Characterization of Compressibility and Compactibility of Poly(ethylene oxide) Polymers for Modified Release Application by Compaction Simulator

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Abstract Poly(ethylene oxide) polymers (PEO) appear to have great potential for controlled release applications. These polymers are hydrophilic with good water solubility, low toxicity, and high swelling capacity. As part of formulation optimization for a large-scale solid dosage form production, physicomechanical characterization of PEO was undertaken using a compaction simulator. Heckel plots for all PEOs were constructed, and yield pressures (P_y) at different punch velocities were calculated from the linear portion of the plots. Low P_y values, increase of P_y with increasing punch speed, upward curvature of the plot, and strain rate sensitivity values indicate that the densification process and consolidation mechanism for PEOs of various molecular weights (0.2 × 10^6 to 7 × 10^6) are identical and follow plastic deformation. PEOs have a high degree of crystallinity (57–85%) and show significant axial recovery (15–25%) upon decompression and ejection. The low P_y values (58–78 MPa) and low mean compaction pressures demonstrate that volume reduction (compressibility) under pressure is excellent. However, due to viscoelastic behavior and large axial expansion, tablets of relatively low tensile strength are produced. These observations suggest the need to blend PEO with highly compressible excipients in order to produce tablets on a high-speed production press.

Modified-controlled-release dosage form design combines the application of polymer chemistry, physicochemical principles of pharmaceutics, and variety of excipients to produce drug delivery systems and optimize therapy by controlling drug entry into the systemic circulation in order to achieve either steady-state drug levels or other clinically desirable input rates. Drug release from such systems is largely influenced by the properties of polymers including swelling erosion, osmotic action, ion-exchange, and diffusion. In the area of solid dosage form design for oral administration, material selection and the stability of system components are highly crucial in the development of a well-characterized, reproducible drug delivery system. Therefore, a better understanding of intrinsic polymer characteristics such as physicochemical and mechanical properties in particular provides criteria for the polymer selection in system design to achieve the desired objectives.

Polyethylene oxide (PEO) is a class of water-soluble linear resins, available over a wide range of molecular weights under the trade name of Polyox. These polymers have been widely used in chemical technology, agricultural engineering, medicine, and the pharmaceutical and food industries because of their aqueous solubilities, high gelation, and low toxicity. Their applications in the controlled-release field are also documented.1 Recent studies demonstrate that PEOs have great potential in the fabrication of controlled-release systems for oral administration because of their unique swelling erosion properties.2,4

Zero-order drug release kinetics from a directly compressed simple tablet or a composite-layered tablet based on PEOs are achievable.5,6 While PEOs have been employed in tablet formulations in research and development, their compressibility and compactibility behavior for large-scale manufacturing has not yet been explored.

The importance of time dependent deformation of pharmaceutical material during compaction has been recognized.7,8 Since it is known that formation of a strong, coherent tablet essentially depends on the process of powder consolidation, in a multicomponent formulation more often the compression behavior of individual components allows a formulation scientist to choose excipients with desired compressibility and compactibility properties for formulation optimization.9

Therefore, it becomes necessary to evaluate the compactibility behavior of PEO's under compression and their consolidation mechanism. This can be accomplished via several means including an instrumented single- or multistation tablet press, a universal testing machine, and a compaction simulator. For example, with the application of different punch velocities the strain rate sensitivity of materials can be determined using the equation derived by Heckel.10,11

The objectives of this study were to investigate the compression behavior of PEO over a wide range of molecular weights using a compaction simulator as well as identifying the effect of punch velocity on the nature of its consolidation. An attempt is also made to compare and correlate various physical properties of PEOs and their molecular weights with their yield pressure, axial recovery, and strain rate sensitivity.

Experimental Section

Materials—Polyethylene oxide with declared average molecular weights of 0.2 × 10^6, 0.3 × 10^6, 0.6 × 10^6, 0.9 × 10^6, 1.0 × 10^6, 2.0 × 10^6, and 4.0 × 10^6, 7.0 × 10^6 (Corresponding Polyox NF grades are WSR N-800H, WSR N-750, WSR 205, WSR-1105, WSR N-12K, WSR 60K, WSR-301, and WSR-303, respectively) were supplied by Union Carbide Corp. The moisture content of all grades of PEO was <1% as indicated by the supplier. All samples were sieved with US standard sieves to obtain a fraction of particle size between 105 and 208 μm. Additionally, bulk samples were also characterized as received for compaction and powder properties as shown in Table 1. These included WSR N-3000 (MW = 0.4 × 10^6), WSR-1105, WSR N-60K, WSR-301, and WSR-303.

Powder Characterization—The powder properties of bulk PEO samples were determined on a powder characterization tester (Hosokawa Micron), which allows the measurement of parameters as listed in Table 1.

Micromeric Characterization—The true density of each PEO sample was determined on a helium pycnometer AccuPyc 1330 (Micrometrics, Norcross, GA), and the average of two runs was recorded. The specific surface area was measured on a Gemini 2360 surface area analyzer (Micrometrics) using the BET equation and gas adsorption.

Thermal Analysis—Differential scanning calorimetry was performed on a Perkin-Elmer DSC-7 calorimeter to determine the melting temperature and crystallinity. The heating rate was 10 K/min, and the initial temperature was 273 K. The melting temperature corresponded to the endotherm's peak. The ratio of the experimental melting enthalpy to the melting enthalpy of perfectly
crystalline polymer ($\Delta h_{\text{cryst}} = 196.6 \text{ J/g}$)\(^{12,13}\) was taken as the degree of crystallinity characterizing the proportion of crystalline phase in PEOs.

### Compaction Profiling
Compaction profiling was carried out using a compaction simulator which has been described in detail elsewhere.\(^{14}\) In brief, the system consists of a Mand Compaction Simulator (Abacus Industries Ltd., formerly Mand Testing Machines Ltd., Stoubridge, U.K.), a Nicolet Model 440 oscilloscope, and a personal computer. The compaction cycle used to drive the simulator was that of a Manesty Betapress, i.e., double-ended compaction (both punches moving) with subsequent automatic ejection, operated at maximum punch tip velocities of 50 and 250 mm s\(^{-1}\). The elastic deformation of the punches and related parts under load was also determined and utilized to correct the compact heights in the die.

The required time-displacement profiles were calculated according to the Rippie and Danielson equation\(^{15}\) derived for a rotary tablet press (Manesty Betapress),

$$Z = [(r_1 + r_2)^2 - (r_3 \sin \omega t - x)^2]^{1/2}$$

where \(Z\) is the vertical displacement of the upper or lower punch at time \(t\); \(r_1\) and \(r_2\) are the radii of the compression rolls and the vertical curvature of the punch head rim, respectively; \(r_3\) is the radial distance between the turret center and the die cavity center (so called “pitch circle”); \(x\) is the horizontal distance between the center of the upper punch and the center of vertical curvature of the punch head rim; \(\omega\) is the turret angular velocity. This equation and, hence, the waveform do not take into consideration the punch head flatness. Hence, the contact time on the simulator is actually shorter than that on the rotary press operating at the same speed. A typical compaction profile (upper punch force as a function of time) generated using the waveform calculated for the Manesty Betapress operating at a punch velocity of 250 mm s\(^{-1}\) is presented in Figure 1.

Compacts were prepared using a constant volume of solid in the die equivalent to 0.225 cm\(^3\) (compact weight = true density $\times$ 225 mg) and flat-faced, 1 cm, round tooling. The nominal thickness of compacts to be produced was set at 2.8, 3.0, 3.2, and 3.5 mm in order to obtain a residual porosity of 2–20%, and seven compacts were prepared at each condition. Thickness, weight, and hardness (tablet hardness analyzer VK 2000, Vankel Corp.) of ejected tablets were determined immediately after production. Tensile strength was calculated according to the method of Fell and Newton.\(^{16}\) The data (loads and displacements of upper and lower punches as a function of time) were down-loaded from the Nicolet oscilloscope to the PC and converted into Microsoft Excel (version 5.0) for further manipulation.

### Processing of Compaction Data
The compaction force–porosity data were analyzed using the Heckel equation, which has been widely employed to characterize the compaction behavior of powders:\(^{3,17}\)

$$\ln \frac{1}{1-D} = KP + A$$  

where \(D\) is the ratio of the apparent density of the compact at pressure \(P\) to the true density of the material. \(K\) is the slope of the linear portion of the plot, and its reciprocal is taken to be the yield pressure \(P_y\); \(A\) is a constant.

The percentage of apparent axial recovery of each ejected compact was calculated according to the equation\(^{18}\)

$$\text{apparent axial recovery} = \frac{H - H_c}{H_c} \times 100\%$$

where \(H_c\) is the minimum thickness of the tablet in the die and \(H\) is the thickness of the tablet after ejection.

### Results and Discussion
Powder flowability is one of the most important parameters that the formulation scientist takes into consideration when developing a solid dosage form, because commercial production of a solid dosage form requires the continuous flow of powder mixes during manufacturing process. According to Carr\(^{19,20}\) powder flowability could be best assessed by four parameters: angle of repose, angle of spatula, compressibility, and cohesiveness. Table 1 outlines all physical characteristics required to characterize PEO flow properties. As shown in Table 1, all samples exhibit a similar angle of repose and good flow characteristics.

<table>
<thead>
<tr>
<th>Powder Properties of Bulk Polyox Samples (^a)</th>
<th>WSRN3000</th>
<th>WSR-1105</th>
<th>WSR-60K</th>
<th>WSR-301</th>
<th>WSR-303</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angle of repose (deg)</td>
<td>35</td>
<td>32</td>
<td>35</td>
<td>30</td>
<td>36</td>
</tr>
<tr>
<td>Angle of fall (deg)</td>
<td>25</td>
<td>31</td>
<td>31</td>
<td>21</td>
<td>29</td>
</tr>
<tr>
<td>Angle difference (deg)</td>
<td>9.7</td>
<td>1.4</td>
<td>4.2</td>
<td>9.5</td>
<td>7.3</td>
</tr>
<tr>
<td>Aerated bulk density (g/mm(^3))</td>
<td>0.53</td>
<td>0.47</td>
<td>0.39</td>
<td>0.51</td>
<td>0.45</td>
</tr>
<tr>
<td>Packed density (g/mm(^3))</td>
<td>0.59</td>
<td>0.5</td>
<td>0.42</td>
<td>0.56</td>
<td>0.47</td>
</tr>
<tr>
<td>Compressibility (%)</td>
<td>23</td>
<td>6.2</td>
<td>7</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Cohesiveness (%)</td>
<td>36</td>
<td>51</td>
<td>69</td>
<td>39</td>
<td>53</td>
</tr>
<tr>
<td>Angle of spatula (deg)</td>
<td>44</td>
<td>37</td>
<td>36</td>
<td>40</td>
<td>39</td>
</tr>
<tr>
<td>Dispersibility (%)</td>
<td>37</td>
<td>28</td>
<td>11</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>Degree of floodability</td>
<td>Fairly high</td>
<td>Fairly high</td>
<td>b</td>
<td>Fairly high</td>
<td>Fairly high</td>
</tr>
<tr>
<td>Floodability index</td>
<td>76</td>
<td>62</td>
<td>57</td>
<td>72</td>
<td>65</td>
</tr>
<tr>
<td>Flowability index</td>
<td>67</td>
<td>72</td>
<td>66</td>
<td>70</td>
<td>71</td>
</tr>
<tr>
<td>Degree of flowability</td>
<td>Good</td>
<td>Good</td>
<td>Normal</td>
<td>Good</td>
<td>Good</td>
</tr>
</tbody>
</table>

\(^a\) No significant differences among lots were observed. Difference was also evident in the cohesiveness of the powder. \(^b\) Tends to flush.
The mechanical properties of polymeric materials depend on their molecular structure, rheological properties, and related parameters such as surface morphology, particle size, glass transition temperature ($T_g$), and degree of crystallinity. Polyethylene oxides (PEOs) are tough, crystalline polymers at room temperature, and their glass transition temperature has been identified around $-60 \, ^\circ C$. Table 2 lists the determined physical parameters of PEOs. The true density values of PEOs are similar, and the degree of crystallinity does not seem to decrease as molecular weight increases. The high crystallinity and smooth symmetric chains make PEOs mechanically strong although their glass transition temperatures are well below $0 \, ^\circ C$. The degree of crystallinity is likely to vary during material processing such as shearing and tableting. Bulk WSRN-80H (MW $0.2 \times 10^6$) as received has a crystallinity of 85%. However, the crystallinity was reduced to 61.2% when compressed at 2000 lb, and when ground for 5 min with a pestle and mortar its crystallinity was reduced to 50.6%. This is probably due to the structural irregularities in the crystal lattice by shearing, slip planes, and stressing. A similar phenomenon has been observed with Avicel PH101 after compression. It should be noted that changes in materials crystallinity during processing may have unpredictable implications in formulation development.

### Heckel Analysis

The results of Heckel analysis of compaction data generated from both bulk and sieved PEO samples are presented in Figures 2 and 3 respectively. The curves for different molecular weight PEOs are overlapped on one another for clarity; for clarity the Heckel plot for WSR-303 (MW $7 \times 10^6$) is represented as an inset in Figure 3. The difference of sieved and bulk sample in Heckel plots will be considered in the following section. All the curves follow the same trend, implying that the molecular weight, chain rigidity, and crystallinity of PEO exert little influence on its compression behavior. At the early stage of compression, repacking of PEO particles occurs followed by a rapid transition into the linear portion of the Heckel plot. The curves become linear as compaction pressure exceeds 10 MPa. On the other hand, when pressure reaches the maximum, the Heckel plot exhibits a pronounced upward curvature, which is a typical characteristic of plasticly deforming polymeric materials. The most striking aspect of the plots is a large reduction in volume at low applied pressures; for instance, the apparent porosity at 100 MPa for WSR-303 is 2%. Above 50 MPa, considerable upward curvature occurs. This kind of upward curvature is often observed at low residual porosity levels and is largely due to greater resistance to compression when porosity approaches zero. In addition, punch velocity can also influence the observed behavior.

Table 3 summarizes yield pressure $P_y$, tensile strength, and axial recovery of PEO compacts. $P_y$ values were determined by linear regression of the region of Heckel plots between 10 and 40 MPa. The low yield pressure values indicate that the material has good compressibility behavior. No correlation was found between $P_y$ and molecular weight. The tensile strengths of PEO compacts were in the range 0.47–1.1 MPa without an apparent relationship with their molecular weight. It appears that, in addition to the possible opposing effect of crystallinity and instantaneous axial elastic recovery, post-compression viscoelastic behavior, particle size distribution, and morphology may also affect tensile strength. In view of the inherent complexity of the densification process and

<table>
<thead>
<tr>
<th>Molecular Wt of PEO</th>
<th>True Density g/cm$^3$</th>
<th>Surface Area (m$^2$/g)</th>
<th>$T_m$ (°C)</th>
<th>Crystallinity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$0.2 \times 10^6$</td>
<td>1.249</td>
<td>1.768</td>
<td>64.6</td>
<td>85.0</td>
</tr>
<tr>
<td>$0.3 \times 10^6$</td>
<td>1.245</td>
<td>1.502</td>
<td>66.0</td>
<td>78.3</td>
</tr>
<tr>
<td>$0.6 \times 10^6$</td>
<td>1.261</td>
<td>2.084</td>
<td>66.0</td>
<td>72.5</td>
</tr>
<tr>
<td>$0.9 \times 10^6$</td>
<td>1.246</td>
<td>2.09</td>
<td>66.2</td>
<td>71.6</td>
</tr>
<tr>
<td>$1.0 \times 10^6$</td>
<td>1.248</td>
<td>1.289</td>
<td>65.7</td>
<td>64.5</td>
</tr>
<tr>
<td>$2.0 \times 10^6$</td>
<td>1.249</td>
<td>1.317</td>
<td>65.6</td>
<td>61.1</td>
</tr>
<tr>
<td>$4.0 \times 10^6$</td>
<td>1.286</td>
<td>2.0</td>
<td>66.9</td>
<td>57.0</td>
</tr>
<tr>
<td>$7.0 \times 10^6$</td>
<td>1.249</td>
<td>1.944</td>
<td>67.8</td>
<td>72.2</td>
</tr>
</tbody>
</table>

*These values were determined on PEO sieved samples. Particle size range was between 105 and 208 μm.
The porosity change of the powder bed during the compression event would also provide some insight into the process of densification and general consolidation mechanism. Figure 4 shows the changes in the porosity of sieved PEO compacts with applied pressure. Since sieved PEOs of all molecular weights studied revealed almost identical compression behavior, only those grades used in recently published work\(^6\) on controlled release are given. As can be seen, the difference in densification curves for various PEOs could not be differentiated, which suggests that high molecular weight PEOs consolidate in the same manner as low molecular weight PEOs irrespective of other physical properties. The consolidation process displayed little variation even though the molecular weight increased 7-fold. In general, porosity of about 2% for all sieved PEOs was achieved around 100 MPa compaction force. Figure 5 demonstrates the change of tensile strength and residual porosity of WSR-12K compacts produced from sieved sample as a function of compression pressure. Increase pressure during the compression process results in more viscous flow, which leads to greater plastic deformation and interparticulate bond formation and, hence, greater tensile strength with significant reduction in residual porosity.

**Effect of Particle Size on PEO Compression Behavior**—Figure 6 presents the comparative effect of selected particle size and bulk material on the shape of Heckel plots for WSR-303 (MW = 7 × 10\(^6\)). It is obvious that the sieved sample, having a narrower size distribution, showed greater resistance to deformation when compared to the bulk sample, with a wider particle size distribution. For the latter, lower compaction pressures were sufficient to achieve residual porosity levels comparable to that of sieved samples. For example, bulk WSR-303 (MW = 7 × 10\(^6\)) compact has a porosity of 0.66% at a pressure of 63 MPa, whereas sieved sample attains a porosity of 2% at a pressure of 100 MPa. The \(P_y\) increased from 64.1 MPa in the case of bulk material to 75.3 MPa for a sieved sample. This is partly due to the

Table 3—Parameters Derived from Compaction Data\(^a\)

<table>
<thead>
<tr>
<th>Molecular Wt of PEO</th>
<th>Yield Pressure (MPa)</th>
<th>Tensile Strength (MPa)</th>
<th>Apparent Axial Recovery(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2 × 10(^6)</td>
<td>77.8</td>
<td>0.66</td>
<td>15.5</td>
</tr>
<tr>
<td>0.3 × 10(^6)</td>
<td>66.8</td>
<td>1.10</td>
<td>15.3</td>
</tr>
<tr>
<td>0.6 × 10(^6)</td>
<td>78.9</td>
<td>0.62</td>
<td>19.0</td>
</tr>
<tr>
<td>0.9 × 10(^6)</td>
<td>73.5</td>
<td>0.64</td>
<td>18.8</td>
</tr>
<tr>
<td>1.0 × 10(^6)</td>
<td>76.9</td>
<td>0.75</td>
<td>18.8</td>
</tr>
<tr>
<td>2.0 × 10(^6)</td>
<td>78.2</td>
<td>0.80</td>
<td>18.5</td>
</tr>
<tr>
<td>4.0 × 10(^6)</td>
<td>58.4</td>
<td>0.47</td>
<td>25.9</td>
</tr>
<tr>
<td>7.0 × 10(^6)</td>
<td>75.3</td>
<td>0.75</td>
<td>17.9</td>
</tr>
</tbody>
</table>

\(^a\) These parameters were calculated from the compact with in-die thickness of 3 mm, and the punch velocity was 250 mm s\(^{-1}\); PEO samples were sieved.

**Figure 4**—Change of porosity in sieved Polyox-WSR in-die compacts of 3 mm thickness at a punch velocity of 250 mm s\(^{-1}\) as a function of compression pressure (X, WSR-1105; •, WSR N-12K; +, WSR-60K; ○, WSR-303).

**Figure 5**—Relationships between tensile strength, residual porosity of sieved WSR-12K compacts, and compression pressure at a punch velocity of 250 mm s\(^{-1}\).

**Figure 6**—Effect of particle size on a Heckel plot of WSR-303 (□, bulk sample; ■, sieved sample; the punch velocity was 250 mm s\(^{-1}\)).
Influence of Punch Velocity on Compression Behavior of PEO—It is known that plastic deformation is a time dependent phenomenon and can be assessed by comparison of Heckel plots at different punch velocities.7,8 Figure 7 shows the Heckel plots of bulk WSR-303 (MW = 7 × 10⁶) generated at two punch velocities. We chose bulk samples instead of sieved fraction in anticipation that bulk powders will eventually be used in production. For material that consolidates plastically, the extent of plastic deformation would be reduced if the time during which the material is held under load is shortened (i.e., dwell time is decreased) with an increase in punch velocity, and the yield pressure (P_y) would also increase. In the case of WSR-303 (MW = 7 × 10⁶), P_y increased from 55.6 MPa at 50 mm s⁻¹ to 68.5 MPa at 250 mm s⁻¹. Similar results were obtained for WSR-1105 (MW = 0.9 × 10⁶) and WSR-301 (MW = 4 × 10⁶). The effect of punch velocities on yield pressures (P_y) and tensile strengths are further summarized in Table 4.

The apparent strain rate sensitivity (SRS) was calculated from the equation ²⁷

\[
\text{apparent SRS} = \frac{P_{y2} - P_{y1}}{P_{y2}} \times 100\% \quad (4)
\]

where P_{y1} is the yield pressure at low punch velocity and P_{y2} is the yield pressure at high punch velocity. High SRS values indicate that the material deforms plastically (i.e., consolidation is time dependent), whereas low SRS values (< 2%) suggest that consolidation is relatively time independent (i.e., brittle fracture).²⁷ Therefore, it is apparent that SRS values depend mainly on punch velocities.

The calculated SRS values for WSR-1105, WSR-301, and WSR-303 bulk samples were 18.5%, 18.9%, and 18.8%, respectively. These values suggest that PEOs are strain rate sensitive and therefore consolidate predominantly by plastic deformation.

Apparent Axial Recovery—Polymeric materials exhibit elastic behavior below their yield stress in conjunction with viscous and/or plastic flow when subjected to external stress above their yield value. When the external stress is removed, they tend to resume their original dimensions to a certain extent (i.e., viscoelastic properties). Both elastic deformation and viscous/plastic flow are directly proportional to the applied stress and the time scale during which the stress has been exerted. This phenomenon has significant implication in tableting compaction.¹⁵,²⁸,²⁹ Table 3 shows that the PEO compacts of all molecular weights underwent a substantial axial recovery in the range of 15–25% during decompression and ejection. It has been reported recently that microcrystalline cellulose, a frequently used excipient which also consolidates mainly by plastic deformation, experiences an axial recovery in the range of 25–40% during decompression.

The apparent axial recovery of WSR-1105 and WSR-301 was 20% at 250 mm s⁻¹ and 8% at 50 mm s⁻¹, respectively. This difference is probably due to the postcompression viscoelastic recovery of the compact (see Figure 8). At relatively high compaction pressure for this particular material (i.e., near zero porosity at pressure < 100 MPa) permanent deformation occurs. A further increase in stress introduces no significant deformation, and the change of strain with stress becomes insignificant.

The apparent axial recovery of WSR N-12K is almost directly proportional to compression pressure up to 60 MPa and then levels off.

In conclusion, these results show that PEOs of different molecular weights behave similarly during a compaction event. The consolidation mechanism dominantly follows plastic deformation as evidenced by various constants derived from the Heckel equation and SRS, and the compacts expen-
rienced significant axial recovery during decompression and ejection. PEOs of different molecular weights require low compression loads to consolidate into a compact and produce relatively soft tablets.

Our observations indicate that PEO polymers need to be blended with highly compactible excipients in order to produce tablets on a high-speed production press.

References and Notes

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