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RESEARCH PAPER

The Compression of Spheres Coated with an Aqueous Ethylcellulose Dispersion

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ABSTRACT

Tablets were compressed from commercial samples of Sugar Spheres NF, Sucrose NF, Corn Starch NF, as well as ground spheres and a physical mixture of ground sucrose plus cornstarch. Additional tablets were compressed from spheres that had been coated with a water-soluble cellulosic polymer solution followed by an aqueous ethylcellulose dispersion. Tableting parameters measured ''in-die'' included work of compression, peak offset time, tablet density, and Young's modulus. Following ejection, tensile strength was determined under diametrical loading. Dissolution of a marker contained in the water-soluble layer was determined for both compressed and uncompressed spheres. Porosities at peak pressure and peak offset times or tensile strength as functions of peak pressure did not differ between tablets compressed from pristine spheres or from ground spheres. Tablets compressed from spheres had higher values for porosity, tensile strength, and peak offset time than those compressed from sucrose or the sucrose : starch mixture. Values for work of compression were higher for tablets compressed from pristine spheres or from starch. This was attributed to the work required for particle deformation and for breaking of the spheres. The greatest elastic recovery during decompression was observed for tablets compressed from pristine spheres or starch. More brittle behavior was observed for tablets compressed from sucrose or the sucrose : starch mixture. Tablets compressed from ground spheres were more brittle than those compressed from the pristine spheres, indicating an effect due to grinding. Most mechanical properties of tablets compressed from the coated spheres were comparable to those of tablets compressed from uncoated spheres. An exception was diametric strain for tablets compressed from spheres coated with the aqueous ethylcellulose dispersion. These values increased since the plasticized ethylcellulose allowed greater distortion of the tablet before failure occurred. The dye marker was released more rapidly *from tablets compressed from spheres coated with the aqueous ethylcellulose dispersion than from comparable uncompressed spheres. At both the 5% and 10% coating levels, spheres coated with the aqueous ethylcellulose dispersion fused into nondisintegrating matrices during compression. Little difference in release rates was seen between the two tablets.*

INTRODUCTION

The coating of drug-loaded spherical particles has become an accepted means of controlling drug delivery (1). Such particles can then be suspended in liquids, filled into sachets, encapsulated into hard gelatin shells, or compressed into tablets. While drug release in the first three dosage forms depends mainly on properties of the drug and the formulation, compression into tablets imparts an additional physical stress to the spheres. Porter and Ghebre-Sellassie have summarized the many considerations in the development and scale-up of membrane-coated spheres (2), and Çelik has reviewed the compaction of microspheres (3).

Spheres or beads may be formed from a mixture of drug plus excipients; the mixture is extruded and spheronized or agglomerated in a pan or rotary fluid bed granulator. Alternately, the drug may be contained in a layer surrounding an inert preformed sphere. Drug-loaded spheres are then coated with water-insoluble films to control or to delay release of the drug. Such films have sufficient strength to withstand processes such as encapsulation, but generally suffer some damage during a tableting process. Numerous studies have investigated means of reducing such compression-induced film damage. Factors considered include variations in sphere composition (4–9), the nature of extrasphere excipients (4–6,9–11), film composition and level (10,12), size of sphere (5,13,14), and compressional force (4,6–11,15). Mechanical properties of spheres and tablets were determined in order to correlate similarities between coating and substrates with reduced severity of compression-induced film damage (4,6,8,10).

Drug release from spheres coated with release-controlling films is dependent on film thickness, which is a function of the amount of coating material applied and the surface area of the substrate. For practical purposes, one applies a known amount of coating to a measured weight of substrate, thereby having no direct control of the surface area. For this reason, the deposition of drug onto the surface of nonpareil beads followed by application of the rate-controlling film has definite advantages since these beads have uniform sphericity, surface properties, and size, thereby providing indirect control over surface area.

This study examines the mechanical properties of tablets compressed from such beads or spheres and their components and examines the effects of representative coatings on these properties.

MATERIALS AND METHODS

Tablets were compressed from Sugar Spheres NF (Nu-Pareil 14/18 mesh, Crompton and Knowles, Mahwah, NJ), Sucrose NF (Canwest Foods, Edmonton, Canada), and Corn Starch NF (St. Lawrence Starch, Mississauga, Canada). Ground samples were prepared by hand using a mortar and pestle, and the physical mixture was prepared by blending the powders in a cube blender (Erweka, Milford, CT), passing the blend through a 16-mesh screen, and blending for an additional period in the cube blender. True densities of the materials were measured by helium pycnometry (Quantachrome Multipycnometer, Boynton Beach, FL). Weight loss was determined following drying at 105°C for 4 hr. Sucrose content of the sugar spheres was determined using the extraction method specified in NF 19. Optical rotation of the aqueous extracts was measured using a polarimeter (Zeiss, Don Mills, Canada), and sucrose concentration was calculated using a calibration curve prepared using aqueous solutions containing known quantities of sucrose.

Sugar spheres were film coated in a fluid bed film coater (Aeromatic Strea-1, Niro Inc., Columbia, MD) using an aqueous solution of hydroxypropylmethylcellulose (HPMC) (Pharmacoat 606, Shinetsu Chemical Co., Ltd., Tokyo, Japan) containing FD&C Yellow #6 (Warner Jenkinson Canada Ltd., Kingston, Canada) as a marker. The coating level was 6.5%. For the balance of this paper, this coat is referred to as HPMC/dye. The spheres were then coated with an aqueous ethylcellulose dispersion (Surelease, Colorcon, West Point, PA). Coating levels for the rate-controlling coatings were 5% and 10%.

Tablets were compressed using an instrumented rotary tablet press (Betapress, Manesty Machines, Liverpool, UK) fitted with a 1.27-cm diameter flat-faced tooling with IPT standard heads at one station. Details of the press instrumentation and data acquisition and analysis have been published previously (16–19). Tablets were

Table 1

Physical Properties of Sugar Spheres and Their Components

Sample	True Density (g/ml)	Loss on Drying (%)
Sucrose	1.584	0.03
Cornstarch	1.480	7.28
Sucrose:starch mixture	1.564	ND
Sugar Spheres (14/18 mesh)	1.482	2.53
Sugar Spheres (14/18 mesh), ground	1.553	ND
Sugar Spheres (HPMC/dye)	1.476	ND
Sugar Spheres (HPMC/dye), ground	1.532	ND
Sugar Spheres (HPMC/dye + 5% Surelease)	1.406	ND
Sugar Spheres (HPMC/dye + 5% Surelease), ground	1.524	ND
Sugar Spheres (HPMC/dye + 10% Surelease)	1.426	ND
Sugar Spheres (HPMC/dye + 10% Surelease), ground	1.490	ND

ND, not determined.

compressed using peak pressures ranging from 25 to approximately 210 MPa. Following ejection, tablet dimensions were measured using a caliper, and the tablet was retained for tensile strength analysis. Tablets were subjected to diametric load using a hardness tester (CT-40, Nottingham, UK). The hardness tester had been instrumented to measure force and the distance traveled by the moving platen. The signals were read by an Apple II Plus computer for analysis.

Release of the dye marker was determined using USP apparatus II operated at 75 rpm. The medium used was water, and the dye concentration was determined spectrophotometrically at 482 nm using a diode array spectrophotometer (Hewlett Packard 8452A, Mississauga, Canada).

RESULTS AND DISCUSSION

Physical Properties of Sugar Spheres and Their Components

Physical properties of the materials are shown in Table 1. The sucrose content of the spheres was found to be 76.6%. For convenience, the physical mixture of sucrose powder and cornstarch was prepared with 80% sucrose. The loss on drying (LOD) values were used to correct for water content in the determinations of the sucrose content of the spheres. Values of true density for powder or ground samples were used in the calculation of tablet porosity.

Compression of Uncoated Sugar Spheres and Their Components

Figure 1 shows the relationship between tensile strength and peak pressure during compression P_{max} for tablets compressed from ground sucrose, cornstarch, pristine spheres, ground spheres, and the sucrose:starch mixture. For each material, there is an approximately linear relationship between tensile strength and P_{max}. At all peak pressures, tablets compressed from the components of the spheres, namely, sucrose, starch, and the sucrose:starch mixture, have lower tensile strengths than tablets compressed from the spheres themselves. However, tablets compressed from ground spheres have similar tensile strengths as the tablets compressed from pristine spheres. The higher tensile strength of the pristine spheres relative to their components can be attributed to their process of manufacture, in which, in the presence of water, powdered sucrose and starch are layered onto sucrose crystals. The solubility of the sucrose permits dissolution and bridge formation on evaporation of the water, leading to the strength of the resulting spheres. The process imparts compressibility to the parent materials, and this compressibility was not reduced by grinding.

Figure 2 shows porosity of the tablets, determined from tablet volume at peak pressure, as a function of the peak pressure. Such plots indicate the ability of a material to consolidate on application of pressure. Sucrose and the physical mixture of sucrose and starch (80:20) showed the smallest change as P_{max} increased. Tablets compressed from both pristine and ground spheres showed a higher

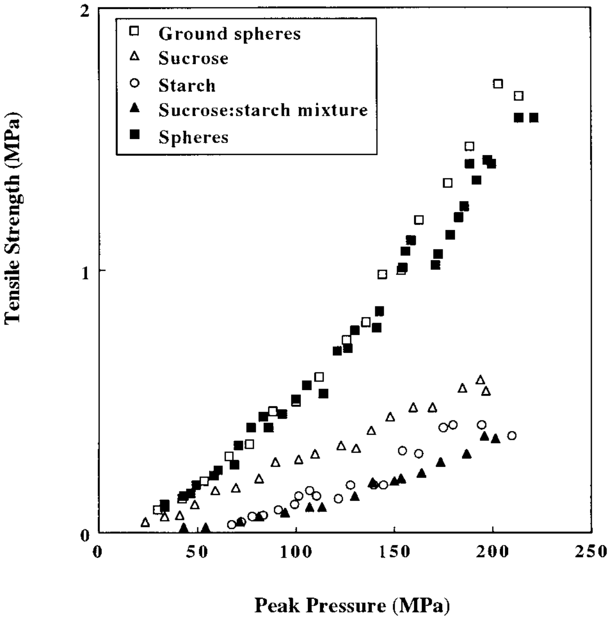

Figure 1. Tensile strength versus peak pressure for tablets compressed from spheres and their components.

rate of reduction in porosity at increasing peak pressures. For tablets compressed from pristine or ground spheres, sucrose, or the sucrose : starch mixture, differences in porosity for peak pressures greater than 125 MPa were minimal. Starch, however, showed a visually different dependence on peak pressure starting from a relatively high porosity at low P_{max} and reducing to a compact with a porosity near zero for peak pressures above 180 MPa. The volume reduction or decrease in porosity does not correlate with interparticulate bonding since the tablets show low tensile strengths.

Figure 2 shows that sucrose and starch have very different relationships between porosity and peak pressure. The relationship of porosity to peak pressure for a physical mixture of sucrose and starch is similar to surcrose itself, yet different from spheres of similar composition. As with tensile strength, the process by which the spheres are manufactured has altered another property of the starting materials, and again, the change was unaffected by grinding.

Figure 3 shows the relationship between peak offset time T_{off} and peak pressure. Scatter in such plots generally does not permit construction of statistically significant regression plots. The examination of the regions of the plot at which data points lay does allow some insight into the behavior of the material on compression. Large peak offset times at low peak pressures (about 6 ms for a turret

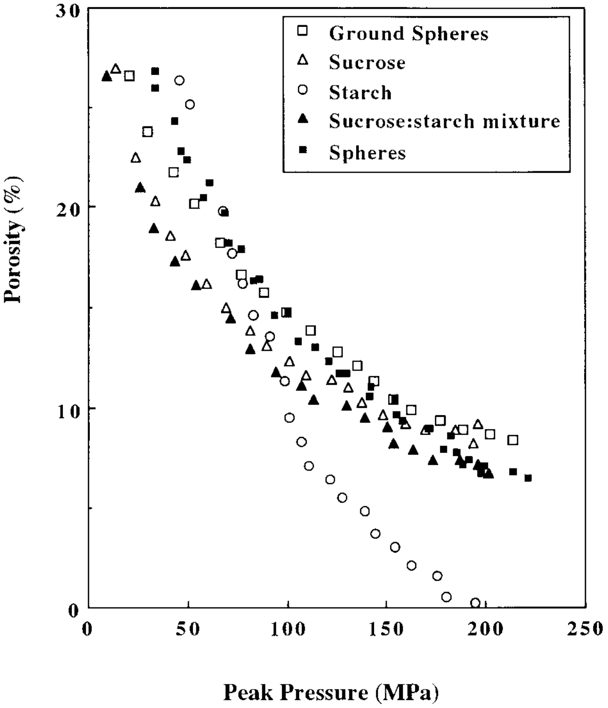

Figure 2. Porosity versus peak pressure for tablets compressed from spheres and their components.

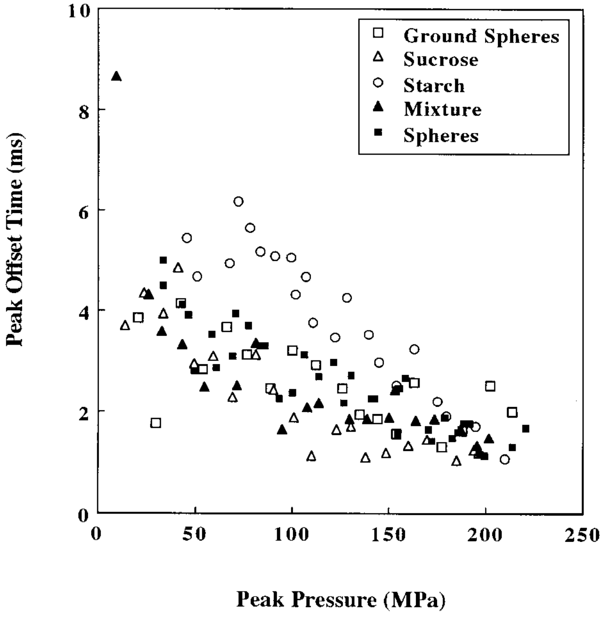

Figure 3. Peak offset time versus peak pressure for tablets compressed from Sugar Spheres NF and their components.

rotation time of 1 s) are characteristic of materials that have a high capacity to flow plastically. For these compacts, the peak offset time approaches zero at high P_{max} as void spaces are filled. Materials with short peak offset times at low pressures have a lower capacity to relieve stress. For compacts in which the material undergoes brittle fracture, the peak offset time typically starts at a low value and decreases with higher P_{max}, but does not approach zero since these compacts have greater ability to retain void spaces at high pressures.

In Fig. 3, values of T_{off} for starch are relatively high at low pressures, indicating a high capacity to flow. This is consistent with Fig. 2, which shows a high rate of porosity reduction. The differences in T_{off} for ground sucrose, pristine spheres, ground spheres, and the sucrose : starch mixture are similar over the entire range of P_{max} indicating similar flow characteristics. Their peak offset times at low P_{max} are relatively low, characteristic of more brittle materials. Values of peak offset times at higher pressures (200 MPa) for all materials show that the compacts have undergone most of their consolidation.

Figure 4 shows the work of compression in relationship to peak pressure for all materials. The sucrose and the sucrose : starch mixture showed little work done to the compact during compression. For ground spheres, the work of compression is similar to that of sucrose and the sucrose : starch mixture, but more work is required for peak pressures above 100 MPa. The work of compression for tablets compressed from the pristine spheres is greater than that for tablets compressed from ground spheres over the entire measured pressure range by about 4 J/g. The difference is due to the work required to break the spheres down into a groundlike state. The apparent constant difference between work values over the range indicates that the breakdown occurs at pressures less than 25 MPa. Starch has the highest work of compression at all peak pressures, consistent with its high degree of volume reduction (Fig. 2).

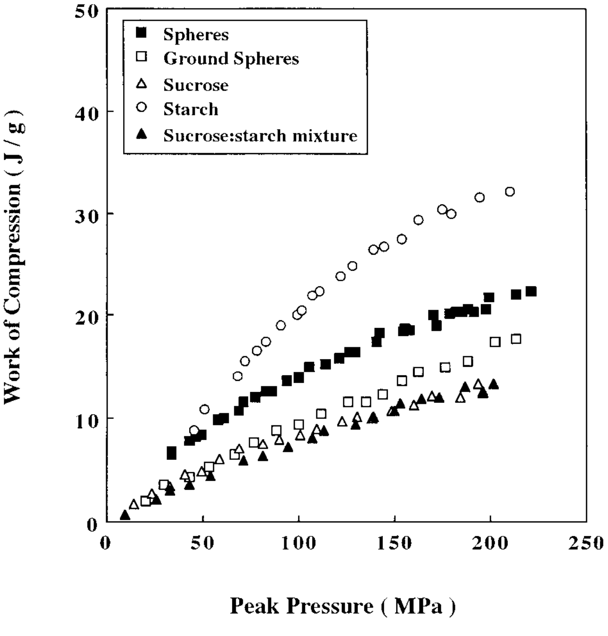

Figure 4. Work of compression versus peak pressure for tablets compressed from Sugar Spheres NF and their components.

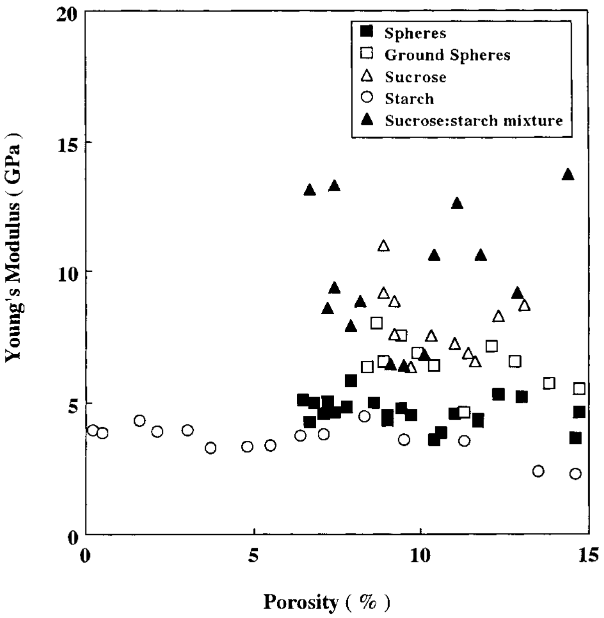

Figure 5. Young's modulus versus porosity for tablets compressed from Sugar Spheres NF and their components.

Figure 5 shows values of Young's modulus with respect to the porosity of the tablets. A low value of Young's modulus indicates a compact that has a high degree of axial expansion during decompression. Starch has the lowest Young's modulus, which indicates the highest degree of elasticity. For example, a 4-mm thick compact compressed from starch at a peak pressure of 200 MPa will expand by about 0.2 mm (5% of the compact thickness at peak pressure). Like starch, compacts compressed from pristine spheres have low values of Young's modulus and expand to about the same degree as starch. The values for Young's modulus for ground spheres and sucrose over the porosity range are very similar. At 200 MPa, when the porosity of both compacts is approxi-

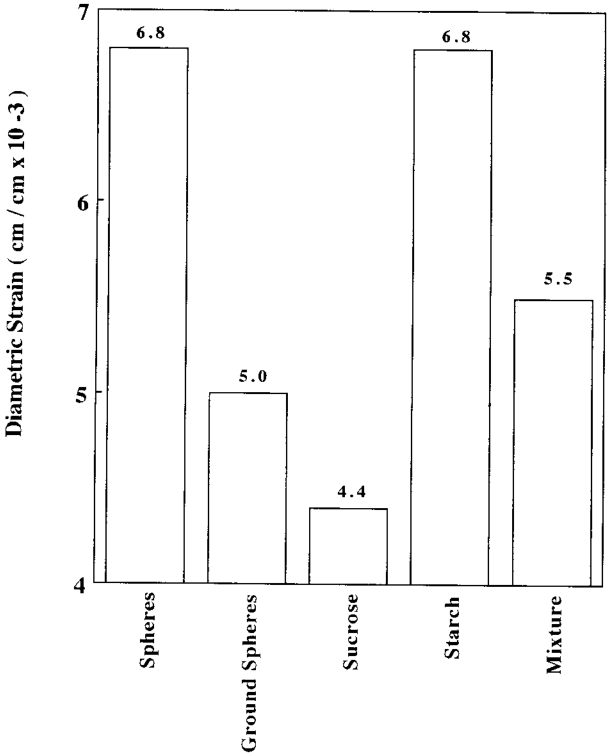

Figure 6. Diametric strain for tablets compressed from Sugar Spheres NF and their components.

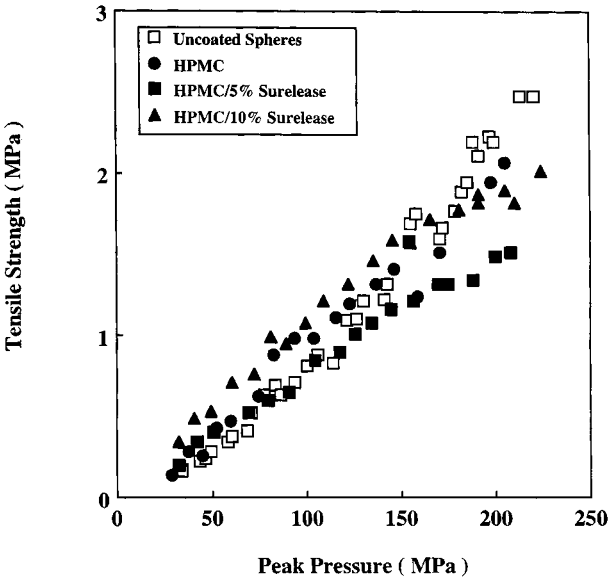

Figure 7. Tensile strength versus peak pressure for tablets compressed from coated and uncoated Sugar Spheres NF.

mately 8%, the value of Young's modulus for each is about 8 GPa. This value is twice that for compacts compressed from starch or the pristine spheres, indicating half as much expansion during decompression. Values of Young's modulus for compacts compressed from the sucrose : starch mixture are also higher than those for the starch or the pristine spheres; however, the high degree of scatter in the data does not permit an accurate estimate of the numerical value.

Diametric strain is a function of the change in tablet diameter during diametric loading in a hardness tester. Brittle materials tend to have low diametric strain, while plastic materials have higher values. Figure 6 shows values of diametric strain for compacts compressed at peak pressures of 150 MPa. Compacts compressed from sucrose have the lowest values for diametric strain, indicating their brittle nature, while values for compacts compressed from starch or the pristine spheres are higher, indicating greater plasticity. Tablets compressed from ground spheres have a low value for diametric strain, indicating a more brittle compact. The diametric strain of the sucrose : starch mixture falls between those of sucrose and starch, indicating a blending of the properties of the parent materials.

Compression of Coated Spheres

Mechanical properties of tablets compressed from coated spheres are generally comparable to the corresponding properties of tablets compressed from uncoated spheres. The presence of the HPMC/dye coating and additional amounts of the ethylcellulose membrane produced few changes in the mechanical properties of these tablets, presumably because the amounts of the coatings are small compared to the mass of the spheres themselves. Figure 7 shows the tensile strength of tablets compressed from coated spheres. Profiles are comparable for all samples at lower peak pressures, while tensile strengths of the tablets compressed from spheres coated with 5% Surelease are slightly lower at higher peak pressures. A similar pattern is seen when the work of compression is plotted against peak pressure in Figure 8. Values are slightly lower for tablets compressed from spheres coated with either 5% or 10% Surelease, but overall, profiles are virtually identical. All samples show similar decreases in porosity (Fig. 9) and peak offset times (Fig. 10) with increases in peak pressure. No discernible patterns were seen for values of Young's modulus in any of the samples.

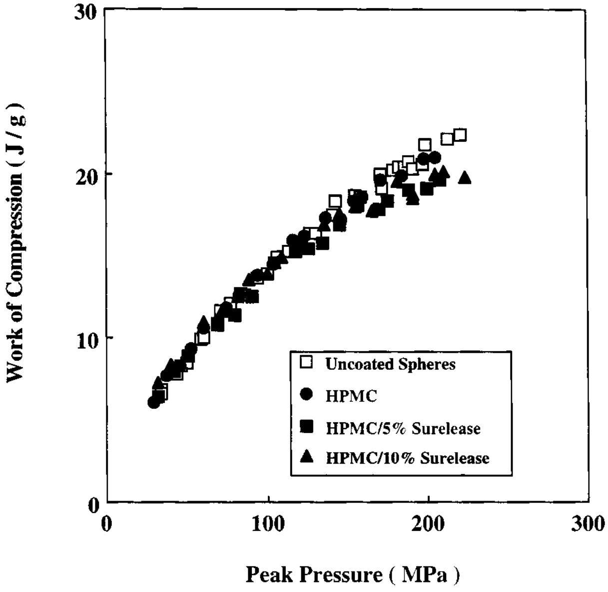

Figure 8. Work of compression versus peak pressure for tablets compressed from coated and uncoated spheres.

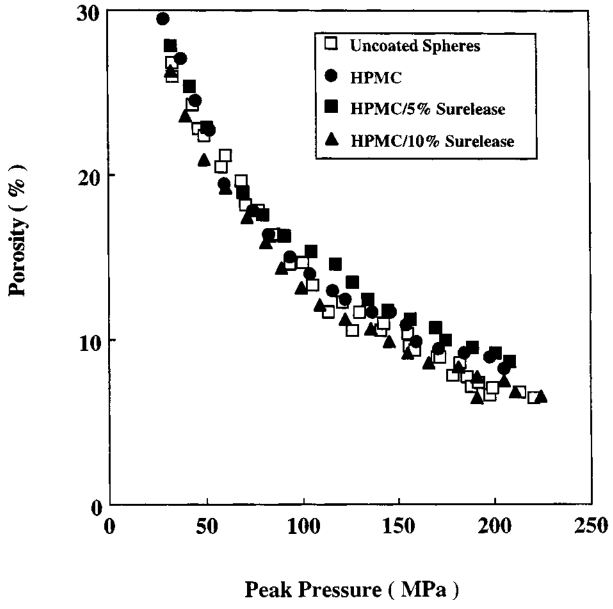

Figure 9. Porosity versus peak pressure for tablets compressed from coated and uncoated spheres.

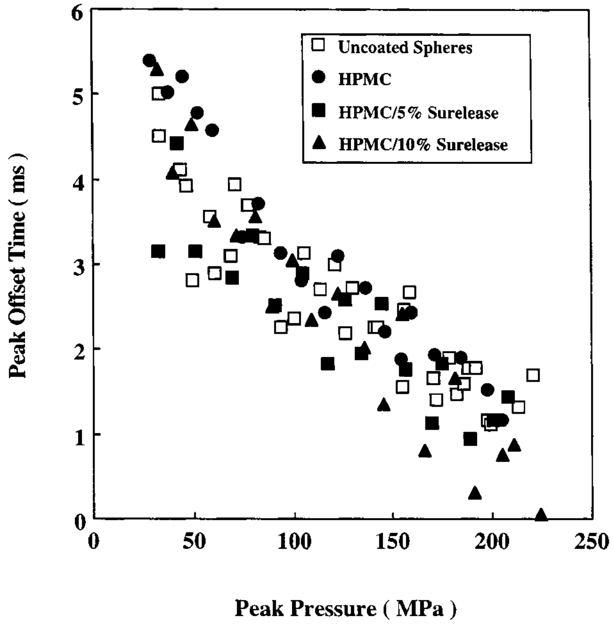

Figure 10. Peak offset time versus peak pressure for tablets compressed from coated and uncoated spheres.

Noticeable differences are seen for tablets compressed from the spheres coated with Surelease when diametric strain is determined. Figure 11 shows values for diametric strain of these tablets along with the values previously seen in Fig. 6. While no apparent difference is seen for the tablets compressed from spheres coated with only HPMC/dye, clear increases are seen for tablets compressed from spheres coated with Surelease. Changes in the values of diametric strain can be attributed to the flexibility of the plasticized ethylcellulose. The presence of this material simply allows greater deformation of the compact to occur prior to failure of the compact.

Dye Release from Coated Spheres

A probe dissolution evaluation was carried out on the uncompressed spheres and the tablets compressed from these spheres to determine any compression-induced changes in the release rates. Dissolution of the dye as a function of time is seen in Fig. 12. Dye dissolution from either compressed or uncompressed spheres coated with only the HPMC/dye layer was rapid. Uncompressed spheres coated with Surelease showed a prolonged release effect, with such effect being greater for the spheres coated with 10% Surelease. Faster release is seen in compacts compressed from these spheres, but little difference

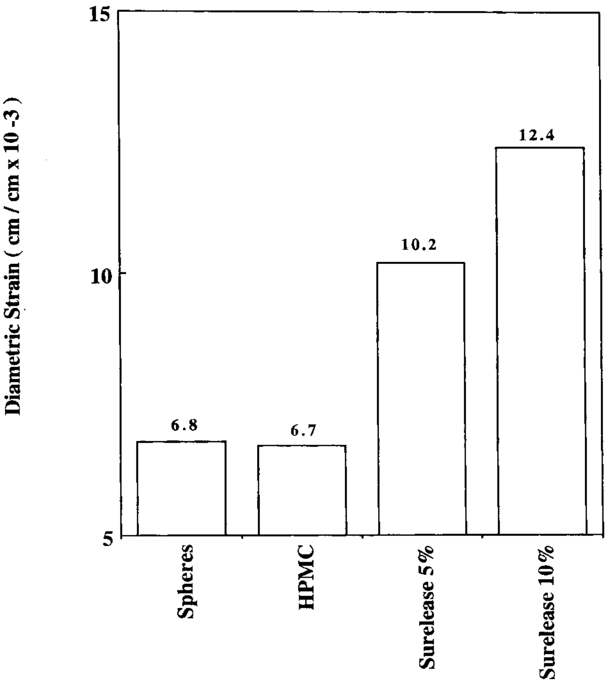

Figure 11. Diametric strain for tablets compressed from coated and uncoated spheres.

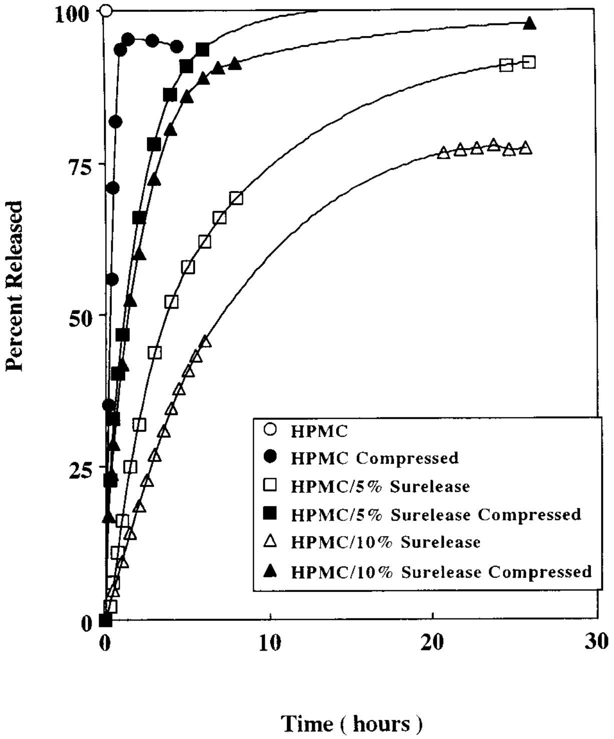

Figure 12. Release profiles of FD&C Yellow #6 from compressed and uncompressed spheres.

is seen between the 5% and 10% coating levels. In both cases, compression had fused the spheres into nondisintegrating compacts that remained intact throughout the dissolution test. Increases in dissolution are attributable to film damage of surface spheres, and the formation of this continuous polymer network explains the greater ability of the compacts to deform, as illustrated by the increases in diametric strain observed during the determination of tensile strength of the compacts.

CONCLUSIONS

Differences between tablets compressed from spheres or their components were attributed to the layering process involved in sphere manufacture as opposed to a simple physical mixing process. The higher work of compression for spheres or starch was attributed to the work involved in particle deformation. The presence of starch in the spheres and the method by which the spheres are formed introduced a flexibility to the material not present in sucrose itself. Such flexibility is lost if the spheres are reduced to powder by grinding.

Most mechanical properties of tablets compressed from the coated spheres are similar to those of tablets compressed from uncoated spheres. This could be anticipated since the bulk of the final sphere is the core itself. Diametric strain during crushing is increased in tablets compressed from spheres coated with Surelease since the plasticized ethylcellulose allows the compact to deform to a greater extent before failure occurs.

Compression of Surelease-coated spheres in the absence of excipients produces a continuous, nondisintegrating matrix. Release of the marker dye is faster than from uncompressed beads due to compression-induced damage to the film, but the formation of the matrix maintains a rate-controlling effect. At the coating levels studied, the formation of the matrix itself is the predominant rate-controlling factor as little difference in release rate is seen between the 5% and 10% coating levels.

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