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Compaction Simulator Study on Pectin Introducing Dwell Time

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ABSTRACT – Although many scientists have used pectin, its feasibility in terms of tablet manufacturability with a high speed machine has never been evaluated. Therefore, compactibility of different pectin types for large scale tableting operation has been evaluated. The compactibility behavior of powder pectins was studied by a compaction simulator. It was found that pectin on its own does not produce tablets of acceptable quality even at a punch velocity as low as 20 rpm (e.g. low tensile strengths, capping and lamination irrespective of applied compression force). Thus, dwell time was introduced and more hard compact was produced as relaxation time in die increases. It was concluded that frequent structural failure observed in both pectin types was due to lack of plastic deformation, poor compactibility and high elastic recovery.

Key words – Pectin, Compactibility, Compaction simulator, Consolidation mechanism, Tableting, Punch velosity, Strain rate sensitivity, Plastic deformation

Pectin has great potential as a tableting excipient and drug carrier to the colon. It is a non-toxic, soluble polysaccharide which passes through the stomach and small intestine with limited digestion but is totally metabolized by the colonic microflora. In the past, drug-pectin matrices coated with pH-dependent polymers have been investigated for possible drug delivery to the colon. It is known that there are various pH sensitive synthetic polymers and prodrugs which have been used[1)] for colonic delivery of drugs. The major substrates for bacterial growth in the human large intestine are polysaccharides (i.e., pectin, starches) and proteins that escape from digestion, azo aromatic molecules, exfoliated cells, mucins and other carbohydrate moieties. These macromolecules are degraded to smaller subunits by variety of hydrolytic enzymes. Thus, drug targeting to the colon is looked at as a potential route[2)] for drug delivery by employing pectin as a drug carrier.

Pectin is non-toxic and almost totally metabolized by colonic bacteria and is present in fruits and vegetables, and consists of D-galacturonic acid and its methyl ester linked via (1-4) glycosidic linkages. It is commercially available and is marketed as low methoxylated (degree of methoxylation 30-37%) and high methoxylated (degree of methoxylation 65-72%) pectin. Various published works suggest that pectin as an excipient and a drug carrier to the colon may be of value.[3-7)] Investigations to assess behavior of pectin tablets and matrix type tablets under conditions mimicking mouth-to-colon transit[8,9)] suggest that both high and low methoxylated pectin formulation can optimally protect a drug from a high susceptibility to enzymatic attack during its transit to the colon.[7)] It is also shown that drug-containing pectin matrices rapidly can be eroded (degraded) in the presence of pectinolytic enzyme[5)] in the dissolution media. Furthermore, as an excipient, viscosity modifier and gelling agent, pectin has been used for the development of controlled release drug delivery design when blended and tabletted with other polymers in a binary or ternary polymeric matrix system.[10,11)]

In general, an ideal excipient for tableting should be free flowing, inert, non-toxic, inexpensive, chemically compatible with drugs, compressible, and have good bonding/consolidation properties. These characteristics are rarely embodied in a single excipient, and in practice, a combination of both brittle and plastic material at predetermined ratios offers advantages over a single material.[12,13)] Furthermore, it is impossible to predict the type and amounts of desired excipients from the knowledge of the compaction properties of the active or individual excipient(s) during the formulation development. Nevertheless, useful conclusions based on the compaction behavior can be drawn when relevant parameters such as porosity changes with increasing pressure, Heckel plots, strain-rate sensitivity values, force-displacement curves and percentage of elastic-recovery of tablets are taken into consideration.[14-18)]

The objectives of the present study were :

(i) to investigate compressibility/compactibility of pectin by itself taken into account for dwell time using a compaction

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simulator under tableting conditions used in production as opposed to compression on a Carver press and (ii) to investigate the influence of punch velocity on compaction behavior and determine the porosity changes.

Experimental

Materials

Pectin Type 170 [designated as low methoxyl pectin with a degree of methoxylation (DM) 30-37%] and Pectin Type 621 [designated as high methoxyl pectin with a DM of 65-72%] obtained from Pectagel Co., Great Neck, NY were used for compaction studies. Magnesium stearate (AMEND Drug & Chemical Co., Irvington, NJ) was used as received.

Methods

Compaction simulator data acquisition and treatment – Compaction Profiling was carried out on a Mand Compaction Simulator (Abacus Industries Ltd., formerly Mand Testing Machines Ltd., Stoubridge, UK), equipped with 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 compression (both punches moving) operated over a range of velocities. Typically, tablet production at 20 rpm is equivalent to a maximum punch tip velocity of about 50 mm/sec with a dwell time comparable to that of rotary presses such as Stokes B2 and a speed of 100 rpm (i.e., punch velocity of 250 $\mathrm{mms^{-1}}$) is equivalent to a dwell time on a typical production press if the punch head flatness is considered. The required time-displacement profiles for the upper and lower punches were calculated according to the Rippie and Danielson equation[19]:

$$Z = [(r_1 + r_2)^2 - (r_3 \sin\ \omega t - x_2)^2]^{1/2} \tag{1}$$

where Z is the vertical displacement of the punch (upper or lower) at time t; r_1, r_2, r_3, and x_2 are mechanical constants of the tablet press, while ω is the turret angular velocity. This equation, and hence the waveforms, do not take into consideration the punch head flatness. These waveforms were used to characterize and interpret behavior of pectin types. Pure pectin samples failed to form intact tablets due to poor compactibility. Hence, waveforms with increased dwell time (flatness considered) were also used for compaction profiling of pure pectin types.

Compacts were prepared using a constant volume of pectin powder in the die equivalent to 0.225 $\mathrm{cm^3}$ (compact weight = true density × 225 mg). 1 cm die and flat faced round tooling were used. Seven compacts of different pectin samples and their blends were compressed to obtain a residual porosity in the range of 2-20% at each compaction speed. Thickness, weight and hardness (Tablet Hardness Analyzer VK 2000, Vankel Corp.) of tablets were measured immediately after ejection unless otherwise indicated. The data (loads on and displacements of upper and lower punches as a function of time) from 3 representative compaction cycles at each test conditions were subsequently down-loaded from the Nicolet Oscilloscope to the PC and converted into Microsoft Excel (version 5.0) for further manipulation. Tensile strength of tablets was calculated according to the method of Fell and Newton.[20]

Analysis of compaction data – Many techniques and compaction equations have been used to characterize the consolidation behavior of pharmaceutical solids.[21-23] However, due to the complexity of the compressional process, many of the expressions have been shown to have limitations. A simple and most widely used approach is analysis of Heckel plots which can be constructed according to Heckel equation[24, 25]:

$$\ln\frac{1}{1-D} = KP + A \tag{2}$$

where D is the ratio of the density of the powder mass at pressure P to the true density of the powder mixture(i.e., relative density). The reduction in porosity or the resistance to volume reduction is reflected by the slope (K) of the profile and A is a constant. The yield pressure, Py, is usually calculated as the reciprocal of the linear portion slope 'K' of the Heckel plot.

Although the Heckel equation has limitations, it has been successfully and widely used by many authors to differentiate between compression by brittle fracture and plastic deformation.[24,26]

Results and Discussion

Force-time profiles for normal and prolonged dwell time – A typical upper punch force profile during compression cycle at a compaction speed of 20 rpm for both pectins under normal and prolonged dwell time are shown in Figure 1. As can be seen, the force-time peak under normal dwell time condition is not symmetrical for both pectin types (i.e., slightly skewed). For example, the calculated area under the curve for the compression and decompression phases for high and low methoxylated pectins (Figure 1) are $\mathrm{AUC_{comp}}$ 312.5 and 298.1 KN · sec and $\mathrm{AUC_{decomp}}$ 192.8 and 201.1 KN · sec, respectively. The accuracy of AUC values and interpretation of complex events that occur during decompression phase are highly questionable, however, the determination of degree and intensity of symmetry between the phases of compression and decompression may be of value. It is reported that for fully elastic

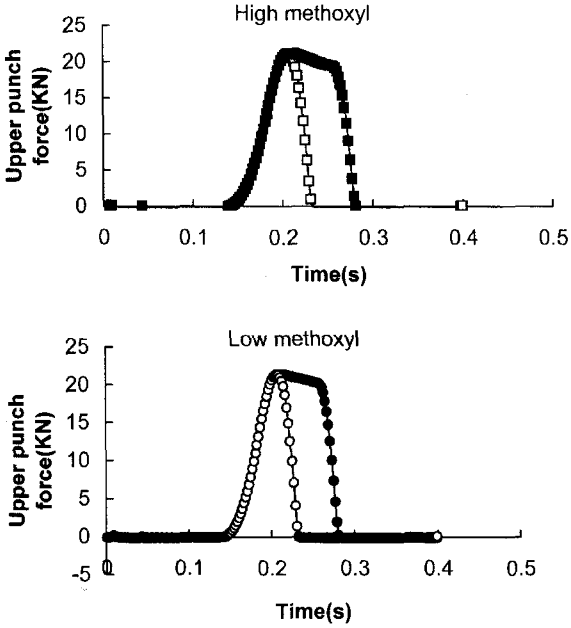

Figure 1–Representation of Upper Punch Force versus time for high and low methoxylated pectin samples at 20 rpm generated under normal (□, ○) and prolonged (■, ●) dwell time.

body (steel ball), the force-time profile is symmetrical.[27)] Synonymous behavior has been observed for plastically deforming (i.e., Avicel PH 101, PH 102, and Klucel) and brittle (i.e., Emcompress and lactose) materials in relation to 'peak offset time' or 'punch stress maxima'.[27,28)] These reports indicate that the duration of 'peak offset time' or 'punch stress maxima' is longer for materials that consolidate by plastic flow while short values are characteristics of brittle fracture behavior. The latter materials do not show intense symmetrical pressure-time profiles at the point where the derivative of pressure with respect to time is zero, while under similar conditions, viscoelastic substances show an apparent asymmetrical pressure-time profiles.[27,29)] Figure 1 may indicate that pectin is rigid and brittle material. When prolonged dwell time is used (as shown in Figure 1), significant reduction in peak upper punch force is apparent (declining slopes during dwell time). This phenomena is likely to be associated with internal stress relaxation (ie., changes in the magnitude of the stress distribution within the compact), and reduction in porosity (as shown in Figure 2).

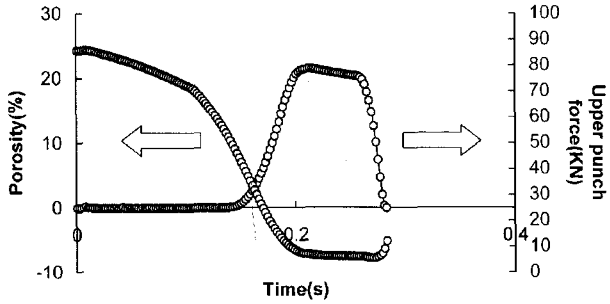

Figure 2–Residual Porosity of high methoxylated pectin sample under prolonged dwell time versus consolidation profile for thickness 3.0. Tablets were produced at 20 rpm (N=3).

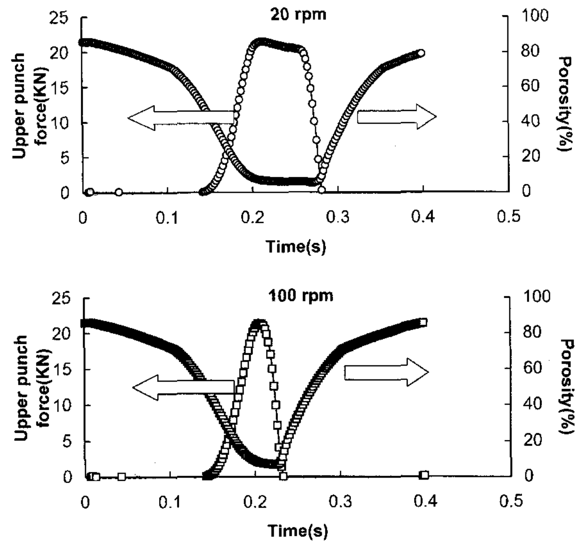

Figure 3–A typical consolidation profile and porosity changes(b) for high methoxylated pectin produced at 20 rpm and 100 rpm to a constant thickness of 3.0 mm.

Heckel analysis and Influence of punch velocity on compression behavior of pectin – Figure 3 is the representative consolidation profiles for high methoxylated pectin at compaction speed of 20 and 100 rpm keeping the in-die thickness at 3.0 mm. The variation of consolidation gradients are significantly different ($p < 0.05$) from each other. This clearly signifies that pectin has some degree of viscoelastic properties. The calculated mean yield values 'Py' (using the linear portion of the profile from 25 MPa to 125 MPa, r^2=0.9999 based on linear regression analysis) at 20 and 100 rpm are 200 and 213 MPa, respectively. These values are relatively large and indicative of great resistance to compression and volume reduction. In general, a low value of Py (steep slope) reflectes low resistance to pressure, good densification and easy compression. A low Py value however, may not significantly reflect that compact has acceptable tensile strength. In the case of pectin, the Py values at both punch velocities are relatively large. This indicates that pectin resists consolidation. The nature of consolidation mechanism can be best described by the apparent strain rate sensitivity (SRS) value.[15)] This is calculated by using the equation value[15)]:

$$\text{Apparent SRS} = \frac{Py2-Py1}{Py2} \times 100\% \tag{3}$$

where Py1 and Py2 are the calculated yield pressures at low and high punch velocities respectively. The calculated strain rate sensitivity (SRS) for pectin derived from profiles, presented in Figure 3 was 6.1%. A low SRS value suggestes that the material consolidation is large by brittle fracture. The corresponding porosity profiles are also given in Figure 3. In the original work value,[15)] determination of SRS values were based on constant punch velocities of 0.033 and 400 mms^{-1} using saw-tooth waveforms and SRS values for a variety of materials were in the range of 1.8 to 54.1. High values of SRS indicate that material is strain rate sensitive, a property was seen with plastically deforming materials while low SRS values are associated with brittle fracture substances. In contrast to pectin, plastically deforming materials such as PEO[14)] (MW : 7×10^6, SRS=18.5%) and Avicel PH 101 value[15)] (SRS=38.9 %), exhibit high SRS values.

Conclusions

From the evidence provided in this study, it may be concluded that pectin which is a hard, rigid material, on its own does not produce intact compacts when the compaction speed is greater than 20 rpm. The cause of this may be related to low plastic flow as reflected by small changes in porosity at higher applied pressures, low strain rate sensitivity values and large axial recovery after ejection. When compressed at very high compaction pressures, some increase in tensile strength at the compaction speed of 20 rpm could be achieved in the case of high methoxylated pectin. When dwell time is applied, these blends of pectin might have been expected to provide excellent compacts at all punch velocities and compaction pressures although pectin by itself exhibited a low strain rate sensitivity (e.g. a brittle material). The frequent structural failures (lamination and capping) observed in all pectin types could be attributed to lack of plastic deformation, poor compactibility and high elastic recovery. High methoxylation resulted in more coherent, still weak compacts. Examination of compaction profiles presented here may be useful for research scientists who are involved in use of pectin as a drug carrier. Pectin can also be used as formulation "finger-prints" and may aid in troubleshooting.

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