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The powder flow and compact mechanical properties of two recently developed matrix-forming polymers

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Abstract

The powder flow and compact mechanical properties of two recently developed matrix-forming polymers were determined. The polymers are cross-linked high-amylose starch (Contramid) and poly(acrylic acid) (Carbopol EX507), and their properties were compared with those of two established matrix-forming polymers, hydroxypropyl methylcellulose (Methocel K100LV) and hydroxypropyl cellulose (Klucel EXF). The particle morphology, size distribution and true density of the four materials were quite different and they exhibited measurable performance differences with respect to powder flow, compact ductility, compact elasticity and compact tensile strength. Recommendations for formulating solid dosage forms with each of these excipients were made, based on a consideration of their physical properties and their anticipated processing performance.

Introduction

Polymers are frequently used in the production of matrices for controlled-release dosage forms (Mathiowitz 1999). In addition to needing those properties necessary for controlled drug delivery (e.g. gel forming ability, high microviscosity) these materials are required to have particulate and mechanical properties that allow them to be conveniently manufactured into final dosage forms. These properties include, but are not limited to, adequate powder flow and the ability to form mechanically robust compacts (Alderborn & Nystrom 1995).

It is usually desirable to use conventional pharmaceutical tableting operations for manufacturing controlled-release matrix dosage forms. Thus, this paper describes a comparison of the physical properties of four matrix-forming polymers with respect to their suitability for conventional tableting operations. Typically, the properties of as-received matrix-forming polymers are not optimal for such manufacturing operations (e.g. they often exhibit a very high degree of plasticity).

The materials considered in this work are two recently developed excipients, cross-linked high-amylose starch (Contramid) and poly(acrylic acid) (Carbopol EX507), and two well-established matrix-forming materials, hydroxypropyl methylcellulose (Methocel K100LV) and hydroxypropyl cellulose (Klucel EXF). The potential advantages of the newer excipients over those already in use are considered, and the attributes of these materials that may require modification by processing or the use of additional functional excipients are identified.

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Materials and Methods

Contramid, a granulated cross-linked high-amylose starch, and Carbopol EX507, a dry granulated acrylic acid polymer, have recently been developed for controlled-release tablet applications, and were supplied as samples by Labopharm Inc. and B. F. Goodrich, respectively. (The Carbopol EX-507 studied was an experimental lot. The product has recently been commercialized as Carbopol 71G and has a slightly different particle size distribution.) Details of the polymer manufacturing procedures and their possible applications can be obtained directly from the suppliers. Hydroxypropyl methylcellulose is a well-studied matrix-forming polymer, and the grade used in this work was Methocel KV100LV (Dow Chemical). Hydroxypropyl cellulose (Klucel EXF; Hercules Inc.) was selected as an alternate cellulose-derived matrix former. This particular grade has been specially formulated with a small mean particle size to promote uniform blending with other formulation ingredients.

Photomicrographs of each material were taken with a Jeol JSM-5800 scanning electron microscope (Jeol USA Inc., MA). The photographs were taken at a working distance of 10 mm with an accelerating voltage of 5 kV. Optical microscope images of the contramid particles were obtained with an Olympus SZX12 microscope at a magnification of 10 ×. The true densities of the samples were determined with a helium pycnometer (Quantachrome Inc., FL) operated at 20°C according to the manufacturer's recommended methods. The particle size distribution of each powder was determined using a Sympatec Helos/Rodos laser diffraction particle size analyser (Sympatec Inc., NJ) with dry powder dispersion capability. The powder dispersion pressure was 2.0 bar with direct feed into the dispersion funnel. The optical concentration was maintained over the range 8–12%. Bulk and terminal tapped densities were determined using a VanKel tapping device fitted with a 100-mL glass measuring cylinder (VanKel, NC). The Hausner ratio was calculated as the direct ratio of the tapped and bulk densities (Hausner 1967). Powder flow was assessed using a custom-built plate-type shear cell that has been described previously (Hiestand & Wilcox 1968). A two-point determination of the effective angle of internal friction was performed at 20°C and 50% relative humidity, using normal stresses of 75.6 and 104.9 g cm^{-2}. All determinations were made in duplicate and mean values are reported.

Samples for mechanical testing were approximately 5-g rectangular compacts measuring $1.9 \times 1.9 \times 1.0$ cm^3. They were formed by uni-axial compression using a custom-built hydraulic press that permitted gradual triaxial decompression of the samples and produced practically flawless compacts (Hiestand & Smith 1984). The punch and die surfaces were sparingly lubricated with magnesium stearate suspended in methanol (approx. 5%). Indentation hardness determinations were performed in "dynamic" mode (approx. 1500 mm s^{-1} impact speed) using a pendulum impact device and in "quasi-static" mode (approx. 0.008 mm s^{-1} impact speed) with a custom-built indentation tester (Hiestand & Smith 1984). The spherical indentors were 2.54 cm in diameter and 65.6 g in mass, and the pendulum length was 92.3 cm with a release angle of 30°. Quasi-static indentation forces were selected to produce indentations of a similar size to the dynamic indentation test. The compact indentations were measured using a stylus-type profilometer (Federal Products, RI) and the dent depth, dent diameter, apparent radius of curvature and rebound height were used to calculate the indentation hardness and elastic modulus of the compacts (Hiestand & Smith 1984). The tensile strength of the compacted samples was determined with a custom-built tensile tester (Hiestand & Smith 1984). Tensile failure was observed for all the rectangular compacts when compressed between flat-faced platens at a speed of 0.041–0.002 mm s^{-1}. Specially modified punch and die sets permitted the formation of compacts with a centrally located hole (0.11 cm diam.), which could be used to act as a stress concentrator during tensile testing. This capability permitted the determination of a "compromized" compact tensile strength and thus facilitated an assessment of the defect sensitivity of each compacted material. At least two replicate determinations were performed for each mechanical testing procedure and mean values are reported.

Results and Discussion

Powder characteristics

The poly(acrylic acid) particles were too large to be examined by electron microscopy and so were examined by light microscopy instead. It was noted that they were regular, dense and had a smooth surface (Figure 1). The scanning electron micrographs for the cross-linked starch, hydroxypropyl methylcellulose and hydroxypropyl cellulose samples are shown in Figures 2–4. The cross-linked starch consisted of collapsed spherical particles typical of those produced by spray-drying processes. In contrast to the newer matrix-forming polymers, the hydroxypropyl methylcellulose and hydroxypropyl cellulose samples each comprised frag-

Figure 1 Optical microscope image of poly(acrylic acid) (Carbopol EX507).

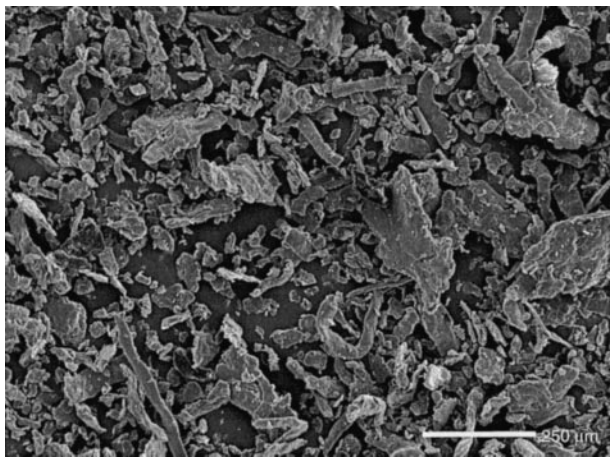

Figure 3 Photomicrograph of hydroxypropyl methylcellulose (Methocel K100LV).

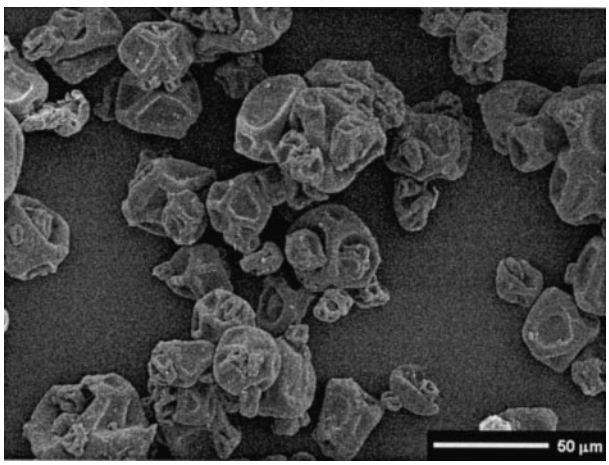

Figure 2 Photomicrograph of cross-linked high-amylose starch (Contramid).

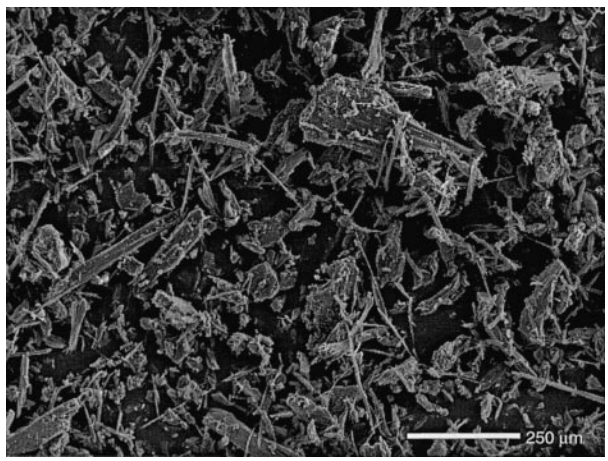

Figure 4 Photomicrograph of hydroxypropyl cellulose (Klucel EXF).

mented fibrous particles that had an irregular surface morphology. Using helium pycnometry, important differences in the true densities of the four materials were detected (Table 1). Since the materials all have a similar chemical composition, these differences most likely reflect differences in their molecular weight distribution, degree of branching, cross-linking and crystalline order.

The particle size distributions of the excipients are compared in Figure 5 and Table 1. Since the particles were not perfectly spherical for any of the materials, these particle size data should only be considered to indicate relative particle size differences. The largest particles were clearly those of the granulated poly(acrylic acid); the other excipients all had very similar particle size distributions. The Contramid sample was labelled as ''granulated'', but no large agglomerates were detected by scanning electron microscopy or laser diffraction size analysis. The bulk and tapped densities of the polymer samples are given in Table 2. The poly(acrylic acid) had a higher bulk density than the other materials (presumably because it was dry granulated) and the tapped densities of all four polymers were quite similar.

Based on the differences in particle morphology, true density, bulk and tapped density, and particle size for the four matrix-forming polymers, it was expected that

Table 1 Mean particulate properties of the matrix-forming polymer samples (s.d. all less than 0.005 g mL^{-1} or 0.5 μm).

Material	True density (g mL^{-1})	Median particle size (μm)	10th percentile size (μm)	90th percentile size (μm)
Cross-linked high-amylose starch	1.19	76	28	360
Poly(acrylic acid)	1.43	354	29	648
Hydroxypropyl methylcellulose	1.30	66	22	192
Hydroxypropyl cellulose	1.21	85	12	247

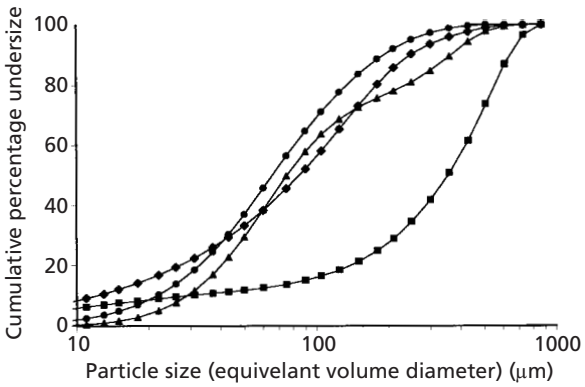

Figure 5 Mean particle size distributions of matrix-forming polymer samples: ▲, cross-linked high-amylose starch; ■, poly(acrylic acid); ●, hydroxypropyl methylcellulose; and ◆, hydroxypropyl cellulose. (Error bars are smaller than the symbols in all instances).

their powder flow properties would be quite different. This was confirmed by the wide range of values obtained for the effective angle of internal friction (Table 2). The lower the value of this parameter, the more easily the powder flows. The two cellulose polymers, with their fibrous particle morphology, had the worst powder flow, with the small particle size grade of hydroxypropyl cellulose exhibiting particularly poor powder flow. The cross-linked starch appeared to have a slight "glidant" action in the shear cell, since its angle of internal friction was significantly lower than would be expected from its macroscopically observed behaviour. Not surprisingly, in the shear cell, the large, granulated, regular particles of the poly(acrylic acid) were observed to flow very easily. The Hausner ratio has been used as an indicator of powder flow by some workers (Abdallah & Geldart 1999), but for the materials considered in this work, there was no obvious correlation between this parameter and the measured angle of internal friction. Interestingly, the poly(acrylic acid) did have the lowest Hausner ratio (consistent with its microscopically observed flow performance in the shear cell), and the hydroxypropyl methylcellulose had a higher Hausner ratio than the hydroxypropyl cellulose, as might be expected from its relative particle size distribution.

Compact mechanical properties

Based on experience with a wide range of pharmaceutical excipients, drug substances and formulations, the mechanical properties of the matrix-forming polymers were assessed. The matrix-forming polymers were considered with respect to their use in direct-compression or granulated formulations where they will typically comprise between 30 and 80 % of the total tablet weight. So as to be able to directly compare their mechanical properties, the materials were each compressed into compacts with an identical porosity (Alderborn & Nystrom 1995). This porosity (15 %) is typical of many solid oral dosage forms.

Table 2 Mean bulk properties of the matrix-forming polymer samples (s.d. all less than 0.005 g mL^{-1}).

Material	Bulk density (g mL^{-1})	Tapped density (g mL^{-1})	Hausner ratio	Angle of internal friction (°)
Cross-linked high-amylose starch	0.35	0.46	1.31	30
Poly(acrylic acid)	0.51	0.58	1.14	33
Hydroxypropyl methylcellulose	0.32	0.56	1.75	38
Hydroxypropyl cellulose	0.30	0.47	1.57	45

Table 3 Mechanical properties of matrix-forming polymer compacts (at a compact porosity of 15%) (mean and s.d.).

Material	Dynamic indentation hardness (MPa)	Quasi-static indentation hardness (MPa)	Elastic modulus (GPa)	Tensile strength (MPa)	Compromised tensile strength (MPa)
Cross-linked high-amylose starch	35 (< 1)	8 (< 1)	0.2 (< 0.1)	1.4 (< 0.1)	1.0 (0.1)
Poly(acrylic acid)	242 (23)	70 (1.7)	6.6 (0.5)	5.5 (< 0.1)	3.0 (0.3)
Hydroxypropyl methylcellulose	129 (26)	26 (< 1)	0.8 (< 0.1)	3.3 (< 0.1)	3.0 (< 0.1)
Hydroxypropyl cellulose	53 (< 1)	5 (< 1)	0.4 (< 0.1)	1.4 (< 0.1)	1.4 (< 0.1)

The dynamic indentation hardness values shown in Table 3 indicate the relative plasticity of each material, with low values indicating high plasticity or "ductility". Clearly, the cross-linked starch and the hydroxypropyl cellulose had the greatest ductility, and they were able to rapidly absorb energy by permanently deforming when loaded at a relatively fast rate. This is normally considered to be a material attribute since plasticity permits the permanent deformation of particles and can increase the bonding area between them. Based on our experience with other very high ductility excipients (e.g. poly(ethylene glycol)), the extremely low dynamic indentation hardness of the cross-linked starch may also lead to "flow" of the material between the punch and die during pharmaceutical tableting operations, and this is obviously an undesirable occurrence. Hence, the hydroxypropyl cellulose probably had the optimal dynamic indentation hardness of the four materials considered. Under quasi-static loading conditions, the four polymers displayed a similar overall trend in ductility, and, as is seen with most pharmaceutical materials, they had a lower resistance to indentation under quasi-static loading than under dynamic loading. This decrease in indentation hardness with loading rate will be considered in more detail later.

The elastic moduli of the polymer compacts, determined from the results of the quasi-static indentation hardness tests (Hiestand & Smith 1984), indicate that the poly(acrylic acid) had a significantly greater elasticity than the other materials (Table 3). This may be a disadvantageous property for commercial tablet manufacturing operations because significant reversible deformation of compacts can be the cause of tablet lamination problems (Ritter & Sucker 1980). To offset this material deficiency, the poly(acrylic acid) was able to form compacts with a much greater tensile strength than the other materials, even when compromised by the presence of a controlled flaw which acts as a stress concentrator or crack initiation point (Table 3). The hydroxypropyl methylcellulose also formed compacts with a high tensile strength, while having a lower elastic modulus and greater ductility (usually considered attributes for tablet compression operations). The elasticity and tensile strength of the two other materials were typical of many other compressible excipients and were considered to be acceptable for normal tablet formulation applications.

The ductility, elasticity and strength of the polymer compacts need to be carefully balanced to achieve optimal performance for any given tableting application. One way of evaluating the relative importance of these properties is by using the "tableting indices" proposed by Hiestand (Hiestand & Smith 1984). These are a series of simple ratios between the parameters listed in Table 3; they were calculated and are presented in Table 4 for the four matrix-forming polymers. The brittle fracture index reflects the relative magnitude of the two tensile strength measurements and indicates on a scale of zero to unity, the fracture resistance of each material. A low value is desirable since this shows that the compacted material is relatively insensitive to the presence of macroscopic flaws or defects. In a sense, this parameter is providing similar information to that obtained from classic fracture mechanics measurements (Kendall & Gregory 1987). For the materials studied in this work, it is clear that the non-cellulose-based polymers were the most susceptible to failure initiated at compact defects, and this mode of failure will probably be a very significant one for compacts formed from the poly(acrylic acid). The two bonding indices (Table 4) are the ratios of the tensile strength to the indentation hardness values and they indicate whether the compacts have the strength and ductility to withstand either a dynamic load ("worst case") or a quasi-static load ("best case"). In both cases, the higher the value, the greater the combined strength and ductility and the more likely a compact will be to withstand external stresses without failing (e.g. during tablet decompression

Table 4 Tableting indices for matrix-forming polymer compacts (at a compact porosity of 15%).

Material	Brittle fracture index	Bonding index (worst case) $\times 10^2$	Bonding index (best case) $\times 10^2$	Viscoelastic index
Cross-linked high-amylose starch	0.17	3.9	17	4
Poly(acrylic acid)	0.42	2.3	8	3.5
Hydroxypropyl methylcellulose	0.06	2.6	13	5
Hydroxypropyl cellulose	0.00	2.7	29	11

Table 5 Summary of properties of matrix-forming polymers and their compacts (at a compact porosity of 15%) (+ indicates desirable performance, − indicates undesirable performance).

Material	Powder flow	Ductility	Elasticity	Tensile strength	Brittleness	Bonding
Cross-linked high-amylose starch	+	++	+	+	−	++
Poly(acrylic acid)	+	+	−	+++	−−	++
Hydroxypropyl methylcellulose	−	+	+	++	++	++
Hydroxypropyl cellulose	−−	+++	+	+	+++	++

or handling). This viewpoint presumes that permanent deformation of a compact without failure is an acceptable outcome following the application of an external load (in compression or tension). For all the materials considered, the magnitudes of the bonding indices were such that the mechanical strength of their compacts during normal tableting operations should not be in question (Table 4). For comparison, the common tableting excipient microcrystalline cellulose, typically, has a worst case bonding index of between 200 and 400, depending on the supplier and the grade tested (Williams et al 1997). The last tableting index of interest is the viscoelastic index which is simply the ratio of the two hardness values (Table 4). This parameter provides an indication of the sensitivity of a material to the loading rate during the indentation measurements. A high value is indicative of a strongly time-dependent viscoelastic response. This behaviour may be desirable for pharmaceutical tablet manufacturing to some extent, but extremely high viscoelasticty can, in theory, lead to problems during the high-speed compression of tablets for commercial use. This is unlikely to be a problem for the poly(acrylic acid), the cross-linked starch and the hydroxypropyl methylcellulose, but may be a potential liability when working with compacts of hydroxypropyl cellulose (Table 4).

By comparing the trends in Tables 1–4, it should be possible to determine if there are any links between the particulate properties and mechanical properties of the matrix-forming polymers. Notably, the two cellulosic polymers produced compacts with the lowest brittle failure tendency, suggesting that the fibrous particle morphology might impede the propagation of cracks through the compacts. Otherwise, there were no clear correlations between particle size, morphology or density and any of the mechanical properties of these polymers. Presumably, the effects of chemical structure, molecular weight, percentage crystallinity, degree of substitution, branching and cross-linking were sufficient to mask any effects on the mechanical properties as a result of the particulate properties of these materials.

Obviously, an optimal matrix tablet needs to be "manufacturable" using conventional processing operations, and it should, in addition, be able to resist normal handling and shipping stresses. The dosage form should also remain intact and resist mechanical shock and erosion when in the hydrated state in the gastrointestinal tract. We have not considered the in-vivo performance of the four polymers studied; however, it is apparent that none of the materials considered has an optimal combination of flow and mechanical properties even in the "dry" state (Table 5). This it not unusual among excipients, and it is thus expected that some additional approaches will need to be used with any formulation containing these materials to produce a robust and optimally performing system. In the case of the poly(acrylic acid), the addition of excipients with greater ductility should be considered to offset the

elasticity and brittleness of this material, especially in matrix applications where the polymer would be expected to form a significant portion of the final formulation. With the cross-linked starch, a particle size enlargement step, such as wet granulation, may be helpful to reduce the tendency for brittle failure of the matrix tablets. When using hydroxypropyl methylcellulose to formulate a matrix-type tablet it may, likewise, be desirable to perform a wet granulation operation to improve the flow and increase the ductility of the formulation. Finally, with the hydroxypropyl cellulose, significant measures will probably be required to promote powder flow in its formulations (e.g. addition of a glidant). Not considered in this work, for obvious reasons, is the influence of the drug substance on the properties of formulations containing these matrix-forming polymers. It is usual that excipients are selected to have complimentary properties to the drug substance and thus no one excipient can be expected to be suitable for use with all drug candidates. From the results presented here, it can be seen that the four polymers used in this work present a diverse range of properties and together they can provide most of the excipient selection options that are desired when developing matrix-type controlled-release dosage forms.

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