties of its wet mass (Shah et al., 1995). It has a very high internal porosity and a large surface area due to randomly aggregated filamentous microcrystals. The high internal porosity and large surface area provide highly absorbent and moisture retaining properties which are essential to the extrusion process. The

retained moisture acts as a lubricant during extrusion and helps to manipulate the pellet shape during spheronization. The physical properties of microcrystalline cellulose, such as moisture content, particle size, density, morphology and surface area, have been shown to play an important role in the quality of pellets made by extrusion/spheronization (Sonaglio et al., 1995). These authors studied the microcrystalline cellulose from two commercial sources (Avicel<sup>®</sup> PH 101 and Microcel<sup>®</sup> MC 101) and concluded that acceptable pellets can be prepared using microcrystalline cellulose from the two sources. However, the difference in their particle size resulted in varying amounts of water needed for the process.

At the present time, microcrystalline cellulose is the only pelletization aid of choice that has been studied extensively for pellet preparation by extrusion/spheronization due to its unique properties. An extensive search of literature showed that very few studies were even conducted to evaluate other excipients for this application. Lindner and Kleinebudde (1994) studied the production of pellets using powdered cellulose and microcrystalline cellulose and reported that the former gave pellets with higher porosity and faster dissolution rate. Other studies have been reported using materials with functional application in pellets, such as chitosan (Goskonda and Upadrashta, 1993; Tapia et al., 1993), hydroxypropyl cellulose (Kleinebudde, 1993), glycerin palmitostearate and gelucire 50/02 (Edimo et al., 1993), glyceryl monostearate (Blanche et al., 1995), cross-linked carboxymethyl cellulose sodium (Iannuccelli et al., 1993), pH adjusters (Bianchini et al., 1992) and sodium lauryl sulphate (Mesiha and Valles, 1993). However, in all these studies, microcrystalline cellulose was used as the major pelletization aid. In the majority of these studies, water was used as the wet massing liquid. In one of the studies, pellets were prepared using water/ethanol mixtures as the wet massing liquid (Millili and Schwartz, 1990). These authors reported that the pellets became stronger and harder with increasing amounts of water, however, the pellet compressibility was relatively better with higher amounts of alcohol. In other studies, alcohol was used as the wet massing liquid for the extrusion of effervescent granules (Gamlen, 1986; Lindberg et al., 1987, 1988).

The objective of the present study was to characterize two cellulose ethers, hydroxypropyl methylcellulose and hydroxyethyl cellulose, for their physical properties, such as particle size, size distribution, bulk and tapped densities, surface area, moisture content and surface morphology, which play a critical role in the ability of a material to act as extrusion/spheronization aid. In addition, inter-lot variability of the excipients was investigated because it is known to play an important role in the manufacture of product with desired attributes.

Another objective of this study was to investigate the feasibility of their pelletization by extrusion/spheronization and to relate it to their physical properties with microcrystalline cellulose as the reference material.

## 2. Materials and methods

### 2.1. Materials

Two cellulose ethers, hydroxypropyl methylcellulose (HPMC) (Methocel<sup>®</sup> E6P, Dow Chemical, Midland, MI) and hydroxyethyl cellulose (HEC) (Natrosol<sup>®</sup> 250 HHX, Aqualon, Wilmington, DE), were chosen as the excipients for physical characterization and pelletization for this study. Microcrystalline cellulose (MCC) (Avicel<sup>®</sup> PH 101, FMC, Philadelphia, PA) was used as the reference material for comparison purposes. Hydroxypropyl cellulose (HPC) (Klucel<sup>®</sup> EXF, Aqualon) was used as the binding agent and isopropyl alcohol (IPA) was used as the wet massing liquid.

### 2.2. Physical characterization

The moisture content determination of the powder materials was carried out using a moisture analyzer (Computrac<sup>®</sup>, model Max 50, Arizona Instruments, Tempe, AZ), set at a temperature of 105°C using a 5 g sample. The moisture content data of the powder materials are the mean of three determinations (Table 1).

The bulk and tapped densities of the powder materials were determined by standard methods.

Table 1  
Moisture content (%) of HPMC, HEC and MCC powders

| Lot | HPMC        | HEC         | MCC         |
|-----|-------------|-------------|-------------|
| A   | 1.64 ± 0.02 | 5.25 ± 0.03 | 4.06 ± 0.4  |
| B   | 1.62 ± 0.04 | 4.97 ± 0.04 | 4.42 ± 0.3  |
| C   | 1.95 ± 0.02 | 4.46 ± 0.06 | 3.80 ± 0.05 |

± Values indicate S.D. (*n* = 3).

The tapped density was performed with 1000 taps using a tapped density tester (J. Engelsmann, Ludwigshafen, Germany). The bulk and tapped density data were used to calculate the Hausner's flowability (Hausner, 1967) and Carr's compressibility (Carr, 1970) indices. The bulk and tapped density data are given in Table 2, while the Hausner's flowability and Carr's compressibility indices are given in Table 3.

The particle size analysis was performed using a Malvern<sup>®</sup> Master sizer (Malvern<sup>®</sup> Instruments, Southborough, MA) equipped with MSX dry powder feeder. The median particle size data are the mean of three determinations and are summarized in Table 4. The particle size distribution is also graphically depicted in Fig. 1.

The surface area of the cellulosic materials was determined by the multi-point BET adsorption method (Gemini II, model 2370, Micromeritics<sup>®</sup> Instruments, Norcross, GA) using nitrogen as the adsorbate gas. The powder samples were degassed for 16–18 h under nitrogen at 80°C to remove the pre-adsorbed gases and vapors from the surface of the powder material. Multi-point measurements were made at five partial pressures, ranging between 10–30% for the adsorbate gas. The surface area data are the mean of three determinations (Table 5).

Table 2  
Bulk/tapped density (g/ml) of HPMC, HEC and MCC powders

| Lot | HPMC      | HEC       | MCC       |
|-----|-----------|-----------|-----------|
| A   | 0.53/0.66 | 0.50/0.66 | 0.35/0.48 |
| B   | 0.46/0.64 | 0.47/0.64 | 0.31/0.48 |
| C   | 0.44/0.66 | 0.51/0.68 | 0.35/0.51 |

Table 3  
Hausner's flowability and Carr's compressibility indices for HPMC, HEC and MCC powders

| Lot | HPMC      | HEC       | MCC       |
|-----|-----------|-----------|-----------|
| A   | 1.25/19.7 | 1.32/24.2 | 1.37/27.1 |
| B   | 1.39/28.1 | 1.36/26.6 | 1.55/35.4 |
| C   | 1.36/26.7 | 1.33/25.0 | 1.46/31.4 |

The surface morphology of the powder samples was examined using a Hitachi scanning electron microscope. The accelerating voltage was 10 kV and the working distance was 15 mm. The images at various magnifications were photographed. The photomicrographs were examined for any differences in the surface morphology of the powder samples (Figs. 2–4).

### 2.3. Pellet preparation

The composition of the placebo pellet formulations was as follows: HPMC, HEC or MCC (95%), HPC (5%) and IPA (q.s). The pelletization batch size was 500 g.

The HPMC, HEC and MCC powders were granulated with 10% HPC solution in IPA in a planetary mixer (Hobart<sup>®</sup> N-50, Hobart, North York, Ont.). Additional IPA was added as

Table 4  
Malvern<sup>®</sup> particle size analysis data for HPMC, HEC and MCC powders

| Material | Lot | Particle size ( $\mu\text{m}$ ) |                  |                 |
|----------|-----|---------------------------------|------------------|-----------------|
|          |     | D(v, 0.5)                       | D(v, 0.9)        | D(v, 0.1)       |
| HPMC     | A   | 64.4 $\pm$ 0.30                 | 158.2 $\pm$ 0.64 | 24.3 $\pm$ 0.79 |
|          | B   | 111.9 $\pm$ 1.79                | 254.0 $\pm$ 3.62 | 33.0 $\pm$ 1.07 |
|          | C   | 83.6 $\pm$ 1.38                 | 200.6 $\pm$ 4.05 | 27.5 $\pm$ 0.64 |
| HEC      | A   | 96.9 $\pm$ 0.95                 | 230.6 $\pm$ 9.97 | 40.8 $\pm$ 1.75 |
|          | B   | 103.4 $\pm$ 0.93                | 230.1 $\pm$ 2.06 | 43.7 $\pm$ 0.70 |
|          | C   | 110.1 $\pm$ 3.22                | 252.6 $\pm$ 2.33 | 44.0 $\pm$ 1.18 |
| MCC      | A   | 64.6 $\pm$ 0.46                 | 142.2 $\pm$ 0.85 | 25.7 $\pm$ 0.20 |
|          | B   | 65.5 $\pm$ 0.99                 | 151.6 $\pm$ 2.44 | 24.2 $\pm$ 0.21 |
|          | C   | 60.1 $\pm$ 0.17                 | 137.0 $\pm$ 0.73 | 23.3 $\pm$ 0.05 |

$\pm$  Values indicate S.D. ( $n = 3$ ); D(v, 0.5) = 50 percentile; D(v, 0.9) = 90 percentile; and D(v, 0.1) = 10 percentile of the particles.

needed, to achieve consistency of the wet mass suitable for extrusion/spheronization. The wet mass was immediately passed through a radial basket type extruder (Nica<sup>®</sup>, model E-140, Niro-Aeromatic, Columbia, MD) using 1 mm screen and processed in a spheronizer (Nica<sup>®</sup>, model S-320, Niro-Aeromatic). The speed of the feeder and extruder was 120 and 100 rpm, respectively. The spheronizer speed was 600 rpm and the residence time was 6 min. The pellets were dried in a forced air-circulation oven at 40°C (Despatch<sup>®</sup>, Minneapolis, MN) to a moisture content of < 3%, as determined by Computrac<sup>®</sup> set at 105°C.

### 2.4. Pellet evaluation

The size analysis of the pellets was carried out by sieve analysis using a nest of sieves containing mesh #s 12, 14, 16, 18, 20, 25 and 30. The sample size was 100 g and the shaking time was 5 min. The mean pellet size and size distribution data are summarized in Table 6 and graphically presented in Fig. 5.

Pellet hardness was determined by Pharmatest<sup>®</sup> hardness tester (model PTB 501, Key International, Englishtown, NJ) on a sample of 10 pellets from the 14/16 sieve fraction. The pellet hardness data are summarized in Table 6.

The pellet friability was carried out using a friabilator equipped with an 8" diameter abrasion drum containing 12 baffles. A 10 g pellet sample (14/16 sieve fraction) was placed in the friabilator drum containing 200 glass beads of 4 mm diameter. The speed of the friabilator was 20 rpm. The friabilator was rotated for 10 min and the percent weight loss of the pellets was determined. The pellet friability data are given in Table 6.

The bulk and tapped densities of the pellets were determined by standard methods. The tapped density was performed with 1000 taps using a tapped density tester (J. Engelsmann, Ludwigshafen, Germany). The bulk and tapped density data are summarized in Table 6.

The sphericity index (shape factor) of the pellets was determined by image analysis carried out using a stereomicroscope (Olympus Zoom Stereomicroscope, model SZ-Tr, Olympus, New Hyde Park, N.Y.) interfaced via a video camera

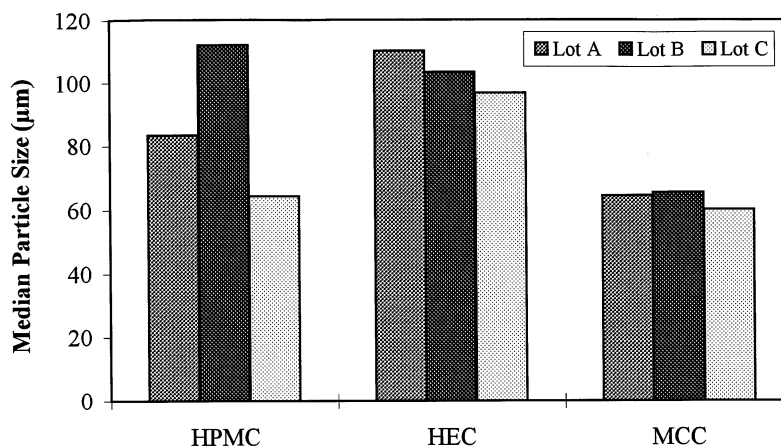


Fig. 1. Median particle size for HPMC, HEC and MCC.

(model JE 3010, Javelin Systems, Torrance, CA) to a personal computer loaded with a commercially available software program (Sigma<sup>®</sup> Scan Pro, Jandel Scientific, San Rafael, CA). The sphericity index of the pellets is calculated by the software using the following relationship:

$$\text{Sphericity index} = \frac{4 \pi (\text{Projected area})}{(\text{Perimeter})^2}$$

The image analysis is based on the consideration that a perfect sphere has a shape factor of 1.000, and a shape factor of < 1.000 indicates deviation from sphericity. At least 50 pellets were scanned for image processing and analysis. The sphericity of all the pellets under study was normalized taking nonpareil seeds as standard. The sphericity index of the placebo pellets of HPMC, HEC and MCC is given in Table 6, and their stereomicroscopic images are shown in Fig. 6, Fig. 7 and Fig. 8, respectively.

Table 5  
Surface area (m<sup>2</sup>/g) of HPMC, HEC and MCC powders

| Lot | HPMC            | HEC             | MCC             |
|-----|-----------------|-----------------|-----------------|
| A   | 0.2669 ± 0.0008 | 0.0782 ± 0.0158 | 1.0443 ± 0.0229 |
| B   | 0.2443 ± 0.0154 | 0.0653 ± 0.0145 | 0.9963 ± 0.0156 |
| C   | 0.2134 ± 0.0020 | 0.0707 ± 0.0010 | 1.0326 ± 0.0159 |

± Values indicate S.D. (*n* = 3).

The dissolution study on the pellets was carried out using the standard USP apparatus II (Vankel, Edison, NJ) in 900 ml of purified water maintained at 37 ± 0.5°C. The paddle speed was set at 100 rpm. The weight of the pellets used was 300 mg/vessel.

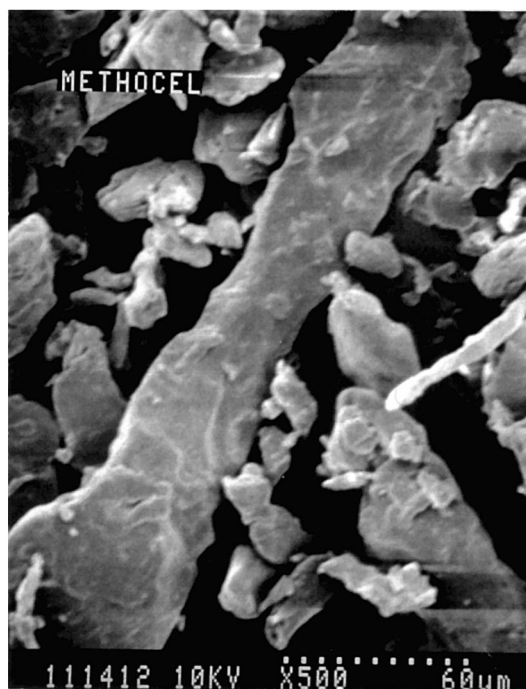


Fig. 2. Scanning electron photomicrograph of HPMC.



Fig. 3. Scanning electron photomicrograph of HEC.

### 3. Results and discussion

The physical characterization of powder excipients is extremely important, since physical properties play a critical role in the formulation, processing, in vitro and in vivo performance of the finished dosage forms. The results of the physical characterization will relate back to the parameters associated with the performance of the formulation and process and should give information that will ensure the successful production of each and every batch of the product.

The two cellulose ethers, HPMC and HEC, were chosen for physical characterization and subsequent pelletization by extrusion/spheronization because of their similarity in morphology and chemical make-up to MCC, as well as their wider regulatory acceptance and use in pharmaceutical applications.

#### 3.1. Moisture content

The moisture content data of three different lots of HPMC, HEC and MCC are given in Table 1. The determination of the moisture content at different temperatures ranging from 100 to 150°C with 10°C increment gave similar results. Therefore, all further determinations were carried out at 105°C for the cellulosic excipients as well as the pellets. The moisture analysis data indicate that the moisture content of the three celluloses was consistent with very little lot-to-lot variation. The moisture content of the wet mass and its distribution in the powder mass is an important variable, especially in the extrusion/spheronization process (Bains et al., 1991; Hasznos et al., 1992; Baert and Remon, 1993; Fielden et al., 1993; Otsuka et al., 1994; Jerwanska et al., 1995). The moisture content of the major excipient determines the amount of wet massing liquid to be added for successful extrusion/spheronization and to obtain pellets with desired characteristics. Higher variability in moisture content among excipient lots will lead to variability in the wet massing liquid requirement,

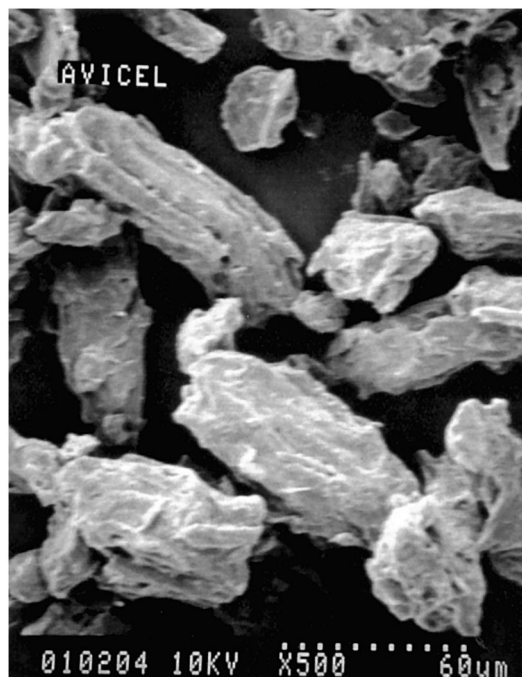


Fig. 4. Scanning electron photomicrograph of MCC.

Table 6  
Physical properties of HPMC, HEC and MCC pellets

| Property                           | HPMC            | HEC             | MCC             |
|------------------------------------|-----------------|-----------------|-----------------|
| Mean pellet size ( $\mu\text{m}$ ) | 1400            | 1700            | 1750            |
| Geometric standard deviation       | 1.17            | 1.36            | 1.40            |
| Hardness (kp)                      | $0.9 \pm 0.4$   | $0.8 \pm 0.2$   | $0.7 \pm 0.2$   |
| Friability (%)                     | 0.87            | 1.21            | 0.30            |
| Bulk/tapped density (g/ml)         | 0.46/0.49       | 0.46/0.50       | 0.54/0.58       |
| Sphericity index (shape factor)    | $0.93 \pm 0.04$ | $0.81 \pm 0.06$ | $0.93 \pm 0.05$ |

$\pm$  Values indicate S.D. Tablet hardness is mean of 10 determinations and shape factor is mean of at least 50 determinations.

leading to a process that will be difficult to control to achieve reproducible pellet quality and quantity. Although water was not used as the wet massing liquid in the present placebo pellet formulations, the moisture content of the starting materials will significantly influence the optimum amount of isopropyl alcohol required for wet massing, since the latter is miscible with water in all proportions.

### 3.2. Bulk and tapped densities

Bulk and tapped densities and the other derived parameters, i.e. Hausner's flowability and Carr's compressibility indices, for the different lots of the cellulosic excipients studied are listed in Tables 2 and 3. The data are in good agreement with those reported in the literature (Wade and Weller, 1994). The examination of the bulk and tapped density data (Table 2) indicates that the lot-to-lot variability was minimal for the three excipients. The bulk and tapped densities of HPMC and HEC were higher than those of MCC, whereas the compressibility of MCC was higher than the other two celluloses (Table 3). The Hausner's flowability index, which is the ratio of tapped density to bulk density, ranges from 1.25 to 1.55 for the three materials studied. Since higher Hausner's flowability index indicates poorer powder flow, one may conclude from the data that HEC and HPMC will exhibit relatively better flow properties as compared to MCC. The compressibility of the starting material is an essential property to be considered in such specialized applications as extrusion/spheronization because higher compressibility will yield denser and less

friable pellets, which is desirable for subsequent coating applications. Although the compressibility of HPMC and HEC is relatively lower as compared to MCC, it might be adequate to produce acceptable pellets. In addition, relatively higher bulk and tapped densities of HPMC and HEC as compared to MCC make these two cellulose ethers suitable for extrusion/spheronization process.

### 3.3. Particle size

The results of the particle size analysis for HPMC, HEC and MCC are summarized in Table 4 and graphically presented in Fig. 1. From the particle size data, it can be seen that there was a considerable degree of variability in particle size from lot-to-lot for HPMC and HEC as compared to MCC. The median particle size for MCC for the three lots was in the range of 60 to 65  $\mu\text{m}$ , whereas that for HPMC and HEC ranged from 65 to 112  $\mu\text{m}$  and 97 to 110  $\mu\text{m}$ , respectively. The results of median particle size of MCC agree with the values reported in the literature (Wade and Weller, 1994) and those provided by the excipient manufacturer.

The particle size distribution of the excipients has direct impact on the pellet size distribution due to the direct relationship of particle size with the wet massing liquid requirement. The particle size of the excipients also has vital influence on the extrusion characteristics of the wet mass (Fielden et al., 1989), as well as the size and sphericity of the pellets (Newton et al., 1993; Wan et al., 1993). MCC, a commonly used excipient for this application, exhibited a very narrow size

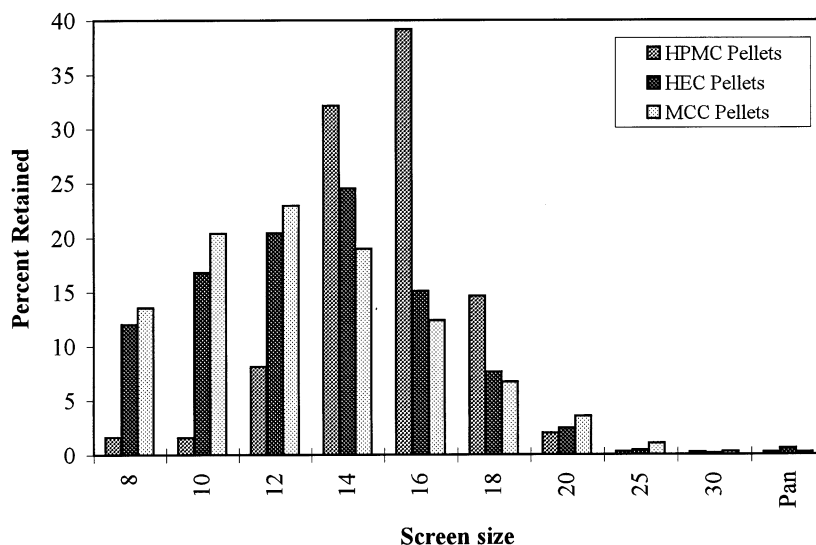


Fig. 5. Size distribution of HPMC, HEC and MCC pellets.

distribution and smaller lot-to-lot variability in median particle size as compared to HPMC and HEC.

Since HPMC and HEC, the two cellulose ethers under study, are primarily meant to be used in the solution form for coating and granulation applications, their particle size and size distribution is not critical. However, particle size and size distribution of the pelletization aids are important properties because these are known to influence the critical liquid requirement of the powder mass during wetting. In general, smaller particle size results in larger surface area and therefore higher

wet massing liquid requirement. The wet massing liquid level is very critical to achieving pellets of desired quality, sphericity and yield in the extrusion/spheronization process (Elbers et al., 1992). Optimum moisture content and distribution are desirable in order to produce a dense extrudate and to lubricate the wet mass during extrusion. Poorly wetted masses create excessive pressure and friction in the extruder, ultimately resulting in pellets that crumble and, consequently, too many fines are produced. Masses that are overwet, on the other hand, produce larger pellets and pellets with a wider size distribution.

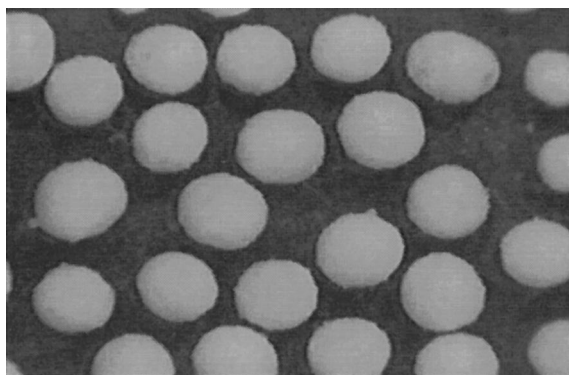


Fig. 6. Stereomicroscopic images of HPMC pellets (5 × magnification).

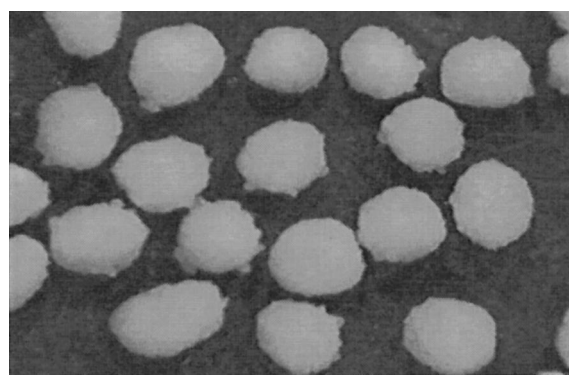


Fig. 7. Stereomicroscopic images of HEC pellets (5 × magnification).



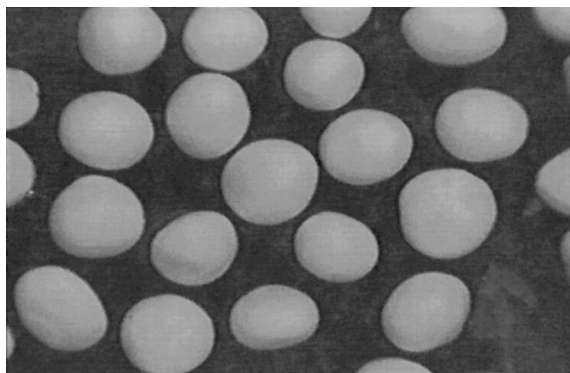


Fig. 8. Stereomicroscopic images of MCC pellets ( $5\times$  magnification).

### 3.4. Surface area

The surface area data for HPMC, HEC and MCC are given in Table 5. The intra-lot variability for HPMC was smaller as compared to the inter-lot variability. However, for HEC, the intra-lot variability was relatively much higher as compared to HPMC, whereas inter-lot variability was smaller. The surface area data of HPMC and HEC are neither reported in the literature nor were available from the excipient manufacturers. For MCC, the intra- and inter-lot variability was much smaller as compared to HPMC and HEC. The surface area of HPMC was about three to four times larger than that of HEC which, in part, can be attributed to the difference in their median particle size and size distribution. Also, the surface area of MCC was more than four times larger than that of HPMC and  $\approx 15$  times that of HEC. The results of surface area determination obtained for MCC agree with those reported in the literature (Nakai et al., 1977; Zografi et al., 1984). The minimal variation among different lots and narrower particle size distribution of MCC makes it a better excipient for extrusion/spheronization, as particle size plays a critical role in obtaining a product of satisfactory attributes. A close examination of the particle size and surface area data reveals some disagreement between the results. The median particle size for one of the lots of HPMC and MCC was 64.4 and 64.6  $\mu\text{m}$ , respectively, and their surface area was 0.2669

and 1.0443  $\text{m}^2/\text{g}$ , respectively. Despite the fact that their median particle size is the same, MCC exhibited a 4-fold larger surface area than HPMC. This difference may be attributed to the difference in the surface morphology and porosity of these materials. MCC is manufactured to have higher porosity and therefore, higher compressibility (Wallace, 1990). The comparatively smaller surface area observed for HPMC may be due to the less porous and more dense particles resulting from the manufacturing process. For HEC, however, some correlation was observed between the particle size and the surface area; its relatively larger particle size correlated with its smaller surface area, which may be attributed to its long fiber like particles as observed under the microscope and from the photomicrographs (Figs. 2–4).

The surface area of powder material has a profound influence on its critical liquid requirement during wet massing and therefore, on the ability of the material to undergo extrusion/spheronization. The larger surface area results in a larger number of bridges that form between the particles during wet massing leading to an increased liquid requirement (Kristensen and Schaefer, 1987). This is an important property that should be monitored in order to obtain a pellet product that has consistent quality attributes.

### 3.5. Scanning electron photomicrographs

The photomicrographs of HPMC, HEC and MCC are shown in Figs. 2–4, respectively. These photomicrographs exhibit the typical shape of cellulosic materials, i.e. long, fibrous or granular particles and appear to be similar in overall shape. However, the size and the surface morphology of the three cellulosic materials appear to be different. HEC appears to have more elongated, smoother particles than HPMC and MCC. The MCC particles appear to contain more fractures and irregular cavities as compared to either HPMC or HEC. This might have partly contributed to the larger surface area observed for MCC as compared to HPMC and HEC.

### 3.6. Pelletization

The preliminary trials of pelletization by extrusion/spheronization with the three cellulosic excipients, HPMC, HEC and MCC, using water as the wet massing liquid, were successful only in the case of MCC due to its unique water absorbing and retaining characteristics (Baert et al., 1992). HPMC and HEC could not be extruded/spheronized because both the materials turned into a tacky mass, owing to their solubility in water. In order to avoid the tackiness, water was substituted by IPA as the wet massing liquid. This was done primarily because the three cellulosic materials were practically insoluble in IPA and therefore did not cause tackiness. Secondly, IPA is widely accepted in pharmaceutical formulations. Although MCC is a water-insoluble material and is generally wet massed with water, it also was granulated using IPA for the reasons of consistency and comparison.

In the subsequent preliminary trials with IPA as the wet massing liquid, the three cellulosic materials were successfully extruded/spheronized, however, the pellets exhibited very high friability. The pellets crumbled back to powder during drying and subsequent handling. In order to avoid this problem, use of some of the widely used binders was investigated. Unlike some other binders, HPC is soluble in IPA and during preliminary trials, it yielded pellets with acceptable friability as well as hardness for all the cellulosic excipients. Therefore, it was used as the binder. HPC was used as a solution in IPA since it was more effective as a binder in solution form than in dry powder form. Very few studies have been reported where a non-aqueous liquid instead of water was used as the wet massing agent. In some studies, alcohol or hydro-alcoholic mixtures (Lindberg et al., 1987, 1988; Millili and Schwartz, 1990; Elbers et al., 1992) and 2-propanol (Schroder and Kleinebudde, 1995) were used as the granulating liquid. The pellets prepared using larger amounts of 2-propanol were reported to disintegrate faster as compared to those prepared with smaller amounts of 2-propanol and this was attributed to the decreased particle–particle bonding with increasing levels of propanol (Schroder and Kleinebudde,

1995). Millili and Schwartz (1990) have shown that pellets were formed when granulated with binary mixtures of ethanol (up to 95%) and water but not with absolute alcohol. The pellets reportedly became stronger and harder as the mole fraction of water in the hydro-alcoholic mixture for wet massing was increased. The compaction studies of these pellets showed that pellets prepared using water were not very compressible, whereas pellets prepared with 95% alcohol showed excellent compressibility. Neau et al. (1996) utilized chemical interaction between electrolytes and Carbopol® 974P to reduce the tackiness of the latter in a pellet formulation. The authors were able to successfully prepare chlorpheniramine maleate/MCC pellets containing up to 55% w/w of Carbopol® 974P by incorporating strong electrolytes, such as sodium chloride, calcium chloride, magnesium chloride and aluminum chloride.

In the present study, the three cellulosic materials, HPMC, HEC and MCC, were used alone without any aid except a binder. The extrusion/spheronization process variables, such as feeder speed (120 rpm), extruder speed (100 rpm), spheronizer speed (600 rpm) and residence time (6 min), were kept constant for all the formulations in order to avoid the influence of process parameters on the pellet properties. The amount of wet massing liquid required to produce satisfactory pellets was 190 ml in the case of MCC, 500 ml in the case of HEC and 800 ml in the case of HPMC for a 500 g batch. The pellet size distribution for the three formulations is shown in Fig. 5. The size distribution of MCC and HEC pellets was comparable, the majority of pellets being in the 8/16 sieve size. However, for HPMC, 90% of the pellets fell in the 12/18 sieve size, which indicates relatively smaller size of HPMC pellets. The other properties, such as hardness, bulk and tapped densities, friability and sphericity index, of the pellets of the three celluloses are given in Table 6. It appears from the data that the pellets of the three cellulosic materials had acceptable properties, such as hardness, friability, density and sphericity. The pellets should have satisfactory hardness and friability so that they can withstand handling of pellets during routine manufacturing

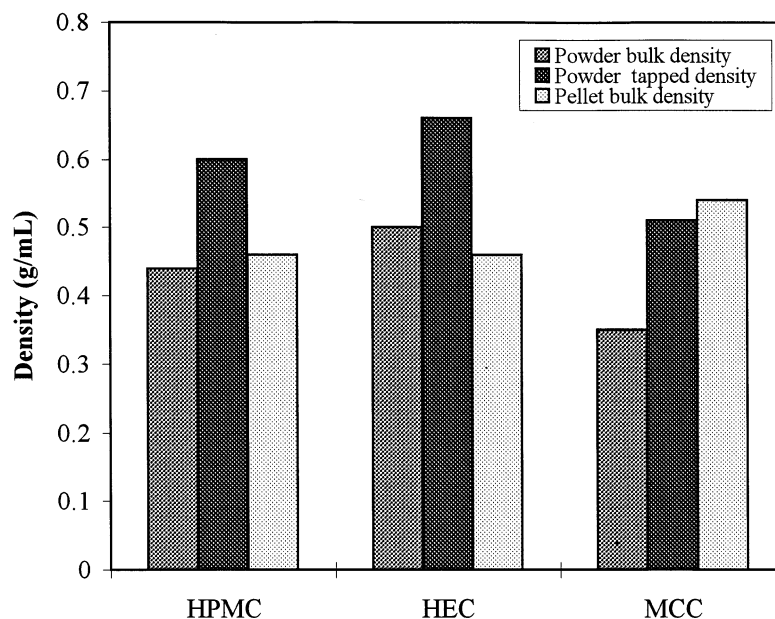


Fig. 9. Bulk and tapped densities of HPMC, HEC and MCC powders and pellets.

operations, such as transfer between the containers, encapsulation, coating, etc. The hardness of the pellets was similar for the three pellet formulations. However, there were differences in their friability. The friability index of MCC, HPMC and HEC pellets was 0.30, 0.87 and 1.21%, respectively. The stereomicrographs of the images of HPMC, HEC and MCC pellets substantiate the pellet friability values (Figs. 6–8). It is evident from the pellet images that the surface of the MCC pellets was much smoother as compared to that of HPMC and HEC pellets. The surface roughness increased in the order of MCC to HPMC to HEC pellets, which corresponded to the friability of their pellets. From these observations, it may be inferred that the rougher and more irregular surface of the pellets will result in relatively higher friability. However, the pellet friability index of the three materials which ranged from 0.3 to 1.2% appeared to be acceptable for subsequent pellet coating in a fluid-bed equipment.

The bulk and tapped density data of HPMC, HEC and MCC powders and their pellets are summarized in Tables 2 and 6, respectively, and

are graphically depicted in Fig. 9. Each of the three cellulosic materials exhibited a significant increase in the density after tapping, however, only MCC showed an increase in density after pelletization. In the case of MCC, its powder tapped density was similar to the pellet bulk density, whereas in the cases of HPMC and HEC, it was the powder bulk density which was close to the pellet bulk density. These density data clearly indicate that MCC gets densified after extrusion/spheronization, even when wet-massed using a non-aqueous solvent which was not observed in the case of HPMC and HEC.

The sphericity index (shape factor) data of HPMC, HEC and MCC pellets are summarized in Table 6. The pellets of all the three materials appear to be nearly spherical when compared to nonpareil seeds. On the shape factor scale of 0.000–1.000, where a shape factor of 0.000 indicates a cylindrical object and 1.000 indicates a perfect sphere, the MCC and HPMC pellets had sphericity index of 0.93, whereas the HEC pellets had a sphericity index of 0.81. The relatively lower sphericity of the HEC pellets can be attributed to the rougher and irregular surface of the pellets (Fig. 7).

The smoothness of pellet surface is dependent on the amount of wet massing liquid. Baert and Remon (1993) have shown that the pellet surface gets smoother with increasing amount of the wet massing liquid. These authors were able to conclude from photomicrographs that pellets containing 80% MCC and 20% theophylline monohydrate made with 115% water were rounder and smoother compared to the pellets made using 75% water. The authors also observed folding phenomenon of the extrudate with lower liquid level instead of end-rounding phenomenon reported by Rowe (1985). Based on their observations, Baert and Remon proposed that the pellet formation occurs initially by rope-folding of the extrudate, followed by twisting and formation of a shape similar to a dumb-bell. Further twisting breaks the dumb-bell into two parts with a central cavity which is closed on further spheronization resulting in spherical pellets. However, in the present study, pelletization appeared to occur by the mechanism described by Rowe (1985). The extrudate broke on the friction plate of the spheronizer into small cylinders which went through several shape changes, i.e. cylinders with rounded ends, dumb-bells, ellipsoids and finally spheroids.

Hellen et al. (Hellen et al., 1993a,b), working with a formulation containing mannitol (75%), MCC (20%) and caffeine (5%), reported that surface morphology of the pellets was a function of the amount of wet massing liquid level; the higher the amount of the liquid, the smoother the pellets. The authors reported the presence of small crumbs on the surface of the pellets and was unable to explain their existence by means of any process variables. The authors made an assumption that the plasticity of the wet mass was just adequate to produce spherical pellets, but was insufficient to produce a smooth surface. The authors also did not find any correlation between surface smoothness and shape of the pellets.

The surface smoothness of the pellets may be attributed to the particle size of the starting powder materials. The particle size plays a significant role in the preparation of pellets by influencing the critical liquid requirement of the powder mass (Fielden et al., 1993), the extrusion/spheronization

properties of the wet mass (Fielden et al., 1989) and finally the physical properties of the pellets, such as size and sphericity (Wan et al., 1993) and morphology of the pellets. The median particle size of MCC, HPMC and HEC powders was 60.1, 83.6 and 110.1  $\mu\text{m}$ , respectively. Based on the observations of this study, it can be inferred that powder materials with relatively smaller particle size will yield pellets with smoother surface. Accordingly, the relatively larger particle size of HEC contributed to the rougher pellet surface which eventually contributed to the higher pellet friability.

A correlation between the particle size and surface area is not established for MCC and HPMC. Despite comparable particle size of the two materials, the much larger surface area of MCC as compared to HPMC is due to the porous nature of MCC, as evident from the photomicrographs (Figs. 2 and 4). Also, no correlation was observed for the surface area of HPMC, HEC and MCC and their wet massing liquid requirement to produce satisfactory pellets. It has been reported that the number of liquid bridges formed between the powder particles is a function of the particle size and therefore the surface area, and leads to its increased critical liquid requirement and granule strength (Kristensen and Schaefer, 1987). Consequently, the larger surface area of the powder will exhibit higher critical liquid requirement. However, the liquid requirement for MCC, HPMC and HEC decreased with increased surface area, contrary to what is expected. Based on this observation, it can be concluded that surface area of the powder excipient is not the only contributing factor in its critical liquid requirement. Rather, there are other forces which act at the powder–liquid interface which determine the critical liquid requirement of the powder material. One possibility is the differences in the surface energetics at the solid–liquid interface of the three materials. The surface energetics play a major role in several different areas of pharmaceutical interest, such as dissolution of solid dosage forms, wet granulation, suspension formulation, product stability and film-coating (Buckton, 1988).

The physical behavior of the pellets in water in the dissolution flask for the three pellets was

observed to be different. The HPMC pellets immediately absorbed water without significant swelling, stuck together and formed a single mass at the bottom of the dissolution flask. In contrast, HEC pellets absorbed water, exhibited significant swelling and stayed intact without adhering to each other; the swollen pellets eroded and finally dissolved in the dissolution medium. The MCC pellets stayed intact and separate without swelling. Such behavior can be attributed to the differences in the aqueous solubility and the viscosity of the three celluloses. The behavior of the HPMC pellets can be explained in terms of the lower viscosity grade (6 cps for a 2% solution) of the polymer used for pelletization. However, the HEC was of 3400–5000 cps (1% solution) viscosity. Since higher viscosity or higher molecular weight grades of cellulosic polymers form gels of higher viscosity and higher gel stability compared to lower viscosity grades, the HEC pellets exhibited higher degree of swelling and intactness in the dissolution medium for a longer period of time as compared to HPMC pellets. The MCC pellets stayed intact because of its insolubility in water.

#### 4. Summary and conclusions

The inter and intra-lot variability in moisture content and bulk and tapped densities of the three cellulosic excipients, HPMC, HEC and MCC, was found to be very small. The Hausner's flowability index data suggest that HPMC and HEC will exhibit relatively better flowability as compared to MCC. The relatively higher bulk and tapped density of HPMC and HEC, as compared to those of MCC, make them suitable for processes involving densification, such as extrusion/spheronization. Although the bulk and tapped densities of MCC were lower as compared to HPMC and HEC, MCC has higher compressibility, which resulted in MCC pellets with higher bulk and tapped density as compared to HPMC and HEC pellets (Table 6). However, the inter-lot variability in particle size and surface area, both of which play critical role in the wet massing liquid requirement of the excipient, was much larger for HPMC and HEC as compared to MCC. A minimal variation

in the particle size and surface area of the powder excipients is required for not only extrusion/spheronization but also for other applications, especially in the solid dosage form technology. Hence, the higher variability observed in the particle size and surface area of HPMC and HEC emphasizes the need for the availability of these materials with tighter specifications. The median particle size of the three materials did not correlate with their surface area, which may be attributed to the difference in their surface morphology. Also, the critical liquid requirement of the three cellulosic materials cannot be correlated with such physical properties as particle size and surface area. The observed difference in the wet massing liquid requirement of the three cellulosic materials may, in part, be due to difference in their surface properties, such as surface energetics. These differences could not be explained in terms of the routine tests conducted.

It appears from the pellet evaluation data that the pellets of desirable attributes can be prepared from HPMC and HEC using IPA as the wet massing liquid by extrusion/spheronization. MCC also yielded pellets of acceptable attributes, even with IPA. However, the critical liquid requirement of MCC was much smaller as compared to HPMC and HEC. Another part of the study on these materials, using mixer torque rheometer, evaluates the critical liquid requirement of these three materials and the effect of amount of wet massing liquid on the rheological behavior of their wet masses.

During dissolution, the HPMC and HEC pellets absorbed water producing a viscous gel matrix and dissolved or eroded, unlike MCC pellets which stayed intact in the dissolution medium. This behavior may be useful in some specialized applications where complete water-solubility of all the formulation excipients is desired. Since the cellulose ethers are available in a wide range of viscosity grades and hydration rates, another possible application of the water-soluble polymers will be in controlled-release dosage form development, where the drug release can be modified from pellets without the application of any rate-controlling membrane coatings by appropriate selection of the pellet formulation components.

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